

ACTIVE A

Effects of Addition of Clopidogrel to Aspirin in
Patients with Atrial Fibrillation who are
Unsuitable for Vitamin K Antagonists

Disclosures

- The presenter has the following relationships:
 - Research grants from, Portola, AstraZeneca, Boston Scientific, St. Jude Medical
 - Lecture and or consulting fees from Sanofi-Aventis, Bristol Myers Squibb, Behringer-Ingelheim, St. Jude Medical

Vitamin K Antagonists in AF

- Reduce stroke by 38%, compared to aspirin
- Recommended in high risk patients with AF
- Only 40-50% of ideal patients receive VKA in Western countries
 - Many patients considered unsuitable
 - Due to poor INR control, concern about bleeding
 - Patient preference

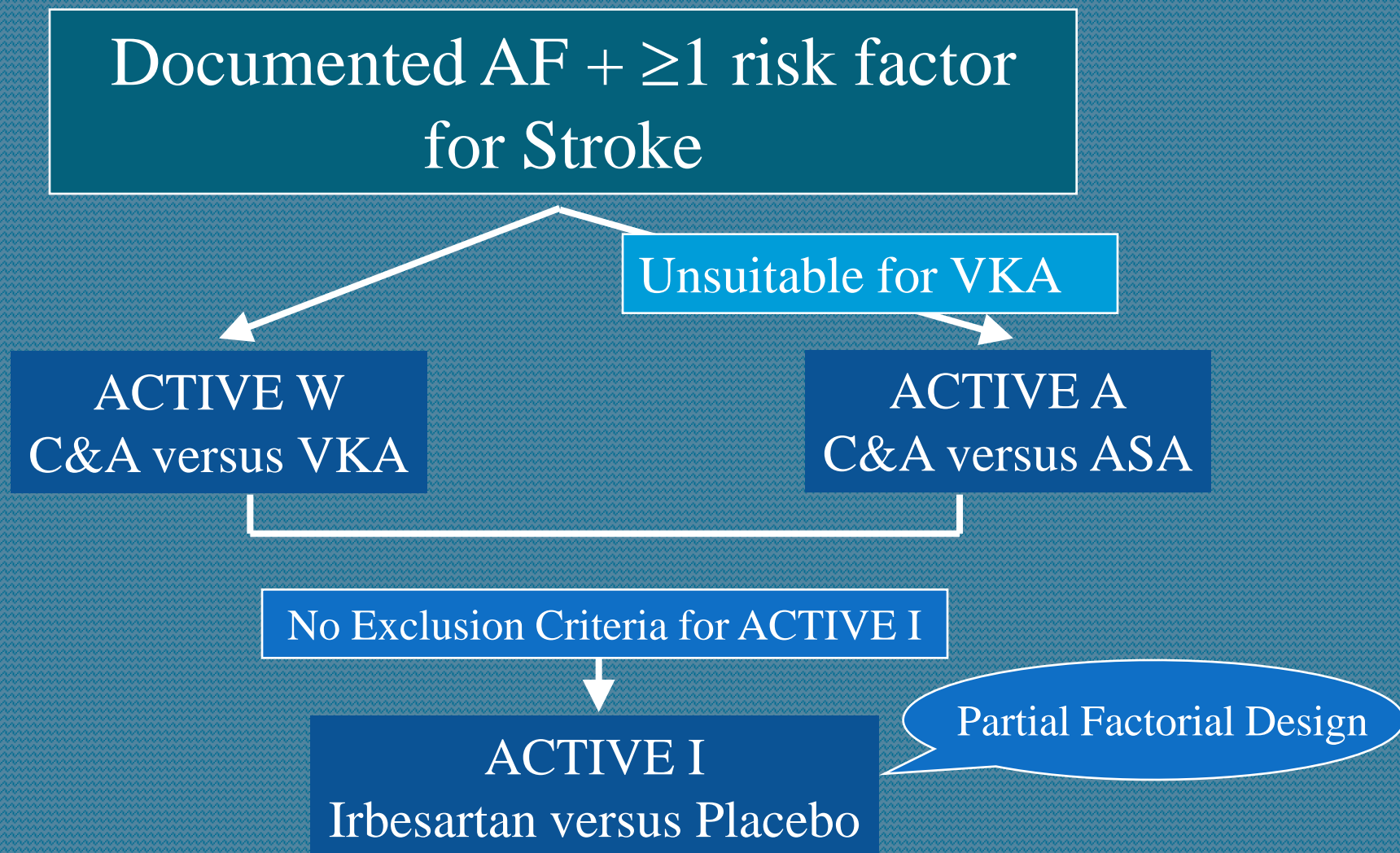
Antiplatelet Therapy in AF

- Increased platelet activation in AF
- Aspirin reduces stroke in AF by 22%
- Addition of clopidogrel to aspirin achieves greater suppression of platelet activity
- Addition of clopidogrel to aspirin reduces vascular events in ACS, with acceptable risk of bleeding

