Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

*Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators**

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*Members listed at end of report

Department of Neurology, University of Essen, Hufelandstrasse 55, 45122 Essen, Germany (Prof H C Diener MD); **Department of Neurology, CHUV, Lausanne, Switzerland** (Prof J Bogousslavsky MD); **Department of Neurology, Yale University School of Medicine, New Haven, CT, USA** (Prof L M Brass MD); **Divisione Medicina II, Ospedale Vimercate, Milano, Italy** (Prof C Cimminiello MD); **Department of Neurology, University Medical School of Debrecen, Hungary** (Prof L Csiba MD); **Department of Neurology, University of Helsinki, Finland** (Prof M Kaste MD); **Stroke Department, University of Lille, Lille, France** (Prof D Leys MD); **Service of Neurology, Hospital General Universitario de Alicante, Spain** (Prof J Matias-Guiu MD); **Department of Medicine II, Johannes Gutenberg University Mainz, Mainz, Germany** (Prof H J Rupprecht MD)

Correspondence to:
Prof Hans-Christoph Diener
h.diener@uni-essen.de

Summary

Background **Clopidogrel was superior to aspirin in patients with previous manifestations of atherothrombotic disease in the CAPRIE study and its benefit was amplified in some high-risk subgroups of patients. We aimed to assess whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of vascular events with potentially higher bleeding risk.**

Methods **We did a randomised, double-blind, placebo-controlled trial to compare aspirin (75 mg/day) with placebo in 7599 high-risk patients with recent ischaemic stroke or transient ischaemic attack and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day. Duration of treatment and follow-up was 18 months. The primary endpoint was a composite of ischaemic stroke, myocardial infarction, vascular death, or rehospitalisation for acute ischaemia (including rehospitalisation for transient ischaemic attack, angina pectoris, or worsening of peripheral arterial disease). Analysis was by intention to treat, using logrank test and a Cox's proportional-hazards model.**

Findings **596 (15.7%) patients reached the primary endpoint in the group receiving aspirin and clopidogrel compared with 636 (16·7%) in the clopidogrel alone group (relative risk reduction 6.4%, [95% CI –4·6 to 16·3]; absolute risk reduction 1% [–0·6 to 2·7]). Life-threatening bleedings were higher in the group receiving aspirin and clopidogrel versus clopidogrel alone (96 [2·6%] *vs* 49 [1·3%]; absolute risk increase 1·3% [95% CI 0·6 to 1·9]). Major bleedings were also increased in the group receiving aspirin and clopidogrel but no difference was recorded in mortality.**

Interpretation **Adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack is associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding is increased by the addition of aspirin.**

Introduction

Antiplatelet therapy is a proven component of secondary prevention in patients with transient ischaemic attack or ischaemic stroke.[1] In the CAPRIE trial,[2] clopidogrel was superior to aspirin in the overall population of patients with recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease, reducing the relative risk for the primary endpoint (ischaemic stroke, myocardial infarction, or vascular death) by 8·7% versus aspirin (p=0·043). For the subgroup of patients with ischaemic stroke as the qualifying event the relative risk reduction was 7·3% and not significant. However, the CAPRIE study was not designed to specifically address this subgroup of patients. In post-hoc analyses, the benefit of clopidogrel was shown to be amplified in high-risk subgroups, including patients with a history of previous ischaemic stroke or myocardial infarction,[3] those with diabetes,[4] those with previous cardiac surgery,[5] and those receiving lipid-lowering therapy.[6] In patients with a history of previous ischaemic stroke or myocardial infarction before their qualifying event, clopidogrel produced a relative risk reduction of 14·9% versus aspirin for the primary CAPRIE endpoint.

Findings of randomised controlled trials in patients with coronary manifestations of atherothrombosis (CURE, CREDO)[7,8] have shown the sustained benefit of clopidogrel on top of standard treatment including aspirin. These therapeutic benefits were all obtained with an acceptable increase in the risk of major bleeding complications.[7,8] These trials provided the rationale to undertake MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients), to find out whether aspirin added to clopidogrel would further reduce the risk of recurrent ischaemic vascular events in high-risk patients after transient ischaemic attack or ischaemic stroke. The potential bleeding risk after addition of aspirin to clopidogrel in some stroke populations, such as in small-vessel disease (patients with lacunar stroke), could not be estimated from previous cardiology trials. Here, we report the main findings from the MATCH trial.

