Fisher pp 275-282 15/7/05 12:05 pm Page 1

Should all diabetic patients receive aspirin? Results from recent trials

NICK BARWELL, GILLIAN MARSHALL, CLAIRE MCDOUGALL, ADRIAN JB BRADY, MILES FISHER

Abstract

Atherosclerotic cardiovascular disease (CVD) is common in patients with diabetes, and antiplatelet therapy has been the cornerstone of preventative therapy for many years. The majority of the evidence for the use of aspirin in patients with diabetes comes from subgroup analysis of major secondary prevention trials. Secondary prevention data from the Antiplatelet Trialist's Collaboration meta-analysis suggests that the benefit derived from aspirin is similar in diabetic and non-diabetic populations. In the general population, data from primary prevention studies have shown the benefit of aspirin in terms of cardiovascular mortality, but there is little evidence to suggest that aspirin is beneficial in terms of total or cardiovascular mortality for primary prevention in a diabetic population. Clopidogrel may have advantages over aspirin and combined therapy may be superior for certain types of coronary artery disease and stroke, although this is offset by an increased risk of haemorrhage in the latter setting. The use of aspirin in the prevention of CVD in patients with diabetes should therefore be focused on those with a history of vascular events or aggressively treated hypertension.

Key words: diabetes, aspirin, antiplatelet therapy, cardiovascular disease.

Br J Cardiol 2005;**12**:275–82

Introduction

Antiplatelet therapy is commonly prescribed in the primary and secondary prevention of cardiovascular disease. Diabetes, particularly type 2 diabetes, is associated with increased cardiovascular risk, and significant cardiovascular mortality. Evidence for the efficacy of antiplatelet therapy in patients with diabetes has been almost exclusively derived from subgroup analysis of large trials, often involving relatively small numbers of diabetic subjects and frequently lacking adequate statistical power in that subgroup. Some of the results have been counter-intuitive to our expectation of the benefit of antiplatelet therapy in such an alleged high-risk group. This review asks the question 'Should all diabetic patients receive aspirin?' and focuses on recent evidence that specifically pertains to subjects with diabetes.

Table 1 summarises recent key clinical studies in primary and secondary prevention with antiplatelet agents. These studies include diabetic patients.

Summary of previous antiplatelet studies

In 1994 the Antiplatelet Trialists' Collaboration meta-analysis included 145 randomised controlled trials covering nearly 100,000 patients.[1] Overall, the end point of 'vascular event', defined as non-fatal myocardial infarction (MI), non-fatal stroke or vascular death, was significantly reduced by 25% in a composite 'high-risk' group of subjects with prior MI, acute MI, prior stroke/transient ischaemic attack (TIA) or 'other high risk'.

In 29 of these trials, data for individual subjects was available according to diabetes status. In 4,502 diabetic subjects with vascular disease, vascular events as defined above, were reduced from 22.3% to 18.5%, with 38 events prevented per 1,000 patients treated, compared with control (figure 1). A second analysis examined seven trials where patients were recruited because they had diabetes and presumed high vascular risk (n=1,365), and there was no benefit from antiplatelet therapy. The authors suggested that the trends in several subgroups, including diabetes, suggested possible benefit, but close examination of the diabetes data, if anything, suggests a possible negative effect of antiplatelet therapy, with a vascular event rate of 4.9% in the antiplatelet group and 4.4% in the control group.

Concerns about the safety of aspirin in hypertensive patients led to inclusion of aspirin 75 mg or placebo therapy in the Hypertension Optimal Treatment (HOT) trial.[2] In the general study population (n=17,289), aspirin therapy significantly reduced major cardiovascular events, and the greatest reduction was of non-silent MI (2.3 *vs.* 3.6, p=0.002), and the diabetic subgroup (n=1,501) achieved greater benefit (2.5 MI prevented/1,000 patient-years compared with 1.5 in non-diabetic group). Total and cardiovascular mortality was not reduced overall or in the diabetic subgroup.

