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## Glycemic control, blood pressure control, and aspirin therapy in diabetes: An overview of the ACCORD, ADVANCE, VADT, UKPDS, POPADAD, and JPAD studies.

Several important clinical trials published in 2008 have evaluated management strategies for patients with type 2 diabetes. The ACCORD and STENO-2 studies were the subject of a previous update (April 2008) available on [www.RxFacts.org](http://www.RxFacts.org), that should be read in conjunction with the following material. This update provides a summary and comparison of the ACCORD, ADVANCE, and VADT trials of intensive glycemic control; the results of a 10-year follow up to the UKPDS study of glycemic control and blood pressure (BP) control; and the POPADAD and JPAD studies of aspirin therapy.

### The studies

- **ACCORD** (Action to Control Cardiovascular Risk in Diabetes, New England Journal of Medicine, June 2008)<sup>1</sup>
- **ADVANCE** (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation, New England Journal of Medicine, June 2008)<sup>2</sup>
- **VADT** (Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes, New England Journal of Medicine, Jan 2009)<sup>3</sup>
- **UKPDS** (United Kingdom Prospective Diabetes Study (glucose control), New England Journal of Medicine, Oct 2008)<sup>4</sup>
- **UKPDS** (United Kingdom Prospective Diabetes Study (BP control), New England Journal of Medicine, Oct 2008)<sup>5</sup>
- **POPADAD** (The Prevention of Progression of Arterial Disease and Diabetes, BMJ, Oct 2008).<sup>6</sup>
- **JPAD** (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes, JAMA, Nov 2008).<sup>7</sup>

Large trials, such as UKPDS, have found reductions in diabetes-related outcomes with intensive glucose control, supporting the idea that the lower the HbA1c, the better. In 2008, however, evidence emerged that raised questions about this “lowest is best” approach (see Table). In the ACCORD study, patients who were assigned to a target HbA1c level under 6% had an increased risk of mortality. On the other hand, there was no increase in mortality in the intensive treatment arms of the ADVANCE or VADT studies.

Intensive glucose control did not significantly reduce macrovascular events in ACCORD, ADVANCE, or VADT. There was a significant reduction in microvascular events with intensive glucose control in ADVANCE, primarily as a consequence of a reduction in nephropathy. In contrast, there was no significant reduction in microvascular events in the VADT study.

|   | ACCORD <sup>1</sup>             | ADVANCE <sup>2</sup>         | VADT <sup>3</sup>                                      |
|---|---------------------------------|------------------------------|--|
| No. of patients   | 10,251                          | 11,140                       | 1,791  |
| Mean age, years   | 62                              | 66                           | 60   |
| Duration of diabetes, years   | 10                              | 8                            | 11   |
| History of CVD, %   | 35                              | 32                           | 40   |
| BMI, kg/m <sup>2</sup>  | 32                              | 28                           | 31   |
| Median baseline HbA1c   | 8.1%                            | 7.2%                         | 9.4%   |
| Target HbA1c  | < 6.0% vs. 7.0–7.9%             | < 6.5%                       | < 6.0% vs. a planned difference of 1.5% between groups |
| Median follow-up  | 3.5 years (trial stopped early) | 5 years                      | 5.6 years  |
| <b>Outcomes (intensive glycemic control compared to standard control)</b> |                                 |                              |  |
| HbA1c achieved  | 6.4% vs. 7.5%                   | 6.5% vs. 7.3%                | 6.9% vs. 8.4%  |
| Macrovascular events  | Not significantly different     | Not significantly different  | Not significantly different                            |
| Microvascular events  | Not measured                    | <b>Significant reduction</b> | Not significantly different                            |
| Death (CV)  | <b>Significantly increased</b>  | Not significantly different  | Not significantly different                            |
| Death (all causes)  | <b>Significantly increased</b>  | Not significantly different  | Not significantly different                            |

These trials provide conflicting evidence of mortality risk with intensive glycemic control (i.e., targeting HbA1c levels well below 7%). There was no clear reason for the increased mortality in the ACCORD trial; patients in the standard-therapy group used fewer drugs and drug combinations, but their increased mortality was not attributable to any single drug or drug class.