Patients and methods

Patients

Between December, 2000, and April, 2002, we enrolled individuals at 507 centres (stroke units and neurology

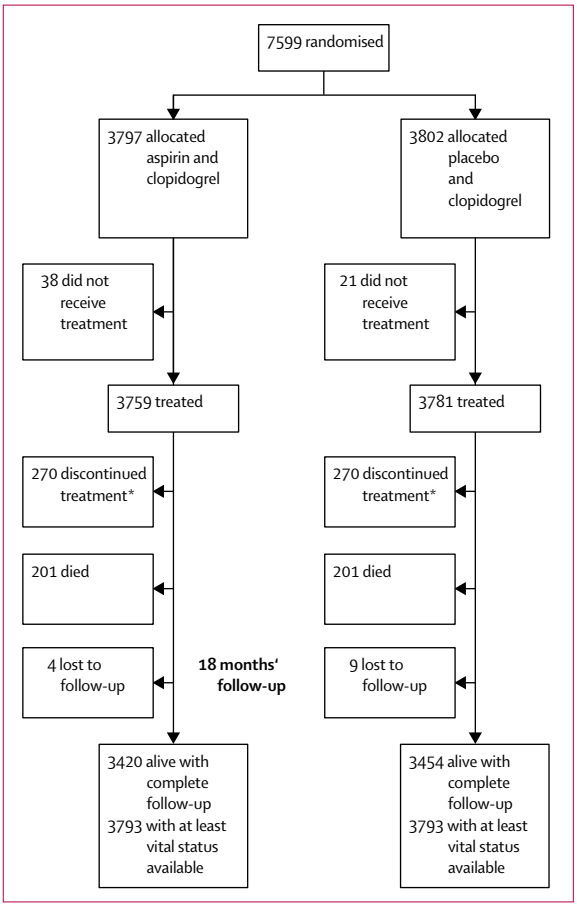


Figure 1: **Trial profile**
*For a reason other than endpoint or adverse event.

departments) in 28 countries. Patients were eligible for inclusion in the study if they had had an ischaemic stroke or transient ischaemic attack in the previous 3 months and had one or more of five additional risk factors—previous ischaemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease—within the previous 3 years. We categorised ischaemic stroke with the TOAST classification.[9] Major exclusion criteria were: age younger than 40 years; severe comorbid conditions; increased risk of bleeding (clinical evidence of severe hepatic insufficiency, current peptic ulceration, history of systemic bleeding, or other history of bleeding diathesis or coagulopathy); scheduled for major surgery or vascular surgery; and contraindications for aspirin or clopidogrel. An independent ethics review was completed and patients gave written informed consent. Follow-up of the last patient was completed in October, 2003.

Procedures

Detailed descriptions of the study methodology and organisation and baseline demographic characteristics of the study population have been published elsewhere.[10] Patients were randomly allocated either aspirin 75 mg once daily or matching placebo tablet; furthermore, all patients received clopidogrel 75 mg once daily. Treatment allocation was done centrally, with an interactive voice-response system (by phone) and was based on a computer-generated list of treatment numbers. Study treatment was started on the day of randomisation and continued for 18 months. After the randomisation visit, follow-up visits were scheduled at 1, 3, 6, 12, and 18 months. These visits were supplemented by monthly follow-up telephone calls to the patient.

The primary endpoint was the first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular death (including haemorrhagic death of any origin), or rehospitalisation for an acute ischaemic event (including unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularisation, or transient ischaemic attack). Secondary endpoints included individual and various combinations of each of the outcomes forming the primary endpoint, and any death and any stroke. Evaluation criteria for safety included incidence of

	Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)
Mean (SD) age (years)	66·5 (9·9)	66·1 (9·9)
Women	1415 (37%)	1406 (37%)
Qualifying event		
Transient ischaemic attack	797 (21%)	808 (21%)
Ischaemic stroke	3000 (79%)	2994 (79%)
Mean (SD) time from qualifying event to randomisation (days)	26·7 (25·3)	26·4 (24·8)
<7 days	736 (19%)	705 (19%)
7 days to 1 month	1857 (49%)	1897 (50%)
⩾1 month (31 days)	1204 (32%)	1200 (32%)
Modified Rankin scale*		
None to slight disability (0–2)	2197 (73%)	2201 (74%)
Moderate disability (3)	455 (15%)	426 (14%)
Severe disability (4 and 5)	348 (12%)	367 (12%)
TOAST classification*		
Cardioembolism	61 (2%)	76 (3%)
Large-artery atherosclerosis	1019 (34%)	1020 (34%)
Small-vessel occlusion	1590 (53%)	1558 (52%)
Stroke of other determined cause	33 (1%)	36 (1%)
Undetermined cause	287 (10%)	304 (10%)
Risk factors and medical history		
Previous ischaemic stroke (before qualifying event)†	1011 (27%)	970 (26%)
Previous transient ischaemic attack (before qualifying event)	716 (19%)	726 (19%)
Previous myocardial infarction†	174 (5%)	189 (5%)
Angina pectoris†	482 (13%)	457 (12%)
Symptomatic PAD†	388 (10%)	388 (10%)
Hypertension	2972 (78%)	2973 (78%)
Diabetes mellitus†	2598 (68%)	2599 (68%)
Hypercholesterolaemia	2126 (56%)	2154 (57%)
Past or current smoker	1825 (48%)	1772 (47%)

Data are number of patients (%) or mean (SD). PAD=peripheral arterial disease. *For patients randomised after an ischaemic stroke only. †Risk factors defined as inclusion criteria.