Diabetes Clinic, Glasgow Royal Infirmary, 84 Castle Street, Glasgow, G4 0SF.
Nick Barwell, Research Fellow
Claire McDougall, Research Fellow
Miles Fisher, Consultant Physician

Department of Cardiology, Queen Elizabeth Building, Glasgow Royal Infirmary, Alexandra Parade, Glasgow, G4 0SF.
Gillian Marshall, Research Fellow
Adrian JB Brady, Consultant Cardiologist

Correspondence to: Dr Miles Fisher
(email: miles.fisher@northglasgow.scot.nhs.uk)

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

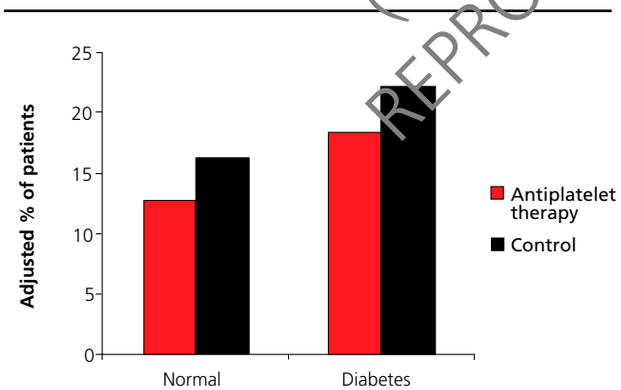
Table 1. Results of end points for all subjects and subjects with diabetes in key primary prevention studies and secondary prevention studies with antiplatelet agents

	Drug	Total subjects n=	Diabetic subjects n= (%)	Primary end point all	Primary end point diabetes	Other events all	Other events diabetes	Comments
'Primary' prevention								
HOT	Aspirin 75 mg *vs.* placebo	19,193	1,501 (8%)	Reduced major CV events from 10.5% to 8.9%	"about the same"	Reduced all MI from 3.6% to 2.3%	Data not provided	Increased non-fatal bleeds with aspirin
Primary Prevention Project	Aspirin 100 mg *vs.* placebo	4,495	1,031	Reduced combined end point (CV death, MI, stroke) from 2.8% to 2.0%	Insignificant effect (4.3% to 3.9%)	Reduced total cardiovascular events 8.2% to 6.3%	Insignificant effect (11.5% to 10.2%)	Extra patients with diabetes included in the diabetes analysis
Secondary prevention/clopidogrel								
CAPRIE	Clopidogrel 75 mg *vs.* aspirin 325 mg	19,185	3,866 (20%)	Reduced combined end point (CV death, MI, stroke) from 5.8% to 5.3% per year	Data not provided	Reduced extended end point (including bleeding) from 12.7% to 11.8%	Reduced extended end point (including bleeding) from 17.7% to 15.6%	
CURE	Aspirin *vs.* aspirin plus clopidogrel 300 mg then 75 mg	12,562	2,840 (22%)	Reduced combined end point (CV death, MI, stroke) from 11.4% to 9.3% per year	Reduced combined end point from 16.7% to 14.2%			
MATCH	Clopidogrel 75 mg *vs.* clopidogrel 75 mg plus aspirin 75 mg	7,599	5,197 (68%)	Insignificant effect on composite of stroke, MI, CV death, re-hospitalisation from 16.7% to 15.7%	Insignificant reduction from 16.8% to 15.1%			Increased life-threatening bleeds with the combination

Key: CV = cardiovascular; MI = myocardial infarction

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

Figure 1. Absolute effects of antiplatelet therapy on vascular events in the 29 trials in high-risk patients with separate information available on each patient subdivided by presence or absence of diabetes. Data from Antiplatelet Trialists' Collaboration[1]



In 2002, the Antiplatelet Trialists' Collaboration group produced an updated meta-analysis including more recent trials, and therefore a larger number of diabetic patients.[3] The bulk of this increase came from the Early Treatment Diabetic Retinopathy Study (ETDRS). This study of 3,711 subjects aimed to determine the safety of aspirin, 650 mg daily, in diabetic patients, particularly with respect to diabetic eye disease, and also collected data on cardiovascular events and mortality.[4] The study population can be considered primarily as a primary prevention or 'low risk' secondary prevention group in terms of cardiovascular risk, as patients with uncontrolled hypertension or a significant prior cardiovascular event with poor five-year prognosis were excluded. With an average follow-up period of five years, there was no significant reduction in total or cardiovascular mortality. Similar to the HOT study a significant 17% reduction in symptomatic myocardial infarction was observed.

The 2002 Antiplatelet Trialists' Collaboration meta-analysis (including ETDRS data) again found no significant benefit in antiplatelet therapy for patients with uncomplicated diabetes in nine trials of patients thought to be 'high-risk' due to co-existing diabetes.

