

## Antiplatelet therapy in diabetes

MARIA KRAW, M.D.

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality in diabetes. Patients with type 2 diabetes have a 2- to 4-fold increased risk of CVD that is present even before the development of fasting hyperglycemia. Patients with diabetes, but without a previous myocardial infarction (MI), have a risk of MI that is as high as non-diabetic patients with a previous MI.<sup>1</sup> In addition, the mortality following MI and stroke is 2 and 3 times higher, respectively, in patients with diabetes. Approximately 65% of deaths in patients with diabetes are due to CVD.<sup>2,3</sup>

In addition to traditional risk factors such as smoking, hypertension, hyperglycemia, and dyslipidemia, the accelerated atherosclerosis seen in diabetes may be caused by a procoagulant state. Patients with diabetes have evidence of endothelial dysfunction, increased susceptibility for thrombosis, reduced fibrinolysis, and increased platelet aggregation.<sup>4</sup> This issue of *Endocrinology Rounds* reviews the platelet dysfunction seen in diabetes, the pharmacology of antiplatelet agents, the evidence for the use of antiplatelet agents in the primary and secondary prevention of CVD in patients with diabetes, and concludes with recommendations on the use of these agents in patients with diabetes.

### Platelet dysfunction in diabetes

Cardiovascular events often occur following disruption of atherosclerotic plaque and superimposed thrombosis. Plaque rupture exposes thrombogenic components, such as collagen, von Willebrand factor, lipids, macrophages, and tissue factors. Platelets become activated following adherence to the exposed collagen and von Willebrand factor and recruit additional platelets by synthesizing thromboxane A<sub>2</sub> (TXA<sub>2</sub>) and releasing adenosine diphosphate (ADP). Platelet activation then induces a conformational change in glycoprotein IIb/IIIa that ligates fibrinogen, leading to the cross-linking of adjacent platelets.

Patients with diabetes have a variety of alterations in platelet function that can predispose them to increased platelet activation and thrombosis. These alterations include:

- a 2-fold increase in platelet turnover due to decreased platelet survival time and an increased entry rate of new platelets into the circulation<sup>5</sup>
- enhanced platelet aggregation, largely as a result of increased TXA<sub>2</sub> synthesis<sup>6</sup>
- decreased inhibition of platelet aggregation by TXA<sub>2</sub> antagonists<sup>7</sup>
- a correlation between fasting plasma glucose and TXA<sub>2</sub> synthesis<sup>7</sup>
- altered platelet membrane fluidity due to nonenzymatic glycation,
- increased binding of fibrinogen to platelet receptors<sup>8</sup>
- platelets have elevated storage and release of plasminogen activator inhibitor-1 (PAI-1), an endogenous inhibitor of fibrinolysis.<sup>9</sup>

### Antiplatelet agents

A variety of antiplatelet agents have been developed that target the different steps in platelet activation (Figure 1). Aspirin permanently inactivates prostaglandin G/H synthase, which is responsible for the synthesis of thromboxane, a major platelet aggregation factor. Aspirin is rapidly absorbed in the stomach and small intestine with peak plasma levels occurring 30-40 minutes after ingestion, while enteric-coated preparations can take up to 3-4 hours. As little as 100 mg of aspirin almost completely inhibits TXA<sub>2</sub> synthesis in normal human platelets, and since anucleated platelets are incapable of synthesizing new enzyme, this inhibition persists for the lifespan of the platelet (average of 8-12 days in normal subjects).

Agents such as ticlopidine and clopidogrel irreversibly inhibit the ADP receptor on platelets, blocking ADP-dependent platelet activation. The use of ticlopidine is limited by bone marrow suppression, diarrhea, and rash. Frequent follow-up of blood counts is necessary due to the increased risk of severe reversible neutropenia and thrombotic thrombocytopenic



