No More Heart Disease—Addressing Major Modifiable Risk Factors in Type 2 Diabetes

Claude K Lardinois, MD, FACP, MACN

Emeritus Professor of Medicine, Division of Endocrinology, University of Nevada School of Medicine

Abstract

Cardiovascular disease (CVD) is the leading cause of death among people with type 2 diabetes, yet much of the population remains unaware of the risk. People with diabetes are two to four times more likely to develop CVD due to a variety of risk factors. Large studies have shown that 85–90 % of patients with CVD have one or more of the traditional modifiable risk factors. Important modifiable risk factors include obesity, physical exercise, nutritional factors, alcohol consumption, tobacco smoking, vitamin D, psychosocial factors, dyslipidemia, hypertension, albuminuria, and dysglycemia. This article will review the impact that each of these modifiable factors has on CVD risk. The importance of aspirin therapy will also be addressed in light of the results of a number of studies that failed to demonstrate a convincing cardioprotective benefit of low-dose aspirin in patients with type 2 diabetes. Gene polymorphisms are also emerging as important contributors to CVD development, but will not be addressed in this article.

Keywords

Cardiovascular disease, type 2 diabetes, vitamin D, hypertension, dyslipidemia, albuminuria, dysglycemia, aspirin

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Correspondence: Claude K Lardinois, MD, FACP, MACN, Department of Medicine, 1700 Aquila Avenue, Reno, NV 89509-3101. E: lardinois@sbcglobal.net

Individuals with diabetes have twice the incident myocardial infarction (MI) rate as the general population, and survival rates are lower among individuals with diabetes once they have an adverse cardiovascular event.[1] Women with diabetes and cardiovascular disease (CVD), regardless of menopausal status, have a four- to sixfold increase in the risk of developing CVD, whereas men with diabetes have a two- to threefold increased risk of CVD compared to women and men without diabetes.[2] Women with diabetes also have poorer prognosis after an MI, have higher risk of death from CVD than men, and typically receive less aggressive treatment to achieve treatment goals.[3] The landmark INTERHEART study showed that no matter where you live, how old you are, or what you look like, 90 % of first myocardial infarctions suffered by men and 94 % in women can be attributed to nine modifiable risk factors.[4] Adding other important modifiable risk factors such as vitamin D intake and albuminuria will undoubtedly increase that percentage. Therefore, CVD can be substantially reduced by aggressively identifying and treating the major modifiable risk factors: obesity, physical exercise, nutritional factors (consumption of fruits and vegetables), consumption of alcohol, smoking, vitamin D intake, psychosocial factors, dyslipidemia, hypertension, albuminuria, and dysglycemia.

Obesity

Obesity is associated with an increased risk for developing CVD. In obese individuals, adipose tissue releases a variety of factors that are involved in the development of insulin resistance. Obesity has long been recognized as fueling the epidemic of diabetes; risk variances estimate that obesity accounts for 60–90 % of the risk.[3] The combination of physical inactivity (hypoactive foot) and overeating (hyperactive fork), known as 'foot and fork dysorder,' contributes substantially to the development of diabetes, primarily type 2.[5] Weight reduction and maintenance at a lower bodyweight are best achieved by reducing caloric intake and increasing physical activity. Behavior modification is important to maintain weight reduction and thus requires long-term follow-up and monitoring. Pharmacologic weight-loss drugs have limited use in the management of obesity, but may help some patients. Morbidly obese people with severe obesity-related health problems may benefit from bariatric surgery.

Physical Exercise

Hypoactive foot is another well-recognized risk factor for the development of diabetes and CVD. Despite common knowledge that exercise is healthy, more than 60 % of American adults are not regularly active, and 25 % are not active at all. Nearly half of young people (12–21 years of age) are not vigorously active, and this disturbing trend will continue to increase as schools eliminate physical activity from their curriculums. Moreover, although many people enthusiastically embark on vigorous exercise programs, most do not sustain their participation. The processes of developing and maintaining healthier habits are as important to study as the health effects of these habits. It is important for people to find a balance

between food intake and physical activity and it is critical to stay within daily calorie needs. Daily physical activity is important, with the appreciation that 60 minutes a day may be required to prevent weight gain and an additional 30 minutes a day may be required to sustain weight loss. Children and adolescents should be encouraged to be physically active for 60 minutes daily.