Hypothesis of ACTIVE A

In patients with AF, unsuitable for VKA therapy, addition of clopidogrel to aspirin will reduce the risk of major vascular events, at acceptable risk of major bleeding

Design of ACTIVE



Patient Eligibility

- Eligibility criteria for ACTIVE A and ACTIVE W were identical
 - Documented AF
 - One or more risk factors for stroke
 - Absence of major risk factor for bleeding
- Investigators selected patients for either study based on assessment of suitability for VKA

ACTIVE A Study Treatments

- All patients received aspirin at a recommended daily dose of 75-100 mgs
- Patients were randomized, double blind, to clopidogrel, 75 mg per day, or matching placebo

Outcomes and Statistical Power

- Primary outcome was a composite of major vascular events:
 - Stroke, myocardial infarction, non-CNS systemic embolism or vascular death
- Secondary outcomes
 - Stroke
 - Major hemorrhage
- 7500 patients planned to achieve 88% power to detect 15% reduction in primary outcome (1600 events)

Study Conduct

- 33 Countries, 580 centers
- 7554 patients enrolled between June 2003 and May 2006
- Final follow up in November 2008
 - Median follow up 3.6 years
 - Follow up was complete in 99.4% of patients

Reasons for Enrolment in ACTIVE A

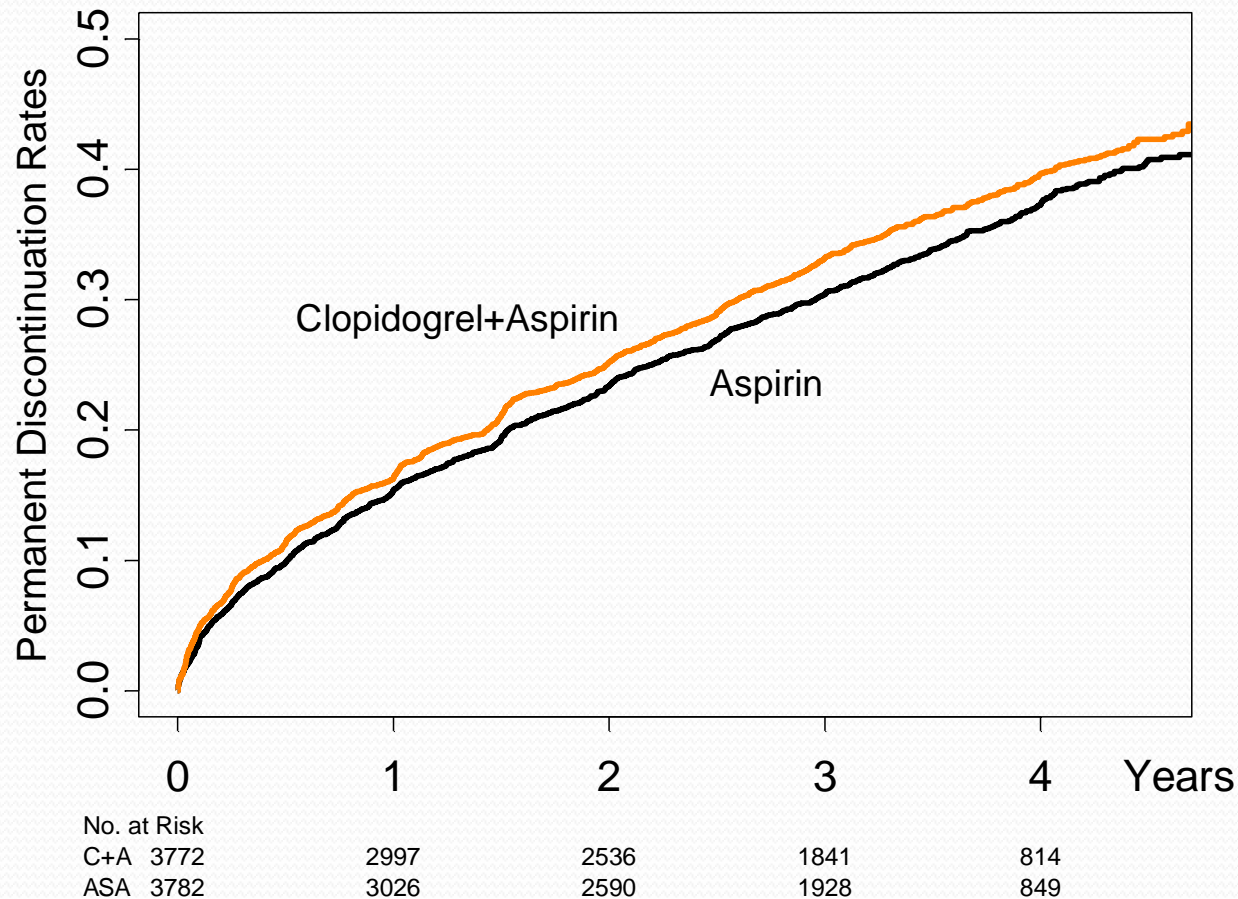
Relative risk factor for bleeding*	23%
Physician assessment that patient is inappropriate for VKA	50%
Patient Preference Only	26%