Leading with Innovation  
Serving with Compassion

**ST. MICHAEL'S HOSPITAL**  
A teaching hospital affiliated with the University of Toronto



### Members of the Division of Endocrinology and Metabolism at St. Michael's Hospital

LAWRENCE LEITER, MD (HEAD)  
EDITOR, *ENDOCRINOLOGY ROUNDS*

GILLIAN BOOTH, MD

PHILIP CONNELLY, PHD

CHRISTINE DERZKO, MD

JEANNETTE GOGUEN, MD

AMIR HANNA, MD

SOPHIE JAMAL, MD

DAVID JENKINS, MD, PHD

ROBERT JOSSE, MD

TIM MURRAY, MD

DOMINIC NG, PHD, MD

ROBERT PATTEN, MD

LETICIA RAO, PHD

WILLIAM SINGER, MD

ROBERT VOLPE, MD

VLAD VUKSAN, PHD

QINGHUA WANG, MD, PHD

TOM WOLEVER, MD, PHD

MINNA WOO, MD, PHD

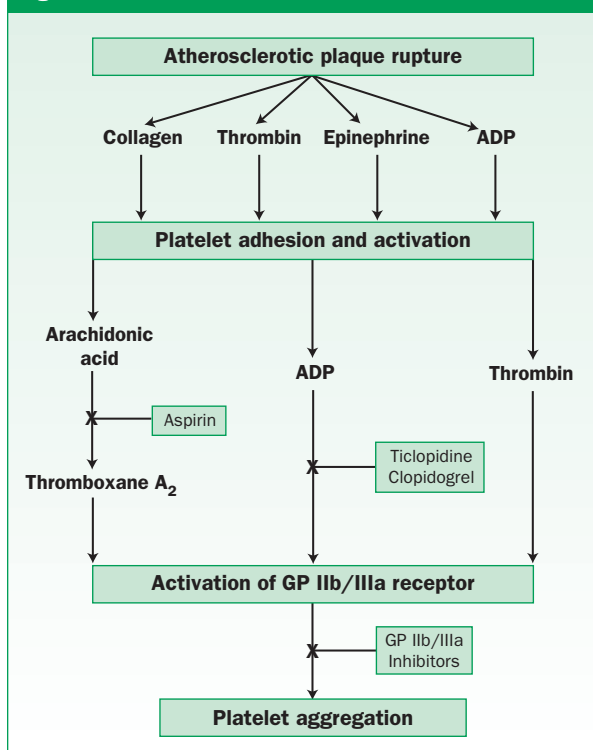
ROBERT ZEMAN, MD

St. Michael's Hospital  
6121-61 Queen St. E.  
Toronto, Ont. M5C 2T2  
Fax: (416) 867-3696

The editorial content of *Endocrinology Rounds* is determined solely by the Division of Endocrinology and Metabolism, St. Michael's Hospital, University of Toronto.

Available on the Internet  
[www.endocrinologyrounds.ca](http://www.endocrinologyrounds.ca)

**Figure 1: Platelet Activation**



Plaque disruption leads to the release of thrombogenic factors that adhere to platelets and activate platelet synthesis of adenosine diphosphate (ADP) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>). This leads to the exposure of the GP IIb/IIIa receptor, which binds fibrinogen, leading to platelet aggregation. Aspirin blocks the synthesis of TXA<sub>2</sub> while ticlopidine and clopidogrel block the platelet ADP receptor. GP IIb/IIIa receptor antagonists block the final common pathway of platelet aggregation.

purpura. As with aspirin, however, these drugs inhibit only one mechanism of platelet activation, leaving several alternative pathways for intraluminal platelet aggregation to occur.

The platelet glycoprotein (GP) IIb/IIIa receptor antagonists such as abciximab, eptifibatide, and tirofiban inter-

fere with the final common pathway of platelet aggregation – the exposure of the GP IIb/IIIa receptor on the platelet. These agents, which are small peptide or nonpeptide molecules, bind the receptor and block fibrinogen binding.

### **Trials of antiplatelet agents in reducing CVD in patients with diabetes**

Given the platelet dysfunction seen in diabetes, a variety of primary, mixed primary and secondary, and secondary prevention trials have investigated whether aspirin therapy reduces the increased risk of CVD (Table 1). Aspirin is the most commonly studied antiplatelet agent, although recent trials have used drugs such as ADP and GP IIb/IIIa receptor antagonists or combination therapy with aspirin and dipyridamole. There are studies looking exclusively at patients with diabetes, but most of the data are from trials reporting on subgroups of diabetic subjects.

#### **Primary prevention with aspirin**

The U.S. Physicians Health Study<sup>10</sup> followed 22,071 male physicians, randomized to receive either 325 mg aspirin every 2 days or placebo, for about 5 years. MI occurred in 1.2% of aspirin-treated men vs 2.2% of those on placebo (relative risk [RR] 0.56, 95% confidence interval [CI], 0.45-0.70,  $P < 0.00001$ ). There was a non-significant increased risk of stroke (RR 1.22; 95% CI, 0.93-1.60;  $P = 0.15$ ) mostly due to an increase in hemorrhagic strokes (RR 2.14; 95% CI, 0.96-4.77;  $P = 0.06$ ). There was no change in total cardiovascular mortality. Subgroup analysis performed in 533 men with diabetes showed the RR of MI was 0.39 in those assigned to aspirin therapy, with MI occurring in 4.0% of those assigned to aspirin therapy vs 10% of those assigned to placebo.

