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Diabetes and cardiovascular disease: Changing the focus from glycemic control to improving the long-term survival

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Abstract

Diabetes is the fifth leading cause of death worldwide and contributes to leading causes of death, cancer and cardiovascular disease including coronary heart disease, stroke, peripheral vascular disease and other vascular disease. While glycemic management remains a cornerstone of diabetes care, the co-management of hypertension, atherosclerosis, cardiovascular risk reduction and prevention of long-term consequences associated with diabetes are now well recognized as essential to improve long-term survival. Clinical trial evidence substantiates the importance of glycemic control, LDL-cholesterol lowering therapy, blood-pressure lowering, control of albuminuria, and comprehensive approaches targeting multiple risk factors to reduce cardiovascular risk. This article presents a review of the role of diabetes in pathogenesis of atherosclerosis and cardiac dysfunction, recent evidence regarding degree of glycemic control and mortality, and available evidence for a multi-faceted approach to improve long-term outcomes for patients.

Introduction

Diabetes is a devastating disease that affects more than 25.8 million people in the United States and more than 330 million people worldwide (<http://www.diabetes.niddk.nih.gov/dm> and <http://www.who.int>). The Centers for Disease Control and Prevention estimates that nearly 26% of US adults are obese and nearly 8% of the population has diabetes (<http://www.cdc.gov/diabetes>). Diabetes is the fifth leading cause of death worldwide and contributes to leading causes of death, cancer and cardiovascular disease. More than 90% of individuals with diabetes have type 2 diabetes mellitus, which could be prevented by behavioral modification including improved nutrition and increased physical activity^{1–4}. People with diabetes have a nearly 40 percent incidence of cardiovascular disease including coronary heart disease, stroke, peripheral vascular disease, and other vascular disease (<http://www.cdc.gov/diabetes>). In addition, there is an excess risk of cancer. In 2001, the estimated decrease in life expectancy for people with diabetes in the UK was 10 years for people with type 2 diabetes and 20 years for people with type 1 diabetes (www.dh.gov.uk/en/Publicationsandstatistics). More recent statistics for the United States suggest a decrease in life expectancy of 8.5 years⁵. The excess mortality attributable to diabetes in 2000 was 2.9

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million (5.2%) globally, and up to 8% in the US⁶. Age of onset, duration of diabetes, and functional status are predictors of excess mortality^{7, 8}. This background defends the need to prevent diabetes and treat preventable causes of premature death in people with diabetes.

The majority of clinical trials assessing cardiovascular and all-cause mortality in people with diabetes have focused on individual interventions including treatment of glucose, hypertension, cholesterol and anti-platelet therapy. In each instance, intervention has proven beneficial. Multi-pronged interventional studies provide evidence for coordinated treatment of cardiovascular risk factors resulting in cardiovascular risk reduction^{9–11}. We will provide an overview of the pathophysiology of cardiovascular disease in diabetes and outline the evidence for treatment of multiple cardiovascular risk factors in the prevention of morbidity and mortality related to diabetes.

Epidemiological evidence supports the thesis that diabetes adds to the impact of individual risk factors such as hypertension and hyperlipidemia for the prediction of excess cardiovascular disease. Prospective longitudinal studies such as Framingham, MRFIT, the Physicians Health Study, and the Nurses' Health Study each demonstrated that in the context of diabetes, there was a greater risk of cardiovascular disease for a given blood pressure or cholesterol level^{12–14}. These observations led to prospective investigation of cohorts with and without diabetes for cardiovascular disease. In these studies, such as the East-West study, the incidence of cardiovascular disease in people with greater than 5 years of diabetes and in the 55 to 65-year-old age range, was equivalent to cardiovascular risk in persons with previous myocardial infarction¹⁵. These data sets were replicated in some, albeit not all, other studies and populations, leading to the clinical impression that diabetes should be considered a cardiovascular risk equivalent. While this may not be universally true in younger populations of people with diabetes, for the general clinician, patients with diabetes should be treated expectantly and cardiovascular risk should be addressed aggressively. Recently, a post hoc analysis of the ADVANCE trial indicated that routine clinical parameters including age at diagnosis, duration of diabetes, sex, pulse pressure, treated hypertension, atrial fibrillation, retinopathy, HbA1c, urinary albumin/creatinine ratio and non-HDL cholesterol predicted CVD in diabetes¹⁶.

One of the most consistent and unacceptable observations across interventions in people with and without diabetes is that while both groups benefit from blood pressure lowering or cholesterol-lowering, excess mortality remains in the diabetic cohort. This observation indicates the need for research into additional targets for intervention in diabetes and the importance of comprehensive in risk factor modification for people with diabetes. Multiple risk factor intervention studies such as Steno-2 and Look AHEAD suggest an impressive impact of simultaneous multiple risk factor intervention^{11, 17}. These studies do not have a non-diabetic comparator group, so it is not possible to tell whether they decreased cardiovascular risk to that of the general population. In this review, we will provide background data on the efficacy of risk factor intervention singly and in combination for people with diabetes to support our recommendation for coordinated risk factor modification in all people with diabetes.

