DIPYRIDAMOLE MAY BE USED SAFELY IN PATIENTS WITH ISCHAEMIC HEART DISEASE

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SUMMARY It is thought that up to 50% of patients with cerebrovascular disease will have concurrent ischaemic heart disease. Dipyridamole co-formulated with aspirin has been shown to increase the relative reduction in risk of second stroke in patients with prior stroke/transient ischaemic attack beyond that obtaining with aspirin alone. We have sought to resolve the question of whether dipyridamole treatment increases the risk of cardiac adverse events in patients with co-existing ischaemic heart disease. The published literature, periodic safety update reports, the randomised controlled trials of antiplatelet agents in stroke prevention and those including dipyridamole in cardiovascular indications, have been reviewed and analysed. The early reports of serious adverse cardiac effect attributable to dipyridamole occurred in patients with severe coronary artery disease using dipyridamole as a stress test adjunct to cardiac imaging. The randomised controlled trials databases show no evidence of mortality and only isolated cases of significant cardiac morbidity attributable to dipyridamole at recommended oral doses in patients with ischaemic heart disease. We conclude that patients with cerebrovascular and mild to moderate concomitant ischaemic heart disease may be treated safely with dipyridamole for the secondary prevention of stroke.
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Dipyridamole has recently been approved for use in secondary prevention of ischaemic stroke and transient ischaemic attack (TIA). It is thought that up to 50% of patients with cerebrovascular disease also have concomitant ischaemic heart disease. A recent analysis[1] of the second European Stroke Prevention Study[2] investigating the proportion of patients who had ischaemic heart disease as diagnosed by history and/or ECG finding revealed that 35% of the total patient entry (6602) had evidence of ischaemic heart disease.

Dipyridamole is also a coronary vasodilator as evidenced by its intravenous use as a pharmacological alternative to exercise stress testing in patients with ischaemic heart disease who are being investigated generally to determine the need for revascularisation procedures. Dipyridamole administered by short intravenous infusion as a stress test prior to thallium imaging of the myocardium, by virtue of what has been called the 'steal' syndrome, allows visualisation of myocardium subtended by the stenotic coronary artery. Thus, the drug in this instance is being used to create relative myocardial ischaemia so as to assist diagnosis. A very large database has shown that the procedure is no more hazardous to the patient than exercise testing.[3] There have been relatively few published case reports[4,5] of angina, myocardial infarction (MI) or cardiac death, in patients with ischaemic heart disease who have received dipyridamole at currently recommended oral doses. In all the cases reported, the patients appeared to have severe coronary artery disease. Dipyridamole by mouth is advised only with caution in patients with severe coronary artery disease, unstable angina or in the period immediately following MI.

In view of the increased likelihood of patients with ischaemic heart disease being treated with dipyridamole for the secondary prevention of ischaemic stroke/TIA, it appears useful to review the cardiac safety of the drug, given that other coronary vasodilators have also been reported to be associated with the precipitation of angina pectoris and/or MI, i.e. sumatriptan, nicotine, nifedipine, diltiazem[6] and, most recently, sildenafil.[7]

SOURCES AND METHODS

A number of sources have been used in compiling this review and include the relevant published literature, formal periodic safety update reports for Persantin® (oral forms), Asasantin® Retard/Aggrenox® (the combination of modified release dipyridamole and aspirin) and Persantin® ampoules, a mortality review[8] from the randomised controlled trials of dipyridamole documented in the Antiplatelet Trialists Collaboration report, and the results of recent large-scale randomised controlled trials including dipyridamole in Boehringer Ingelheim's clinical trials database.

Periodic safety update reports are now required for all medicines in the EU following the issuing of a marketing authorisation and at regular intervals thereafter, culminating in five-yearly reports that are reviewed at the time of renewal of the product licence. Thus a pharmacoepidemiological

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approach is taken by the marketing authorisation holder and by regulators in considering the clinical importance of spontaneously reported individual adverse events occurring in association with drug treatment and their relevance to the exposure. Regular assessments of benefit and risk can therefore be made and, when appropriate, amendment to drug labelling. Signals generated from spontaneous reports of all sources may lead to the necessity for more formal epidemiological studies or for drug surveillance studies. Periodic safety update reports include line listings of suspected adverse drug reactions reported and individual medical assessments of all these whenever they are serious or otherwise noteworthy. These reports have been written for all formulations that include dipyridamole: for the older formulations these are five-yearly reports and for the combination of modified-release dipyridamole with aspirin, being a new product, these are six-monthly reports. All have been submitted to the relevant regulatory authorities. It is acknowledged that spontaneous reporting of suspected adverse reactions may significantly understate the occurrence of side-effects and thus that periodic safety update reports may be subject to under-reporting bias.

