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SECOND EDITION

Handbook of Clinical Trials in Ophthalmology



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Handbook of
CLINICAL TRIALS IN OPHTHALMOLOGY

Second Edition

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CHAPTER 3

Clinical Trials in Diabetic Retinopathy-I

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WISCONSIN EPIDEMIOLOGICAL STUDY OF DIABETIC RETINOPATHY (WESDR)[1-8]

Purpose

- To describe the prevalence, incidence, and progression of diabetic retinopathy and its component lesions and to determine the incidence of visual impairment in a large population-based cohort.
- To determine the relationships between incidence and progression of diabetic retinopathy and risk factors in this cohort.
- To provide information on healthcare delivery and quality of life in persons with diabetes.

Background

Population-based epidemiologic data on the incidence and progression of diabetic retinopathy are important in developing approaches to preventing diabetic retinopathy, in medical counseling and rehabilitative services.

Description

The WESDR was an epidemiological study of a cohort of diabetic patients receiving their medical care in an 11-county area in Southern Wisconsin (Health Service Area 1) from 1979 to 1980. 452 of the 457 physicians who provided primary care to diabetic patients in this area participated in the study. The 452 physicians kept lists of all their diabetic patients for whom they provided primary care from July 1, 1979, to June 30, 1980. During this 1-year period, 10,135 diabetic patients were identified. A sample of 2,990 persons were selected for the baseline examination. This sample was composed of two groups:

1. The first consisted of all patients with diabetes diagnosed before 30 years of age who took insulin (1,210 patients); this group was referred to as "*younger onset*."
2. The second group consisted of a probability sample of 1,780 persons of the 5,431 patients who met the eligibility criteria of having diabetes

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diagnosed at 30 years of age or older and who had the diagnosis confirmed by a casual or a postprandial serum glucose level of at least 11.1 mM or a fasting serum glucose level of at least 7.8 mM on at least two occasions. This group was referred to as "*older onset*." The latter group was stratified by the duration of disease (<5 years, 576 persons; 5–14 years, 579 persons; and >15 years, 625 persons). Of these, 824 were taking insulin and 956 were not.

Of the 2,990 eligible patients, 2,366 (79.1%) participated in the baseline examination from 1980 through 1982. The younger-onset cohort was re-examined in 1984–1986, 1990–1992, 1994–1996, and 2000–2002, whereas the older-onset cohort was re-examined in 1984–1986 and 1990–1992 and interviewed in 1994–1996. Stereoscopic photographs of the Diabetic Retinopathy Study's seven standard fields were taken of each eye.

Results

- In the WESDR, 71% of younger-onset persons had retinopathy, 23% had proliferative diabetic retinopathy (PDR), and 10% had Diabetic Retinopathy Study high-risk characteristics (DRS-HRC) for severe visual loss.[1] Data from the WESDR also showed that diabetic retinopathy was infrequent before puberty. When adjustment was made for other factors, such as duration of diabetes, glycemic control, and blood pressure, younger-onset subjects who were postmenarchal in the WESDR were 3.2 times as likely to have diabetic retinopathy as those who were premenarchal.
- In the older-onset group, 50% had retinopathy, 5% had PDR, and 2% had DRS-HRC.[2]
- Six percent of the younger- and 5% of the older-onset subjects had clinically significant macular edema (CSME).[3]
- In younger- and older-onset persons, both the frequency and the severity of retinopathy and CSME increased with increasing duration of diabetes.[3]
- Glycated hemoglobin (HbA1c) was associated with the incidence and progression of diabetic retinopathy, progression to PDR, and the incidence of CSME.[6] The incidence and progression in each quartile of HbA1c were similar in both younger- and older-onset participants. This suggested that it was the level of glycemia and not the type of diabetes that is important in determining the risk of progression of retinopathy. A 1% increase in HbA1c was also associated with a 25–40% higher risk of incident visual loss, gross proteinuria, lower-extremity amputation, and ischemic heart disease death in both the younger- and the older-onset groups.
- Data from the WESDR have shown associations of high blood pressure, lipid levels, and the presence of gross proteinuria with retinopathy.