Role of diabetes in progression of cardiac and vascular disease

Atherosclerosis is more common in people with diabetes, the atherosclerotic burden is higher and the mortality is greater after a cardiovascular event, acute myocardial infarction, stroke or peripheral vascular disease^{18, 19}. In addition, people with diabetes have a higher incidence of congestive heart failure and greater loss in cardiac contractile function for the same size myocardial infarction leading to excess congestive heart failure^{20–22}. Each of these conditions will be briefly reviewed in relationship with diabetes.

Atherosclerosis in diabetes

Atherosclerosis is the development of complex lipid-laden lesions in the vasculature with the potential to contribute to cardiovascular events including myocardial infarction, stroke and peripheral vascular disease (reviewed in²³⁻²⁵). The blood vessel wall is lined by endothelium which overlies vascular smooth muscle cells while the vessel itself is surrounded by adventitia which includes fibroblasts, adipocytes, and other cells. The classical model of atherosclerosis progression includes injury to the endothelium by circulating factors such as hyperglycemia, hyperlipidemia, inflammatory cytokines, reactive oxygen species, excess flow-mediated stress (hypertension), cigarette smoke or environmental toxins. Injured endothelium changes vascular cell phenotype. The normal endothelial cell phenotype is anti-atherogenic: healthy endothelial cells have tight junctions preventing entry of lipoproteins into the subendothelial space; in response to shear stress, endothelial cells secrete nitric oxide leading to flow-mediated vasodilation. Furthermore, platelets and monocytes will not adhere to healthy endothelial cells; tissue plasminogen activator, a thrombolytic protein, is secreted by healthy endothelial cells. With injury, endothelial cell tight junctions are weakened, allowing egress of lipoproteins into the subendothelial space; there is decreased function of endothelial nitric oxide synthase leading to decreased vasodilatory nitric oxide secretion and increased expression of endothelin-1 leading to increased vasoconstriction; endothelial cells express adhesion molecules which attract and activate platelets and monocyte/macrophages; in addition, production of plasminogen activator inhibitor type I, a pro-thrombotic protein, is increased in injured endothelium²⁶⁻³³. Taken together, this series of changes in endothelial function leads to a feed-forward pro-inflammatory phenotype (Fig 1 – Figure 1 from Reusch/Wang 2011). In addition to the specific changes outlined above, there is increased reactive oxygen species, cytokines and growth factors leading to smooth muscle cell proliferation and foam cell formation³⁴. More recently, the role of the adventitia, recruitment of inflammatory cells, and stimulation of adventitial neovascularization have added to the complexity of progression of the atherosclerotic plaque³⁵⁻³⁷. Diabetes accelerates plaque progression in hypertensive and dyslipidemic animal models. In human subjects, endothelial dysfunction predicts cardiovascular disease (reviewed in³⁸).

Cardiac Dysfunction

Congestive heart failure is increased in diabetes as illustrated by the Framingham study and the Strong Heart Study^{39, 40}. In addition, people with diabetes have an increased incidence of recurrent MI or hospitalization for heart failure after a first MI⁴¹. Individuals with diabetes without coronary artery disease experience an excess burden of cardiac dysfunction ranging from subclinical left ventricular hypertrophy to clinically apparent diabetic cardiomyopathy, which is more pronounced in women than in men⁴². Interestingly, in diabetes, especially in women, CHF hospitalization often occurs in people with increased LV mass and preserved systolic function^{43, 44}. This excess burden of CHF contributes to disability and mortality in people with diabetes.

Much work has been done recently to clarify the etiological factors contributing to the progression of diabetic cardiomyopathy (reviewed in^{45, 46}). In clinical terms, it appears that the inability of the myocardium to efficiently use fuel (lipid or carbohydrate) underlies diabetic cardiomyopathy. Free fatty acids are the preferred fuel of the myocardium at rest. With exertion, healthy myocardium switches to the use of carbohydrates which will generate more ATP for a given amount of oxygen. This is termed metabolic flexibility. In diabetes, there is decreased metabolic flexibility and increased incomplete oxidation of fatty acids leading to production of aldehydes and reactive oxygen species which are toxic to the myocardium^{46, 47}. Much remains to be clarified regarding the precise etiology of this decreased metabolic flexibility, but it is suggested that insulin resistance in the myocardium

(decreased reliance on insulin regulated glucose utilization) and limited perfusion of the myocardium contribute to the progression of diabetic cardiomyopathy. In its end stage, persistent excess of reactive oxygen species leads to inflammation and fibrosis much as it does in the adventitia of the vessel wall. In recent data from our laboratory, it is evident that subclinical cardiac dysfunction occurs early in diabetes and is present in adolescents with both type 1 and type 2 diabetes^{48, 49}. Little is known about the impact of clinical interventions on cardiac dysfunction in diabetes. It is well established that hypertension and physical inactivity contribute to cardiac dysfunction. As such, it is expected that antihypertensive and physical activity interventions will improve cardiac function. A more recently appreciated contributor to cardiac dysfunction may be arterial stiffness. Arterial stiffness is often seen with hypertension, but can persist even when hypertension is treated. Overall, it predicts mortality⁵⁰.