The mortality reviews were prepared following a regulatory question regarding an unexpected mortality benefit seen in the first European Stroke Prevention Study (ESPS)[9] which was not apparent in the second ESPS, where the dose of dipyridamole was higher (400 mg *vs* 225 mg daily) and the dose of aspirin was lower (50 mg *vs* 990 mg daily). Individual trials of antiplatelet treatment suffered from being underpowered with respect to vascular endpoints over many years and especially with respect to ischaemic stroke until the first and second ESPS were performed, where the event rate postulated was then reassessed at an interim blinded analysis so as to confirm sample size. It follows, therefore, that none of the stroke trials was originally powered for mortality. While a reduction in mortality might be expected as a result of reducing events from which patients may die, this has only been confirmed in the meta-analyses of the antiplatelet trialists collaboration,[8,10,11] when very large numbers of randomised patients from all studies are available.

Accordingly, two main sources of data have been used: all randomised placebo-controlled trials of dipyridamole in vascular indications using oral treatment ≥28 days and all randomised placebo-controlled trials of antiplatelet agents in secondary prevention of stroke. In providing the principal outcome measures of overall mortality, vascular and non-vascular deaths, the outcome data from the antiplatelet trialists collaboration reports were used, together with the Boehringer Ingelheim database for the second ESPS. The data for CAPRIE were derived from the publication.[12] An additional statistical analysis comparing the mortality outcomes of the first and second ESPS has also been performed.[13]

A third source of placebo-controlled randomised data are available from post-hoc interrogation of the second ESPS database. In the trial, extensive patient demographic characteristics were collected per protocol, so a number of subgroup analyses were possible based upon prior risk factors. In particular, and relevant to this report, it has been possible to assess outcome in safety terms in patients known to have prior ischaemic heart disease as well as the qualifying stroke or TIA indicative of cerebrovascular disease. Patient histories specifically included questioning as to prior heart disease, angina, MI etc, and electrocardiograms formed part of initial patient assessments. An analysis has recently been published[1] from the population of the second ESPS with known ischaemic heart disease (35%) of 6602 patients and in those known to have had prior MI (13.5%) as to reports of angina pectoris/aggravated angina, MI and death (all-cause). Further, a recently completed randomised, controlled trial[14] of modified-release dipyridamole in some 400 patients with stable angina (PISA) also provides an additional source of information regarding cardiac adverse events encountered during the trial.

RESULTS

Literature reports

Concerns were first raised about the safety of dipyridamole in patients with ischaemic heart disease by Keltz *et al*[4] in 1987 and Vecchi *et al*[5] in 1990, who reported anginal pain in patients with ischaemic heart disease upon single dosing with oral dipyridamole at 75-100 mg. The authors were using the drug as an oral alternative to intravenous use as a pharmacological cardiac stress before myocardial imaging. The patients all appear to have had severe coronary artery disease and produced a symptomatic ischaemic reaction to a standard oral dose of dipyridamole. Homma *et al*[15] reported a similar finding following an oral dose of 300 mg dipyridamole, while Marchant *et al*[16] reported the absence of serious reaction to an intravenous dose of 0.5 mg/kg in patients with single vessel disease and with chest pain syndrome and normal coronary arteries. Finally, a very large survey involving more than 73,000 patients undergoing intravenous dipyridamole stress imaging for ischaemic heart disease was reported by Lette *et al*.[3] The authors noted a very low incidence of serious vascular adverse events, including seven cardiac deaths, 13 non-fatal MIs and nine TIAs (considered to be cases of cerebral 'steal') and concluded that the rate of adverse reaction was comparable to that of exercise testing in a similar population. Finally, in a review of drug-induced chest pain and MI, Ottervanger *et al*[6] listed possible adverse events as arrhythmia and conduction disorders, heart failure and myocardial ischaemia, citing predominantly sumatriptan, nicotine and calcium channel blockers.