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Conclusion

The WESDR provided population-based estimates of the prevalence and incidence of diabetic retinopathy. The associations of glycemia and other traditional risk factors with the incidence and progression of retinopathy have been quantitated, and the findings have shown the need for better general medical and eye care delivery for persons with diabetes. These findings have resulted in the development of guidelines and health education programs directed at prevention, and earlier treatment, of diabetic retinopathy.

The findings from the WESDR provided the rationale for the development of guidelines for dilated eye examination by eye doctors experienced in detection and treatment of diabetic retinopathy: at the time of diagnosis in older-onset persons and yearly thereafter and after 5 years' duration of diabetes in younger-onset persons and yearly thereafter. When diabetes is diagnosed before puberty, the first dilated eye examinations should begin after puberty, and if no retinopathy is present, yearly thereafter.

Epidemiologic studies such as the WESDR cannot determine whether reduction of HbA1c would result in lowered risk of progression of retinopathy and other complications with an acceptable risk–benefit ratio. These questions were addressed by two large randomized therapeutic trials of metabolic control: (1) Diabetes Control and Complications Trial (DCCT) and (2) UK Prospective Diabetes Study (UKPDS). These prospective clinical trials demonstrated the efficacy of intensive treatment of diabetes in preventing diabetic retinopathy and other microvascular complications.

DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)[9]

Purpose

To assess the effect of tight glycemic control on complications of diabetes (nephropathy, neuropathy, and diabetic retinopathy) for persons with type 1 diabetes.

Background

Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). This trial examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Description

This multicenter study was conducted from 1983 to 1993 and funded by the National Institute of Diabetes and Digestive and Kidney Diseases. A total of 1,441 patients with type 1 diabetes—726 with no retinopathy at baseline

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(primary-prevention cohort) and 715 with mild retinopathy (secondary-intervention cohort), were randomly assigned to intensive therapy administered either with an external insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring or to conventional therapy with one or two daily insulin injections. The patients were followed up for a mean of 6.5 years, and the appearance and progression of retinopathy and other complications were assessed regularly.

Inclusion Criteria

The major criteria for eligibility included insulin dependence, as evidenced by deficient C-peptide secretion; an age of 13–39 years; and the absence of hypertension, hypercholesterolemia, and severe diabetic complications or medical conditions.

To be eligible for the primary-prevention cohort, patients were required to have had IDDM for 1–5 years, to have no retinopathy as detected by seven-field stereoscopic fundus photography, and to have urinary albumin excretion of <40 mg per 24 hours.

To be eligible for the secondary-intervention cohort, the patients were required to have IDDM for 1–15 years, to have very-mild to moderate nonproliferative retinopathy, and to have urinary albumin excretion of <200 mg per 24 hours.

Results

- In the primary-prevention cohort, intensive therapy (mean HbA1c 7.2%) reduced the risk for the development of retinopathy by 76% as compared with conventional therapy (mean HbA1c 9.0%).
- In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54% and reduced the development of proliferative or severe nonproliferative retinopathy by 47%.
- In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of 40 mg per 24 hours) by 39%, that of albuminuria (urinary albumin excretion of 300 mg per 24 hours) by 54%, and that of clinical neuropathy by 60%.
- The chief adverse event associated with intensive therapy was a two-to-three-fold increase in severe hypoglycemia. Because of this risk, DCCT researchers do not recommend intensive therapy for children under the age of 13 years, people with heart disease or advanced complications, older adults, and people with a history of frequent severe hypoglycemia. Persons in the intensive management group also gained a modest amount of weight, suggesting that intensive treatment may not be appropriate for people with diabetes who are overweight.
- DCCT researchers estimate that intensive management doubles the cost of managing diabetes because of increased visits to a healthcare

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professional and the need for more frequent blood testing at home. However, this cost is offset by the reduction in medical expenses related to long-term complications and by the improved quality of life of people with diabetes.

Conclusion

Intensive therapy effectively delays the onset and slows the progression of microvascular complications of diabetes, namely diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM.

EPIDEMIOLOGY OF DIABETES INTERVENTIONS AND COMPLICATIONS (EDIC)[10]

Purpose

To examine the persistence of the original treatment effects 10 years after the DCCT in the follow-up EDIC study.

