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## Impact of the Prediabetic State for the Treatment of Cardiovascular Disease in Prediabetic Patients

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### Diabetes and coronary heart disease

Patients with both type 1 and type 2 diabetes are at increased risk for coronary heart disease (CHD) and stroke.<sup>1,2</sup> In the United States, Europe and India, the most common cause of cardiovascular disease (CVD) is CHD; however, in Africa, the most common cause of CVD is stroke. In the Framingham data (Figure 1) type 2 diabetes increases the risk of both CHD and stroke. In women with diabetes, relative CVD risk, but seemingly not absolute risk, exceeds that in men.<sup>3</sup> Only some of the increased CVD risk in patients with diabetes can be attributed to other concurrent major risk factors<sup>1,3</sup> as other metabolic abnormalities, eg, hyperglycemia and insulin resistance, probably contribute additional risk. Most literature relating diabetes to CHD risk exists for type 2 diabetes, although cardiovascular complications are prominent in patients with type 1 diabetes as well. Because of the many differences between the two forms of diabetes, analysis is restricted to type 2 diabetes. Recently, Gu et al showed that while CHD mortality declined in non-diabetic subjects in the United States from the 1970s to 1980s, there was little or no decline in CHD mortality in diabetic subjects (Figure 2).<sup>4</sup> This suggests that current risk factor interventions and medical technologies have yet to have important effects in these populations.

Type 2 diabetes is characterized by insulin resistance and, typically, by obesity and the metabolic syndrome. As the disorder progresses insulin therapy may become necessary. Persons with type 2 diabetes who are treated with insulin nonetheless should not be confused with patients having type 1 diabetes who uniformly require insulin.

### Diabetes as a CHD risk equivalent

One concept which has important implications for the treatment of cardiovascular risk factors in type 2 diabetes is whether type 2 diabetes is a CHD risk equivalent. Several European and American guidelines now consider a 10-year risk of manifesting a cardiovascular event of greater than 20% as a CHD risk equivalent. Three lines of evidence support the concept that



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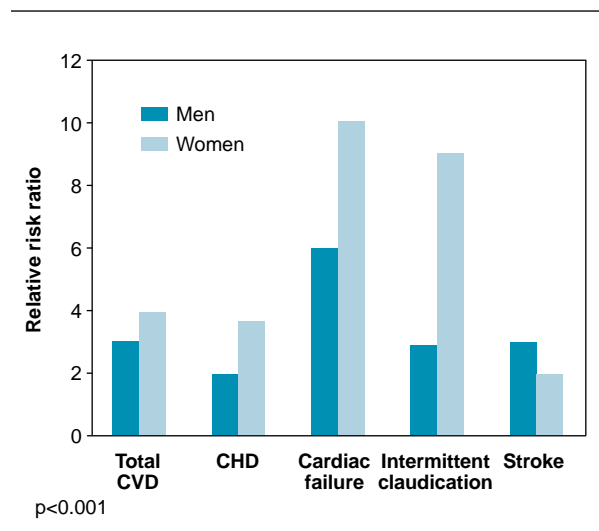
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**Figure 1: Framingham Heart Study 30-year follow up: CVD events in patients with diabetes (ages 35-64).<sup>1</sup>**



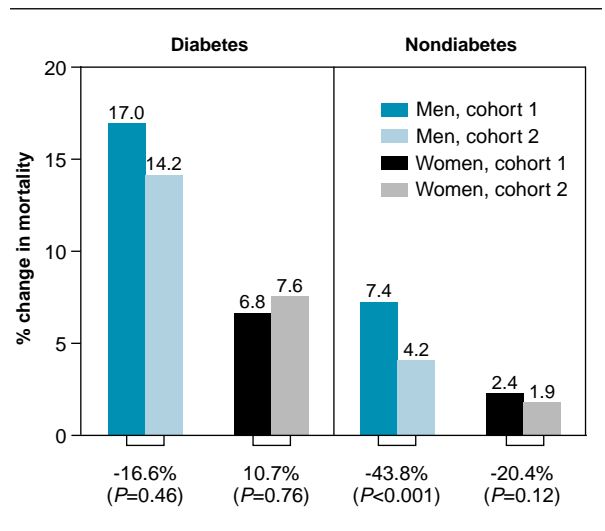
patients with type 2 diabetes from populations with high-average CHD risk are appropriately designated as having a CHD risk equivalent.

