# The Alphabet Soup of Diabetes Research Studies

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## Abstract

This article describes the major studies that are most frequently known by their acronyms. Studies that are completed, currently underway, and anticipated to start soon are included. A description of the study design, outcomes when available, and funding sources is provided. The article also provides references regarding where to find information about participating in upcoming studies.

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The art of care and management of people with diabetes has changed tremendously in the past decade. A combination of new treatment modalities, insights into the causes and potential prevention of the disease, and recognition of the need to empower people with diabetes to be active participants in their management has set the groundwork for better outcomes in the lives of those individuals. The management of diabetes has evolved based on research in the areas of improvement of quality of life, prevention of complications, and the disease itself. Goals for treatment are based on multiple sources of evidence-based research, ranging from areas of basic bench research to the implementation of teaching methods for better adherence to a recommended treatment plan.

Research studies are performed with various outcomes intended. A key concern in all clinical trials, however, is to protect the safety and confidentiality of the participants. Some studies are designed to change clinical practice; others, to get drugs approved for use. The National Institutes of Health (NIH), pharmaceutical companies, foundations, and institutions involved in research are traditional sources of funding.

Study titles are often lengthy and very descriptive of the intent of the study. In order to be efficient in referring to a study, a great deal of thought and effort goes into coming up with an acronym that is both decorative and "catchy" to describe the study. The proliferation of acronyms, along with the use of initials of study sponsors, leads to the alphabet soup often seen in research publications.

Many recent studies that have served as the basis for current studies are known most readily by their acronyms. In this article, we will attempt to describe some of the studies often referred to by a few letters. We will give some of the results of pivotal trials that have changed the way we treat diabetes, as well as some that will change future treatment.

### Past Studies

DCCT, UKPDS, DIGAMI, BARI, DiaLOG, and HOPE are examples of studies that are completed and reported. They are worthy of discussion because they set the groundwork for current and future studies and have changed the treatment guidelines and standards of care for diabetes.

The **D**iabetes **C**ontrol and **C**omplications **T**rial (DCCT) was an NIH-funded trial started in 1987 and concluded in 1993. It compared the effects of intensive insulin therapy with the effects of conventional therapy on early microvascular complications in people with type 1 diabetes. The study population included people with type 1 diabetes with no or minimal signs of secondary complications.

The results of the study demonstrated a markedly decreased occurrence of microvascular complications, including retinopathy, neuropathy, and nephropathy, in the intensely treated group. This greatly changed the way we treat people with diabetes today. The DCCT also illustrated that

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the risk of hypoglycemia needs to be assessed as a complication of intensive therapy. This trial left many unanswered questions related to control and its implications for type 2 diabetes and also the effect of tight glycemic control on macrovascular disease.[1]

The **U**nited **K**ingdom **P**rospective **D**iabetes **S**tudy (UKPDS) was designed to determine which therapies (diet, insulin, sulfonylureas, or metformin) can attain glycemic control in people with type 2 diabetes and whether tight control can decrease complications. The trial, which took place between 1977 and 1997, followed patients every 3 months for 9 years after enrollment. Participants included 4,075 newly diagnosed people with type 2 diabetes with a median fasting plasma glucose level of 207 mg/dl and a median $HbA_{1c}$ level of 9.1%. The participants were randomized after a 3-month high-carbohydrate, low-fat diet to diet alone, insulin, sulfonylurea, or metformin.

The results demonstrated that control of diabetes declined markedly over the 9 years of follow-up. Initially, all patients on a therapeutic agent and having an $HbA_{1c}$ <7% were compared to participants who were on diet therapy After 3 years, however, only about 50% of the participants on oral agents could achieve the goal of <7% with monotherapy, and by 9 years this had decreased to 25%. The conclusion was that the majority of people with type 2 diabetes need multiple therapies to achieve target levels of blood glucose and $HbA_{1c}$ over the long term.[2]

The UKPDS also studied the efficacy of atenolol and captopril in reducing the risk of macrovascular and microvascular complications in type 2 diabetes. Participants were randomized to either captopril or atenolol for tight control of blood pressure, and approximately one-third of the participants were randomized to less tight control of blood pressure.