Aspirin for primary prevention

In the general population, the British Doctors' Trial using a single daily dose of 500 mg of aspirin found no benefit in the risk of first MI in British male doctors with no history of occlusive vas-

Fisher pp 275-282 15/7/05 12:05 pm Page 3

cular disease.[5] Larger studies, such as the US Physicians' Health Study, suggested a significant reduction (44%, p<0.00001) in the risk of first MI with 325 mg of aspirin therapy but, again, there was no reduction in total or cardiovascular mortality.[6] Data from the 39,876 women in the recently published Women's Health Study showed a statistically insignificant reduction in a combined end point of non-fatal MI, non-fatal stroke and fatal cardiovascular disease in women who took aspirin, with a significant reduction in strokes which was a secondary end point.[7] In each of these studies, diabetic subjects represented only 2% of the study group.

Primary Prevention Project

The Primary Prevention Project (PPP) was a randomised, controlled, open trial comparing aspirin 100 mg and vitamin E 300 mg in a 2x2 factorial design,[8] in 4,495 subjects with one or more cardiovascular risk factors (age > 65 years, hypertension, hypercholesterolaemia, diabetes, obesity and family history of premature MI in a first-degree relative) and no history of a vascular event. Aspirin therapy was associated with a significant reduction in risk of cardiovascular death (RRR 44%, p=0.049%) and a significant reduction in a combined end point of all cardiovascular events (RRR 23%, p=0.014).

Post-hoc subgroup analysis of 1,031 diabetic patients in PPP receiving aspirin demonstrated a non-significant reduction in the primary end point of combined cardiovascular death, non-fatal MI, and non-fatal stroke. Indeed, removal of the diabetic patient details from the main analysis in PPP produces more emphatic evidence for the use of aspirin in subjects with other risk factors. Without the diabetic cohort, the study shows a statistically significant 41% reduction in relative risk with respect to the primary end point. Furthermore, analysis of total cardiovascular events (including TIA, angina pectoris, revascularisation etc.) between the two cohorts again shows a small non-significant trend towards benefit in diabetes, but a large and significant benefit in other patients at risk of cardiovascular events (RRR 11% [NS] [diabetes] *vs.* 31% [95% CI 0.53–0.90] [no diabetes]).[9]

Clopidogrel in diabetes mellitus

CAPRIE

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared the efficacy of clopidogrel with aspirin in the secondary prevention of cardiovascular disease. Over 19,000 patients with a history of significant vascular disease were recruited. Entry criteria of thromboembolic stroke, MI or significant peripheral arterial disease ensured a heterogenous group at high risk of further vascular events.[10] The CAPRIE authors reported a significant benefit of clopidogrel over aspirin in relation to the primary outcome (non-fatal MI, non-fatal stroke, or vascular death) with a relative risk reduction of 8.7% (p=0.043).

CAPRIE found clopidogrel to be effective in reducing the incidence of ischaemic stroke, MI or vascular death. However, the benefit to the trial recruitment subgroups (stroke, MI, peripheral arterial disease) was not equal, with the largest and only significant benefit found just in those patients with peripheral arterial disease.[10]

A diabetes subgroup analysis identified 3,866 patients from the CAPRIE cohort.[10] A slightly higher proportion of the diabetic clopidogrel group had hypertension (68% of 1,914 patients) compared with the diabetic aspirin group (64% of 1,952 patients, p=0.025). This study reported an event rate per year of 17.7% in the diabetic patients who received aspirin, and a significantly lower (2.1%, p=0.042) event rate of 15.6% in those on clopidogrel. The primary end point was a composite of vascular death, MI, stroke, or rehospitalisation for ischaemic symptoms or bleeding. Compared with the original CAPRIE primary cluster end point, this is a slightly 'softer' end point. The authors acknowledged the limitations of their composite end point, the study not being sufficiently powered to allow identification of specific individual end points.[11]

CURE/PCI-CURE

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial examined whether the addition of clopidogrel to aspirin therapy in the context of acute coronary syndrome (ACS) improved outcome. In contrast to CAPRIE, which placed the two agents in a head-to-head comparison, CURE examined the role of synergistic antiplatelet therapy in a high-risk cohort.[12]

Aspirin combined with clopidogrel therapy produced a 20% reduction in numbers of patients achieving the first primary end point (composite of cardiovascular death, MI or stroke). With the addition of refractory ischaemia, combined therapy produced a smaller (16%) reduction. The rapid antiplatelet action of clopidogrel appeared to have an impact with a 33% reduction in those achieving the second primary end point in the first 24 hours; in addition, combination therapy appeared to decrease the requirement for thrombolysis or administration of intravenous GP IIb/IIIa inhibitors.