- First, patients with type 2 diabetes have an increased case fatality rate during a myocardial infarction.<sup>5,6</sup> In one large study,<sup>6</sup> the one-year case fatality rate for a first myocardial infarction (from the onset of symptoms, including pre-hospitalization mortality) was 45% in men with diabetes and 39% in women with diabetes, compared to 38% and 25% for non-diabetic men and women, respectively (Figure 3). Of the patients with diabetes who died, 50% of men and 25% of women died before hospitalization. These patients thus would not have benefited from secondary prevention strategies, indicating that management of risk factors in patients with diabetes should precede onset of clinical CHD.

- Second, the overall prognosis for survival is much worse for diabetic patients with established CHD than for non-diabetic CHD patients.<sup>5,6</sup> This observation also points to the need to aggressively prevent CHD in patients with diabetes.

- Third, absolute risk for first major coronary events in patients with type 2 diabetes in high-risk populations approximates that for recurrent events in non-diabetic patients with clinical CHD. For example, in a Finnish population-based study,<sup>7</sup> the seven-year incidence of myocardial infarction (fatal and nonfatal) among 1373 non-diabetic subjects with and without prior myocardial

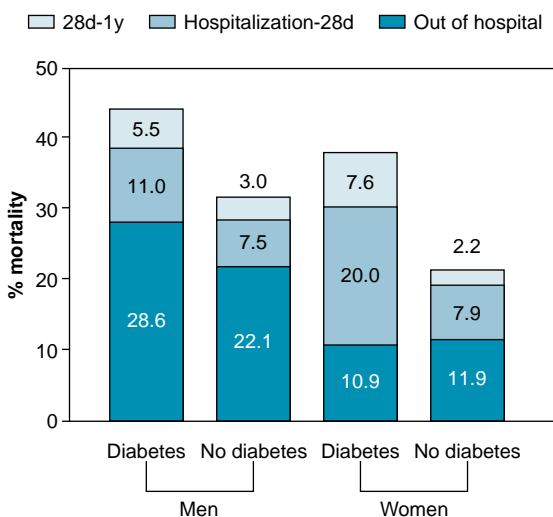
**Figure 2: Changes in CAD mortality rates in patients with and without diabetes.<sup>4</sup>**



infarction at baseline was 18.8% and 3.5%, respectively ( $p < 0.001$ ). In contrast, in 1059 type 2 diabetic subjects, the seven-year incidence rates of myocardial infarction in diabetic subjects with and without prior myocardial infarction at baseline were 45% and 20.2% respectively ( $P < 0.001$ ) (Figure 4). The hazard ratio for CHD death for diabetic subjects without prior myocardial infarction as compared with non-diabetic subjects with prior myocardial infarction was not significantly different from 1.0 (hazard ratio, 1.4; 95% confidence interval, 0.7-2.6) after adjustment for age and sex, suggesting similar risks of infarction in the two groups. After further adjustment for total cholesterol, hypertension, and smoking, this hazard ratio remained close to 1.0 (hazard ratio, 1.2; 95% confidence interval, 0.6-2.4). Thus, in the Finnish population, which is known to be a high-risk population, patients with type 2 diabetes have as high a risk of a myocardial infarction as do non-diabetic patients with previous myocardial infarction. In this study,<sup>7</sup> diabetes was also equal to CHD in predicting the future risk of stroke. These results were confirmed in new data from the OASIS study.<sup>8</sup> However some patients with type 2 diabetes (like patients with pre-existing CHD) may have a lower CHD risk.