EVIDENCE FROM CLINICAL TRIALS

The East-West trial was a pivotal trial published 15 years ago that changed the way clinicians approached cardiovascular risk in diabetes¹⁵. In this trial, the 7-year incidence of myocardial infarction was examined in 2,432 subjects. Subjects with type 2 diabetes but no prior history of myocardial infarction had a risk of cardiovascular death that was similar to individuals with a prior history of myocardial infarction but no diabetes. Furthermore, subjects with both type 2 diabetes and a history of MI had a nearly 3-fold greater risk of cardiovascular death than individuals with a history of MI but no diabetes.

What is the evidence for the impact of glycemic control versus targeting other risk factors on long term survival in diabetes? The next section will outline major trial evidence for intervening in glycemia, cholesterol, blood pressure, and albuminuria on survival in individuals with diabetes. It will end with an overview of evidence from trials examining the impact of multifactorial interventions on survival in diabetes.

Glycemic control – does it matter? How intensive?

Both the DCCT and the UKPDS were large-scale, well-designed and well-conducted randomized trials which showed convincingly that good glycemic control reduces the risk of microvascular complications in both type 1 (A1c of 7% vs. 9%) and type 2 diabetes (A1c of 7% vs 7.9%)^{51, 52}. Since the publication of these initial results in the 1990s, long-term follow-up studies have been performed for both trials, recently demonstrating benefits of good glycemic control on cardiovascular events in both diabetes populations^{53, 54}. There was a “legacy effect” observed in both cohorts, in which the long-term benefits of good glycemic control persisted in the “intensive” arms of each cohort despite regression to a higher A1c during the long follow-up period. It is important to note that what was formerly termed “intensive” control is now considered to be standard of care.

The next major question to be answered became whether tight glycemic control decreases risk for cardiovascular events. This question was addressed in 3 major trials: Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT). ACCORD was stopped prematurely because of an increased risk of mortality in the intervention group⁵⁵. However, this increased risk of mortality with tight glycemic control was not observed in ADVANCE⁵⁶ or VADT⁵⁷, which were completed as planned. Neither ADVANCE nor VADT demonstrated a benefit for tight glycemic control (A1c of <7%) on cardiovascular endpoints compared with what was achieved in the “standard” control group, which reached an A1c of 7.3% in ADVANCE and 8.4% in VADT.

Since publication of these trial results, there has been much discussion of the unexpected increased total mortality observed in ACCORD and post-hoc analyses to understand these findings^{58–64}. Although severe hypoglycemia requiring outside assistance was definitely a risk factor for death in both treatment arms⁵⁹, it may have been a marker for underlying increased risk for mortality in the standard treatment arm while individuals in the intensive treatment were likely to develop severe hypoglycemia merely from the intensive titration regimen. Post-hoc analyses show that the excess mortality in the intensive treatment group cannot be accounted for by hypoglycemia alone, and the increased rate of mortality continued in these subjects after they were transferred to standard treatment⁶². Furthermore, the intensive group had a greater risk for mortality than the standard therapy group only in individuals with A1c greater than 7% and those with the least lowering of A1c during the initial phase of treatment⁶¹ (Fig. 2 – adapted from Figure 2, Riddle 2010). These findings suggest that factors related to resistance to intensification of glycemic control, or higher A1c, NOT lower A1c, were associated with the increased risk observed in the intensive treatment group⁶¹. Interestingly, individuals in the standard treatment group had a much greater risk of severe hypoglycemia with every increment in A1c compared with the intensive treatment group, which suggests that the frequent mild hypoglycemia experienced by subjects in the intensive group may have somehow preconditioned the myocardium, protecting it against the effects of severe hypoglycemia⁵⁹.

Compared to the ACCORD cohort, the ADVANCE cohort had shorter duration of diabetes, lower baseline A1c, markedly fewer individuals on insulin or thiazolidinedione therapy at baseline or at study end, but similar A1c levels reached in the intensive and standard groups. The VADT cohort had a slightly longer duration of diabetes than the ACCORD cohort, with higher baseline A1c (9.4 vs. 8.1%), and greater use of insulin at baseline and study end. Furthermore, the mean A1c levels reached in each group differed; both study groups in ACCORD reached lower mean A1c than in VADT (ACCORD vs. VADT intensive therapy: 6.4 vs. 6.9%, standard therapy: 7.5 vs. 8.4%). However, these differences have not definitively been shown to account for the differences seen in these trial results.