Background

The DCCT demonstrated the powerful impact of glycemic control on the early manifestations of microvascular complications. Contemporary prospective data on the evolution of macrovascular and late microvascular complications of type 1 diabetes are limited.

Description

EDIC was a multicenter, longitudinal, observational study designed to use the well-characterized DCCT cohort of >1,400 patients to determine the long-term effects of prior separation of glycemic levels on micro- and macrovascular outcomes. EDIC is in its 13th year of follow-up. The study is expecting to last until 2016.

Using a standardized annual history and physical examination, 28 EDIC clinical centers that were DCCT clinics followed the EDIC cohort for 10 years. Annual evaluation also included resting electrocardiogram, Doppler ultrasound measurements of ankle/arm blood pressure, and screening for nephropathy. At regular intervals, a timed 4-hour urine sample was collected and lipid profiles were obtained. In addition, dual B-mode Doppler ultrasound scans of the common and internal carotid arteries were performed at years 1 and 6 and at study end. Retinopathy was evaluated by stereoscopic fundus photography in 1,211 subjects at EDIC year 10. Further, three-step progression on the Early Treatment Diabetic Retinopathy Study scale from DCCT closeout was the primary outcome.

Inclusion Criteria

Patients aged 19–45 years, who were participants of the DCCT, were eligible.

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Results

After 10 years of EDIC follow-up, there was no significant difference in mean HbA1c levels (8.07% vs. 7.98%) between the original treatment groups. Nevertheless, compared with the former conventional treatment group, the former intensive group had significantly lower incidences from DCCT close of further retinopathy progression and proliferative retinopathy or worse (hazard reductions, 53–56%; $p < 0.001$). The risk (hazard) reductions at 10 years of EDIC were attenuated compared with 70–71% over the first 4 years of EDIC ($p < 0.001$). The persistent beneficial effects of the former intensive therapy were largely explained by the difference in HbA1c levels during DCCT.

Conclusion

The persistent difference in diabetic retinopathy between former intensive and conventional therapy ("metabolic memory") continues for at least 10 years but may be waning.

UNITED KINGDOM PROSPECTIVE DIABETES STUDY (UKPDS)[11,12]

Purpose

- To determine whether the risk of cardiovascular and microvascular complications in type 2 diabetes can be reduced by intensive blood glucose control.
- In patients with high blood pressure, to determine whether the risk of complications can be reduced by tight control of blood pressure.
- To determine if any specific treatment for type 2 diabetes such as sulfonylureas (first or second generation), metformin, or insulin or anti-hypertensives such as angiotensin-converting-enzyme (ACE) inhibitor (captopril) or β-blocker (atenolol) confer any particular benefit.

Background

Improved blood-glucose control decreases the progression of diabetic microvascular disease, but the effect on macrovascular complications was unknown. Although a higher incidence of microvascular disease has been shown at fasting glucose concentrations >140 mg/dL, epidemiological studies have suggested that the glycemic threshold for an increased risk of cardiovascular disease may be much lower, possibly near the upper limit of the normal range (110 mg/dL). There were no prospective clinical trials that provided firm data indicating whether intensive therapy of type 2 diabetes was advantageous. There was concern that sulfonylureas may increase cardiovascular mortality in patients with type 2 diabetes and that high insulin concentrations (from sulfonylureas or insulin therapy) may enhance atheroma formation.

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The objective of the UKPDS, initiated in 1977, was set up to determine whether improved blood glucose control in people with type 2 diabetes will prevent the complications of diabetes. The UKPDS was also designed to determine whether there are differences between conventional policy (diet therapy) and three different regimens of intensive treatment policy, based on sulfonylurea, metformin, or insulin. A final study report was issued in September 1998, when the median duration of therapy was 11 years.

Description

The UKPDS was a multicenter, randomized, controlled trial. A total of 5,102 people with newly diagnosed type 2 diabetes were enrolled in the UKPDS from 1977 to 1991.