Nutritional Factors—Consumption of Fruit and Vegetables

Several studies have documented that nutritional factors play a key role in reducing CVD. Regular consumption of fruit and vegetables was associated with a 30 % relative risk reduction for myocardial infarction in the INTERHEART study.[4] These results are similar to the findings of the US Nurses Health Study, which also showed that lifestyle modification could potentially avoid more than three-quarters of the risks associated with CVD and strokes in women.[6] The Lyon Heart Study suggested that dietary modification by itself reduced the risk for coronary heart disease (CHD) by about half in patients with CVD.[7]

Nutritional intake should be low in saturated fats, transfats, cholesterol, sodium, and simple sugars. Eating plenty of fruit and vegetables should be encouraged. Both high-carbohydrate and low-fat diets should be avoided because they can exacerbate insulin resistance and dyslipidemia, which can increase CVD risk. The challenge is to educate patients on the importance of substituting monounsaturated and polyunsaturated fats for saturated and transfats while also substituting high-fiber carbohydrates for low-fiber, more processed carbohydrates. The actual distribution of macronutrients may depend on the individual's medical history and what works best in terms of weight management and palatability.

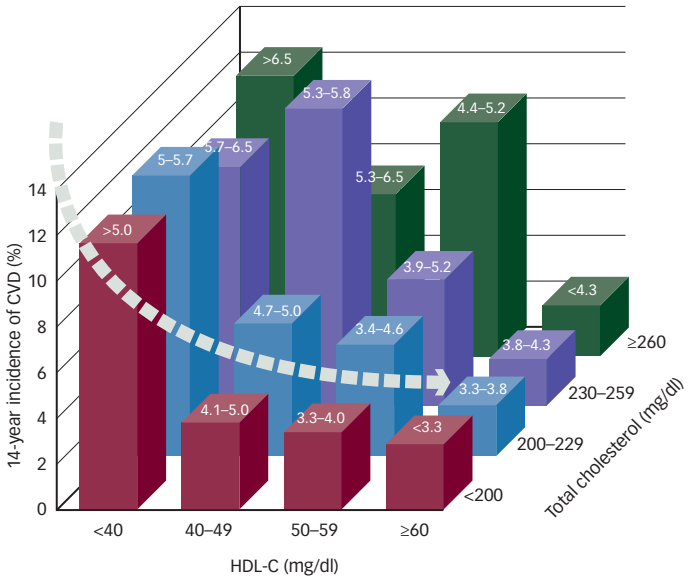
Consumption of Alcohol

Moderate alcohol consumption is associated with reduced all-cause mortality, especially CVD mortality, in the middle-aged and elderly. The reduction in CVD has been partly attributed to a more favorable lipid profile and less thrombogenic platelet function, and there is more recent evidence of favorable changes in glucose metabolism with improved insulin sensitivity and reduced risk for type 2 diabetes.[8] In nine nationally representative samples of US adults, light and moderate alcohol consumption was inversely associated with CVD mortality compared with lifetime abstainers; however, consumption above recommended limits was not associated with a decrease in CVD.[9] The benefits and risks of alcohol consumption must always be considered. However, there is overwhelming evidence that moderate alcohol consumption is associated with reduced CVD and should not be discouraged, even in patients with type 2 diabetes.[10] Moderate drinking is defined as two standard drinks per day for a man and one standard drink per day for a woman, with one standard drink defined as 12 ounces of beer or wine cooler, five ounces of wine, or 1.5 ounces of 80-proof distilled spirits.

Smoking

Smoking is a major risk factor for CVD, with a dose–response correlation between morbidity and mortality and the number of cigarettes smoked. Smokers are insulin-resistant and hyperinsulinemic compared with non-smokers, and these changes can lead to both dyslipidemia and hypertension.[11] One could argue that a major defect leading to increased CVD in smokers is insulin resistance and compensatory hyperinsulinemia, and that the multiple adverse consequences associated with these changes in insulin metabolism are responsible for the accelerated atherogenesis in these individuals. Several large prospective studies also suggest that smoking is linked to the development of type 2 diabetes.[12,13] These findings show that ending smoking should be a national priority.