* Inability to comply with INR monitoring, predisposition to falling or head trauma, persistent BP >160/100, previous serious bleeding on VKA, severe alcohol abuse <2 years, peptic ulcer disease, thrombocytopenia, need for chronic NSAID

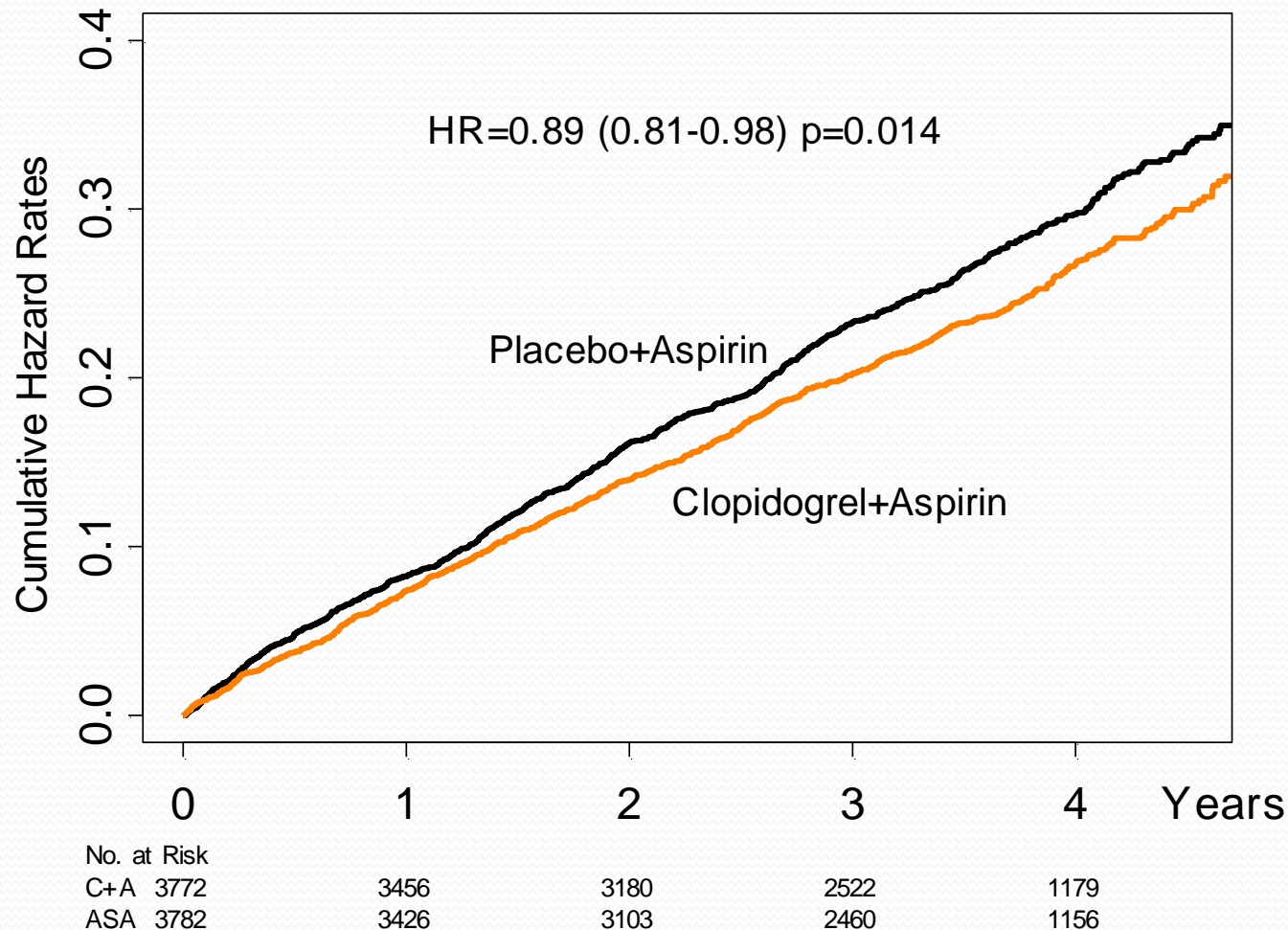
Baseline Demographics

	ACTIVE A	ACTIVE W
N	7554	6706