Possible causes of the higher death rate in the intensive treatment group of ACCORD as compared to ADVANCE and VADT include:

- the magnitude of the reduction in HbA1c
- speed of the reduction in HbA1c (reductions of approximately 1.4% in the intensive therapy group and 0.6% in the standard-therapy group within the first 4 months after randomization)
- differences in drug regimens
- rates of hypoglycemia
- undetected adverse interactions among the various drug classes used at high doses.

## The UKPDS study 10 year follow-up

### Glycemic control

The UKPDS study showed that patients with type 2 diabetes mellitus who received intensive glucose therapy (sulfonylurea or insulin, or metformin in obese patients) had a lower risk of microvascular (renal, retinal) complications than did those treated with diet modification alone. Monitoring was continued for 10 years after the trial to determine whether this improved glucose control persisted, and whether such therapy had a long-term effect on macrovascular (cardiovascular) outcomes.<sup>4</sup>

This long-term follow up revealed that the between-group differences in HbA1c levels were lost after the first year. Despite this, patients in the sulfonylurea–insulin group had reduced 10-year risk for all diabetes-related endpoints (9%,  $P = 0.04$ ) and microvascular disease (24%,  $P = 0.001$ ). Further, risk reductions for MI (15%,  $P = 0.01$ ) and death from any cause (13%,  $P = 0.007$ ) emerged over time. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%,  $P = 0.01$ ), MI (33%,  $P = 0.005$ ), and death from any cause (27%,  $P = 0.002$ ).

In sum, the benefits of an intensive strategy to control blood glucose levels in patients with Type 2 diabetes were sustained for up to 10 years after the cessation of the randomized interventions. Remarkably, these benefits persisted despite the lack of sustained differences in HbA1c between the intensive-therapy group and the conventional-therapy group.

### Blood pressure control

Researchers followed patients in this trial for ten years in order to determine whether the micro- and macro-vascular risk reductions initially achieved with good BP control would be sustained over 10 years.<sup>5</sup>

As with glycemic control (see above), the differences in BP initially achieved between the two study groups (tight BP control vs. less tight BP control) disappeared within 2 years after trial termination. However, the risk reductions found during the trial for diabetes-related endpoints, diabetes-related death, microvascular disease, and stroke in the group receiving tight vs. less tight blood-pressure control were not sustained during the post-trial follow-up.

The finding that the benefits of tight BP control were not maintained once the differences in BP seen during the trial were lost, suggests that good BP control must be continued if its benefits are to be maintained.

## **American Diabetes Association guidelines for glycemic control**

Following publication of these studies, a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association addressed the implications of the ACCORD, ADVANCE, and VADT studies for glycemic control goals.<sup>8</sup> The main recommendations were:

- The lack of significant reduction in CVD events with intensive glycemic control in these studies should not lead to an abandonment of the general target of an HbA1c < 7.0%, because of the well-established benefit of good glucose control on microvascular (renal, retinal) complications.
- Lowering HbA1c to approximately 7% or less reduces the microvascular complications of diabetes. Thus, the goal for most non-pregnant adults in general is an HbA1c < 7%.
- Although randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in cardiovascular disease outcomes, long-term follow-up of the UKPDS trial suggests that treating to a target HbA1c of 7% or less soon after diabetes is diagnosed may cause long-term reduction in risk of cardiovascular disease.

## Summary of glycemic and BP control

### What we already know

- Lowering blood glucose to normal or near-normal HbA1c levels clearly reduces the risk of microvascular complications such as retinopathy and nephropathy.
- The impact of tight glucose control on the risk of macrovascular complications (MI, stroke) or mortality is unclear.

### What the ACCORD, ADVANCE, VADT, and UKPDS studies add

- Intensive versus standard glycemic control did not significantly reduce cardiovascular disease outcomes. In contrast, tight glycemic control was associated with increased mortality in ACCORD.
- Aiming for HbA1c levels near or below 7% soon after the diagnosis of diabetes may reduce the risk of macrovascular disease. Such tight glycemic control may play a more important role before macrovascular disease is well developed than after it has become advanced.
- Any cardiovascular benefit of glucose lowering is probably modest compared with the benefits from treating other CV risk factors such as hypertension and hyperlipidemia. Control of BP must be sustained over time for benefits to be realized.
- Intensive glucose control does appear to reduce the risk of microvascular complications.