Periodic safety update reports

Periodic safety update reports, together with line listings of spontaneously reported suspected adverse drug reactions, have been prepared for the European regulatory agencies in recent time including dipyridamole oral forms (five-year update [1998[17]], together with a two-year update [2000[18]],

Table 1. Distribution of cumulative cardiac adverse event reports by dipyridamole containing formulations for all reporting sources

	Sources			
	Clinical trials	Spontaneous medically confirmed	Medically unconfirmed	Other*
Asasantin Retard/ Aggrenox	53	15	5	2
Asasantin capsules	6	5	1	0
Persantin Retard	36	8	1	7
Persantin tablets	115	15	12	27
Persantin ampoules	104	92	40	30
Total	314	135	59	66

*comprises reports from observational studies, emergency use, authorities, literature and disease registries

written to harmonise with the product international birthday), ampoules (five-year update [1997[19]]) and three six-month PSUs[20-22] for the more recently approved fixed-dose combination of modified-release dipyridamole and aspirin. These reports, which are cumulative over time, contribute to the overall cardiac safety profile in so far as the events reported for the oral dose forms of dipyridamole, including the modified-release form, are few and rarely plausibly related to drug use in almost 4.5 million patient-years of treatment. To date there have been few plausibly related cardiac events reported in association with the use of the aspirin-modified-release dipyridamole combination.

The parenteral form of dipyridamole is being used uniformly on a single dose basis as a pharmacological alternative to cardiac exercise stress testing in conjunction with myocardial imaging. The periodic safety update for this dose form demonstrates well the population that is receiving drug, i.e. patients with ischaemic heart disease, often severe, in whom revascularisation procedures are being considered. Clearly, this test in this population is associated with more risk of cardiac adverse events but not more so than the alternative, i.e. exercise testing. The test also provides useful diagnostic information. However, it may well have been on the basis of such reports that cardiologists have become cautious about coronary vasodilators in general and dipyridamole in particular.

Table 1 shows the distribution over time of adverse cardiac patient events using the relevant WHO preferred term classification.

In clinical trials, adverse events are reported to regulatory authorities on an expedited basis when they meet agreed formal criteria of seriousness and suspected causal relationship to drug treatment and not because of medical relevance or interest. Cases in a company drug safety database also comprise those classified as 'serious' by the criteria prevailing but considered as unrelated as judged on an individual case basis.

A total of 314 'serious' cardiac adverse effects have been reported from clinical trials that involved 10,885 patients who received current medication. Trials in indications not specifically associated with atheroma were only four in number and included 556 patients. Two of these were trials in patients with indwelling arteriovenous shunts, one in a patient with sarcoma and one examining retinal flow in diabetic patients. The remainder were treated in 20 randomised controlled clinical trials involving atheromatous disease, e.g. chronic stable angina, secondary prevention of stroke, post-MI, coronary artery bypass graft, angioplasty, giving an incidence of 0.03% serious adverse cardiac events (irrespective of any suspected causal relationship in individual cases) in 10,329 patients treated. A total of 3304 patients were treated with dipyridamole 200 mg modified release dose form or dipyridamole plus aspirin in the second ESPS, of whom one-third were considered to have a history suggesting probable mild to moderate coronary artery disease. Only 16 adverse cardiac events occurred in 3911 patients treated under investigator-IND studies in the US conducted for the purpose of investigating intravenous dipyridamole infusion as an alternative to stress testing in myocardial imaging tests in patients with moderate to severe coronary artery disease. The remaining patients received dipyridamole on a randomised, controlled basis in peri-procedural studies of vascular interventions including femoropopliteal bypass grafts, coronary artery bypass grafts and angioplasty. One trial investigated the benefit of alteplase in late MI (6-24 hours) in patients also receiving post-infarction dipyridamole. Some studies used oral drug before and after the procedures with intravenous infusions at doses consistent with oral administration in the immediate perioperative period. A measure of double counting of serious cardiac adverse events in patients receiving both oral and i.v. drug, especially in the older case reports, cannot be excluded.