Table 1: **Baseline characteristics**

life-threatening bleeding (defined as any fatal bleeding event; a drop in haemoglobin of ⩾50 g/L; significant hypotension with need for inotropes [haemorrhagic shock]; symptomatic intracranial haemorrhage, or transfusion of ⩾4 units of red-blood cells or equivalent amount of whole blood) and major bleeding (defined as significantly disabling [with persistent sequelae]; intraocular bleeding leading to significant loss of vision; or transfusion of ⩽3 units of red-blood cells or equivalent amount of whole blood).[10]

Statistical analysis

Based on analyses of the CAPRIE database, the annual event rate in the clopidogrel group for the primary study endpoint was predicted to be 13·3%. Therefore, a study that followed up 7600 patients for 18 months would have 80% power to detect a 14% relative risk reduction for the primary endpoint (α=0·05; two-sided test).

The primary efficacy analysis was by intention to treat, based on all patients who were randomised, irrespective of their compliance with the study protocol. Analysis was based on the first occurrence of an event in the primary endpoint at any point during the follow-up period, including events happening after early permanent discontinuation of study drug (at any point during follow-up). We regarded data for patients who were lost to follow-up as censored at the time of last contact. We assessed several covariables—including age, sex, and ethnic origin—for their potential effects on the primary endpoint, including possible interactions with treatment. Hypothesis testing was done with two-sided tests at the 5% significance level. Survival curves for the two treatment groups were compared by a log-rank test. The relative risk reduction for the addition to clopidogrel therapy of aspirin versus placebo was estimated with Cox's proportional-hazards model. Additional analyses for the primary endpoint to investigate the consistency of the primary results included an on-treatment analysis (only treated patients and events from randomisation up to and including 28 days after early permanent discontinuation of study drug).

We based the safety evaluation on the treated population (all patients who were randomised and received at least one dose of study medication). Statistical analysis of safety data was done with Pearson's χ^2 test. No interim analyses were planned or done but the steering committee (unaware of allocations) regularly monitored the event rate. The data safety monitoring board implemented a sequential procedure for monitoring all-cause mortality throughout the study.

Role of the funding source

The MATCH steering committee had overall responsibility for the implementation of the trial. Sanofi-Synthelabo contracted Parexel International (Paris, France) to undertake site monitoring and data management. Sanofi-Synthelabo provided input into the study through three of its employees, who represented the sponsor on the steering committee (representing only one vote from a total of ten) and paid study-related expenses to the other members of the committee. The data safety monitoring board had full access to the database throughout the trial. The steering committee had full access after closure of the database, and final key analyses were done separately and in parallel by the sponsor and by statisticians who worked independently from the sponsor.

	Number (%) with event		Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	p*
	Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)			
Primary outcome†	596 (16%)	636 (17%)	1·0% (−0·6 to 2·7)	6·4% (−4·6 to 16·3)	0·244
Myocardial infarction (fatal or not)	59 (2%)	62 (2%)	..	..	..
Ischaemic stroke (fatal or not)	299 (8%)	319 (8%)	..	..	..
Other vascular death	69 (2%)	74 (2%)	..	..	..
Rehospitalisation for acute ischaemic event	169 (4%)	181 (5%)	..	..	..

*Log-rank test. †Only the first event was counted. For every component of the primary endpoint, only the event regarded as first outcome from the composite was counted.

Table 2: **Primary endpoint analysis**

Results

A total of 7599 patients were randomised: 3802 were allocated placebo and clopidogrel and 3797 aspirin and clopidogrel (figure 1). At 18 months of follow-up, data were available for 7276 patients (96%), including those who died during the study and those alive at the end of the 18-month period of follow-up: 3621 in the aspirin and clopidogrel group and 3655 in the placebo and clopidogrel group. In 13 patients, vital status was not obtained.

Table 1 shows baseline demographics and medical history. Mean time to randomisation was 26·5 days

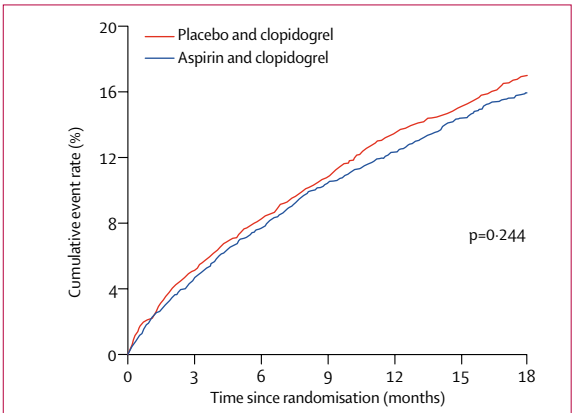


Figure 2: **Kaplan-Meier curves for cumulative rates of primary endpoint events**