These trials comparing the effects of standard glycemic control and tight glycemic control do not show a benefit for further lowering of glycemic targets. There are exceptions to this general conclusion, since certain subgroups may benefit, particularly younger individuals with diabetes duration <10–15 years and without significant cardiovascular disease or nephropathy prior to intensifying glycemic control. However, other subgroups of patients may be harmed by glycemic control that is too intensive (“too little, too late”). Overall, a general goal A1c of 7% should be used for many, if not most patients with diabetes, but this should be individualized to a slightly lower or higher goal depending on other factors such as patient motivation and support systems, risk for hypoglycemia, duration of diabetes, and presence/severity of comorbidities and complications. This individualized approach is consistent with A1c recommendations set forth by the American Diabetes Association (ADA)⁶⁵ and detailed comprehensively in a recently-published position statement from the ADA and the European Association for the Study of Diabetes (EASD) (Diabetes Care 2012 published ahead of print April 19, 2012; doi:10.2337/dc12-0413).

Cholesterol-lowering

Multiple trials have demonstrated that cholesterol-lowering therapy with an HMG-co-A-reductase inhibitor (statin) prevents cardiovascular events in individuals with diabetes, a few of which are outlined below. Secondary prevention of cardiovascular events in diabetes was demonstrated in a subgroup analysis of the 4S (Scandinavian Simvastatin Survival Study) trial⁶⁶, while primary prevention of cardiovascular events by statin therapy in diabetes was confirmed in CARDS (Collaborative Atorvastatin Diabetes Study)⁶⁷. CARDS was a multi-center trial conducted in the United Kingdom and Ireland which included 2,838 subjects

without prior cardiovascular disease randomized to receive placebo versus atorvastatin 10 mg daily for a mean follow-up period of 3.9 years. The trial was terminated 2 years prematurely because of demonstration of benefit for statin therapy on cardiovascular events. Interestingly, a similar trial, the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) did not demonstrate benefit for lowering of LDL below contemporary targets⁶⁸.

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial randomized 9,014 patients with diabetes or impaired fasting glucose, coronary heart disease and total cholesterol between 4.0 – 7.0 mmol/l to placebo vs. pravastatin therapy 40 mg per day for 6 years⁶⁹. This trial demonstrated that secondary prevention with moderate dose statin therapy reduced the risk of any cardiovascular event from 52.7 to 45.2% ($p < 0.008$) in patients with diabetes, preventing one major CHD event (CHD death or nonfatal MI) in 18 patients with diabetes.

The Medical Research Council/British Heart Foundation Heart Protection Study (HPS) examined the effect of cholesterol-lowering with simvastatin 40 mg daily vs. placebo for 5 years in 20,536 high risk individuals⁷⁰. The subgroup of the HPS that included 5,963 adults with diabetes⁷¹ demonstrated that the net lowering of LDL-cholesterol of this simvastatin dose in this cohort was 1 mmol/l. There was a 22% reduction in major vascular events (20.2% in the simvastatin-treated group and 25.1% in the placebo group, $p < 0.0001$). This benefit of LDL-lowering was seen in the 2,912 subjects without occlusive arterial disease at trial entry, and the 2,426 subjects with pretreatment LDL cholesterol < 3.0 mmol/l. This lowering of CVD risk was independent of duration of diabetes, type of diabetes, control of diabetes, age > 65 at entry, hypertension, and total cholesterol < 5.0 mmol/l. The effectiveness of statin therapy was demonstrated for both primary and secondary prevention of cardiovascular events in this trial.

In summary, strong clinical trial evidence establishes that lowering cholesterol with a statin reduces cardiovascular risk in individuals with diabetes.

Blood pressure-lowering

The UKPDS demonstrated that lowering blood pressure from a mean of 160/94 mm Hg at study entry to 144/82 mm Hg reduces the incidence of deaths related to diabetes compared with a group with “less tight” blood pressure control, in which blood pressure was reduced to 154/87 mm Hg⁷². When the macrovascular disease deaths were combined (myocardial infarction, sudden death, stroke and peripheral vascular disease), the tight blood pressure control group experienced a 34% reduction in risk compared to the “less tight” blood pressure control group ($p = 0.019$). These results confirmed results observed in the diabetes subgroup of the Systolic Hypertension in the Elderly Program⁷³. Subsequent studies including ALLHAT⁷⁴, subgroup analysis of the UKPDS⁷², and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)⁷⁵ among others have examined comparative efficacy of different antihypertensive regimens. UKPDS also demonstrated a 56% reduction in risk of heart failure with tight blood pressure control ($p = 0.0043$).