Mean age (years)	71 ± 10	70 ± 9
Male	58%	66%
Mean systolic BP (mmHg)	136 ± 19	133 ± 19
Permanent AF	64%	68%
Baseline VKA use	8.5%	77%
Baseline aspirin use	83%	26%
Prior MI	14%	18%
Prior stroke or TIA	13%	15%
Mean CHADS ₂ score	2.0 ± 1.1	2.0 ± 1.1

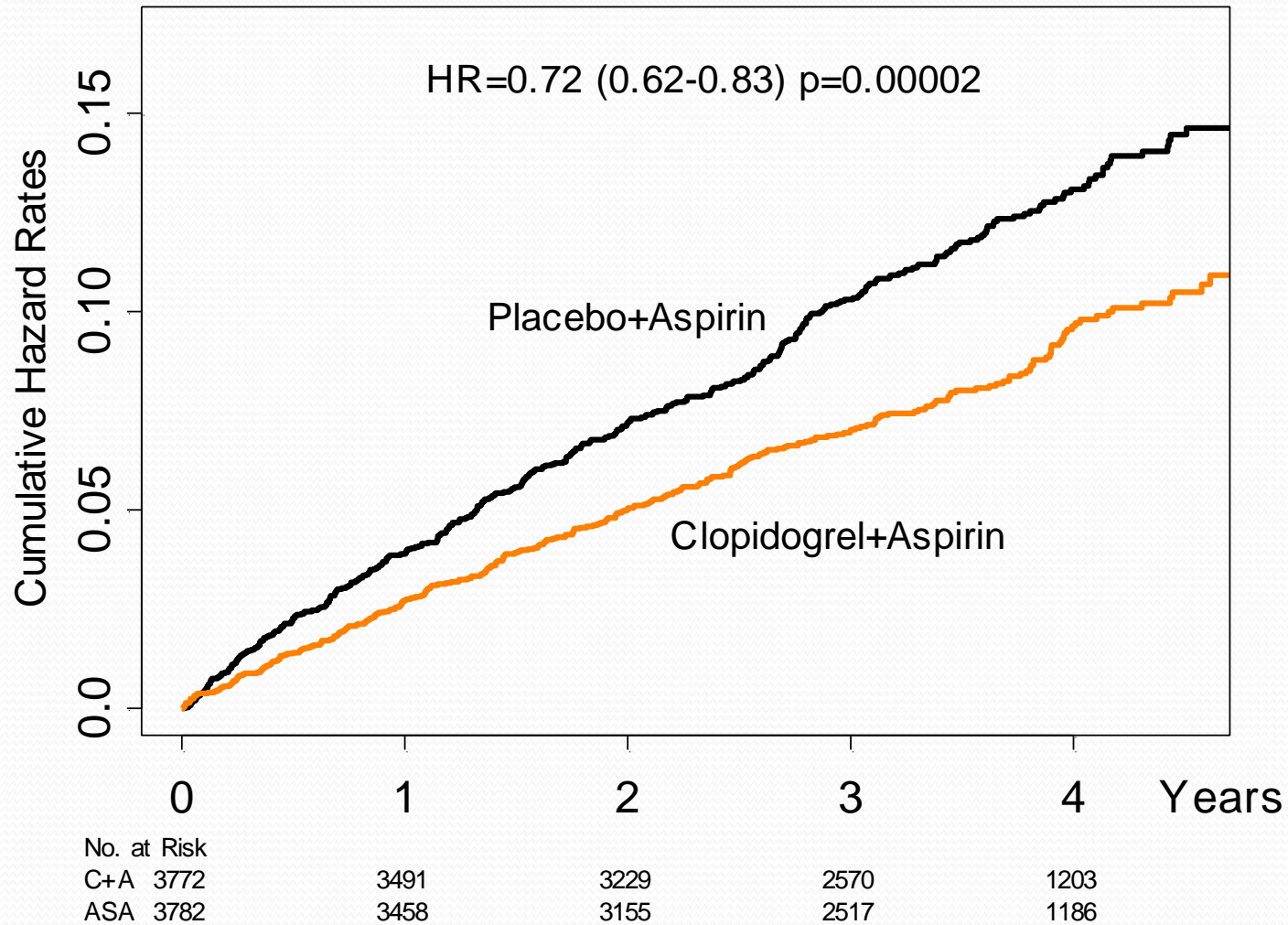
Permanent Study Medication Discontinuation