It has not been possible to associate definitely some 17 cardiac adverse events reported from Canada with a given clinical trial. However, it is known that a randomised controlled trial was conducted at the time the cases were reported in patients receiving dipyridamole plus aspirin at the time of angioplasty. This trial was published in 1988[23] after the trial was stopped because of a greater incidence of post-procedural MI on placebo compared with dipyridamole plus aspirin. By contrast, in 997 angioplasty patients receiving aspirin and heparin and randomised to receive dipyridamole by 12-hour infusion or placebo, a numerical excess of MI occurred on dipyridamole compared with placebo and a numerical benefit in terms of acute vascular occlusion – a neutral outcome. This trial, unpublished, but known as the PECARI trial,[24] was stopped on futility grounds.

Finally, a number of serious cardiac adverse events were reported in the US from investigator-IND studies that were not themselves included in the cohort of 3911 dipyridamole i.v. infusion patients reported by Ranhosky *et al*.[25] Numerator patient totals for these additional study centres are unknown but by their absence have the effect of over-reporting the incidence, as do serious cardiac adverse events that may have occurred more than once in a given clinical trial. Modern methods of accounting avoid these particular pitfalls.

It may reasonably be assumed from the demographic data provided in the reports of these clinical trials that a significant proportion of patients were being operated on for myocardial revascularisation and had significant coronary artery disease before surgery. Whether or not the aspirin was given before or shortly after surgery, the dipyridamole was given before and during the operative period. Acute cardiac outcomes are reported variably in the reports but it is clear the numbers are few and vary from treatment to treatment without suggesting any particular pattern of attribution. In particular, one may conclude that dipyridamole treatment has not induced significant added cardiac risk in the population under study, particularly given the controlled nature of the trials performed.

Reviews of mortality outcomes

The mortality outcomes in the first and second ESPS, as analysed, were different. In the first study, although not powered for mortality, there was a statistically significant reduction in all-cause mortality, there being 108 deaths in 1250 patients receiving the combination of aspirin and dipyridamole and 156 deaths in 1250 patients receiving placebo. By contrast, in the second study, there were 186 deaths in 1650 patients receiving the combination and 204 in 1649 receiving placebo. An obvious difference between the respective studies was the dosing of aspirin, 990 mg versus 50 mg daily, and of dipyridamole, 225 mg versus 400 mg daily. Antithrombotic dose-response for aspirin remains somewhat controversial at low doses (30-100 mg daily) but most authorities are agreed on the absence of further antithrombotic dose-response above 150 mg daily, while higher doses of aspirin appear to be associated with twice the number of serious bleeding events compared with the lower doses. What is less well understood is the question of whether the lower dose of dipyridamole was either more effective or safer than the higher dose.

Accordingly, the homogeneity of the mortality results in the first and second ESPS was tested using Cox survival analysis methods accompanied by descriptive hazard reductions. It thus becomes evident that there were clinically relevant differences in age between and within the two studies (Table 2), given that age is the most powerful predictor of mortality in patients with prior stroke or TIA, themselves the most powerful predictor of second stroke.[2]

It was appropriate, therefore, to control the test for treatment-by-study interaction for a confounding effect of age and to confirm the age-adjusted conclusion by adjusting for all risk factors common to both trials (hypertension, ischaemic heart disease, hypercholesterolaemia, type of qualifying event, >5 units daily alcohol consumption, diastolic and systolic BP, cardiac failure, gastrointestinal disease and previous MI). Endpoints included total mortality, vascular death and non-vascular death. In addition to the intention-to-treat analysis, explanatory analyses of on- and off-treatment mortality were performed.

Table 2. Mean age by study and treatment group

	Mean age (yr)		
Study	**Dipyridamole + aspirin**	**Placebo**	**Difference**
First ESPS	63.25	63.81	-0.56
Second ESPS	66.83	66.60	+0.24
Difference	2.58	2.79	

ESPS, European Stroke Prevention Study

Unadjusted Cox analysis of total mortality yields a non-significant test of treatment-by-study interaction (p=0.081). However, this result is biased by the small imbalances in age favouring the combination in the first ESPS and placebo in the second ESPS. Controlling for this imbalance in age increased the treatment-by-study interaction p-value to 0.19, which is well within the bounds of chance. This finding is confirmed by adjusting for all common risk factors (interaction p=0.203). Thus, part of the seeming difference in treatment effects between the first and second ESPS can be plausibly explained by the small baseline imbalances in age between treatment groups.