There is no published, randomized, controlled trial of aspirin in the primary prevention of vascular events in women. The Nurses Health Study<sup>11</sup> was a prospective cohort study of 87,678 female nurses between the ages of 34-65, of which 11,878 had diabetes. Among women taking 1-6 aspirin per week compared with those not

**Table 1: The effect of antiplatelet agents on the occurrence of vascular endpoints in primary and secondary prevention trials**

Study	Diabetic subjects, N	Antiplatelet agent vs placebo	Endpoint	Event rate % patients with event		Relative risk (95% CI)	p value
				Active group	Placebo group		
Physicians Health Study <sup>10</sup>	533	ASA 325 mg every second day	Myocardial infarction	4.0	10.1	0.39	*
Early Treatment Diabetic Retinopathy Study <sup>12</sup>	3711	ASA 650 mg daily	Myocardial infarction	13.0	15.3	0.83 (0.66-1.04†)	0.04
			Stroke	5.0	4.2	1.17 (0.79-1.73†)	0.32
			Cardiovascular mortality	13.1	14.8	0.87 (0.70-1.10†)	0.12
Hypertension Optimal Treatment <sup>14‡</sup>	1501	ASA 75 mg daily	Myocardial infarction	2.3	3.6	0.64 (0.49-0.85)	0.002
			Stroke	4.1	4.2	0.98 (0.78-1.24)	0.88
			Cardiovascular mortality	3.7	3.9	0.95 (0.75-1.20)	0.65
Antiplatelet Trialists Collaboration <sup>15</sup>	1200	§	Vascular events**	18.5	22.3	0.75	0.002
Antithrombotic Trialists Collaboration <sup>16</sup>	4961	§	Vascular events**	15.7	16.7	††	NS

\* Not reported

† 99% Confidence Interval

‡ although not separately reported, the benefit in the diabetic subgroup was the same as in the whole HOT population (n = 18,790)

§ antiplatelet agent vs. placebo

\*\* non-fatal MI, non-fatal stroke, vascular death

†† although not reported numerically, 99% confidence interval crosses 1.0 in figure representation

taking aspirin, there was an age-adjusted RR of MI of 0.68 ( $P=0.005$ ). After adjustment for cardiovascular risk factors, the RR was 0.75 ( $P=0.04$ ). There were no alterations in stroke risk and no apparent reductions in risk among women taking  $>6$  aspirin per week. The results of the ongoing Women's Health Study, which is comparing 100 mg of aspirin every 2 days versus placebo in 40,000 US female healthcare professionals, will evaluate this question in a randomized, controlled trial setting.

### Mixed primary and secondary prevention trials

The Early Treatment Diabetic Retinopathy Study (ETDRS)<sup>12</sup> was a mixed primary and secondary prevention trial of aspirin in 3,711 men and women, aged 18 to 70 years, with diabetes and diabetic retinopathy. Participants were randomized to treatment with 650 mg aspirin daily or to placebo. Approximately 30% of subjects were classified as having type 1 diabetes, 31% had type 2, and 39% were classified as "mixed" when the type could not be definitely determined. The study population was at high risk of MI given their elevated cholesterol and HbA<sub>1C</sub> and long duration of diabetes. Approximately 49% had a history of CVD.

Over the entire follow-up period (mean follow-up 5 years), fatal or nonfatal MIs occurred in 13.0% of the aspirin-treated group and in 15.3% of the placebo-treated group (RR 0.83; 99% CI, 0.66-1.04;  $P=0.04$ ). More patients assigned to aspirin had fatal or nonfatal strokes (5.0% vs 4.2%; RR 1.17; 99% CI, 0.79-1.73;  $P=0.32$ ). There was no difference in cardiovascular mortality (13.1% and 14.8%; RR 0.87; 99% CI, 0.70-1.10;  $P=0.12$ ), amputations, need for dialysis, or renal transplantation among the 2 treatment arms. Aspirin-placebo differences were similar among men and women and among the 3 diabetes classification groups.