Primary Outcome (Stroke, MI, non-CNS Systemic Embolism, Vascular Death)



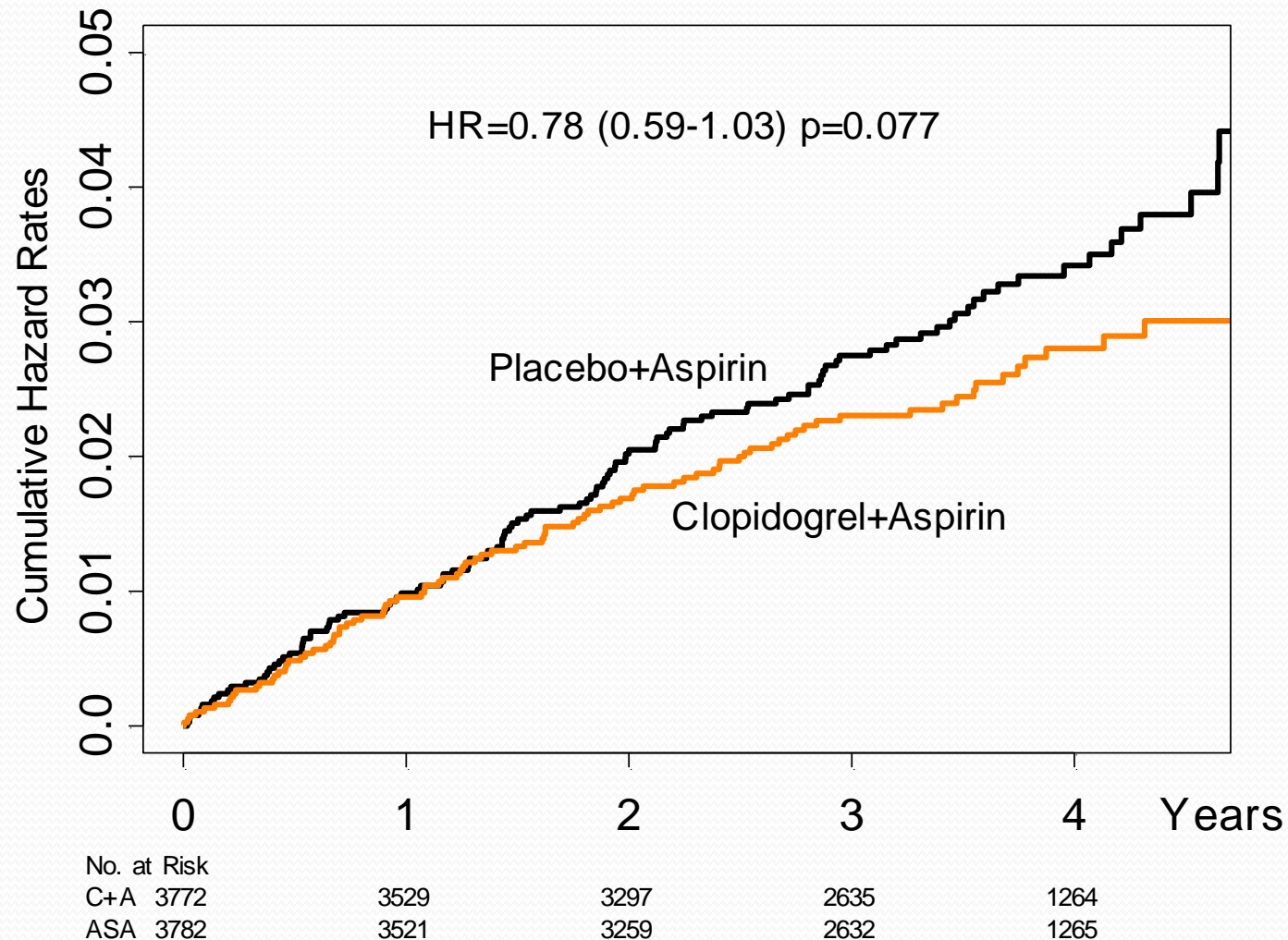
Stroke



Components of the Primary Outcome

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Primary	832	6.8	924	7.6	0.89	0.81-0.98	0.014
Stroke	296	2.4	408	3.3	0.72	0.62-0.83	<0.001
MI	90	0.7	115	0.9	0.78	0.59-1.03	0.08
Vascular Death	600	4.7	599	4.7	1.0	0.89-1.12	0.97
Non-CNS systemic embolism	54	0.4	56	0.4	0.96	0.66-1.40	0.84

