CHD prevention in people with type 2 diabetes: The role of low-dose aspirin

Roger Gadsby

People with diabetes have a risk of myocardial infarction, stroke and cardiovascular death that is at least two- to four-fold greater than that of age- and sex-matched people without diabetes (Scottish Intercollegiate Guidelines Network, 2001). The life expectancy of both men and women diagnosed as having type 2 diabetes at age 40 is reduced by 8 years relative to people without diabetes (Kanters et al, 1999) and by an average of 20 years for people with type 1 diabetes relative to those without (Department of Health, 2001). Most of these premature deaths are from cardiovascular disease (Kanters et al, 1999). This article looks at the evidence which suggests that aspirin therapy could lower these risk factors in people with diabetes.

The *National Service Framework for Diabetes: Standards* (NSF; Department of Health [DoH], 2001) states that people with diabetes who have established cardiovascular disease (CVD) can benefit from the secondary prevention measures recommended in the NSF for coronary heart disease (CHD; DoH, 2000), including treatment with low-dose aspirin, beta-blockers and lipid-lowering agents.

The Scottish Intercollegiate Guideline Network (SIGN) guidelines recommend that aspirin, at a dose of 75 mg per day, should be given routinely and continued long-term in people with diabetes and coronary heart disease (CHD; SIGN, 2001). They also state that the addition of 'clopidogrel 75 mg [Plavix, Sanofi-Aventis and Bristol-Myers Squibb] daily to usual aspirin therapy should be considered for those with diabetes and a history of CHD when presenting with acute coronary syndromes.'

The National Institute for Health and Clinical Excellence (NICE, formerly known as the National Institute for Clinical Excellence) guidelines on managing blood pressure and blood lipids in type 2 diabetes suggest that, for people with manifest cardiovascular disease, aspirin 75 mg daily should be offered (NICE, 2002).

These guideline recommendations are consistent, and fairly straightforward to apply in practice.

Data for people who have established heart disease should be on the practice CHD register. They should be receiving the full range of secondary prevention measures including aspirin.

Antiplatelet therapy in people with diabetes: Evidence from trials

There is evidence from at least five randomised controlled trials of the benefits of aspirin in the primary prevention of CVD in high-risk people without pre-existing CVD (Peto et al, 1988; Hansson et al, 1989; Steering Committee of the Physicians' Health Study Research Group, 1989; the Medical Research Council's General Practice

Article points

1. People with diabetes have a risk of myocardial infarction, stroke and cardiovascular death that is at least two- to four-fold greater than that of age- and sex-matched people without diabetes.
2. Recommendations for the use of antiplatelet therapy to reduce such risks are consistent across UK guidelines.
3. These guidelines are fairly straightforward to implement in practice.
4. However, it is clear that a large-scale trial on the effect of low-dose aspirin in primary prevention of cardiovascular events in people with diabetes is needed.

Key words

- Anti-platelet therapy
- Aspirin
- Cardiovascular disease
- Coronary heart disease
- Guidelines

Roger Gadsby is a GP in Nuneaton and Senior Lecturer at The Warwick Diabetes Centre.

Research Framework, 1998; de Gaetano and the Collaborative Group of the Primary Prevention Project, 2001). A meta-analysis of pooled data from these studies showed that aspirin therapy reduced the risk of CVD by 28% with no significant effects on total mortality and stroke (Hayden et al, 2002).

Despite the known high cardiovascular risk of people with diabetes, clear evidence of the benefit of antiplatelet therapy in this population without previous CHD is lacking. A meta-analysis of pooled data from approximately 5000 people included in nine trials failed to show a clear benefit of antiplatelet therapy in people with diabetes, with a non-significant 7% proportional reduction in serious vascular events (Antithrombotic Trialists' Collaboration, 2002).

Recently there has been a sub-group analysis of 1031 people with diabetes included in the Primary Prevention Project (PPP) from Italy (Sacco et al, 2003). This showed a lower effect on primary prevention of CVD with low-dose aspirin in people with diabetes, a non-significant 10% reduction, as opposed to those with other cardiovascular risk factors who had a significant 41% reduction. Sacco and colleagues suggest that the antiplatelet effects of aspirin in people with diabetes may be overwhelmed by aspirin-insensitive mechanisms of platelet activation and thrombus formation. Other reasons that might explain the non-significant result include: the trial may not have had sufficient power; and its design included looking at the effect of vitamin E (which had no effect on reducing CVD risk at all), which may have adversely influenced the result (Colwell, 2003).

It is clear that a large scale trial on the effect of low-dose aspirin in primary prevention in people with diabetes is urgently needed to resolve these questions.

However, the conclusion of the editorial commentary by a USA-based author (Colwell, 2003) on Sacco and colleagues' paper is that healthcare professionals should still implement the consensus guidelines (from the American Diabetes Association, the American Heart Association and the US Preventive Services Task Force) on aspirin for primary prevention of cardiovascular events in people with diabetes.

Risks associated with aspirin therapy

In the PPP trial, 28.2% of people assigned to aspirin stopped it by the conclusion of the trial; the authors presume that this was because of side effects of gastrointestinal symptoms (Sacco

et al, 2003). This drop-out rate is similar to that seen in other trials of aspirin therapy. Aspirin, even in low doses, is associated with adverse events, primarily of gatsrointestinal tract bleeding. These risks appear to be unrelated to the risks of CVD. So there is considerable variation in the overall risk–benefit ratio for an individual as those with low CVD risk will be at the same risk level of gastrointestinal bleeding as those at high CVD risk.