Figure 1: Link Between Total Cholesterol to High-density Lipoprotein Cholesterol Ratio and Risk for Cardiovascular Disease



There is a high risk for cardiovascular disease (CVD) when the ratio is >5; the risk attenuates once the ratio is <5. HDL-C = high-density lipoprotein cholesterol.
Source: Castelli et al., 1986.[24]

Vitamin D

There is accumulating evidence that vitamin D has important physiologic effects in cardiomyocytes, vascular smooth-muscle cells, and the vascular endothelium. Recent studies have shown that vitamin D is associated with increased CVD, above and beyond established CVD risk factors. Low levels of 25-hydroxyvitamin D (25-OHD), the principal circulating storage form of vitamin D, are associated with myocardial infarction and congestive heart failure and are also linked to impaired glucose tolerance and type 2 diabetes. During the last decade, it has become clear that vitamin D deficiency is highly prevalent in the general population throughout the world, with the prevalence as high as 90 % in patients with type 2 diabetes associated with obesity.[14–16]

It is, therefore, imperative to recognize that vitamin D deficiency is common and undesirable, especially in patients with type 2 diabetes. An intake of at least 1,500–2,000 IU of vitamin D_3 is required to maintain an optimal 25-hydroxyvitamin level of 30–38 ng/ml. Current recommended daily allowances of 400–800 IU for vitamin D_3 are clearly inadequate. It is important to appreciate that vitamin D is a fat-soluble vitamin, and a low level of 25-OHD may require a 'loading' dose of vitamin D to reach an optimal level. A 25-OHD level <10 ng/ml requires a loading dose of 50,000 IU daily for six weeks followed by a maintenance dose of 2,000 IU per day. A level between 11 and 20 ng/ml

Table 1: Primary Dyslipidemia Endpoints of 21 Landmark Lipid Trials

Study	n	TC/HDL Ratio			LDL-C		Drug(s)	Reduction of Events (%)
		Baseline	Pre	Post	Pre	Post		
LRC-CPPT	3,806	290/46	6.30	5.52	214	190	Bile resins	19
WOSCOPS	6,595	272/44	6.18	4.71	192	142	Pravastatin	31
HHS	4,081	289/47	6.15	4.82	297	174	Gemfibrozil	34
AFCAPS	6,605	221/36	6.14	4.71	150	115	Lovastatin	37
BIP	3,090	215/35	6.06	4.96	149	139	Bezafibrate	0
LIPID	9,014	218/36	6.06	4.74	150	113	Pravastatin	24
4S	4,444	261/46	5.67	3.97	188	122	Simvastatin	34
HPS	20,536	228/41	5.57	4.67	131	104	Simvastatin	18
VA-HIT	2,531	177/32	5.53	5.00	113	113	Gemfibrozil	22
CARE	4,159	209/39	5.36	4.08	139	100	Pravastatin	24
Pre TC/HDL-C <5								
A TO Z	4,497	185/39	4.72	3.13	112	66	Simvastatin	0
ALLHAT	10,355	224/48	4.67	3.69	146	104	Pravastatin	0
ACCORD	5,518	175/38	4.60	3.66	100	81	Simvastatin/fenofibrate	0
FIELD	9,795	195/43	4.53	3.72	119	94	Fenofibrate	0
PROSPER	5,804	220/50	4.40	3.15	147	100	Pravastatin	24
IDEAL	8,888	197/46	4.28	3.06	122	80	Atorvastatin/simvastatin	0
ASCOT	10,305	212/50	4.26	3.26	133	90	Atorvastatin	10
AIM-HIGH	3,398	142/35	4.06	3.00	71	64	Simvastatin/niaspan	0
CARDS	2,838	207/54	3.83	3.31	118	82	Atorvastatin	0
JUPITER	17,802	185/49	3.80	2.60	108	55	Rosuvastatin	20
TNT	10,001	175/47	3.72	3.26	97	80	Atorvastatin	0