After an initial treatment with diet alone for 3 months, people with raised fasting blood glucose were randomly allocated to one of various treatment policies. People with fasting plasma glucose < 6 mmol/L, who were asymptomatic, were allocated to a *conventional* policy, primarily with diet alone. When marked hyperglycemia developed, they were allocated to *nonintensive* pharmacological therapy. People with fasting plasma glucose 6.1–15 mmol/L, who were asymptomatic, were allocated to an *intensive* policy group aiming for near-normal glucose control, with two different sulfonylureas tablets, or to insulin. Overweight people could also be randomized to metformin, as an additional option.

People with raised blood pressure as well as diabetes were randomly allocated to a policy aiming for *tight* blood pressure control (<150/85 mm Hg), using two treatments, an ACE inhibitor (captopril) or beta-blocker (atenolol), or to a *less tight* blood pressure control (<180/105 mm Hg).

Inclusion Criteria

Subjects with fasting plasma glucose concentrations of >108 mg/dL (6.0 mmol/L) on two occasions were eligible.

Study Measures

These included follow-up of patients to major fatal and nonfatal clinical endpoints and recording of surrogate endpoints, namely clinical and biochemical markers, e.g., urine albumin, retinal photographs, and visual acuity.

Results

- Intensive blood glucose control reduces the risk of progression of diabetic retinopathy by 17%, need for laser photocoagulation surgery by 29%, development of vitreous hemorrhage by 23%, and risk of legal blindness by 16% and early kidney disease by 33%. In addition, there was some evidence, albeit inconclusive, that it reduced the risk of myocardial infarction and it reduced the risk of requiring a cataract extraction.

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- All three therapies were similarly effective in reducing HbA1c and had equivalent risk reduction for major clinical outcomes compared with conventional policy.
- Better blood pressure control reduces the risk of death from long-term complications of diabetes by a third, strokes by more than a third, and serious deterioration of vision by more than a third. In addition, improved blood pressure also decreased the progression of the small blood vessel disease of diabetes.
- ACE inhibitors and beta-blockers were each shown to be effective in reducing the risk of any diabetes-related endpoint, diabetes-related deaths, and microvascular endpoints.

Conclusion

The complications of type 2 diabetes, previously often regarded as inevitable, could be reduced by improving blood glucose and/or blood pressure control. Intensive blood glucose control and tight blood pressure control reduce the risk of diabetic complications, the greatest effect being on microvascular complications.

APPROPRIATE BLOOD PRESSURE CONTROL IN NIDDM (ABCD)[13,14]

Purpose

- To compare the effects of intensive blood pressure control with moderate control on the prevention and progression of diabetic nephropathy, retinopathy, cardiovascular disease, and neuropathy in non-insulin-dependent diabetes mellitus (NIDDM).
- To determine the equivalency of the effects of a calcium channel blocker (nisoldipine) and an ACE inhibitor (enalapril) as a first-line antihypertensive agent in the prevention and/or progression of these diabetic vascular complications.

Description

ABCD was a prospective, controlled, randomized, double-blinded clinical trial of 950 patients with NIDDM conducted from 1993 to 1998. All patients were seen at the Colorado Prevention Center, the site of the ABCD trial, for follow-up visits.

The study consisted of two study populations aged 40–74 years, 470 hypertensive patients (diastolic blood pressure of ≥ 90.0 mm Hg at the time of randomization) and 480 normotensive patients (diastolic blood pressure of 80.0 mm Hg at the time of randomization). Patients were randomized to receive either intensive antihypertensive drug therapy (target diastolic pressure of 75 mm Hg) or moderate antihypertensive drug therapy (target

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diastolic pressure of 80–89 mm Hg). Patients were also randomized to nisoldipine or enalapril, with open-label medications added if further blood pressure control was necessary.

Inclusion Criteria

Hypertensive subjects, defined as having a baseline diastolic blood pressure of ≥90 mm Hg, were included.

Study Measures

The primary outcome measure was glomerular filtration rate as assessed by 24-hour creatinine clearance. Secondary outcome measures were urinary albumin excretion, left ventricular hypertrophy, retinopathy, and neuropathy. Cardiovascular morbidity and mortality were also evaluated.