In this high-risk group with diabetic retinopathy, of which 26% had proliferative changes, the study also examined the effect of photocoagulation on ocular events; participants underwent serial retinal exams and stereophotographs. Although aspirin therapy did not prevent the development of high-risk proliferative retinopathy, there was no increased risk of vitreous hemorrhage.<sup>13</sup>

The Hypertension Optimal Treatment (HOT)<sup>14</sup> trial was designed to evaluate optimum target diastolic blood pressure ( $\leq 90$ ,  $\leq 85$ , or  $\leq 80$  mm Hg) and the potential benefit of low-dose aspirin (75 mg/d vs placebo) in high-risk hypertensive individuals. The study followed men and women 50- to 80-years-old (mean 61.5 years), 8.7% of whom had a history of CVD, for a mean of 3.8 years. The study included a subset of 1,501 patients with diabetes out of a total of 18,790 patients.

The aspirin-treated group had a 15% reduction in pooled cardiovascular events ( $P=0.03$ ) and a 36% reduction in MI ( $P=0.002$ ). Although there was no difference in stroke incidence, cardiovascular mortality, or fatal bleeds among the 2 treatment groups, nonfatal major bleeds (risk ratio 1.8,  $P<0.001$ ) and minor bleeds (risk ratio 1.8) were significantly more frequent in the aspirin-treated group. Specific data on the diabetic subgroup were not included, however, the results were reportedly similar to those of the study population as a whole.

### Secondary prevention trials

Antiplatelet therapy has been studied extensively in the secondary prevention of stroke, MI, and peripheral vascular disease. In 1994, the Antiplatelet Trialists' Colla-

boration<sup>15</sup> reported a meta-analysis of 145 prospective trials of antiplatelet therapy that were published before 1990 and included about 70,000 high-risk patients (history of MI, stroke, or transient ischemic attack [TIA], or with a positive cardiovascular history). They showed a 25% reduction in vascular events (nonfatal MIs, nonfatal strokes, or vascular deaths) in this group. In the diabetic subgroup of about 1200 subjects, the event rate was reduced from 22.3% to 18.3% in the placebo- vs the aspirin-treated group, a reduction comparable to that seen in those without diabetes (16.4% vs 12.8%,  $P<0.00001$ ). Thus, treating 1000 high-risk diabetic patients with an antiplatelet agent would prevent  $38 \pm 12$  events ( $P<0.02$ ).

The renamed Antithrombotic Trialists' Collaboration<sup>16</sup> recently reported a repeat meta-analysis of 195 randomized trials of antiplatelet therapy published up to 1997. Of the 135,000 high-risk patients assigned to antiplatelet therapy, serious vascular events occurred in 10.7% as opposed to a 13.2% event rate in those on placebo, a proportional reduction of 22% ( $\pm 2\%$ ). Among 4,951 diabetic subjects (3.7% of the total population) from 9 different trials, serious vascular events were reduced from 16.7% in the placebo group to 15.7% in those on an antiplatelet, a nonsignificant 7% ( $\pm 8\%$ ) proportional reduction. The addition of the ETDRS<sup>13</sup> data to the overview likely diminished the statistical significance seen in the earlier 1994 meta-analysis. The authors concluded that antiplatelet therapy may still be of benefit in those diabetic patients who are at increased risk of a first vascular event, such as those with proteinuria. They also cautioned against dismissing the benefit of aspirin in patients with diabetes based on subgroup analysis, particularly in light of the increased cardiovascular risk in these patients.

### Combination antiplatelet therapy

Trials of combination antiplatelet therapy in the secondary prevention of stroke and peripheral vascular disease in patients with diabetes have not demonstrated significant reductions in events. These studies combined aspirin with another antiplatelet agent, dipyridamole (DP), a phosphodiesterase inhibitor. The European Stroke Prevention Study<sup>17</sup> randomized 1,861 patients with previous ischemic cerebral lesions to either a combination of 75 mg DP and 330 mg aspirin, 3 times a day, or placebo. Overall, the trial revealed a 38% decrease in stroke with the combination treatment compared with placebo. The diabetic subgroup (216 patients) receiving the DP-aspirin combination had a 39% reduction in the primary endpoint (death and stroke) and a 48% reduction in the risk of stroke, compared to a 23% and 32% reduction, respectively, in the nondiabetic subgroup (1,645 patients). Although the risk of events was greater in diabetic than in nondiabetic subjects, the risk reduction seen in the diabetic group was not statistically significant.