More recently, the ACCORD study group investigated whether further lowering of blood pressure resulted in additional reduction in a primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes⁷⁶. Four thousand seven hundred thirty-three subjects with type 2 diabetes were randomized to intensive therapy or standard therapy and followed for a mean of 4.7 years. The mean systolic BP decreased to 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard therapy group. By the end of the follow-up period, there was no benefit demonstrated for further lowering systolic blood pressure below 120 mm Hg.

In summary, strong clinical trial evidence demonstrates the beneficial effects of blood pressure control in all individuals with diabetes. However, there is no evidence for aggressive lowering of systolic blood pressure below 120 mm Hg in individuals without albuminuria or other evident renal complications of diabetes.

Control of albuminuria

The presence of microalbuminuria in diabetes correlates with risk for progression to diabetic nephropathy as well as risk for cardiovascular events. However, the published trials were not designed to separate the effects of reducing albuminuria from improvements in glycemia or blood pressure. The LIFE study evaluated urinary albumin-to-creatinine ratio over 4.7 years in patients with diabetes, hypertension and left ventricular hypertrophy⁷⁷. The urinary albumin-to-creatinine ratio (UACR) during treatment with atenolol or losartan was closely related to the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, and stroke, with a 2-fold increased risk with the highest quartile of UACR compared with the lowest quartile.

A longitudinal study examining 216 patients with type 2 diabetes and microalbuminuria over 8 years showed that patients who achieved significant improvements in microalbuminuria had an adjusted risk of first renal or cardiovascular event of 0.41 (95% CI 0.15–0.96), with significantly lower cumulative incidence of death from and hospitalization for renal or cardiovascular events ($p=0.0019$)⁷⁸. Improvement in microalbuminuria was defined as shift to normoalbuminemia or a 50% or greater reduction in microalbuminuria compared with baseline. The group who achieved improvement in microalbuminuria had lower systolic blood pressure and BMI when compared to the “nonreduction” group and also when compared to baseline, prior to any interventions. This study was not designed to determine which interventions were most effective in reducing microalbuminuria.

The Microalbuminuria, Cardiovascular and Renal Outcomes - Heart Outcomes Prevention Evaluation (MICRO-HOPE) trial was a substudy of the HOPE trial consisting of 3577 subjects with diabetes age 55 and older, with or without known cardiovascular disease, who were randomized to receive ramipril or placebo for 5 years^{79, 80}. The HOPE trial itself included 9297 subjects with known cardiovascular disease or diabetes plus at least one other cardiovascular risk factor. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. There were preplanned analyses to determine whether ramipril delayed or prevented microalbuminuria or overt nephropathy in participants with diabetes. HOPE demonstrated that the ramipril group had a relative risk of the primary outcome of 0.78, and relative risk of death from any cause 0.84. Of the total HOPE cohort, 1956 had microalbuminuria, making up approximately 21% of each treatment group. The effect of ramipril to decrease cardiovascular endpoints was demonstrated whether subjects did or did not have microalbuminuria. MICRO-HOPE showed similar results in the subgroup of subjects with diabetes, with a relative risk reduction of 25% for the primary outcome, and total mortality of 24% in the ramipril group. The rate of increase in urine albumin/creatinine ratio was significantly lower in the ramipril group, but since blood pressure was also affected by ramipril, it is unclear whether these effects on albuminuria were independent of improvement in blood pressure.

Physical activity

Increased physical activity is associated with reduced risk for cardiovascular disease in diabetes. In a long-term, prospective study of 3,708 individuals with diabetes followed for 18.7 years, moderate or high levels of physical activity at baseline were associated with decreased total and cardiovascular mortality⁸¹. The beneficial effects of physical activity were demonstrated regardless of BMI, blood pressure, total cholesterol and even smoking.

Multifactorial interventions

The Look AHEAD trial is designed to assess the long-term effects of an intensive lifestyle intervention in obese or overweight individuals with type 2 diabetes⁸². The intensive lifestyle intervention arm includes weight loss with decreased caloric intake and increased physical activity compared with a control group receiving diabetes support and education. A total of 5145 subjects with diabetes are participating in this ongoing study, and subjects have now been followed for over 10 years. The interim trial data demonstrate that an intensive lifestyle intervention resulting in a 5.3% weight loss, increased fitness, and improvements in blood pressure, HDL-cholesterol and triglycerides compared with placebo, can be sustained over 4 years⁸³. Whether this improvement in multiple cardiovascular risk factors with intensive lifestyle intervention will translate to a reduction in cardiovascular events is still unknown.