Thus, consensus guidelines usually suggest giving aspirin to people with diabetes who are at higher levels of risk due to factors other than CHD, such as blood pressure and lipid levels. People with uncontrolled hypertension are at an increased risk of a cerebral bleed (Antithrombotic Trialists' Collaboration, 2002). This risk could be exacerbated by aspirin and guidelines, therefore, state that it should only be given if hypertension is controlled.

Aspirin in primary prevention: Guidelines for people with type 2 diabetes

Systolic blood pressure should be maintained at ≤145 mmHg before and during aspirin therapy for primary prevention (NICE, 2002). Seventy-five milligrams should be considered for all patients who have diabetes and well-controlled hypertension whose risk of a coronary event is estimated to be >20 % over 10 years (SIGN, 2001). For people with a 10-year coronary risk greater than 15 %, offer aspirin 75 mg daily.

Practicalities of calculating CHD risk in people with diabetes

It is difficult to accurately calculate the risk of CHD in people with diabetes. Most GP clinical computing systems contain a CHD risk calculator, which automatically calculates the 10-year risk of a CHD event, basing it on the variables of patient age, sex, smoking history, total cholesterol to HDL-cholesterol ratio, systolic blood pressure and presence or absence of diabetes. These risk calculators are usually based on the Joint Societies' CHD risk engine (Wood et al, 1998) which uses data from the Framingham Heart Study, which was made up of people from a Caucasian background, few of whom had diabetes. As a result the risk of CHD in people with diabetes could be underestimated (McEwan et al, 2004). The risk tables will

Page points

1. A new risk engine specific to type 2 diabetes has been developed from the UK Prospective Diabetes Study data-set which incorporates diabetes-specific variables and gives an approximate margin of error for each estimate.
2. There is debate about the trial evidence for the use of low-dose aspirin in primary prevention of cardiovascular events in people with diabetes.
3. Aspirin use has not been made a quality standard for diabetes quality points in the new General Medical Services contract.
4. However, there are Scottish Intercollegiate Guideline Network and National Institute for Health and Clinical Excellence guidelines to support its use in people with diabetes who have a greater than 15–20% risk of CHD and controlled hypertension over 10 years.

certainly do this in people with diabetes from an Indo-Asian background, who have a higher risk of CHD than Caucasian people. The risk tables are not applicable to people with type 1 diabetes or those with microalbuminuria, who are known to be at very much higher risk.

A new risk engine specific to type 2 diabetes has been developed from the UK Prospective Diabetes Study (UKPDS) data-set which incorporates diabetes-specific variables and gives an approximate margin of error for each estimate (Stevens et al, 2001). The problem is that the UKPDS risk engine is not, as yet, incorporated into many GP clinical computer systems.

Conclusion

As has been described, there is debate about the trial evidence for the use of low-dose aspirin in primary prevention of cardiovascular events in people with diabetes. Aspirin use has not been made a quality standard for diabetes quality points in the new General Medical Services contract. However, there are SIGN and NICE guidelines to support its use in people with diabetes who have a greater than 15–20% risk of CHD and controlled hypertension over 10 years.This calculation is made automatically on many GP clinical computing systems when data is gathered at a practice diabetes clinic appointment. It is possible, therefore, to make the prescribing decision to give low-dose aspirin at the appointment. It has been calculated that 80% of non-symptomatic adults with type 2 diabetes would fulfil the guideline criteria for aspirin prescribing for primary prevention (Wood et al, 1998). ■

Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *British Medical Journal* **324**(7329): 71–86

Colwell JA (2003) Aspirin for primary prevention of cardiovascular events in diabetes. *Diabetes Care* **26**(12): 3349–50

de Gaetano G, Collaborative Group of the Primary Prevention Project (2001) Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet* **357**(9250): 89–95

Department of Health (DoH; 2000) *Coronary heart disease: National Service Framework for Coronary Heart Disease: modern standards and service models*. DoH, London

DoH (2001) *National Service Framework for Diabetes: Standards*. DoH, London

Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al (1989) Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* **351**(9118): 1755–62

Hayden M, Pignone M, Phillips C, Mulrow C (2002) Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* **136**(2): 161–72

Kanters SD, Banga JD, Stolk RP, Alga A (1999) Incidence and determinants of mortality and cardiovascular events in diabetes mellitus: a meta-analysis. V*ascular Medicine* **4**(2): 67–75

McEwan P, Williams JE, Griffiths JD, Bagust A, Peters JR, Hopkinson P, Currie CJ (2004) Evaluating the performance of the Framingham risk equations in a population with diabetes. *Diabetic Medicine* **21**(4):318–23

Medical Research Council's General Practice Research Framework (1998) Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* **351**(9098): 233–41

National Institute for Health and Clinical Excellence (NICE; 2002) *Management of Type 2 Diabetes - management of blood pressure and blood lipids (Guideline H)*. NICE, London

Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K et al (1988) Randomised trial of prophylactic daily aspirin in British male doctors. *British Medical Journal* **296**(6618): 313–6

Sacco M, Pellegrini F, Roncaglioni MC et al (2003) Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* **26**(12): 3264–72

Scottish Intercollegiate Guidelines Network (SIGN; 2001) *SIGN Publication No. 55: Management of diabetes*. SIGN, Edinburgh

Steering Committee of the Physicians' Health Study Research Group (1989) Final report on the aspirin component of the ongoing Physicians' Health Study. *New England Journal of Medicine* **321**(3): 129–35

Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group (2001) The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clinical Science* **101**(6): 671–9

Wood D, Durrington P, Poulter N, Rees A, Wray R (1998) Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* **80**(suppl 2): 1–29