A Veterans Administration Cooperative study<sup>18</sup> examined the effect of aspirin 325 mg and DP 75 mg versus placebo, 3 times daily, in a group of 231 men with Type 2 diabetes who either had a recent amputation for gangrene or active gangrene. There was no significant difference in the primary endpoint of death from atherosclerotic vascular disease or amputation of opposite extremity for gangrene, or in the secondary endpoints of total mortality, all amputations, or MIs. Subgroup analysis did yield a statistically significant difference in strokes and TIAs (8.2% in the drug-treatment group vs 19.0% in the placebo group,  $P=0.02$ ).

## Thienopyridine derivatives

The platelet-inhibiting properties of the thienopyridine derivatives have been studied in the secondary prevention of micro- and macrovascular disease. The TIMAD<sup>19</sup> (Ticlopidine MicroAngiopathy of Diabetes) study assessed the use of ticlopidine (1000 mg daily) on the progression of nonproliferative diabetic retinopathy in 425 patients followed for 3 years. Although patients were excluded if they had cardiovascular disease requiring anti-aggregating therapy, specific data on macrovascular outcomes were not reported. The ticlopidine-treated group had a less severe progression of retinopathy ( $P=0.04$ ), and among those with Type 1 diabetes, there was a reduction in annual microaneurysm progression ( $P=0.03$ ). Adverse effects of neutropenia, diarrhea, and rash were associated with ticlopidine therapy.

The CAPRIE (Clopidogrel vs Aspirin in Patients at Risk for Ischemic Events) trial<sup>20</sup> assessed the relative efficacy of clopidogrel (75 mg) versus aspirin (325 mg) once daily in a population of 19,185 patients with atherosclerotic vascular disease, 20% of whom had diabetes. The annual risk of ischemic stroke, MI, or vascular death was decreased in the group treated with clopidogrel (5.32%) compared with aspirin (5.83%) (RRR 8.7; 95% CI, 0.3-16.5;  $P=0.043$ ). Adverse effects such as rash, diarrhea, major bleed, and neutropenia were similar in both groups. Because there were no data reported on the diabetic subgroup, it is unclear whether patients with diabetes benefited in a similar manner.

## Glycoprotein IIb/IIIa inhibitors

Several studies using abciximab, a chimeric monoclonal antibody against the glycoprotein complex GP IIb/IIIa, have been carried out in patients with diabetes, particularly following percutaneous revascularization, a procedure associated with poor outcomes in diabetic patients.<sup>21</sup> In the Evaluation of PTCA to Improve Long-term Outcome by Glycoprotein receptor blockade (EPILOG) study, where 23% of 2,792 patients had diabetes, abciximab plus heparin after percutaneous revascularization reduced the primary endpoint (30-day mortality, MI, and urgent revascularization) to 6.2% compared to 11.5% in those treated with heparin alone (hazard ratio 0.48; 95% CI, 0.35-0.65;  $P<0.001$ ). Target vessel revascularization, however, was reduced in nondiabetic, but not in diabetic subjects.<sup>22</sup> The EPISTENT study reported on a subgroup of 491 patients with diabetes and found a significant reduction in the 6-month rate of death/MI/need for surgical revascularization (25.2% vs 13.0%;  $P=0.005$ ) in those randomized to stenting plus abciximab versus those receiving stenting alone.<sup>23</sup> The parenteral use of these agents is currently limited to the management of acute coronary syndromes and following percutaneous revascularization, due to their expense and potential for increased bleeding complications.

## Prevalence of regular aspirin use among diabetic patients

Between 1988 and 1994, the third National Health and Nutrition Examination Survey (NHANES III)<sup>24</sup>

studied the use of aspirin in 1,503 adults with self-reported diabetes. An estimated 27% had CVD, whereas an additional 71% had one or more CVD risk factors (family history of heart attack, obesity, hypertension, smoking, albuminuria, or dyslipidemia). Regular aspirin use ( $\leq 15$  times in the previous month) was reported by only 37% of those with CVD and by only 13% of those with one or more risk factors. Thus, of the 98% of diabetic subjects who were potential candidates for aspirin therapy, only 20% took it regularly, a statistic that highlights an important need for patient and physician education in this area.

## General recommendations

### Secondary prevention

Aspirin therapy should be used for secondary prevention in diabetic men and women with evidence of CVD. This includes those with a history of MI, vascular bypass procedures, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina.