Subjects in the Steno-2 study had type 2 diabetes and microalbuminuria. The 160 subjects had a mean age of 55 years and relatively mild diabetes (a quarter were on diet alone, half were on oral agents, and 5–11% were on insulin) but the diabetes was not well-controlled (mean A1c 8.4% versus 8.8% in the intensive- versus conventional-therapy group). They were randomized to receive conventional treatment according to national guidelines, or intensive treatment that included dietary and lifestyle recommendations and targeting multiple risk factors of hyperglycemia, hypertension, dyslipidemia and microalbuminuria, in addition to secondary prevention of cardiovascular disease with aspirin⁸⁴. Over a mean follow-up period of 7.8 years, the improvement in all targeted risk factors was more evident in the intensive-therapy group. Despite not achieving each individual risk factor target, the intensive-therapy group had markedly lower risk for cardiovascular events (hazard ratio 0.47, 95% CI 0.24–0.73) (Fig. 3 – adapted from Figure 2B, Gaede 2003).

When Steno-2 was completed, all of the participants and their diabetes specialists were informed of the beneficial effects of targeting multiple risk factors, and intensive treatment was stopped in that group⁹. A follow-up visit was performed 5.5 years after Steno-2 stopped and showed that the end-of-study differences between groups in A1c, total cholesterol, LDL, triglycerides, blood pressure and urinary albumin excretion had narrowed between the 2 groups (Fig. 4 – Figure 2A from Gaede 2008). Surprisingly, only 30% of patients in the intensive-therapy group died compared to 50 % in the conventional-therapy group, an absolute risk reduction of 20% (p=0.02) (Fig. 5 – adapted from Figure 3A, Gaede 2008). This finding was consistent with what was observed in DCCT/EDIC and the UKPDS Follow-up Study of glycemic control. Interestingly, during the Steno-2 trial, A1c increased from a baseline of 8.8% to 9.0% in the conventional-therapy group and improved from 8.4 to 7.9% in the intensive-therapy group, while decreasing to 8.0% and 7.7% respectively during the follow-up period. These achieved levels of A1c are higher than those targeted in ACCORD, ADVANCE and VADT. Results from Steno-2 and the Steno-2 follow-up study suggest that achieving an A1c of 7.7–7.9% was sufficient to reduce cardiovascular endpoints and all-cause mortality in the context of multi-faceted therapy that includes lifestyle changes and targets other cardiovascular risk factors. Furthermore, although good glycemic control has been demonstrated to be an effective way to reduce cardiovascular morbidity, we do not fully understand the increased total mortality observed in the intensive treatment arm of ACCORD, and current methods for achieving tight glycemic control do not reduce cardiovascular events or mortality, whereas we have strong data (albeit from a small cohort) regarding the beneficial effects of a multifaceted, comprehensive approach to improving cardiovascular risk factors on cardiovascular endpoints and mortality.

CONCLUSION

While epidemiological studies have demonstrated associations between glycemic control and the development of CV disease, a number of confounding variables could account for the association between poor glycemic control and CVD such as blood pressure control, dyslipidemia (increased LDL cholesterol, serum triglyceride level, VLDL and IDL and decreased HDL cholesterol levels) and weight gain, among others. As discussed in other manuscripts in this supplement, although sulfonylureas have been traditionally used as first-line pharmacological therapy for type 2 diabetic patients, different classes of hypoglycemic agents, metformin, thiazolidinediones (TZD's), dipeptidyl peptidase-4 (DPP-4) agonists, glucagon-like peptide-1 (GLP-1) agonists, and insulin can have beneficial effects on CV risk factors. Clinical trial evidence supports good glycemic control, LDL-cholesterol-lowering, blood pressure control, ACE-inhibition, anti-platelet therapy, and increased physical activity to decrease the risk of cardiovascular events and mortality in patients with diabetes. Effective multi-faceted approaches targeting cardiovascular risk factors - dyslipidemia, elevated blood pressure, sedentary lifestyle, high saturated- and trans-fat diet, tobacco use - and emphasizing lifestyle changes such as increasing physical activity are urgently needed to improve long-term survival in our patients with diabetes. The cardiologist's role in improving glucose control and global CV risk reduction in patients with type 2 diabetes mellitus is significant. As the population with type 2 diabetes is increasing, diabetes is becoming increasingly relevant to cardiologists due to the accentuated CV risk inherent with type 2 diabetes mellitus. Achieving global risk reduction through glycemic control as well as CV risk reduction strategies will require continued efforts. This is crucial for patients with type 2 diabetes in whom CVD is a major cause of mortality.