In the CURE study, 2,840 patients were diabetic. As in CAPRIE, the diabetic subgroup suffered a higher vascular event rate than their non-diabetic counterparts. Given an end point of cardiovascular death, non-fatal MI or stroke, 14.2% of those on combined therapy suffered such an event; and 16.7% of the aspirin-only group suffered from a vascular event. The relative benefit of combined therapy over aspirin alone in diabetes narrowly failed to achieve statistical significance.

The PCI-CURE study assessed antiplatelet agent synergy one stage further. CURE study patients requiring percutaneous coronary intervention (PCI) due to refractory or recurring ischaemia were entered into PCI-CURE. Before PCI, patients received aspirin plus placebo or aspirin plus clopidogrel. After coronary stenting, patients all received a thienopyridine (clopidogrel/ticlopidine).

Those receiving combined therapy had multiple benefits. They suffered significantly lower rates of pre-PCI MI and refractory ischaemia, MI, cardiovascular death and urgent revascularisation in the immediate 30 days post-PCI, and in the prolonged follow-up period (eight months). Overall, the administration of clopidogrel (in addition to aspirin) before PCI produced a relative risk of 0.69 (p=0.002) of cardiovascular death or MI. PCI-CURE

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED

Fisher pp 275-282 15/7/05 12:05 pm Page 4

authors comment that the decision to proceed to PCI is influenced by a number of factors, and have adjusted their analysis for covariate factors which are likely to affect the likelihood of a patient proceeding to PCI. The 'propensity score' is a predictive measure of likely PCI requirement. Even after adjusting for these scores, clopidogrel therapy remains beneficial, with an adjusted relative risk of 0.72 (0.53–0.96, p=0.03) of cardiovascular death, or MI from PCI to completion of follow-up.[13]

There were 504 patients with diabetes in the PCI-CURE study. Subgroup analysis of the diabetic cohort detected 101 events (cardiovascular death or MI), with a relative risk of 0.77 (95% CI 0.52–1.15) for the clopidogrel group. The results from the diabetes group certainly lack statistical power due to the small numbers involved. The 'no-diabetes' group appear to derive greater benefit from clopidogrel (relative risk 0.66, 95% CI 0.5–0.87) but this must be viewed in the context of the greater statistical power associated with a greater than four-fold number of subjects in this group.

CLARITY/COMMIT-CCS

The results of two large trials examining the benefits of clopidogrel in acute MI were recently presented at the 2005 meeting of the American College of Cardiology in Orlando U.S. The CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) study randomised 3,491 patients within 12 hours of onset of an ST-elevation MI to clopidogrel or placebo in addition to thrombolytic therapy and aspirin.[14] There was a statistically significant 36% odds reduction in the composite end point of death, re-infarction or occluded infarct-related artery as determined by post-treatment angiography. A 20% reduction in cardiovascular related death, recurrent MI or recurrent ischaemia requiring urgent revascularisation was also demonstrated at 30 days. COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial) enrolled over 45,000 patients with acute MI to clopidogrel or placebo in addition to aspirin for the duration of their hospital stay. This resulted in a 9% relative risk reduction in the primary end point of death, re-infarction or stroke at hospital discharge. As yet, there is no published data regarding diabetic populations within either of these trials but the results are awaited with interest.

MATCH

The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) trial examined the role of combination antiplatelet therapy in ischaemic cerebrovascular disease. MATCH aims to provide information on vascular outcomes and bleeding complications in patients on clopidogrel (75 mg/day) suffering a recent ischaemic neurological event, with at least one further vascular risk factor. The main primary end point consists of a composite of ischaemic stroke, MI, vascular death, or rehospitalisation with acute ischaemic symptoms originating in either the cerebrovascular, coronary or peripheral vascular distribution.