4S = Scandinavian Simvastatin Survival Study; ACCORD = Action to Control Cardiovascular Risk in Diabetes; AFCAPS = Air Force Coronary Arteriosclerosis Prevention Study; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes; ALLHAT = Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; BIP = Bezafibrate Infarction Prevention; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; HPS = Heart Protection Study; IDEAL = Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C = low-desity lipoprotein cholesterol; LIPID = The Long-Term Intervention with Pravastatin in Ischaemic Disease study; LRC-CPPT = Lipid Research Clinics Study Coronary Primary Prevention Trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; TC = total cholesterol; TNT = Treating to New Targets; VA-HIT = Veterans Affairs Cooperative HDL (High Density Lipoprotein) Cholesterol Intervention Trial; WOSCOPS = West of Scotland Coronary Prevention Study.

warrants treatment with 50,000 IU daily for three weeks followed by 2,000 IU daily. If the level is >20 ng/ml, 2,000 IU daily is usually sufficient. It is important to re-check the 25-OHD level after about four to six months to ensure an optimal level. As with any other treatment, if patients fail to continue with the maintenance dose of vitamin D, they quickly revert to their baseline 25-OHD level. Despite the compelling evidence that vitamin D deficiency is associated with increased CVD, prospective randomized controlled trials are warranted to determine whether correction of vitamin D deficiency contributes to the prevention of CVD.

Psychosocial Factors

A large body of literature suggests that psychosocial attributes and stressful events predict the incidence of CVD. The INTERHEART study showed that approximately 30 % of first myocardial infarctions were explained by psychosocial factors such as stress, independently of other well established CVD risk factors.[1] Another study in middle-aged women showed that depression and stress predicted the risk for developing metabolic syndrome by multiple definitions.[17] It is imperative that health professionals begin to identify and treat psychosocial factors, which have been mostly ignored as a 'non-traditional' risk factor for CVD.

Dyslipidemia

A large body of evidence supports a direct relationship between dyslipidemia and CVD. Two of the five National Cholesterol Education Program (NCEP) Adult Treatment Panel III characteristics of the metabolic syndrome are related to lipoproteins: increased triglycerides (TGs) and decreased high-density lipoprotein cholesterol (HDL-C). In fact, the two characteristics most likely to identify patients at risk for insulin resistance are changes in TG and HDL-C levels. A TG/HDL-C ratio >3.5 defines the patients who are most insulin-resistant and at increased risk for a variety of adverse consequences, including type 2 diabetes and CVD.[18]

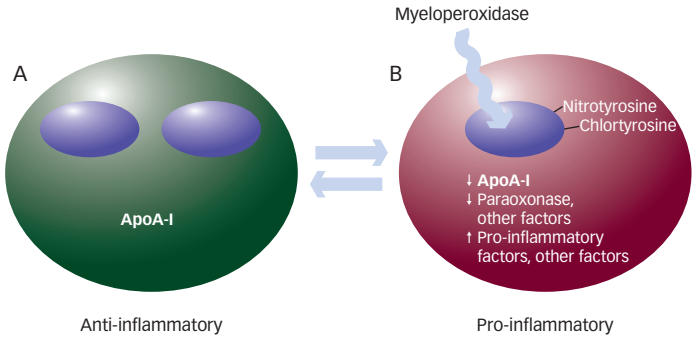
For over two decades, dyslipidemia therapy has focused on low-density lipoprotein cholesterol (LDL-C), which has been identified as a risk factor for CVD in retrospective, prospective, and observational studies. In addition, extensive laboratory and animal research has demonstrated the atherogenic potential of LDL-C.[19,20] However, it is also clear that multiple studies suggest the atherogenicity of TGs and support a protective effect for HDL-C.[21] Scientific evidence points overwhelmingly to the total cholesterol (TC)/HDL-C ratio as the best predictor of CVD events.[22] The European Prospective Investigation into Cancer and Nutrition (EPIC) was a prospective population study of 21,448 participants without diabetes or CVD between 45 and 79 years of age who were followed for 11 years. Completely independently of their LDL-C levels, participants with high non-HDL-C levels, high TG levels, or a TC/HDL-C ratio >5 were at increased CVD risk.[23] The Framingham Heart Study demonstrated a curvilinear increased incidence rate for CVD when the TC/HDL-C ratio was >5, with the CHD risk attenuating as the ratio fell below 5 (see *Figure 1*).[24] *Table 1* outlines the primary