Similarly, analysis of vascular deaths unadjusted and adjusted for age and all common risk factors provides no evidence of unequal effects for the different doses/formulations in the first and second ESPS (interaction p=0.22). Adjustment for age increases the interaction p-value to 0.38. The age-adjusted hazard reduction on dipyridamole and aspirin in vascular death across the two studies is estimated to be a non-significant 17% (p=0.058, 95% CI 1%, 31%) but which may conceal a trend to benefit. Of interest was a surprising 43% unadjusted (42% adjusted) Cox hazard reduction in non-vascular death in the first European Stroke Prevention Study compared with 15% unadjusted (19% age-adjusted) in the second study, although the treatment-by-study interaction was not statistically significant (p>0.15) and this analysis was not pre-specified. The large reduction seen in the first study is not entirely unprecedented in the antiplatelet literature (see below UK TIA Trial). In the ESPS trials, where all patients were followed for two years irrespective of treatment discontinuation, explanatory on- and off-treatment mortality and stroke analyses indicate that chance would seem to have played an important part in the mortality differences. It should be remembered that all-cause mortality was the pre-specified mortality endpoint in both studies. Today, only vascular deaths would be counted for such an endpoint.

Table 3 shows an overall significant difference in relative risk reduction (RRR) of death in the first ESPS, in large measure occurring in patients actually documented as off-treatment (RRR=44.4%, p=0.002). Analysis of the 147 on-treatment deaths in the first ESPS shows a non-significant 21.8% RRR of death for dipyridamole treatment versus placebo (p=0.137). Adjusting for age by Cox analysis lowers the hazard reduction to 19.6% (p=0.188). In the second ESPS, there were 240 on-treatment deaths with the age-adjusted hazard reduction equal to 20.7% (p=0.075 *vs* placebo). Thus the age-adjusted hazard reductions in

Table 3. Annual death rates on treatment, off treatment and overall

	Treatment	Patients (n)	Deaths (n)	Time at risk (yr)	Death rate (%/yr)	Relative risk reduction (%)	p-value
A. Second European Stroke Prevention Study							
Overall	Aggrenox	1650	186	3082	6.03	10.0	0.296
	Placebo	1649	204	3041	6.71		
On treatment*	Aggrenox	1650	106	2310	4.59	16.1	0.174
	Placebo	1649	134	2450	5.47		
Off treatment**	Aggrenox	586	80	772	10.37	12.5	0.418
	Placebo	511	70	591	11.85		
B. First European Stroke Prevention Study							
Overall	Asasantin	1250	108	2333	4.63	32.2	0.002
	Placebo	1250	156	2285	6.83		
On treatment*	Asasantin	1250	65	1769	3.67	21.8	0.137
	Placebo	1250	82	1746	4.70		
Off treatment**	Asasantin	478	43	564	7.63	44.4	0.002
	Placebo	478	74	540	13.71		

*within 30 days after treatment cessation; **more than 30 days after treatment cessation

on-treatment mortality are completely consistent between the two studies.

Although these effects are not statistically significant in the individual trials, combined analysis yields a significant 20.2% age-adjusted reduction in the hazard of on-treatment death on the combination of dipyridamole and aspirin (p=0.027). The off-treatment mortality differences in the first ESPS would appear to have arisen by chance. The same on/off-treatment analysis of stroke shows no anomalous off-treatment results but a consistent 45% on-treatment RRR.

A meta-analysis[26] of mortality outcomes has been performed using the randomised placebo-controlled trials database of dipyridamole in cardio/cerebrovascular indications performed independently or sponsored by Boehringer Ingelheim over the years, where the treatment period was ≥1 month. Eligible studies were those provided for the 1994 antiplatelet trialists collaboration reports. The second ESPS, PISA[14] and studies by Kasahara *et al*[27] and Bran *et al*[28] were the only eligible trials not in the antiplatelet trialists database. Dipyridamole at doses ranging from ≤225 mg daily (31 trials) to ≥300 mg daily (15 trials) was used as monotherapy or in combination with aspirin. The majority of studies were those reported in the antiplatelet trialists collaboration reports, with reference to the original publication if necessary. Outcome data from the second ESPS and PISA came from the respective Boehringer Ingelheim databases. Both these trials have had extensive quality assurance and regulatory audit.

Table 4 and Figure 1 show all-cause mortality rates and estimated RRR over all trials (46) including patient numbers and separated by dose.