In the study, 7,599 patients were randomised to receive clopidogrel plus placebo or clopidogrel plus aspirin (75 mg). Over an 18-month follow-up period, 16% of the combined group suffered an event, which qualified as a primary outcome and 17% of the clopidogrel-only group suffered a primary outcome event. There were equal proportions of MI, ischaemic stroke, other vascular death and rehospitalisation for ischaemia between the groups. This 1% difference in primary outcome achieved represents a relative risk reduction of 6.4% (95% CI –4.6 to 16.3, p=0.244). In addition to this weakly positive trend towards benefit, MATCH reports a higher bleeding rate in the combined group which is likely to offset any benefit from combined antiplatelet therapy.[15]

From the perspective of this review, MATCH provides a relatively large body of evidence as 68% of the MATCH population (n=5,197) had diabetes. Although neither result achieves significance, the diabetic population appears to show a beneficial trend (1.7% lower Event Rate) towards reduced risk of further vaso-occlusive events. In contrast, the non-diabetic population show a trend towards benefit from clopidogrel monotherapy.[15]

Discussion

Aggressive cardiovascular risk factor management allied to good glycaemic control represents optimal management for patients with diabetes. For the secondary prevention of cardiovascular disease, the Antiplatelet Trialists' Collaboration meta-analysis indicates that diabetic patients with established cardiovascular disease show the same benefit with aspirin therapy as their non-diabetic counterparts (figure 1). Data from CAPRIE suggests that clopidogrel therapy may be better than aspirin in diabetic patients but within the context of a softer end point. This was significant due to the inclusion of hospitalisation for ischaemia or bleeding in the composite end point. Both CURE and PCI-CURE suggest a trend towards benefit with combined therapy but lack power to achieve statistical significance for diabetic patients. Although the large diabetic cohort in MATCH potentially shows a beneficial trend from combined therapy, the overall bleeding event rate would preclude duotherapy in diabetic patients with a history of stroke/TIA.

For primary prevention, ETDRS and the diabetic subgroup of PPP found no significant reduction in major cardiovascular events with aspirin therapy but both show a beneficial trend of similar magnitude (around 10%). The HOT trial gives the most positive impetus to the use of antiplatelet therapy as primary prevention in diabetic subjects. The greatest benefit in HOT was a reduction in MI. Cardiovascular mortality was not affected, although such a small cohort (1,501 patients) could never have the statistical power to determine this. Until further evidence is available, it seems reasonable to target antiplatelet therapy on patients where there is evidence i.e. secondary prevention, and patients with treated hypertension. This evidence may come from the ASCEND trial (A Study of Cardiovascular Events in Diabetes) which aims to recruit 10,000 people with diabetes in a randomised 2X2 factorial design of aspirin versus placebo and omega-3 fatty acid supplementation versus placebo for the primary prevention of cardiovascular events in people with diabetes.

Very few of the studies are able to demarcate the type of diabetes, however ETDRS attempts to define the proportion of type

COPYRIGHT MEDINEWS CARDIOLOGY LIMITED REPRODUCTION PROHIBITED

Fisher pp 275-282 15/7/05 12:05 pm Page 5

1 and type 2 diabetics involved in the study. The ETDRS investigators used their own classification system which could be considered to over-classify patients as type 1. The ETDRS population is likely to differ from other study populations as it has a high (80%) proportion of patients classified as suffering from type 1 diabetes. Delineating the type of diabetes may prove to be important as we appreciate the distinct differences between the pathogenesis of accelerated atherosclerosis, particularly with respect to type 2 diabetes.[16]

It would appear counter-intuitive to suggest that antiplatelet therapy is less effective in patients with diabetes. Yet in patients with lower risk/uncomplicated diabetes, available evidence suggests that this is indeed true. The phenomenon of aspirin resistance in the general population has been described, and the findings from the reported studies may suggest a greater degree of aspirin resistance in the diabetic population. Indeed, among heart failure patients, aspirin use may be associated with a worse outcome.[17]

So far, a definitive reason for aspirin resistance among diabetic subjects is not well understood. Infusions of glucose and mannitol into both diabetic and non-diabetic subjects increase platelet reactivity. Increased osmolality and hyperglycaemia appear to increase expression of both p-selectin and GpIIb/IIIa.[18] Type 2 diabetes is associated with increased C-reactive protein (CRP) levels, and is a marker of chronic inflammation.[19] Upregulated macrophage/monocytes are a source of thromboxane A2 production and unlike platelet COX-1, which is irreversibly inhibited by aspirin, have inducible COX-2 which may not be completely inhibited by aspirin.[20] Endothelial dysfunction, particularly associated with type 2 diabetes is characterised by a relative deficiency of endothelial nitric oxide (eNO).[17] In a relative deficit of eNO, platelets are encouraged to aggregate and adhere.

