Macrovascular Risk Reduction in Diabetes: Antiplatelet Therapy

People with diabetes have a 2 to 4 fold higher risk of dying from cardiovascular disease. People with diabetes have a complex procoagulant state, which contributes to the increased risk of atherosclerotic events. Antiplatelet therapy is a simple intervention that can reduce the risk of events in this high-risk population. NHANES III data shows that 27% of people with diabetes are eligible for secondary prevention strategies, while an additional 71% had at least one risk factor for atherosclerotic disease. Thus, basically all persons with diabetes are candidates for antiplatelet therapy, yet only 13% of eligible patients were currently taking aspirin.[1, 2]

Recommendations:

1) People with diabetes who are age 30 or above should be offered aspirin therapy if no contraindications exist to therapy.

2) Dose: 75 to 325mg daily. An enteric-coated product may be used to minimize gastrointestinal side effects

3) If an aspirin allergy is present, clopidogrel may be recommended (75mg/day) for secondary prevention. Currently, no primary prevention trials in people with diabetes have been conducted. In primary prevention patients with multiple risk factors, the risk, benefit, and cost of clopidrogrel must be considered.

Do not use antiplatelet therapy in people with:

1) Bleeding tendency

2) Anticoagulant therapy

3) Recent gastrointestinal bleeding

4) Clinically active hepatic disease

5) Patients at risk of Reye's syndrome

Combination Therapy:

In people with diabetes who have an event on aspirin, aspirin resistance may play a role.[3]

1) The CURE trial used combination therapy with aspirin 75mg to 325mg and clopidogrel 75mg every day. Though over 22% of the patients enrolled had diabetes, the relative risk of an event in subjects with diabetes was not reduced significantly by the combination.

2) No benefit has been shown with the addition of warfarin to aspirin therapy [4]

Secondary Prevention

1) **Anti-platelet Trialists'**
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 308:81-106,1994

    a. Meta-analysis of 145 prospective controlled trials of antiplatelet therapy

    b. Risk reduction of 38±12 vascular events per 1000 diabetics treated (p<0.02)

    c. Placebo rate of events 22.3%, reduced to 18.5% on doses of 75mg to 325mg a day

2) **Early Treatment of Diabetic Retinopathy Study (ETDRS)**
ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus. JAMA 268:1292-1300, 1992

    a. Mixed group of primary and secondary prevention in 3711 diabetics

    b. Dose: 650mg/day or placebo

    c. Results: 9.1% had myocardial infarction (MI) on aspirin vs. 12.3% on placebo

    d. No increase in retinal bleeding was seen on serial eye exams

3) **Hypertension Optimal Treatment (HOT)**
Hansson L, Zanchetti A, 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) randomised trial. Lancet 351:1755-1762, 1998

    a. Mixed primary and secondary prevention trial in hypertensive type 2 diabetics

    b. 1501 diabetics enrolled in study for average of 3.8 years follow-up

    c. Dose: 75mg or placebo

    d. Results: 15% reduction in pooled cardiovascular events (p=0.03), and a 36% reduction in the risk of MI (p=0.002)

4) **Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)**

    a. 19185 persons with recent atherosclerotic event randomized to clopidogrel or aspirin

    b. Dose: clopidogrel 75mg every day, aspirin 325mg every day

    c. 5.32% risk of ischemic stroke, MI, or vascular death with clopidogrel vs. 5.83% for aspirin (p=0.043)

    d. Post-hoc subset analysis of 3866 subjects diagnosed with diabetes by intake questionnaire from investigator5

    e. Composite outcome endpoint was: vascular death, MI, stroke, or hospitalization for angina or bleeding event.

    f. Event rate was 15.6% vs. 17.7%/ year (p=0.042), for clopidrogrel and aspirin respectively. No significant difference in individual outcomes.

    g. Would need to treat approximately 47 individuals with clopidrogrel instead of aspirin to reduce one event.

5) **Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators (CURE)**
N Eng J Med 345:494-502, 2001

    a. 12, 562 subjects who presented to the hospital with an acute coronary syndrome within 24 hours of symptoms

    b. Given aspirin 75mg to 325mg every day plus one time dose of clopidogrel 300mg, followed by 75mg every day vs. aspirin alone

    c. Results: In 2849 subjects who had diabetes, the combination group experienced a 14.2% event rate vs. 16.75% in the aspirin alone group.

    d. Though the relative risk favored addition of clopidogrel, the reduction was not significant

6) **Ticlopidine in Microangiopathy of Diabetes (TIMAD)**
TIMAD Study Group: Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy. Arch Ophthalmol 108:1577-1583, 1990

    a. 435 diabetic with nonproliferative diabetic retinopathy

    b. ticlopidine 250 mg two times a day or placebo

    c. followed up to 3 years

    d. fluorescein angiograms of eyes done

    e. Reduction in progression of retinopathy by 67% (p=0.03) in ticlopidine group vs. placebo

    f. Side effects limit usefulness: 2-3% experience neutropenia, serial CBC's must be followed for a minimum of 3 months

Primary Prevention

1) **Physician's Health Study**
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 321:129-135, 1989

    a. Dose: 325mg every other day or placebo

    b. 22, 071 participants followed for approximately 5 years, 533 had diabetes

    c. Outcome: myocardial infarction in 11/275 (4.0%) on aspirin vs. 26/258 on placebo (10.0%). Relative risk = 0.39 (significance not reported)

References:

1. Rolka DB, Fagot-Campagna A, Narayan KM: Aspirin use among adults with diabetes: Estimates from the Third National Health and Nutrition Examination Survey. Diabetes Care 24:197-201, 2001
2. American Diabetes Association. Position Statement. Aspirin Therapy in Diabetes. Diabetes Care. 25:S78-S79, 2002; Diabetes Care. 2004 Jan;27 Suppl 1:S72-3.
3. Gum PA, Kottke-Marchan K, Poggio ED, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol 88:230-5, 2001
4. Fiore LD, Ezekowitz MD, Rophy MT, et al. Department of veterans affairs cooperative studies program clinical trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 105:557-563, 2002
5. Cannon CP. CAPRIE Investigators. Effectiveness of clopidrogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial). American Journal of Cardiology 90(7):760-2;2002