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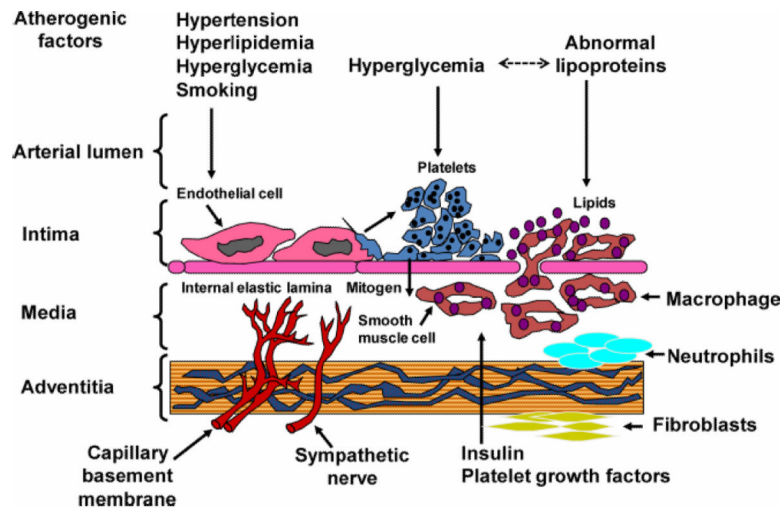


Figure 1.

Diagram of the vascular wall: atherogenesis in the setting of diabetes. Exposure to atherogenic factors such as hyperglycemia, hyperlipidemia, excess flow-mediated stress (hypertension), or cigarette smoke results in over-production of inflammatory cytokines and reactive oxygen species, injuring the endothelium, causing vascular smooth muscle cell phenotype switching, allowing egress of lipoproteins into the subendothelial space, increasing adhesion molecule expression which attracts and activates platelets and monocytes/macrophages, and foam cell formation³⁴. Diabetes accelerates plaque progression.

Reusch and Wang, JCEM 2011, Figure 1

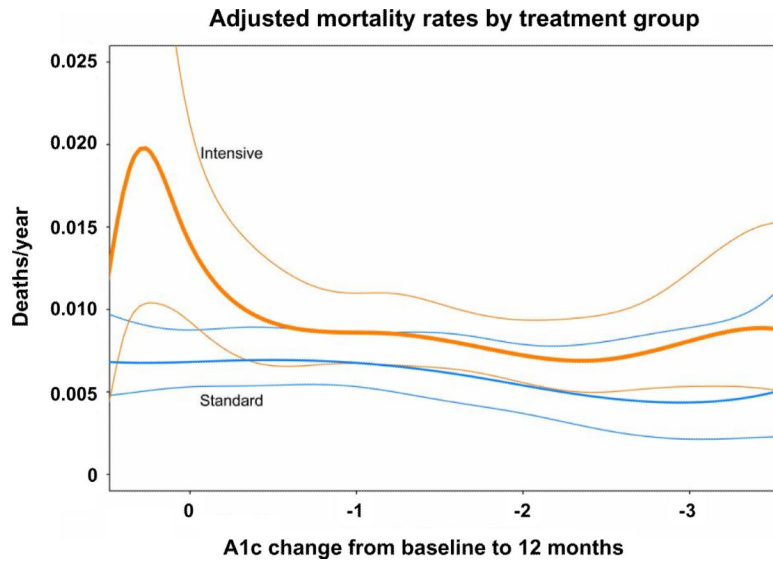


Figure 2.

Complex relationship between A1c and mortality in the ACCORD trial: increased mortality in the intensive-therapy group was concentrated among participants whose A1c decreased the least or did not decrease at all in the first year of intensification of glycemic therapy. The orange lines indicate the intensive treatment group with 95% confidence intervals; the blue lines indicate the standard treatment group with 95% confidence intervals. Adapted from Riddle -Diabetes Care 2010 (Fig. 2)

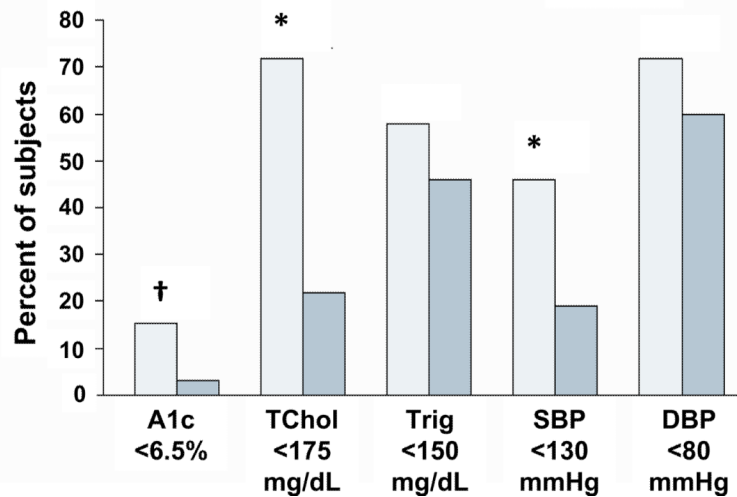


Figure 3.