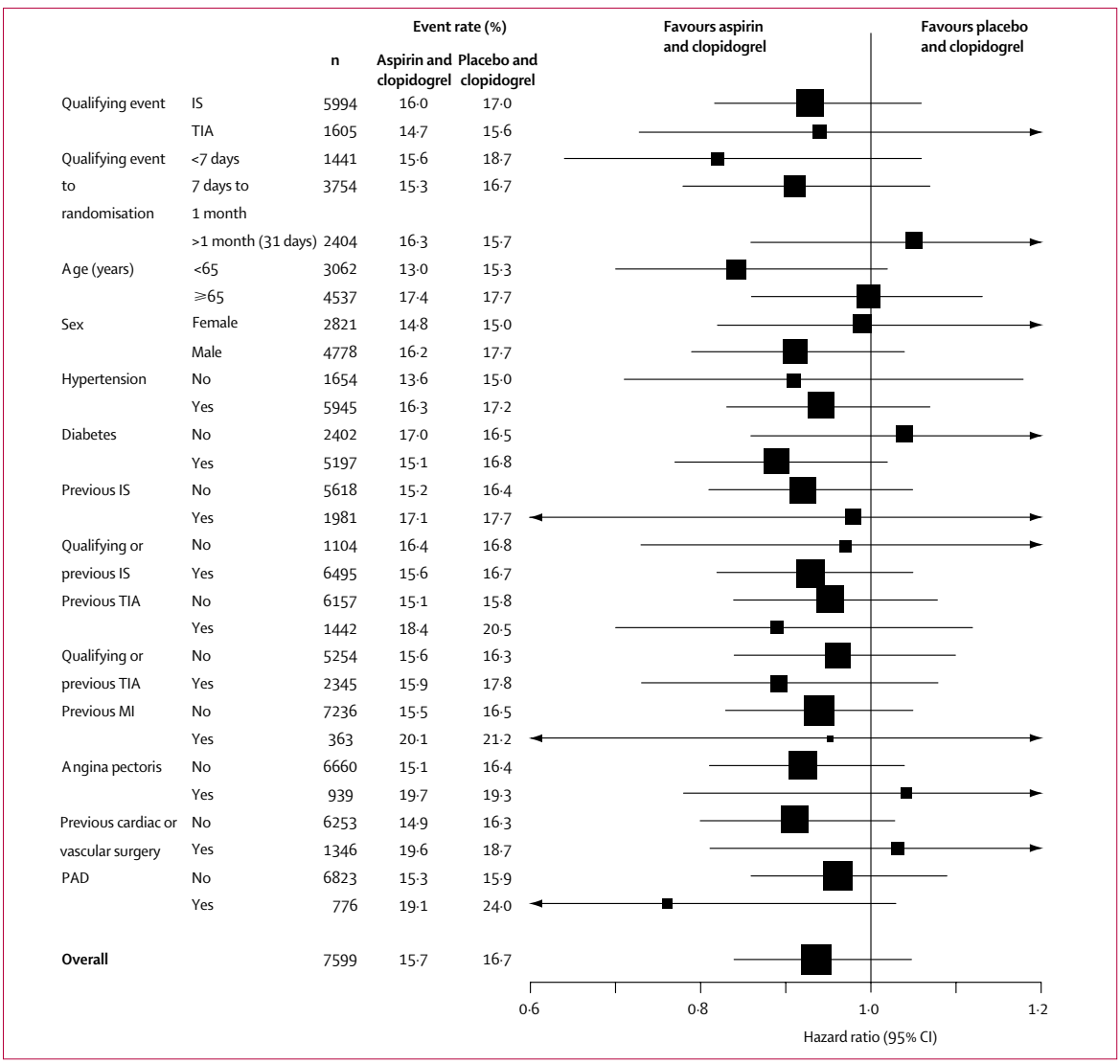


Figure 3: **Rates and relative risks of primary endpoint event in prespecified subgroups**
IS=ischaemic stroke. TIA=transient ischaemic stroke. MI=myocardial infarction. PAD=peripheral arterial disease.

(SD 25). In 5994 patients whose qualifying event was ischaemic stroke, 4398 (73%) had a modified Rankin score of 0–2. According to the TOAST classification system, the principal causes of stroke were small-vessel occlusion (n=3148; 53%) and large-artery atherosclerosis (2039; 34%). The most prevalent risk factors at randomisation were hypertension (78%), diabetes mellitus (68%), and hypercholesterolaemia (56%). 26% of patients had previous ischaemic stroke and 19% had transient ischaemic attack. Most patients (n=6033; 79%) had one additional risk factor, as defined in the inclusion criteria at study entry, and 1496 (20%) had two or more. No imbalance in baseline characteristics was recorded between the two groups.

Table 2 and figure 2 show the primary endpoint analyses. In the placebo and clopidogrel group, the estimated event rate per year for first occurrence of the primary endpoint was 12·7%, consistent with the protocol hypothesis;[10] the on-treatment analysis was consistent with the intention-to-treat analysis (relative risk reduction 9·5%, 95% CI –2·0 to 19·6). Examination of the event rates for the primary endpoint in different predefined patient subgroups indicated a slight favour for adding aspirin to clopidogrel compared with placebo to clopidogrel in most subgroups (figure 3). No interactions were reported between covariates and treatment effect, apart from patient age (p=0·012 for interaction between age and treatment effect). Table 3 shows the secondary endpoint analyses.