dyslipidemia endpoints for 21 landmark lipid trials including the results of the two recent studies: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and Atherothrombosis Intervention in Metabolic Syndrome with low HDL/high Triglycerides and Impact on Global Health Outcomes (AIM-HIGH). One can readily appreciate that when the pre-treatment TC/HDL-C ratio was >5, all but one study showed a significant decrease in the primary endpoint; by contrast, when the pre-treatment TC/HDL-C ratio was <5, little or no reduction in primary endpoints was achieved. Lipid subgroup analysis clearly demonstrated that TGs and HDL-C but not LDL-C played a critical role in primary endpoint reduction.[25] In the Bezafibrate Infarction Prevention (BIP) study, patients with TG >200 mg/dl had a 39.5 % reduction in primary endpoint; there was a 27 % reduction in the primary endpoint in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study in patients with TG >204/HDL-C <42 mg/dl; and in the ACCORD study there was a 31 % reduction in the primary endpoint in the subgroup that had TG >204/HDL-C <34 mg/dl. The baseline total cholesterol/HDL-C ratio in the ACCORD subgroup was 6.37 and fell to 4.53 consistent with the Framingham Heart Study curvilinear increased incidence rate for CVD when the ratio is >5 and attenuating once the ratio is <5. Even the 34 % reduction in primary endpoint in the Helsinki Heart Study increased to 71 % in those patients with TG >200mg/dl. All of these studies reiterate the important association between high TG and/or low HDL-C and CVD risk.

In the Women's Health Study,[26] baseline lipoproteins were measured by nuclear magnetic resonance in 27,673 initially healthy women. The best predictor of a CVD event was the TC/HDL-C ratio, followed by the 'atherogenic' apolipoprotein B (Apo B)/'protective' apolipoprotein A-1 (ApoA1) ratio and TGs. LDL-C was a distant 11th. The INTERHEART study demonstrated another powerful link between ApoB/ApoA1 ratio and risk for myocardial infarction.[4] The ApoB/ApoA1 ratio showed a graded relation with myocardial infarction risk, with no evidence of a threshold, for the top versus the lowest decile of ApoB/ApoA1 ratio. Patients with high TG and/or low HDL-C often have elevated numbers of LDL particles without having elevated LDL-C, again demonstrating that the calculated LDL-C has limited value in assessing CVD risk. The AIM-HIGH study was terminated 18 months early on May 26, 2011 because an interim analysis concluded that the trial will not be able to show a significant difference in cardiovascular outcome event rates between the two study arms. AIM-HIGH was designed to test whether the addition of Niaspan would provide an additional 25 % reduction in CVD events versus simvastatin monotherapy in patients with stable, non-acute established, CVD and well controlled LDL-C. The baseline TC/HDL-C ratio in AIM-HIGH was 4.06 and fell to ~3.0 when the study was stopped. Again illustrating that when the TC/HDL-C ratio is <5 as baseline (see *Figure 1*) difficult to show any further CVD benefit with additional pharmacologic intervention.

Therefore, while a comprehensive assessment of lipids and lipoprotein particle number and size may be useful in some unique cases, the primary measurement determining CVD risk level and assessing a patient's response to therapy should be the TC/HDL-C ratio. Life insurance underwriter companies focus only on TC and TC/HDL-C when determining CVD risk. If the TC is less than 200 and your TC/HDL-C ratio is <5 you get a preferred policy. As the TC and ratio increase your premium increases as well. The companies do not look at LDL-C or triglycerides. Patients with a TC/HDL-C ratio >5 are at increased risk for CVD and should be treated

Figure 2: Model of Bi-directional Conversion of High-density Lipoprotein Cholesterol from Anti-inflammatory (A) to Pro-inflammatory (B)