### Primary prevention

The use of aspirin in diabetic patients with no evidence of CVD should be based on their overall risk of CVD. Those with established cardiovascular risk factors, such as those listed below, should have the underlying risk factor appropriately managed.

- family history of premature CVD
- cigarette smoking
- hypertension
- obesity
- albuminuria
- dyslipidemia (LDL-C  $>2.5$  mmol/L, total cholesterol/HDL-C ratio  $>4$ , triglycerides  $>2$  mmol/L).

Given their increased risk, it would appear prudent to treat such individuals with aspirin for the primary prevention of CVD, even in the absence of clinical trial data confirming benefit in these subgroups.

### Age

Although the U.S. Physician's Health Study<sup>10</sup> included men between the ages of 40 and 70, the benefit of aspirin therapy in the reduction of MI was only seen in the subgroup  $>50$  years of age. The ETDRS<sup>12</sup> studied patients 18- to 70-years-old (83%  $>30$  years), but it is unclear whether there was any difference in outcome based on age, since subgroup analysis based on this variable was not performed. Regardless, no statistically significant difference in cardiovascular events was noted in this trial. Given the unknown rate of events and the unclear benefit of aspirin therapy in diabetic patients  $<50$  years, it is uncertain whether the potential reduction in events outweighs the potential risk of GI toxicity or hemorrhagic stroke. Therefore, decision to use or not use aspirin should be based on the patient's overall cardiovascular risk.

### Antiplatelet agents

The Antithrombotic Trialists' Collaboration<sup>16</sup> showed no difference in vascular event rates in an indirect comparison of different antiplatelet regimens.

Direct comparisons of clopidogrel versus aspirin showed a 10% reduction in events on clopidogrel, although 99% CIs suggest that the true benefit may range from negligible to a 20% reduction.<sup>16</sup> Aspirin would appear to be the best choice, given that it is the most widely studied and most economical. Patients who cannot tolerate aspirin should substitute an alternate antiplatelet agent such as clopidogrel. Antiplatelet agents should not be used in patients with inherited or acquired bleeding disorders, recent gastrointestinal (GI) bleeding, serious renal or hepatic failure. Aspirin should not be used in patients <21 years of age due to an increase in Reye's syndrome.

### Dosage

The optimal dose of aspirin for preventing vascular events was addressed by the Antithrombotic Trialists' Collaboration (Table 2).<sup>16</sup> There was no significant difference in the proportional reduction in vascular events among the different doses of aspirin. Doses of 75 to 325 mg/day were as effective as either higher aspirin doses or another antiplatelet agent.

Aspirin-induced GI toxicity appears to be dose related in the range of 30-1,300 mg/day.<sup>25</sup> A case-controlled trial found that the risk of hospitalization for bleeding peptic ulcers was decreased with lower, daily, prophylactic doses of aspirin:

- 75 mg (odds ratio (OR) 2.3; 95% CI, 1.2-4.4),
- 150 mg (OR 3.2; 95% CI, 1.7-6.5)
- 325 mg (OR 3.9; 95% CI, 2.5-6.3).<sup>26</sup>

Observational studies have shown the relative risk of hospitalization due to upper GI bleeding and/or perforation associated with low-dose (100-300 mg daily) aspirin (RR 2.3; 95% CI, 1.7-3.2) is similar to that seen with other antiplatelet agents (RR 2.0; 95% CI, 1.4-2.7) or with anticoagulants (RR 2.2; 95% CI, 1.4-3.4).<sup>27</sup> The use of buffered or enteric-coated aspirin does not appear to substantially decrease the risk of GI bleeding as demonstrated by a case-controlled trial using average daily doses of  $\leq$  325 mg aspirin where the RR of upper GI bleeding was 2.6 for plain, 2.7 for enteric-coated, and 3.1 for buffered aspirin.<sup>28</sup>

The overview by the Antithrombotic Trialists' Collaboration<sup>16</sup> showed an absolute excess of intracranial hemorrhage of <1 per 1,000 patients per year in high-risk patients on aspirin therapy. The same analysis showed similar risks of a major extracranial bleed with all daily doses of aspirin less than 325 mg (OR 1.7; 95% CI, 0.8-3.3).

Although aspirin results in a similar reduction in CV events among all dosing regimens, GI toxicity does appear to be dose-related. Therefore, the lowest effective dose should be used (75-150 mg daily). Due to the aforementioned increase in platelet turnover and thromboxane synthesis in diabetes, it has been suggested that multiple daily dosing of aspirin may be preferred in diabetic patients, although no clinical endpoint data have confirmed this hypothesis.