Adding aspirin to clopidogrel resulted in significantly more bleeding complications than in the placebo and clopidogrel arm, doubling the number of events (table 4).

No early increase was recorded in life-threatening bleeding and, more specifically, in primary intracranial haemorrhage (figure 4). Symptomatic intracranial haemorrhage was more frequent in the aspirin group than in patients allocated placebo; however, in both treatment arms, no haemorrhagic transformations of ischaemic stroke were reported as life-threatening bleeding,[10] and no significant difference was recorded in the incidence of fatal bleeding. Gastrointestinal bleeds were the most common cause of life-threatening (51 [1·4%] *vs* 21 [0·6%]) and major (42 [1·12%] *vs* 11 [0·29%]) bleeds in patients who were allocated aspirin versus those in the placebo group. Occurrence of non-haemorrhagic adverse events in at least 1% of patients differed significantly between treatments: influenza-like symptoms, abdominal pain, arthralgia, and pruritus were more typical in the placebo and clopidogrel group whereas constipation and anaemia were more frequent in patients allocated aspirin and clopidogrel.

	Number (%) with event		Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	p*
	Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)			
Myocardial infarction, ischaemic stroke, and vascular death	445 (12%)	473 (12%)	0·72% (−0·7 to 2·2)	5·9% (−7·1 to 17·3)	0·360
Myocardial infarction (fatal or not)	73 (2%)	68 (2%)	−0·13% (−0·7 to 0·5)	−7·7% (−49·8 to 22·6)	0·660
Ischaemic stroke (fatal or not)	309 (8%)	333 (9%)	0·62% (−0·6 to 1·9)	7·1% (−8·5 to 20·4)	0·353
Vascular death	124 (3%)	121 (3%)	−0·08% (−0·9 to 0·7)	−2·4% (−31·5 to 20·3)	0·854
Ischaemic stroke (fatal or not) and vascular death	401 (11%)	430 (11%)	0·75% (−0·7 to 2·2)	6·6% (−7·0 to 18·5)	0·324
Any stroke (ischaemic stroke, primary intracranial haemorrhage, or non-classifiable stroke [fatal or not])	339 (9%)	347 (9%)	0·20% (−1·1 to 1·5)	2·0% (−13·8 to 15·6)	0·790
Death (all cause)	201 (5%)	201 (5%)	−0·01% (−1·0 to 1·0)	0·1% (−21·5 to 17·8)	0·992
Non-fatal myocardial infarction, non-fatal ischaemic stroke, rehospitalisation for acute ischaemic event	505 (13%)	546 (14%)	1·06% (−0·5 to 2·6)	7·6% (−4·3 to 18·2)	0·199

*First event counted (independently from the first outcome from the composite of the primary endpoint).

Table 3: **Frequency of secondary endpoint events**

Discussion

In most patients, a consistent reduction of primary and secondary vascular events was recorded with aspirin added to clopidogrel, although the differences were not significant. The relative risk reduction in favour of aspirin in the intention-to-treat population of 6·4% is in the range that was reported in the CAPRIE trial (8·7%).[2] Addition of aspirin to clopidogrel in the MATCH trial resulted in a significantly higher bleeding rate that offset any beneficial effect. No significant increase in fatal bleeding was recorded and mortality was the same in both groups. Besides intracranial haemorrhage, the principal type of major or life-threatening bleeding that was increased by adding aspirin to clopidogrel was gastrointestinal bleeding, most probably indicating the known deleterious effect of aspirin on the gastrointestinal mucosa[11,12] and the associated excess in bleeding risk.[13–16]

Our results of risk of intracranial haemorrhage and gastrointestinal bleeding accord with those reported in the CAPRIE study.[2,17] In the CURE and CREDO trials,[7,8] the combination of clopidogrel and aspirin was clearly superior to aspirin alone for prevention of vascular endpoints in patients with coronary heart disease. Moreover, in these studies, the increase in bleeding risk with the combination was smaller than in MATCH, resulting in a positive benefit to risk ratio. These trials, however, had different designs to MATCH, whereby clopidogrel was added to aspirin treatment; thus, they provided a measure of the benefit to risk ratio of clopidogrel in addition to aspirin, not for aspirin added to clopidogrel as in MATCH. Bleeding complications in MATCH were constant over time, which could indicate that for long-term trials, a time margin exists at which risk outweighs benefit.

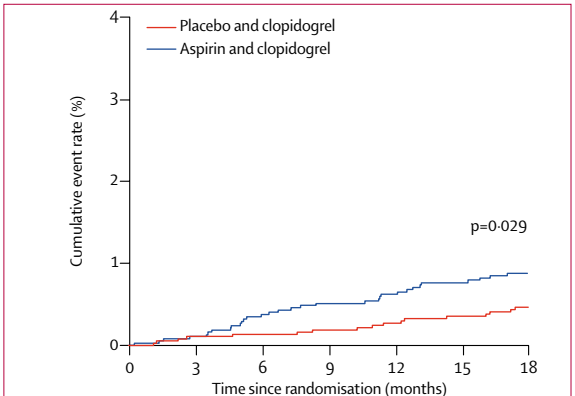
The inclusion criteria in MATCH were designed to select high-risk patients, and most eligible patients could justifiably be expected to have previously received aspirin therapy. Indeed at baseline, 80% of patients in MATCH were receiving aspirin.[10] Based on the amplified benefit of clopidogrel versus aspirin seen in high-risk subgroups of patients in the CAPRIE study[2] and the benefits of the combination of clopidogrel and aspirin in cardiology, clopidogrel was chosen as the comparator in MATCH.