The results showed that captopril and atenolol were equally effective in reducing both blood pressure and macrovascular end points. Neither drug had any specific beneficial or deleterious effect, suggesting that blood pressure reduction itself may be more important than the treatment used to achieve the reduction.[3]

The **H**eart **O**utcomes **P**revention **E**valuation (HOPE) Study was a large, randomized trial comparing ramipril (an angiotensin-converting enzyme [ACE] inhibitor) and vitamin E to placebo in prevention of myocardial infarction (MI), stroke, or cardiovascular death. More than 9,000 women and men over 55 years of age who were at high risk for these conditions were recruited over 18 months starting in December 1993, with treatment lasting 5 years. Key design features of HOPE were inclusion of individuals at high risk of cardiovascular disease (CVD), including people with diabetes (36%) and women (27%) and detailed studies to provide data on the mechanism of benefit. The results showed that treatment with ramipril decreased the rates of death from cardiovascular causes, MI, and stroke.[4]

The **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation (BARI) studied the relative long-term safety and efficacy of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery in patients with multi-vessel disease and severe angina or ischemia who required revascularization and had coronary anatomy suitable for either procedures. Participants were 18–75 years of age. A subgroup of 353 participants had diabetes.

The study was stopped prematurely because of a significant increase in 5-year mortality in patients with diabetes receiving PTCA compared to those undergoing CABG. This resulted in the National Heart, Lung, and Blood Institute (NHLBI) issuing a clinical alert recommending CABG over PTCA for patients on drug therapies for diabetes (type 1 or type 2) and who had multiple coronary blockages and were first-time candidates for either procedure. The clinical alert was prompted by the analysis of the 5-year mortality data from BARI, which showed that the PTCA-treated group of participants who were drug-treated experienced a 35% death rate after 5 years compared to a 19% death rate in participants who had CABG. In the non-drug-treated group and in participants without diabetes, the death rate was 9% in both the CABG and PTCA groups. In addition, after 5 years, 8% of participants who had CABG had to undergo revascularization compared to 54% of those assigned to PTCA.[5,6]

**Dia**betes **L**ist **o**f **G**oals (DiaLOG) was an investigator-initiated, single-site trial with funding from Roche Pharmaceuticals. One hundred fifty people with diabetes participated within 3 months of completing a diabetes education program.

The participants were randomized into two groups. Baseline lipids, $HbA_{1c}$, and blood pressure readings were obtained for all participants. Half of the participants received a copy of a traditional laboratory form that was also sent to the primary care physician. The other half (study group) received an individualized 11 × 17-inch laminated color sheet showing the laboratory results, blood pressure, $HbA_{1c}$, and 6-month goals for those indices and a wallet-sized card bearing the same information. A copy of the DiaLOG card was sent to the primary care physician in addition to the traditional laboratory forms.

After 6 months, $HbA_{1c}$ levels were compared. In the control group, the $HbA_{1c}$ of participants whose baseline $HbA_{1c}$ was >6.9% had dropped an average of 0.77 points. In the study group, which received the DiaLOG sheet and card, the drop in $HbA_{1c}$ in participants with the same original criteria averaged 1.69%. These results were presented at the President's Poster Session of the American Diabetes Association (ADA) Annual Meeting and Scientific Sessions in June 2000 in San Antonio, Texas.[7]

The **D**iabetes Mellitus **I**nsulin-**G**lucose Infusion in **A**cute **M**yocardial **I**nfarction (DIGAMI) study was initiated to address the issue of the higher short- and long-term mortality rate of people with diabetes who suffer an MI. The higher rate of mortality in those with diabetes after MI persists despite advances in management of post-MI care that have reduced overall morbidity and mortality. The DIGAMI study focused on rapid improvement of metabolic control in diabetes patients.

In the study, 620 patients were randomized into two groups. Participants with an acute MI and diabetes were randomly assigned to either insulin-glucose drip or conven-

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tional therapy to determine whether mortality was decreased by tight control both initially and if continued over time. The results showed that insulin-glucose infusion followed by intensive subcutaneous insulin in patients with acute MI and diabetes improves long-term survival. The effect was most apparent in patients who had not previously received insulin treatment and who were at low cardiovascular risk.[8,9]

**Current Trials**

Several large, long-term trials have completed recruitment and are ongoing. Two are the well-known **D**iabetes **P**revention **P**rogram (DPP) and **A**torvastatin as **S**econdary **Prev**en**t**ion of CHD (ASPEN) trial.

ASPEN, sponsored by Parke-Davis, is a 4-year, double-blind, randomized, placebo-controlled study of atorvastatin as secondary prevention of coronary heart disease (CHD) in patients with type 2 diabetes. Its objective is to assess the effect of 10 mg atorvastatin on cardiovascular end points in people with type 2 diabetes and documented CHD.

Participants at entry had a low-density lipoprotein (LDL) cholesterol level ≤160 mg/dl and trigylcerides ≤600 mg/dl. Participants receive either 10 mg of atorvastatin or placebo taken once daily. This study will measure the primary efficacy parameter as the time from randomization to the occurrence of the primary clinical end point (death from any cause, MI, or angina).