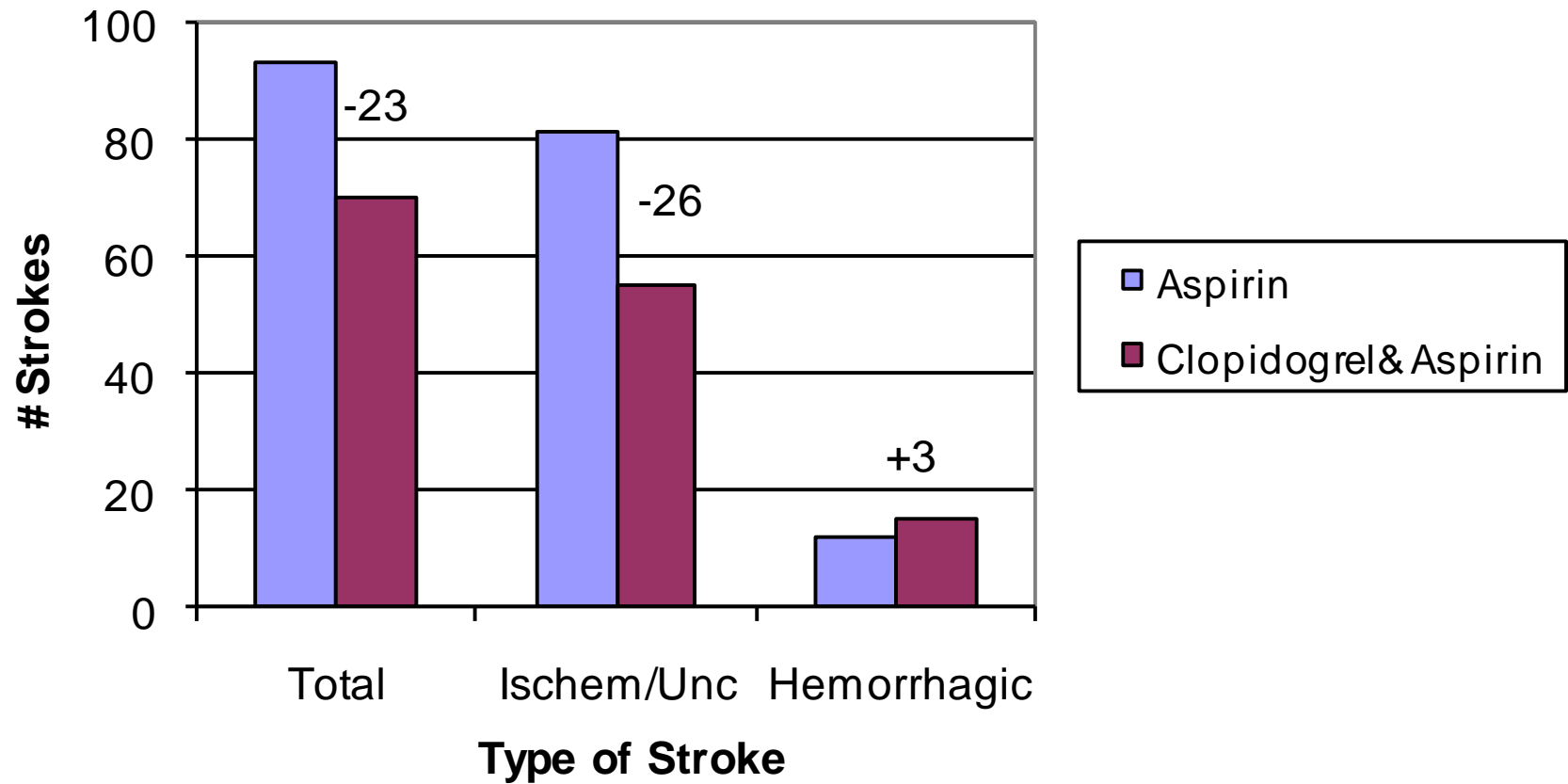
Myocardial Infarction



Stroke Types and Severity

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Ischemic/Uncertain	268	2.1	388	3.2	0.68	0.59-0.80	<0.001
Hemorrhagic	30	0.2	22	0.2	1.37	0.79-2.37	0.27
Non-disabling (mod. Rankin 0-2)	107	0.9	153	1.2	0.70	0.54-0.89	0.004
Disabling or fatal (mod. Rankin 3-6)	198	1.6	267	2.1	0.74	0.62-0.89	0.001

Numbers of Fatal Strokes Prevented



ACTIVE Bleeding Definitions

- Major Bleed
 - an overt bleed requiring ≥ 2 unit transfusion
 - OR
 - severe Bleed
 - drop in hemoglobin of ≥ 5.0 gm/dL
 - hypotension requiring inotropic agents
 - intraocular bleeding leading to substantial vision loss
 - requirement for surgical intervention
 - symptomatic intracranial
 - ≥ 4 unit transfusion
 - fatal

Bleeding

Outcome	Clopidogrel + Aspirin		Aspirin		Clopidogrel + Aspirin versus Aspirin		
	#	rate/ year	#	rate/ year	RR	95% CI	P
Major	251	2.0	162	1.3	1.57	1.29-1.92	<0.001
Severe	190	1.5	122	1.0	1.57	1.25-1.98	<0.001
Fatal	42	0.3	27	0.2	1.56	0.96-2.53	0.07
Intra-cranial	54	0.4	29	0.2	1.87	1.19-1.94	0.006
Extra-cranial	200	1.6	134	1.1	1.51	1.21-1.88	<0.001

Benefits and Risks

1000 patients treated for 3 years

- Will prevent
 - 28 strokes (17 fatal or disabling)
 - 6 myocardial infarctions