How can the differences between this trial and the cardiology trials be explained? First, most patients included in MATCH had lacunar strokes due to microangiopathy, which might not be of pure atherothrombotic origin. Furthermore, an increased bleeding rate has been noted with anticoagulation in patients with small-vessel disease. Second, increased biological activity might not translate into increased benefit, because the rise in bleeding rates could counterbalance the positive effects seen in certain clinical settings. This effect has been shown for oral glycoprotein IIb/IIIa antagonist therapy in the secondary prevention of stroke,[18] although in that case, potent

	Number (%) with event		Difference (%) between aspirin and placebo (95% CI)	p*
	Aspirin and clopidogrel (n=3759)	Placebo and clopidogrel (n=3781)		
Life-threatening bleeding	96 (3%)	49 (1%)	1·26 (0·64 to 1·88)	<0·0001
Fatal bleeding	16 (<1%)	11 (<1%)	0·13 (−0·14 to 0·40)	
Non-fatal bleeding	81 (2%)	38 (1%)	1·15 (0·59 to 1·71)	
Symptomatic intracranial haemorrhage†	40 (1%)	25 (1%)	0·40 (−0·01 to 0·82)	
Primary intracranial haemorrhage	32 (1%)	17 (<1%)	0·40 (0·04 to 0·76)	
Major bleeding	73 (2%)	22 (1%)	1·36 (0·86 to 1·86)	<0·0001
Minor bleeding	120 (3%)	39 (1%)	2·16 (1·51 to 2·81)	<0·0001

*Pearson's χ^2 test. †All symptomatic (and thus primary) intracranial haemorrhages were life-threatening bleeds.

Table 4: **Number (%) of patients with bleeding events**



Patients at risk

Aspirin and clopidogrel	3724	3691	3643	3601	3552	3508	2756
Placebo and clopidogrel	3781	3576	3686	3638	3582	3544	2823

Figure 4: **Kaplan-Meier curves for cumulative rates of primary intracranial haemorrhage**

antiplatelet inhibition was associated with increased mortality, leading to early discontinuation of the trial.

The size of the treatment effect seen in MATCH might be in line with the benefit shown in previous meta-analyses in patients with ischaemic stroke or transient ischaemic attack, in which a 13% relative risk reduction in favour of aspirin versus placebo was described.[19] The effect of aspirin might be also limited in patients with diabetes, as suggested in the primary prevention project.[20]

What are the practical outcomes of the MATCH trial? Because of benefit to risk considerations, the trial did not show additional clinical value of adding aspirin to clopidogrel in high-risk patients with transient ischaemic attack or ischaemic stroke. Additional information on the use of clopidogrel and aspirin combination therapy in patients at low risk of these events will be investigated in the current CHARISMA trial comparing clopidogrel and aspirin with aspirin alone in primary and secondary prevention.[21] Furthermore, data will also be forthcoming in patients with cerebrovascular disease of different causes: acute transient ischaemic attack and minor ischaemic stroke in FASTER, lacunar strokes in Secondary Prevention of Small Subcortical Strokes (SPS3), and ischaemic strokes arising from aortic arch plaques in ARCH.

Contributors

H-C Diener had the idea for the study design, chaired the MATCH steering committee, and wrote the first draft of the manuscript. J Bogousslavsky, L M Brass, C Cimminiello, L Csiba, M Kaste, D Leys, J Matias-Guiu, and H-J Rupprecht contributed towards study design, interpretation of data, and revision of the manuscript.