Table 4. All-cause mortality rates for dipyridamole containing treatments versus placebo

Daily dose (mg)	Patients (n)	Adjusted event rates		RRR (95% CI)
		Dipyridamole	Placebo	
100-225	12,041	7.36%	7.94%	7.6% (-4.5, 18.3)
300-400	7439	10.19%	11.47%	11.4% (-1.4, 22.6)
Overall	19,480	8.42%	9.29%	9.3% (0.7, 17.2)

RRR, relative risk reduction

When the mortality data are separated into vascular death and non-vascular death, the point estimates for RRR regarding vascular deaths remain in favour of dipyridamole, being 7.0% overall, 7.9% for 300-400 mg and 6.5% for ≤225 mg daily. However, the 95% CI for each includes zero. As to non-vascular death, the RRR are large, at 13.2%, 13.7% and 12.5% respectively, in favour of dipyridamole but with wide CI. The adjusted event rates were small, ranging from 1-4%. When the trials including dipyridamole as monotherapy are analysed, the size of the database falls to 5356 patients, but the pattern of mortality is similar with the point estimates favouring dipyridamole but with wide 95% CI.

In order to examine further the apparent reduction in all-cause mortality seen in the first ESPS, of which a major element was an implausible but significant difference in non-vascular death, analysis of all the antiplatelet stroke trials listed in the collaboration report in 1994 was performed in a similar way to the dipyridamole randomised controlled trial database. Twenty trials were identified comparing antiplatelet treatment with placebo.[29] Apart from the first ESPS, no trial showed a reduction in relative risk of all-cause mortality, while the pooled data (n=18,217) gave adjusted mortality rates of 11.25% for antiplatelet treatment versus 12.77% for placebo. This gives a statistically significant

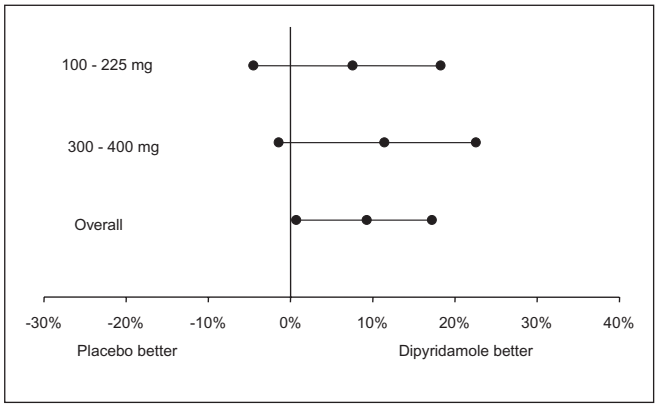

Figure 1. Estimates of relative risk reductions (with 95% CIs) for all-cause mortality over all trials with dipyridamole-containing treatments versus placebo

RRR of 12.2% (95% CI 4.6, 19.2) for the pooled analysis. The relative risk of vascular death was reduced by 9.4% with a CI (-0.3, 18.1) just failing to reach significance. Surprisingly, analysis of non-vascular mortality gave a significant reduction in relative risk of 18.4% (CI 4.5, 30.2), the adjusted event rates being 3.31% for antiplatelet treatment and 4.06% for placebo. Inspection of the individual trials shows that apart from the first ESPS one other trial of almost equal size also gave a significant and implausible reduction in non-vascular death, namely the UK TIA trial,[30] with a non-vascular death rate almost identical to the first ESPS. The RRR for the UK TIA trial was 43% (CI 11, 63) on event rates of 2.5% for aspirin and 4.4% on placebo. The figures for the first ESPS were RRR 42% (CI 9, 63) on event rates of 2.3% for the combination and 4.0% for placebo. Thus the first ESPS is not unique in providing an implausible mortality outcome. One would conclude for future studies that only vascular death is relevant to the analysis of such trials with respect to treatment benefit, while for individual drug trials clearly all-cause mortality counts are needed for safety reasons.