The original 4-year study is scheduled to end in 2003. There is a planned extension so that all participants will be enrolled for at least 4 years and up to 7 years depending on when each entered the trial.

The principal objective of the DPP, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), is to prevent or delay the development of type 2 diabetes in those people at risk for development of the disease. This trial includes 4,000 participants with impaired glucose tolerance (IGT). Participants were identified by screening populations known to be at high risk for IGT and type 2 diabetes (i.e., those with a family history of diabetes, the elderly, overweight individuals, women with a history of gestational diabetes, and minority populations with a high incidence of diabetes, including African Americans, Hispanic Americans, Asian and Pacific Island Americans, and Native Americans).

Originally, participants were randomized into either lifestyle intervention or one of three medication groups, metformin, 500 mg twice a day; troglitizone, 400 mg daily; or placebo. The lifestyle group has a goal of 7% reduction in body weight and 150 minutes of exercise per week. In June 1998, the use of troglitizone was discontinued in the study. However, those participants continue to be followed.

Medication group participants are seen quarterly and have fasting glucose measurements performed semiannually. All participants are tested annually with a 75-g glucose tolerance test. Participants will be followed from 3.5 to 6 years. The trial is expected to end in June 2002, and results will be reported shortly thereafter.[10]

**Newer Trials**

The trials discussed in the previous section have completed their recruitment phase and are now ongoing. A myriad of other trials addressing important clinical issues are now recruiting patients. To be successful, they need a valid study design and complete enrollment. A discussion of all of the new trials is beyond the scope of this article. We have instead selected a few trials that we anticipate will have an impact on the diabetes community at large.

The **D**iabetes **P**revention **T**rial—IDDM (DPT-1) is a multicenter trial jointly sponsored by the NIDDK, National Center for Research Resources, National Institute of Allergy and Infectious Diseases, National Institute of Child Health and Human Development (NICHD), Office of Research on Minority Health, and Office of Research on Women's Health. It is designed to identify nondiabetic first- and second-degree relatives of individuals with type 1 diabetes who are at high risk for developing type 1 diabetes based on islet cell antibodies and intravenous glucose tolerance testing.

DPT-1 will examine whether type 1 diabetes can be prevented or delayed in humans with insulin injections or insulin capsules. Participants are enrolled in one of two studies based on their degree of risk for developing diabetes over the next 5 years. The Insulin Injection Trial includes individuals with a >50% chance of getting diabetes. These participants inject low doses of insulin twice a day. Once a year, they are admitted to a hospital for 4 days of insulin therapy. The Oral Insulin Trial includes individuals with a 25–50% chance of developing diabetes. They will take insulin capsules orally. Within each study, half of the participants will be randomly assigned to an insulin treatment group, and half will be placed in a control group to which no insulin is given.

DPT-1 investigators are still looking for participants with first- or second-degree relatives with type 1 diabetes. Individuals may qualify if they are 3–45 years of age and have a brother or sister, child, or parent with type 1 diabetes, or are 3–20 years of age and have a cousin, uncle or aunt, nephew or niece, grandparent, or half-sibling with type 1 diabetes.

The study involves 9 medical centers and more than 350 clinics in the United States, Canada, and Puerto Rico. More information about site location can be obtained by calling 1-800-HALT DM1 (800-425-8361).[10]

The **H**yperglycemia and **A**dverse **P**regnancy **O**utcomes Study (HAPO) is jointly sponsored by the ADA, NICHD, and NIDDK. This trial will examine the effects of hyperglycemia on pregnancy outcomes. It is a population-based study attempting to recruit all pregnant women at 16 sites. It aims to recruit 25,000 women of all cultural and ethnic backgrounds.

The study's primary hypothesis is that hyperglycemia during pregnancy, less severe than diabetes mellitus, is associated with increased risk of adverse maternal, fetal, and neonatal outcomes that are independently related to the degree of metabolic disturbance. The study will examine glucose tolerance in the third trimester of pregnancy and aims to establish internationally acceptable criteria for the diagnosis and classification of gestational diabetes mellitus. Additional

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information can be found on the ADA Web site (http://www.diabetes.org).

The **Gen**etics of **N**on-**I**nsulin **D**ependent Diabetes (GENNID) study is sponsored by the ADA. Its goal is to understand why type 2 diabetes runs in families and to determine what genes cause diabetes. Thirteen centers across the country are involved in the trial.