MATCH investigators

Steering committee—H C Diener, Essen, Germany (Chair); J Bogousslavsky, Lausanne, Switzerland; L Brass, New Haven, CT, USA; C Cimminiello, Milano, Italy; L Csiba, Debrecen, Hungary; M Kaste, Helsinki, Finland; D Leys, Lille, France; J Matias-Guiu, Alicante, Spain; H J Rupprecht, Mainz, Germany; and F Bigonzi, A Denys, and D Roome (representatives from Sanofi-Synthelabo).
Adjudication committee (Dresden, Germany)—R von Kummer, (Chair); G Gahn; D Mucha; A Müller, H Reichmann; A Schmeißer; T Schwarz; O Wunderlich; and S Helm.
Data safety monitoring board—J M Orgogozo, Bordeaux, France (Chair); J D Easton, Providence, USA; C Fieschi, Rome, Italy; W Hacke, Heidelberg, Germany; A Whitehead, Reading, UK (statistician).
Statistical analyses—D Dukovic for Sanofi-Synthelabo; M Buyse and G Sturbois from International Drug Development Institute working independently for the data safety monitoring board.
Principal investigators
Australia (227 patients): C Bladin; D Crimmins; S Davis; G Donnan; J Frayne; D Freilich; D Gillies; A S Zagami; G Hankey; G Herkes; N Ingham; C Levi; S Read; D Schultz; J Watson; M Williams.
Austria (89 patients): F Aichner; M Brainin; W Lalouschek; C Schmidauer; R Schmidt.
Belgium (175 patients): S Blecic; P Cras; P Caekebeke; P De Deyn; J De Reuck; P Desfontaines; P Laloux; R Madou; A Michotte; A Peeters; W Robberecht; B Sadzot; G Vanhooren.
Canada (182 patients): N Bayer; M Beaudry; L Berger; R Cote; H Desai; V Hachinski; L H Lebrun; G Moddel; J W Norris; A Penn; S Phillips; D Selchen; A Shuaib; D Simard; D Spence; P Teal; A Turpie; T Winder.
Czech Republic (508 patients): M Bar; J Bauer; E Ehler; Z Kadanka; L Kamenik; L Kotik; J Neumann; J Polivka; V Prochazka; O Skoda; J Sroubek; K Urbanek; G Waberzinek; D Weberová.
Denmark (146 patients): G Andersen; K Elleman; S Husted; H Iversen; J O Jarden; E Jensen; H Kraemmer Nielsen; P Petersen; D Rasmussen; T Sørensen; B Traberg Kristensen; K Virring Sørensen; M Worm.
Estonia (44 patients): S Haldre; A Kreis.
Finland (177 patients): V M Ala-Hurula; M Hillbom; T Jolma; M Kaislakoski; M Kaste; E Kinnunen; K Koivisto; J Puranen; A Rissanen; J Sivenius; I Tarvainen.
France (458 patients): P Amarenco; A Autret; M Bataillard; J Boulliat; M G Bousser; H Cambon; S Canaple; J P Caussanel; F Chedru; F Chollet; P Clavelou; T De Broucker; R Decombe; H Decousus; X Ducrocq; E Ellie; Y M Frances; G Géraud; M Giroud; B Guillon; M Hommel; H Hosseini; T Rosolacci; F Nicoli; P Labauge; C Lucas; M H Mahagne; J L Mas; L Milandre; T Moulin; F Mounier-Véhier; J P Neau; Y Onnient; M Pages; J F Pinel; G Rancurel; G Rodier; E Roullet; G Said; C Tannier; P Trouillas; J M Warter; F Ziegler.
Germany (853 patients): E Bartels; P Berlit; T Brandt; O Busse; W Christe; G Deuschl; H C Diener; W Dippold; K M Einhäupl; F Erbguth; A Ferbert; G Gahn; M Görtler; H Griese; M Grond; R Haberl; G Hamann; A Hartmann; W D Heiß; M Hennerici; A Hetzel; M Horn; R W C Janzen; J Jörg; M Kaps; C Kessler; J Klingelhöfer; A Lindner; P Marx; S Meves; S Müller-Jensen; C Neumann; B Griewing; J Noth; G Ochs; W Oertel; V Rammler; S Ries; E B Ringelstein; D Schneider; R Schneider; A Schwartz; M Schwarz; G Seidel; E Stark; M Stöhr; H Schütz; A Thie; C Weiller; B Widder; H Wiethölter; O Witte.
Greece (120 patients): C Karageorgiou; A Kyritsis; I Milonas; A Papadimitrou; A Plaitakis; K Vemmos.
Hong Kong (62 patients): R T F Cheung; L R S Wong.
Hungary (384 patients): A Csanyi; L Csiba; M Csornai; P Dioszeghy; A Fazekas; S Horvath; G Jakab; K Karsay; S Komoly; P Köves; V Nagy; J Nikl; I Sagi; J Semjen; P Soltesz; N Szegedi.
Israel (156 patients): N Bornstein; B Gross; Y Herishanu; S Honigman; Y Lampel; R Milo; M Rabey; A Reches; J Streifler; D Tanne; D Yarnitsky.
Italy (427 patients): M Balestrino; L Bartolomei; N Battistini; L Belloi; E Bottacchi; P Bovi; A Carolei; A Cavallini; G Cazzato; V Crespi; L Ferini-Strambi; C Frattola; C Gandolfo; G L Gigli; A Gomitoni; E Grasso; A Guccione; D Guidetti; M Guidotti; D Inzitari; G L Lenzi; G Micieli; L Murri; R Musolino; E Natalè; G Orefice; G Orlandi; M Paciaroni; A Pirisi; M Poloni; L Provinciali; ML Sacchetti; I Santilli; L Scarzella; O Scarpino; A Spissu; R Sterzi; M Venti; GVinci; V Toso.
Lithuania (226 patients): I Bickuviene; V Budrys; A Kirkutis; V Pauza; A Sciupokas.
Netherlands (303 patients): P J van den Berg; J Boiten; P J A M Brouwers; J H A de Keyser; P L M de Kort; M de Waal; J C den Heijer; P J Dippel; J J M Driesen; C L Franke; C J Gijsbers; R J Hertzberger; P H E Hilkens; D J Kamphuis; L J Kapelle; P J Koudstaal; J Lodder; E S Louwerse;