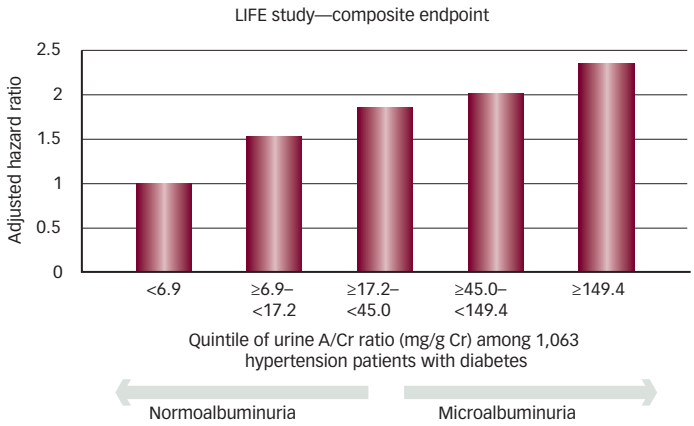


ApoA = apolipoprotein A.

aggressively. Based on the Framingham Heart Study, a ratio < 4 appears to capture most of the CVD benefit, but a prospective randomized clinical trial is required to delineate the 'ideal' ratio in minimizing CVD. Measuring the ApoB/ApoA1 ratio is another option, but it is not as readily available. Non-HDL-C is another potential treatment target. Non-HDL-C is your total cholesterol minus your HDL-C. Non-HDL-C measures all atherogenic apolipoprotein B-containing lipoproteins, not just LDL-C therefore predicting cardiovascular risk better than LDL-C alone. When triglycerides are 200 to 500 mg/dl, non–HDL-C is >30 mg/dl higher than LDL-C due to elevated levels of triglyceride rich lipoproteins. For this reason, the National Cholesterol Education Program Adult Treatment Panel III set the goal for non–HDL-C 30 mg/dl higher than the LDL-C goal (LDL-C + 30). Baseline levels and subsequent changes in LDL-C are frankly irrelevant when assessing CVD risk and the potential benefit of therapy. Furthermore, TC, HDL-C, ApoB, and ApoA1 levels in the fasting and post-prandial states are virtually identical, so patients do not need to fast for eight to 12 hours before testing. This is in major contrast to LDL-C, which is a calculated number derived from subtracting the HDL-C and TG/5 from the TC. Food intake can significantly affect TG levels, resulting in profound differences in the LDL-C value.

Many lines of evidence indicate that HDL-C protects the artery wall against the development of atherosclerosis and subsequently CVD by promoting reverse cholesterol transport via the adenosine triphosphate (ATP)-binding cassette transporter A1 pathway. Recent studies, however, suggest that in the presence of inflammation HDL-C can accumulate oxidized lipids and proteins that make it proatherogenic/dysfunctional.[27,28] Myeloperoxidase (MPO), a heme protein released by phagocytes, interacts with hydrogen peroxide and chloride to generate a powerful oxidant hypochlorous acid (HOCL). MPO converts tyrosine into a stable product, 3-chlorotyrosine. Chlorination of the phenolic ring of tyrosine may have clinical relevance because elevated 3-chlorothyrosine products have been detected in LDL-C isolated from human atherosclerotic lesions. Furthermore, HOCL selectively targets tyrosine residues in ApoA1, which accounts for 70 % of the total protein content of HDL-C. Increased 3-chlorotyrosine levels in HDL impair the ability of HDL apolipoproteins to remove cholesterol from macrophages in the artery wall. Nitration of specific ApoA1 tyrosine residues also impairs HDL function. In other words, chlorination and nitration of specific

Figure 3: Albuminuria Assessment in Patients with Hypertension and Diabetes Improves Cardiovascular Risk Stratification



Albuminuria predicts cardiovascular risk at levels below current definition. A = albumin; Cr = creatinine.

ApoA1 tyrosine residues promotes atherogenesis by counteracting the established antiatherogenic effects of native HDL and the ATP-binding cassette transporter A-1 pathway (see *Figure 2*).