In conclusion, patients with diabetes are at higher risk of premature cardiovascular events. Yet, in answer to our initial question, we would conclude from available evidence that aspirin therapy is not indicated in all diabetic patients. Aspirin at a dose of 75 mg should be targeted at those with existing cardiovascular disease, or tightly controlled hypertension and diabetes, as the benefit of primary prevention with antiplatelet therapy in all people with diabetes remains to be proven. The widespread addition of clopidogrel should be limited to specific situations, such as people expected to undergo PCI, or as part of the management of acute MI.

Conflict of interest

NB, GM, and CM: none declared. MF has served on advisory panels for Bristol-Myers Squibb and Sanofi-Synthelabo. AB has received research grants from AstraZeneca UK, Merck Sharp & Dohme UK, Pfizer UK, Bristol-Myers Squibb UK, Bayer Germany, Sanofi UK and Servier France.

Editors' note

This is the third article in the 'Cardiovascular drugs in diabetes' series. Previous articles covered:

Key messages

- Antiplatelet therapy and aspirin in particular has not been conclusively shown to reduce cardiovascular death when given for primary prevention to people with diabetes, but may reduce or delay the onset of first non-fatal vascular events
- Diabetic subjects with a history of vascular disease derive at least as much benefit from secondary preventative antiplatelet therapy as the rest of the population
- The combination of aspirin plus clopidogrel has limited benefits in secondary prevention, with a possible decrease in significant vascular events in patients requiring percutaneous intervention for coronary ischaemia, and decreased readmission rates for recurrent ischaemic symptoms
- Routine combination of aspirin and clopidogrel is not yet recommended in patients with existing cerebrovascular disease

- Should all diabetic patients receive a statin? (*Br J Cardiol* 2004;**11**:455-60)
- Should all diabetic patients receive an ACE inhibitor? (*Br J Cardiol* 2005;**12**:130-4)

The final article in the series will cover 'Should all diabetic patients receive a beta blocker?'.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81-106.
2. Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: prinicipal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;**351**:1755-62.
3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ* 2002;**324**:71-86.
4. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *JAMA* 1992;**268**:1292-301.
5. Peto R, Gray R, Collins R *et al*. Randomised trial of prophylactic daily aspirin in British male doctors. *BMJ* 1988;**296**:313-16.
6. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989;**321**:129-35.
7. Ridker PM, Cook NR, Lee I-M *et al*. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;**352**:1293-304.
8. Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* 2001;**357**:89-95.
9. Sacco M, Pellegrini F, Roncaglioni MC *et al*. on behalf of the PPP Collaborative Group. Primary prevention of cardiovascular events with

Continued on page 282

COPYRIGHT MEDINEWS CARDIOLOGY LIMITED REPRODUCTION PROHIBITED

Fisher pp 275-282 15/7/05 12:05 pm Page 6

Continued from page 280

low-dose aspirin and vitamin E in type 2 diabetic patients. *Diabetes Care* 2003;**26**:3264-72.
10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329-39.
11. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002;**90**:625-8.
12. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment Elevation. *N Engl J Med* 2001;**345**:494-502.
13. Mehta SR, Yusuf S, Peters RJG *et al*. for the Clopidogrel in Unstable Angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous intervention: the PCI-CURE study. *Lancet* 2001;**358**:527-33.
14. Sabatine MS, Cannon CP, Gibson CM for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352**:1179-89.
15. Diener H-C, Bogousslavsky J, Brass LM *et al*. on behalf of the MATCH Investigators. 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. *Lancet* 2004;**364**:331-7.
16. Hayden MR, Tyagi SC. Is type 2 diabetes mellitus a vascular disease (atheroscleropathy) with hyperglycaemia a late manifestation? The role of NOS, NO and redox stress. *Cardiovasc Diabetol* 2003;**2**:2.
17. Cleland JG, Findlay I, Jafri S *et al*. The Warfarin/Aspirin Study in heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148**:157-64.
18. Keating FK, Sobel BE, Schneider DJ. Effects of increased concentrations of glucose on platelet reactivity in healthy subjects and in patients with and without diabetes mellitus. *Am J Cardiol* 2003;**92**:1362-5.
19. Nystrom T, Nygren A, Sjoholm A. Persistent endothelial dysfunction is related to elevated CRP levels in type 2 diabetic patients after acute myocardial infarction. *Clin Sci* 2005;**108**:121-8.
20. Halushka MK, Halushka PV. Why are some individuals resistant to the cardioprotective effects of aspirin? Could it be thromboxane A2? *Circulation* 2002;**105**:1620-2.

COPYRIGHT MEDINEWS (CARDIOLOGY) LIMITED REPRODUCTION PROHIBITED