Results

The mean blood pressure achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate control group.

- During the 5-year follow-up period, no difference was observed between intensive versus moderate blood pressure control and those randomized to nisoldipine versus enalapril with regard to the change in creatinine clearance.
- Intensive therapy demonstrated a lower overall incidence of deaths, 5.5 versus 10.7%, $p = 0.037$. Over a 5-year follow-up period, there was no difference between the intensive and moderate groups with regard to the progression of diabetic retinopathy and neuropathy.
- Analysis of the 470 patients in the trial who had hypertension (baseline diastolic blood pressure, >90 mm Hg) showed similar control of blood pressure, blood glucose and lipid concentrations, and smoking behavior in the nisoldipine group (235 patients) and the enalapril group (235 patients) throughout 5 years of follow-up. Using a multiple logistic-regression model with adjustment for cardiac risk factors, it was found that nisoldipine was associated with a higher incidence of fatal and nonfatal myocardial infarctions (total of 25) than enalapril (total of 5) (risk ratio, 9.5; 95% confidence interval, 2.3–21.4). However, the use of nisoldipine versus enalapril had no differential effect on diabetic retinopathy and neuropathy.

Conclusion

Blood pressure control of 138/86 or 132/78 mm Hg with either nisoldipine or enalapril as the initial antihypertensive medication appeared to stabilize renal function in hypertensive type 2 diabetic patients without overt albuminuria over a 5-year period. The more intensive blood pressure control decreased all-cause mortality.

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Table 1: Summary of epidemiological studies in diabetic retinopathy.

Title	Purpose	No of patients	Inclusion criteria	Outcome measure	Result/conclusion
WESDR (1979)	Prevalence, incidence, and progression of diabetic retinopathy and its component lesions along with visual loss	2,990	Patients with diabetes diagnosed before 30 years of age Diabetics diagnosed at 30 years of age or older	–	71% of younger-onset persons had retinopathy In the older-onset group, 50% had retinopathy 6% of the younger- and 5% of the older-onset subjects had CSME Both the frequency and the severity of retinopathy and CSME increased with increasing duration of diabetes
DCCT (1983)	Effect of tight glycemic control on complications of diabetes for persons with type 1 diabetes	1,441	IDDM, age 13–39 years, absence of hypertension, hypercholesterolemia, and severe diabetic complications	Appearance and progression of retinopathy and other complications over 6.5 years	Intensive therapy delays the onset and slows the progression of microvascular complications of diabetes (diabetic retinopathy, nephropathy, and neuropathy) in IDDM
EDIC	To examine the persistence of the original treatment effects 10 years after the DCCT	1,400	Patients aged 19–45 years, who were participants of the DCCT	Appearance of micro- and macrovascular complications (presently in 13th year follow-up)	The persistent difference in diabetic retinopathy between former intensive and conventional therapy continues for at least 10 years but may be waning

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Title	Purpose	No of patients	Inclusion criteria	Outcome measure	Result/conclusion
UKPDS (1977)	Improved blood glucose and blood pressure control in type 2 diabetes for preventing the complications of diabetes	5,102	Newly diagnosed type 2 diabetes patients	Follow-up of patients to major fatal and nonfatal clinical endpoints	Intensive blood glucose control and tight blood pressure control reduce the risk of diabetic complications, the greatest effect being on microvascular complications
ABCD (1993)	Intensive blood pressure control versus moderate control in the prevention and progression of nephropathy, retinopathy, cardiovascular disease, and neuropathy in NIDDM	950	Hypertensive subjects with NIDDM were included	Glomerular filtration rate as assessed by 24-hour creatinine clearance	The more intensive blood pressure control decreased all-cause mortality

(ABCD: Appropriate blood pressure control in NIDDM; CSME: clinically significant macular edema; DCCT: Diabetes Control and Complications Trial; EDIC: Epidemiology of Diabetes Interventions and Complications; IDDM: insulin-dependent diabetes mellitus; NIDDM: non-insulin-dependent diabetes mellitus; UKPDS: UK Prospective Diabetes Study; WESDR: Wisconsin Epidemiological Study of Diabetic Retinopathy)

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