### Bottom Line

- It is important to treat elevated HbA1c, and the greatest clinical benefit of good glycemic control may occur early in the course of the disease. A reasonable HbA1c target is 7% for most patients. This goal should be individualized in selected patients such as the frail elderly and pregnant women.

## Aspirin therapy

Aspirin has for years been a mainstay of cardiac prevention, with clear evidence from randomized controlled trials that it can reduce the incidence of myocardial infarction in patients with existing cardiac disease. Diabetes is generally thought to be coronary artery disease “risk equivalent” and thus aspirin has generally been recommended for most patients with diabetes, including those without known vascular disease. However, two recent large trials have raised new questions about the role of aspirin in primary prevention. Their findings are summarized below, along with an overview of current recommendations.

## **The POPADAD study**

The POPADAD study<sup>6</sup> evaluated whether 100 mg of aspirin daily is effective in preventing cardiovascular events in patients with diabetes and asymptomatic peripheral arterial disease. It enrolled 1,276 adults (mean age 60) with type 1 or type 2 diabetes but no symptomatic cardiovascular disease. Approximately 10% of participants were using insulin.

About a third of study subjects were current smokers and another third were previous smokers. Time since diagnosis of diabetes was approximately 6 years, median BMI was 29, systolic BP was approximately 145 mm Hg, mean HbA1c was 8%, and median LDL was 121 mg/dL.

The 2 primary outcome measures were:

- (1) death from coronary heart disease or stroke; and
- (2) any of the following: death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischemia.

Median follow-up was almost seven years.

In this trial, aspirin conferred no significant benefit in terms of either outcome measure. The rate of death from any cause was 14.7% in patients randomized to aspirin and 15.8% in controls, the difference was not statistically significant. The rate of gastrointestinal bleeding was 4.4% with aspirin and 4.9% in controls, also non-significant. The study also randomized patients to receive an anti-oxidant ( $\alpha$ -tocopherol 200 mg, ascorbic acid 100 mg, pyridoxine hydrochloride 25 mg, zinc sulphate 10 mg, nicotinamide 10 mg, lecithin 9.4 mg, and sodium selenite 0.8 mg) or placebo. That, too, had no effect on cardiovascular outcomes.

## **The JPAD study**

Like POPADAD, the JPAD study<sup>7</sup> examined the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes. It randomized 2,539 patients with type 2 diabetes and no history of atherosclerotic disease to receive either 81 or 100 mg aspirin per day or placebo.

The primary outcome measure was any atherosclerotic event.\* Secondary endpoints studied included each primary endpoint and combinations of primary endpoints, as well as death from any cause. Median follow-up was 4 years.

In this primary prevention study of patients with type 2 diabetes, low-dose aspirin did not reduce the incidence of total atherosclerotic events, (coronary, cerebrovascular, and peripheral vascular) compared to placebo. However, deaths from MI or stroke were significantly reduced in the low-dose aspirin group (1 death vs. 10 deaths,  $p = 0.0037$ ), though all-cause mortality was not significantly reduced. Gastrointestinal bleeding occurred in 12 patients in the aspirin group and 4 patients in the placebo group ( $p$  value not stated). There was no significant difference in the composite outcome of hemorrhagic stroke and severe gastrointestinal bleeding.

\*death from coronary, cerebrovascular, and aortic causes; nonfatal acute myocardial infarction; unstable angina; newly developed exertional angina; nonfatal ischemic and hemorrhagic stroke; transient ischemic attack; or nonfatal aortic and peripheral vascular disease (arteriosclerosis obliterans, aortic dissection, mesenteric arterial thrombosis)

## Summary of aspirin therapy

### What we already know

- The benefit of aspirin for patients with diabetes who have **known cardiovascular disease** is well established. Patients with established CV disease should be treated with aspirin unless there is a compelling contraindication.
- The benefit of aspirin for diabetic patients **without known cardiovascular disease** is less well established.
- Aspirin can cause important gastrointestinal morbidity.

### What POPADAD and JPAD add

- These studies add to the uncertainty about the efficacy of aspirin for the **primary** prevention of cardiovascular events in type 2 diabetes, but do not diminish its established usefulness in secondary prevention.

### The Bottom Line

- The benefit of aspirin for the primary prevention of cardiovascular events in patients with diabetes is unclear. An individual clinical decision must be made weighing the degree of cardiovascular risk and the risk of bleeding.

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**These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.**

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