Safety data from recent randomised controlled trials

The final element in this review of the cardiac effects of dipyridamole lies within the randomised evidence relating to dipyridamole trials. The population entering second ESPS was screened for evidence of concomitant ischaemic heart disease by history, systematic enquiry and by routine ECG. Evidence of risk factors for stroke/TIA was also collected. Analysis of the demographic data shows that 35.0% of the total second ESPS population had historical and/or ECG evidence of ischaemic heart disease (2319/6602) and that 13.5% (891/6602) had historical and/or ECG evidence of MI. Each subgroup was distributed evenly across the four treatment groups in the second ESPS. Analyses of subgroups were performed on an intention-to-treat basis together with an explanatory on-treatment basis. The data were also, as in the main trial, analysed on a factorial basis and by comparing treatment groups. The incidences of angina pectoris, MI and death could then be established for the study as a whole and for the subpopulations.

Angina pectoris occurring within the second ESPS as a whole was reported by 8.4% (ITT) of the population and by 7.3% in the explanatory analysis. Among those with a history of ischaemic heart disease the respective incidences were 15.5% and 13.1%, and among those with previous MI at baseline, 14.9% and 17.2%. Factorial analysis and χ^2 testing for homogeneity of the incidences by treatment group show no evidence of adverse effects attributable to treatment, either for angina or for subsequent MI or death. The data have been published elsewhere.[1]

The PISA trial referred to earlier included 400 patients with chronic stable angina randomised to six months treatment with modified-release dipyridamole 200 mg b.d. or placebo, using standard treadmill exercise testing and endpoints representative of antianginal effect. All patients were receiving single, double or triple regular antianginal medication (β-blockers, calcium channel blockers and/or long-acting nitrates). Against this treatment background dipyridamole was unable to show any additional antianginal effects. However, analysis of adverse events reported during the trial confirmed the absence of initial dipyridamole-related adverse cardiac effects in terms of angina or MI and showed no excess of such events subsequently in the dipyridamole treatment group compared with the placebo treatment group, suggesting that 'steal' phenomena were not occurring in the population investigated.[14]

DISCUSSION

Drugs with vasodilating effects upon the coronary vasculature have over the years been associated with concerns regarding the precipitation of potentially serious ischaemic cardiac events. A recent review by Ottervanger *et al*[6] confirms that adverse cardiac effects have been associated with several drugs that have vasomotor effects. Most recently, reports have appeared in the literature regarding the effects of sildenafil in patients with ischaemic heart disease using the drug for its intended purpose. Dipyridamole was introduced originally for the management of angina and myocardial ischaemia. A meta-analysis by Sacks *et al*[32] involving published randomised trials of dipyridamole versus placebo had seemed supportive. Two published reports suggested a possible hazard with dipyridamole at approved oral doses in patients with severe coronary artery disease being investigated by cardiac imaging, while a large study of intravenous use of dipyridamole as a pharmacological alternative to exercise testing at quite different doses suggested an ischaemic hazard attributable to the investigational use that was acceptable, compared with that attributable to exercise testing.

With the recent findings of effective secondary prevention of stroke and TIA arising from the two large-scale ESPS trials, wider use of dipyridamole in a population expected to have a 30-50% incidence of concomitant ischaemic heart disease may be anticipated. A comprehensive review of the cardiac safety of dipyridamole has therefore been performed. The evidence from a variety of sources has been examined and additional analyses of the relevant data performed. The most powerful evidence arises from the second ESPS database in which the concomitant presence of ischaemic heart disease was sought systematically, and analysis of which does not suggest cardiac hazard attributable to dipyridamole in respect of patients who may have mild to moderate disease. A further randomised placebo-controlled trial (PISA), now published,[14] also shows no excess cardiac risk attributable to treatment with dipyridamole using the modified-release preparation at 200 mg b.d.

Investigation of the dipyridamole randomised controlled trial database in patients with cardiovascular and cerebrovascular conditions provides reassurance with regard to overall and to vascular mortality. The apparent difference in mortality outcomes in the first and second ESPS have been

investigated and age difference shown to be a relevant confounder. Comparable non-significant reductions in vascular mortality, as expected from trials of this size, were attributable to active treatment, while a significant but implausible difference in non-vascular deaths is shown to have occurred also in another large-scale stroke prevention trial, the UK TIA study, and suggests that all-cause mortality should only be used for safety purposes in large-scale drug trials.

The dipyridamole product labelling already includes an appropriate caution in respect of patients with severe coronary artery disease, unstable angina and recent MI, who may be at risk of ischaemic event provoked by dipyridamole. However, this review provides ample evidence that dipyridamole may be used safely for the secondary prevention of stroke and TIA, even in patients with concomitant ischaemic heart disease.

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