### Conclusion

Patients with diabetes have a 2- to 4-fold increased risk of morbidity and mortality from CVD. Platelet dysfunction in diabetes may contribute to this

**Table 2: Indirect comparison of aspirin doses reducing vascular events in high-risk patients in the Antithrombotic Trialists' Collaboration<sup>16</sup>**

Aspirin doses, mg/d	Trials, No.	Patients, No.	Odds Reduction, %
500-1500	34	22 451	19 $\pm$ 3
160-325	19	26 513	26 $\pm$ 3
75-150	12	6 776	32 $\pm$ 6
<75	3	3 655	13 $\pm$ 8

increased risk. The use of antiplatelet agents, specifically aspirin, has been found to decrease this risk in a variety of primary and secondary prevention trials. Therefore, aspirin should be used in all diabetic patients with evidence of CVD, as well as those in whom atherosclerotic risk factors place them at increased likelihood of cardiovascular events.

*Dr. Maria Kraw is an Endocrinology and Metabolism Fellow at the University of Toronto.*

### References

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakson M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-234.
2. Stamlet J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-444.
3. Wingard DL, Barrett-Conner E. Heart disease and diabetes. In: National Diabetes Data Group. *Diabetes in America*. 2nd ed. Washington, DC: Government Printing Office 1995:429-48.
4. Sobol AB, Watala C. The role of platelets in diabetes-related vascular complications. *Diabetes Res Clin Pract* 2000;50:1-16.
5. DiMinno G, Silver MJ, Cerbone AM, Murphy S. Trial of repeated low-dose aspirin in diabetic angiopathy. *Blood* 1986;68:886-891.
6. Davi F, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 1990;322:1769-74.
7. Halushka PV, Rogers RC, Loadholt CB, Colwell JA. Increased platelet thromboxane synthesis in diabetes mellitus. *J Lab Clin Med* 1981;97:87-96.
8. Winocour PD, Bryszewska M, Watala C, et al. Reduced membrane fluidity in platelets from diabetic patients. *Diabetes* 1990;39:241-244.
9. Jokl R, Klein RL, Lopes-Virella MF, et al. Release of platelet plasminogen activator inhibitor 1 in whole blood is increased in patients with type 2 diabetes. *Diabetes Care* 1995;18:1150-1155.
10. 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;321:129-135.
11. Manson JE, Stampfer MJ, Colditz GA, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA* 1991;266:521-527.
12. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *JAMA* 1992;268:1292-1300.
13. Chew EY, Klein ML, Murphy RP, Remaley NA, Ferris FL. Early Treatment Diabetic Retinopathy Study Research Group report no. 20. Effect of aspirin on vitreous/preretinal hemorrhage in patients with diabetes mellitus. *Arch Ophthalmol* 1995;113:52-55.
14. Hansson L, Zanchetti AI, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998;351:1755-1762.
15. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized 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.
16. 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.

17. Sivenius J, Laakso M, Riekkinen P, Smets P, Lowenthal A. European Stroke Prevention Study: effectiveness of antiplatelet therapy in diabetic patients in secondary prevention of stroke. *Stroke* 1992;23: 851-854.
18. Colwell JA, Bingham SF, Abraira C, et al. Veterans Administration Cooperative Study on antiplatelet agents in diabetic patients after amputation for gangrene: II. Effect of aspirin and dipyridamole on atherosclerotic vascular disease rates. *Diabetes Care* 1986;9:140-148.
19. TIMAD Study Group. Ticlopidine treatment reduces the progression of non-proliferative diabetic retinopathy. *Arch Ophthalmol* 1990;108:1577-1583.
20. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996;348:1329-1339.
21. Kip KE, Faxon DP, Detre KM, et al. Coronary angioplasty in diabetic patients: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 1996;94:1818-1825.
22. Kleiman NS, Lincoff AM, Kerckhoffs DJ, et al. Diabetes mellitus, glycoprotein IIb/IIIa blockade and heparin. Evidence for a complex interaction in multicenter trial. *Circulation* 1998;97:1912-1920.
23. Marso SP, Lincoff AM, Ellis DL, et al. Optimizing the percutaneous interventional outcome for patients with diabetes mellitus. Results of the EPIS-TENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trials) diabetic substudy. *Circulation* 1999;100:2477-2484.
24. Rolka DB, Fargot-Campagna A, Venkat Naraya KM. Aspirin use among adults with diabetes: estimates from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2001;24:197-201.
25. Patrono C, Collier B, Dalen JE, et al. Platelet-active drugs: the relationship among dose, effectiveness and side effects. *Chest* 2001;119:395-635.
26. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ* 1995;310:827-830.
27. Garcia-Rodriguez LA, Cattaruzzi C, Troncon MG, et al. Risk of hospitalization for upper gastrointestinal bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med* 1998;158:33-39.
28. Kelly JP, Kaufman DW, Jurgelson JM, et al. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413-1416.