Hypertension

Hypertension is the number one cause of death in the world. Diabetes increases the risk for CVD by a factor of two to three at every level of systolic blood pressure. Large-scale randomized, controlled trials have documented the benefits of blood-pressure-lowering treatment on the risk for macrovascular and microvascular complications and on survival among patients with type 2 diabetes.[29–32] Even at a systolic blood pressure of 120 mmHg, there was a significantly higher CVD mortality in patients with type 2 diabetes compared with patients who did not have diabetes.[33] Therefore, the results of ACCORD, the first randomized trial to state that a strategy of lowering blood pressure is better in patients with type 2 diabetes, came as something of a surprise.[34] Lowering blood pressure to normal levels (<120 mmHg), below current recommended levels, did not significantly reduce the risk for fatal or non-fatal CVD events compared with a blood pressure <140 mmHg. Although there were 17 % fewer cardiovascular events in the intensive group (n=208) compared with the standard group (n=237), the results did not reach statistical significance (p=0.55). However, there was a significant 40 % reduction in the risk for stroke (p=0.01).

Why did the ACCORD study not show a CVD benefit compared with other clinical trials? The study may have been underpowered. The event rate was only half what was expected (~2 %/year), and the mean duration of 4.7 years may not have been of sufficient duration to capture a difference between the two groups. The reduced power was reflected in the relatively wide confidence interval, which does not exclude a 27 % benefit for the primary endpoint. Furthermore, even though both groups were considered to be at high risk for CVD, the aggressive treatment of other major CVD risk factors may have lowered the absolute risk to a point from which it was difficult to demonstrate further incremental benefit from more aggressive treatment of blood pressure. The TC/HDL-C ratio was 3.70 in the intensive therapy group and 3.57 in the standard therapy group, and glycated hemoglobin (HbA_{1c}) was 7.6 % in both groups at the last visit. In addition, at the end of the study in both groups there were fewer patients smoking and most patients were on aspirin therapy. Based on the lack of overall clinical benefit in ACCORD, a systolic blood pressure goal of <120 mmHg may not be justified in every patient with type 2 diabetes. However, if there is a personal or family history of CVD or stroke, the patient is unable to tolerate lipid-lowering therapy and/or aspirin, and the patient has unacceptable glycemic control and smokes, a systolic blood pressure goal of <120 mmHg is recommended.

Albuminuria

Albuminuria is an independent risk factor for CVD in men and women with diabetes or hypertension, the general population, and those with established CVD. Albuminuria is an indicator of generalized endothelial injury, a hallmark of systemic atherosclerosis. A 24-hour urine albumin excretion rate ≤30 mg or an albumin/creatinine ratio (ACR) ≤30 mg/g is defined as normoalbuminuria, between 30 and 300 mg as microalbuminuria, and >300 mg as macroalbuminuria.[35] It is important to appreciate that these definitions were derived from studies that looked at the risk of a patient progressing to end-stage renal disease, and they are not applicable for the assessment of CVD and cerebrovascular disease risk. Treatments that decrease albuminuria, particularly agents that inhibit the renin–angiotensin system, reduce CVD in patients with diabetes and hypertension. Numerous studies have shown that increased albumin excretion, even at near 'normal' levels, was associated with increased CVD mortality and stroke. The Losartan Intervention for Endpoint (LIFE) reduction in hypertension study demonstrated that to achieve an adjusted hazard ratio of 1.0 for CVD risk, the optimal ACR had to be <6.9 mg/g, which is well below the normal definition of 30 mg/g (see *Figure 3*).[36] The Heart Outcomes Prevention Evaluation (HOPE) and Health Survey of Nord-Trondelag II (HUNT II) studies also showed a significant decrease in CVD mortality when ACR levels were maintained at <7.3 mg/g and <6 mg/g, respectively.[37,38] In the HOPE study, albuminuria was the most important independent, predictive variable for the combined endpoint of CVD death, myocardial infarction, and stroke. Critical health professionals have thus begun to appreciate that albuminuria, like hypertension and dyslipidemia, is an important modifiable CVD risk factor. Urine ACR should be measured and treated if the ACR is >7 mg/g. Any albumin in the urine is abnormal, so terms such as 'micro' and 'macro' are less meaningful when it comes to CVD and should be abandoned.