- At a cost of 20 (non-stroke) major bleeds (3 fatal)

Conclusions

Addition of clopidogrel to aspirin in high risk AF patients, unsuitable for VKA:

- Reduces major vascular events
- Primarily due to a reduction in stroke
- With an increase in major bleeding

It provides an important benefit to many patients, at an acceptable risk

Back up Slides

Understanding ACTIVE A and ACTIVE W

Treatment	Control	Study	RRR for Stroke
VKA	Aspirin	Meta-analysis *	-38 %
VKA	Clopidogrel & aspirin	ACTIVE W (ALL)	-42%
VKA	Clopidogrel & aspirin	ACTIVE W (Naïve)	-29%

*Hart RC et al. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have non-valvular AF . Ann Intern Med 2007; 146: 857-67

Benefits and Risks: Compared to Warfarin

Effects	Warfarin versus Aspirin	Clopidogrel & Aspirin versus Aspirin
	Meta-analysis* (RRR)	ACTIVE A (RRR)
Reduction in stroke	- 38%	-28%
Increase in intra-cranial bleed	+128%	+87%
Increase in extra-cranial bleed	+70%	+51%

*Hart RC et al. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have non-valvular AF . Ann Intern Med 2007; 146: 857-67

ACTIVE A and W: Stroke Rates and Risk Reductions

Treatment	VKA	C+A	Aspirin
ACTIVE W (Rate per year)	1.4	2.4	--
ACTIVE A (Rate per year)	--	2.4	3.3
RRR versus Aspirin	-58%	-28%	--
RRR versus C+A	-42%	--	--