## Abstract of Interest

### Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients

ANTITHROMBOTIC TRIALISTS' COLLABORATION. *BMJ* 2002;324:71-86

**Objective:** To determine the effects of antiplatelet therapy among patients at high risk of occlusive vascular events.

**Design:** Collaborative meta-analyses (systematic overviews).

**Inclusion criteria:** Randomised trials of an antiplatelet regimen versus control or of one antiplatelet regimen versus another in high risk patients (with acute or previous vascular disease or some other predisposing condition) from which results were available before September 1997. Trials had to use a method of randomisation that precluded prior knowledge of the next treatment to be allocated and comparisons had to be unconfounded that is, have study groups that differed only in terms of antiplatelet regimen.

**Studies reviewed:** 287 studies involving 135 000 patients in comparisons of antiplatelet therapy versus control and 77 000 in comparisons of different antiplatelet regimens.

**Main outcome measure:** "Serious vascular event": non-fatal myocardial infarction, non-fatal stroke, or vascular death.

**Results:** Overall, among these high risk patients, allocation to antiplatelet therapy reduced the combined outcome of any serious vascular event by about one quarter; non-fatal myocardial infarction was reduced by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth (with no apparent adverse effect on other deaths). Absolute reductions in the risk of having a serious vascular event were 36 (SE 5) per 1000 treated for two years among patients with previous myocardial infarction; 38 (5) per 1000 patients treated for one month among patients with acute myocardial infarction; 36

(6) per 1000 treated for two years among those with previous stroke or transient ischaemic attack; 9 (3) per 1000 treated for three weeks among those with acute stroke; and 22 (3) per 1000 treated for two years among other high risk patients (with separately significant results for those with stable angina ( $P=0.0005$ ), peripheral arterial disease ( $P=0.004$ ), and atrial fibrillation ( $P=0.01$ )). In each of these high risk categories, the absolute benefits substantially outweighed the absolute risks of major extracranial bleeding. Aspirin was the most widely studied antiplatelet drug, with doses of 75-150 mg daily at least as effective as higher daily doses. The effects of doses lower than 75 mg daily were less certain. Clopidogrel reduced serious vascular events by 10% (4%) compared with aspirin, which was similar to the 12% (7%) reduction observed with its analogue ticlopidine. Addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone. Among patients at high risk of immediate coronary occlusion, short term addition of an intravenous glycoprotein IIb/IIIa antagonist to aspirin prevented a further 20 (4) vascular events per 1000 ( $P<0.0001$ ) but caused 23 major (but rarely fatal) extracranial bleeds per 1000.

**Conclusions:** Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischaemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischaemia, peripheral arterial disease, or atrial fibrillation. Low dose aspirin (75-150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed. *BMJ* 2002;324:71-86.

## Upcoming Meetings

17-20 November 2002

### American Heart Association Scientific Sessions 2002

Chicago, Illinois

CONTACT: [www.scientificsessions.org](http://www.scientificsessions.org)

Tel: 800 650-9839

Fax: 800 521-6017

10-12 January 2003

### American Diabetes Association

#### 50<sup>th</sup> Annual Advanced Postgraduate Course

New York, New York

CONTACT: [www.diabetes.org](http://www.diabetes.org)

Tel: 703 549-1500 ext. 2453

Email: [meetings@diabetes.org](mailto:meetings@diabetes.org)

30 March – 2 April 2003

### American College of Cardiology

#### 52<sup>nd</sup> Annual Scientific Session

Chicago, Illinois

CONTACT: [www.acc.org/2003ann\\_meeting/home/home.htm](http://www.acc.org/2003ann_meeting/home/home.htm)

Tel: 800 253-4636 or 301 897-2697

Change of address notices and requests for subscriptions to *Endocrinology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to [info@snellmedical.com](mailto:info@snellmedical.com). Please reference *Endocrinology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above.

This publication is made possible by an educational grant from

# Aventis Pharma