J U R Niewold; P H H Pop; P J M Raedts; E A C M Sanders; H M A van Gemert; H B C Verbiest; E P Vries; R J G M Witjes; E J Wouda.
Norway (105 patients): C Eika; E Ellekjaer; B Indredavik; R Kloster; I Lofsnes; R Ofstad; S Roalso; Y Ronning; O Rosjo; R Solhoff; L Thomassen.
Poland (561 patients): M Arciuch; A Czlonkowska; W Drozdowski; W Fryze; J Huczynski; A Klimek; J Kochanowski; J Kotowicz; W Kozubski; B Ksiazkiewicz; A Kuczynska; H Kwiecinski; M Lyczywek-Zwierz; Z Maciejek; A Niewodniczy; P Nowacki; S Ochudlo; K Pierzchala; J Pniewski; R Podemski; K Selmaj; J Slawek; A Stepien; M Strzelecka-Gorzynska; A Szczudlik; A Wajgt; P Zaleski.
Portugal (199 patients): M Cândido; C Correira; L Cunha; J Ferro; J Fontes; J Grilo Gonçalves; R Martins; M Rojão; V Salgado.
Singapore (136 patients): H M Chang; N V Ramani.
Slovenia (56 patients): A Grad; B Meglic.
Spain (848 patients): L C Alvaro; J Alvarez-Sabín; A Arboix; F Barriga; F Cañadillas; J Castillo; A Chamorro; J A Cortés Laiño; A Cubero; A Dávalos; J Díaz; E Díez-Tejedor; J A Egido; O Fernández; A Fernández Barreiro; J Gállego; A Gil-Nuñez; A Gil-Peralta; J González; F Gracia; J M Trejo; D Jiménez-Hernández; C Jiménez-Martínez; C Jiménez-Ortiz; N Vilá; A Lago; J M Lainez; J Larracoechea; J F Martí Massó; J L Martí-Vilalta; J Masjuan; E Mostacero; R Navarro; M Rebollo; J Romero; J Roquer; F Rubio; J Sánchez-Herrero; J Sancho-Riegger; J Tejada; J Vivancos.
Sweden (72 patients): E Bertholds; M Crisby; S Karlsson; B Leijd; J E Olsson; P Palmqvist; J Radberg; T Strand; R Unden-Goransson; N G Wahlgren; T Wallen.
Switzerland (148 patients): R Baumgartner; J Beer; J Bogousslavsky; A Gallino; B Hess; H J Hungerbühler; P Lyrer; P Maire; H Mattle; F Müller; H Schaad; R Sztajzel; B Tettenborn; P Vuadens.
Taiwan (55 patients): J S Jeng; S B Jou.
UK (293 patients): A Al-Memar; J Bamford; D Barer; P Bath; B Bhowmick; M Brown; S Ellis; L Erwin; G Ford; C Gray; P Humphrey; D Jenkinson; K Lees; G Lowe; R MacWalter; H Markus; K Muir; P Murphy; H Rodgers; T Rudd; D Sandeman; A Sharma; H Shetty; P Tyrrell; G Venables; J Wade; L Warburton; M Watt.
USA (589 patients): G Albers; M Alberts; R Atkinson; K Becker; J Belden; R Bell; A Bernstein; J Biller; J Brandes; J Brillman; A Callahan; R Chan; C Chaves; T Chippendale; W Clark; B Coull; B Dandapani; P Davis; T Devlin; W Felton; W Felton; K Furie; B Gheorghiu; J Gilroy; G Graham; J Grotta; T Habiger; J Hanna; J Harris; W Holt; S Horowitz; B Jacobs; C Kase; R Kelley; H Kirshner; E Labadie; S Laowattana; L Lennihan; K Levin; R Libman; D Liefer; G Locke; P Lyden; K Madden; S Malenbaum; S Markind; E Marsh; J McDowell; F McGee Jr; R Meckler; P Mitsias; M Nash; K Ng; F Nichols; M Pato; C Perkins; T Perkins; LC Pettigrew; P Reynolds; R Sacco; H Sachdev; M Sauter; J Schechter; A Segal; D Sherman; C Sila; S Silliman; R Stephens; D Thaler; A Turel; J Wilterdink; R Zweifler.

Conflict of interest statement

HCD is or has been a consultant or speaker for AstraZeneca, GlaxoSmithKline, Pfizer, Boehringer Ingelheim, BASF, Abbott, Novartis, Parke-Davis, MSD, Servier, Sanofi-Synthelabo, Bayer, Fresenius, and Janssen Cilag. LMB has been a consultant or speaker for Bristol Myers Squibb, Merck, Sanofi-Synthelabo, Solvay, Ono, AstraZeneca, and Wyeth and has received grants for research from Bristol Myers Squibb and Sanofi-Synthelabo.

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