Dysglycemia

CVD in patients with diabetes is clearly associated with the degree of hyperglycemia. However, there remains an unanswered question in diabetes management: does the targeting of near normal levels reduce the rate of CVD? The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study[39] showed that a high two-hour glucose concentration was associated with an increased risk for CV mortality, independently of the level of the fasting glucose. The observational EPIC study demonstrated an increased risk for CVD and total mortality as the HbA_{1c} increased.[40] Two large glucose trials showed that intensive glucose control in patients with type 2 diabetes reduced the progression of microvascular disease,[41,42] but the effect on macrovascular complications remains uncertain. Three recent studies, the Action in

Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, the ACCORD study, and the Veterans Affairs Diabetes Trial (VADT), failed to show any significant decrease in CVD events despite rather intensive glucose control.[43–45] The ACCORD trial was terminated early because of a significant increase in deaths in the intensive-therapy group.

Why did the three recent studies fail to show a CVD benefit? Aggressive lowering of glucose substantially increases the frequency of hypoglycemia, the most important adverse effect of intensive glucose management. Severe episodes can be accompanied by confusion, disorientation, convulsions, coma, permanent impairment of brain function, and even death. Patients with type 2 diabetes who experience symptomatic and severe hypoglycemia have an increased risk for death, regardless of whether their diabetes is controlled or not. Hypoglycemia is associated with abnormal prolonged cardiac repolarization with increased QT intervals and QT dispersion (torsades de pointes).[46]

Therefore, the recommendation that the HbA_{1c} goal for selected individual patients be as close to normal (<6 %) as possible must be targeted without causing significant hypoglycemia. The most appropriate candidates include those with a short duration of diabetes (<12 years), long life expectancy, and no significant CVD. For patients with a history of severe hypoglycemia, limited life expectancy, or long-standing diabetes in which it is difficult to reach normal glycemia, a less stringent HbA_{1c} goal must be considered. Health professionals must understand that hypoglycemia is not benign and must carefully assess the risk–benefit of intensive glucose control when it comes to overall diabetes management. Metformin should be the cornerstone of treatment of patients with type 2 diabetes. Dual therapy with an incretin mimetic or dipeptidyl peptidase-4 (DPP-4) inhibitor has proven HbA_{1c} reduction with minimal risk for hypoglycemia.[47] It is crucial not to let the patient become 'glucocentric' or to forget there are several other very important, modifiable risk factors to address that have proven benefit in decreasing CVD.

Aspirin

Aspirin is effective in reducing CVD events and mortality among patients who have suffered acute myocardial infarction or ischemic stroke. For primary prevention, however, the balance is less clear because the risks of aspirin versus the benefits are generally an order of magnitude lower than in secondary prevention.[48] Diabetes patients without prior CVD and patients without diabetes but with established CVD have a similar increase in CVD events. Such results prompted the classification of diabetes as a CVD 'risk equivalent' necessitating aggressive antiatherosclerosis management, including aspirin.[49] However, a number of recently published randomized trials failed to demonstrate a cardioprotective of aspirin in patients with diabetes.[50]

Why did aspirin therapy fail to demonstrate a benefit? One possibility is that increased utilization of cardioprotective therapies such as statins and angiotensin-converting enzyme (ACE) inhibitors in these contemporary trials minimizes the effect size of aspirin on ischemic events. In addition, aspirin is considerably less effective in reducing platelet reactivity in patients with diabetes than in control subjects and the response of platelets to aspirin was inversely associated with HbA_{1c}. Protein glycation may attenuate the ability of aspirin to acetylate target platelet proteins in patients with diabetes.

These findings suggest that patients with type 2 diabetes may have 'aspirin resistance.'[51] Therefore, low-dose aspirin (70–100 mg), which was used in many of the large-scale studies, may be inadequate in providing effective inhibition of platelet reactivity, thus limiting its ability to reduce CVD events. Given these findings, a universal recommendation for low-dose aspirin in patients with type 2 diabetes is not evidence-based. Whether higher-dose regimens (162–325 mg) will demonstrate a benefit is unknown. Aspirin remains the most commonly prescribed cardiovascular medication; thus, it behooves us to determine the optimal strategy for using this life-saving medication, especially in patients with type 2 diabetes.

Conclusion

CVD remains the leading cause of death in patients with type 2 diabetes. Lifestyle modifications, including more physical activity and reduced calorie intake, must be encouraged. The reduction in CVD can be predicted from easily measurable and modifiable risk factors. Preventing even a small number of cases would have a major impact on reducing healthcare costs. ■

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