The GENNID study centers are currently looking for families to participate. Participants must have at least one sibling willing to participate and must have one parent who has never had diabetes. GENNID has already collected detailed family histories and a broad array of data on 170 pedigrees, all of which contain at least one affected sibling pair. At present, information on a total of 650 affected individuals and ~1,200 total subjects has been collected. Information about participating sites can be found on the Web at http://www.diabetes.org/research/Gennid/ClosestGENNIDCenter.asp.

**A D**iabetes **O**utcome **P**rogression **T**rial (ADOPT) is a multicenter trial sponsored by SmithKline Beecham Pharmaceuticals. It aims to demonstrate whether rosiglitazone prevents the decline in pancreatic ß-cell function. It is designed to evaluate and compare the effects of treatment with rosiglitazone, metformin, or glyburide on glycemic control in patients with newly diagnosed type 2 diabetes.

This 4-year trial includes subjects between 30 and 70 years of age with diabetes diagnosed <2 years ago, who are on diet therapy, and who have a fasting plasma glucose of 126–240 mg/dl. For information on study sites, call 888-914-7400 or visit the Web site at www.newdiabetes.com.

**Future Studies**

Much remains unknown about CVD in people with diabetes. New treatments are becoming available to decrease the rate of CVD, but the efficacy and cost of the various interventions are unknown. Macrovascular complications are the leading cause of morbidity and mortality in people with diabetes. Fifty to sixty percent of people with diabetes have deaths related to CVD. This is two to four times higher than the rate of CVD-related deaths among those without diabetes.

Three large NIH trials that are not yet open for patient recruitment will attempt to address these issues.

The **S**tudy of **H**ealth **O**utcomes and **W**eight-Loss (SHOW) is sponsored by NIDDK, NHLBI, the National Institute of Environmental Health Sciences, and the National Institute of Nursing Research. The study question relates to interventions designed to produce weight loss in patients with type 2 diabetes and whether weight loss improves health. The study design and outcome measures are still in development.

This multicenter trial will be conducted at 16 sites in the United States. The protocol will include 6,000 people with type 2 diabetes. Participants must have type 2 diabetes and be between 18 and 75 years of age. Recruitment is expected to begin sometime in 2001. More information will become available as the study approaches its recruitment phase.

The **A**ction to **C**ontrol **C**ardi**o**vascular **R**isk in **D**iabetes (ACCORD) study, sponsored by NHLBI, is designed to evaluate the use of standard versus more aggressive treatment of established risk factors for CVD and glycemia in preventing major cardiovascular events in people with type 2 diabetes. It will also evaluate the cost of treatments. Protocol development is still ongoing but expected to be finalized in the next few months.

This trial is scheduled to begin recruitment in the near future. Participants must have type 2 diabetes and be considered at high risk for cardiovascular disease on the basis of age or evidence of subclinical arteriosclerosis. There are currently 7 clinical networks and approximately 63 sites in the United States and Canada participating. Expect to see more information, including a toll-free phone number for information, as the trial nears.

The **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation II (BARI-II) trial is an NIH-sponsored multicenter follow-up to the BARI trial. It aims to examine the safety and efficacy of new angiographic cardiac interventions in patients with diabetes relative to CABG. It also aims to determine the impact of glucose control on the outcome of these interventions.

At this writing, working groups were still finalizing the protocol, and the vanguard (pilot) centers hoped to start recruitment toward the end of 2000, with all centers starting recruitment in early 2001. BARI-II will include patients with coronary artery disease and diabetes who are treated with oral agents. All participants will receive therapy for tight blood pressure, lipid, and glycemic control. However, patients will be randomized to receive insulin or an insulin-sensitizing agent and randomized either to bypass surgery or angioplasty with stent placement. The Web site www.ClinicalTrials.gov lists some site information. Look for more information as the start of recruitment approaches.

**Summary**

Clinical trials provide us with a tremendous amount of information that affects the way we treat patients. When properly designed, they answer our hypotheses about a given diagnosis. Over the years, we have discovered that tight control of diabetes limits the progression of microvasculsar disease, and subsequently we have changed our standards of care. The importance of clinical trials cannot be overestimated.

Current trials are designed to determine whether we can prevent the onset of disease and to identify better treatments. Each day, more trials are developed. Information on ongoing clinical research trials can be obtained from the ADA, NIH, and American Association of Clinical Endocrinologists Web sites.

In order for the many ongoing and planned trials to be successful in gathering this crucial data, they first must achieve complete enrollment, and the results must be carefully scrutinized for scientific merit and clinical application. As we find ourselves swimming in the alphabet soup of today's important research studies, we must always keep the safety of our patients as our highest priority.

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