Targeting of multiple risk factors in Steno-2. The intensive-therapy group had better control of multiple risk factors in Steno-2 compared with the standard-therapy group, but a significant proportion of participants did not achieve target levels for risk factors, and only 1 individual achieved all of the targets. Despite this, there was a 20% risk reduction in cardiovascular events in the intensive-therapy group. Light bars indicate the intensive-therapy group; shaded bars represent the conventional-therapy group. Comparison of intensive- with conventional-therapy group: * $p < 0.05$; † $p < 0.10$. A1c, hemoglobin A1c. TChol, total cholesterol. Trig, triglycerides. SBP, systolic blood pressure. DBP, diastolic blood pressure
adapted from Gaede 2003 (Fig 2B)

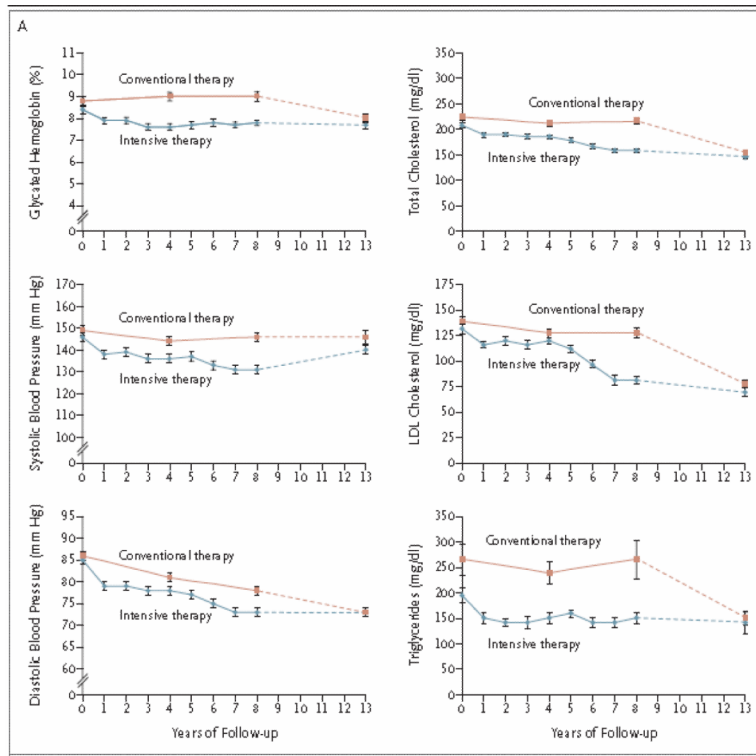


Figure 4. Steno-2 follow-up study. During the follow-up period, control of multiple cardiovascular risk factors converged between the intensive- and conventional-treatment groups. Gaede 2008, Figure 2A

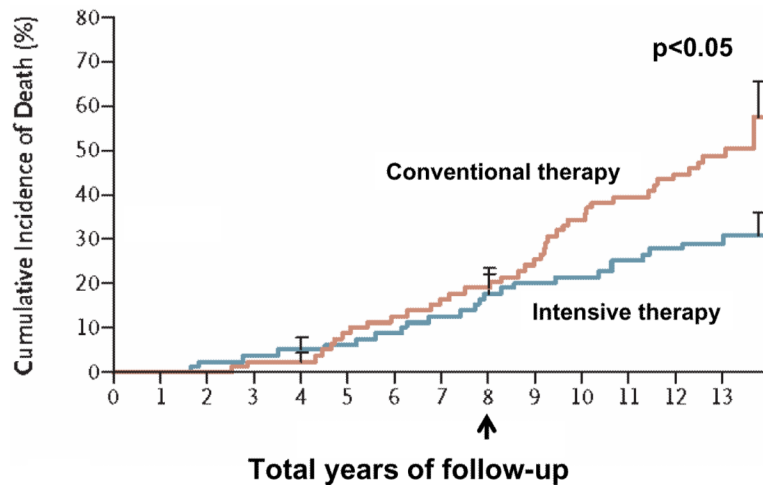


Figure 5.

Long-term effect of intensive control of multiple risk factors in the Steno-2 follow-up study. Despite a narrowing of differences in A1c, total cholesterol, LDL, triglycerides, blood pressure and urinary albumin excretion between treatment groups during the 5.5-year follow-up period, the intensive-therapy group had a markedly decreased cumulative risk of cardiovascular mortality compared with the conventional group, highlighting the importance of targeting multiple cardiovascular risk factors to increase long-term survival among individuals with diabetes. Arrow indicates timepoint for completion of Steno-2 study, and beginning of Steno-2 follow-up study. $P < 0.05$ for comparison of cumulative incidence of death between groups adapted from Gaede 2008 (Fig 3A)