Moreover, in a major clinical trial, the United Kingdom Prospective Diabetes Study (UKPDS),<sup>9</sup> the absolute 10-year risk for major CHD events was 15-20%, depending on the subgroup. Although this percent-

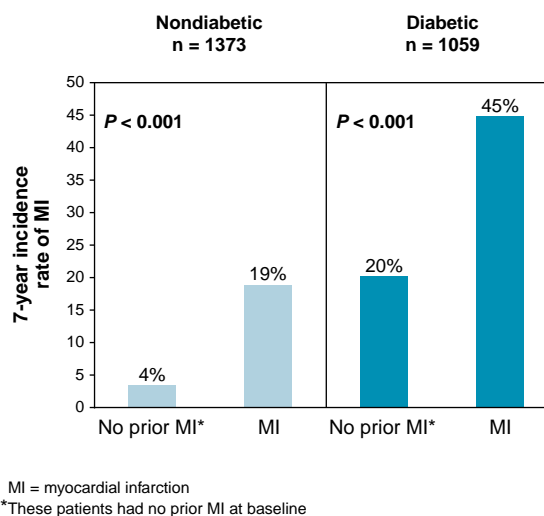
**Figure 3: 1-year mortality in diabetic and nondiabetic subjects after a first MI.<sup>6</sup>**



age was below 20% in some subgroups, it must be recognized that the patients in this trial had a diagnosis of diabetes made relatively recently; also, they were less obese, on average, than most patients with type 2 diabetes in the United States and Europe. In those with higher BMIs (>30 kg/m<sup>2</sup>), 10-year risk exceeded 20%. Finally, it is well known that patients participating in clinical trials manifest a lower risk during the trial than does the population at large. Thus, UKPDS results are consistent with the concept that patients with type 2 diabetes belong in the category of CHD risk equivalent. In another large clinical trial (HOPE),<sup>10</sup> patients with type 2 diabetes who did not manifest CHD at the entry had an annual rate of major coronary events of about 2.5% (10-year risk = 25%). In HOPE, diabetic patients had an additional risk factor, were older than UKPDS patients at entry, and seemingly had a higher baseline risk. However, UKPDS and HOPE trial results are consistent with the epidemiologic data supporting the concept that patients with type 2 diabetes belong in the category of CHD risk equivalent.

In some low-risk populations, the presence of type 2 diabetes in isolation may not raise the level of risk to that of a CHD risk equivalent. One example may include patients of oriental ancestry. In contrast, type 2 diabetes is accompanied by a very high risk for CHD in persons of South Asian origin.<sup>11</sup>

**Figure 4: Type 2 diabetes and CHD: 7-year incidence of fatal/nonfatal MI (East West Study).<sup>7</sup>**

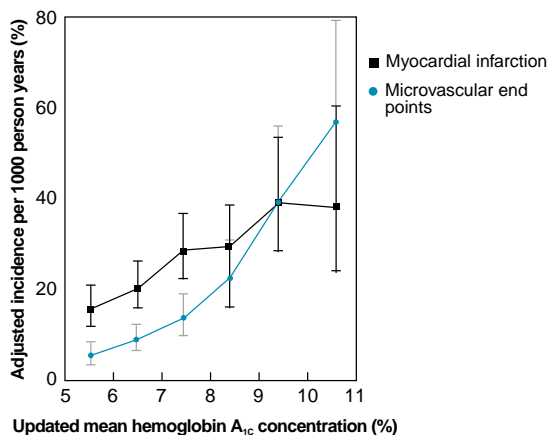


Classification of diabetes as a CHD risk equivalent implies that enhanced benefit will be achieved from aggressive LDL-lowering and blood pressure-lowering therapies since the absolute risk of coronary heart disease is high in type 2 diabetic subjects and clinical trials have suggested that the benefits of cardiovascular risk factor interventions are at least as great in diabetic subjects as in non-diabetic subjects.

### Glycemia and CHD in diabetic subjects

Even if type 2 diabetes represented a CHD risk equivalent, it still would not mean that type 2 diabetic subjects would need more aggressive standard cardiovascular risk factor management unless the excess risk of cardiovascular disease remained after control of glycemia. The relationship of glycemia to CHD risk in diabetic subjects has been long disputed.<sup>12,13</sup> In the UKPDS,<sup>9</sup> intensive glycemic control was associated with a larger reduction in microvascular events (25%) than in myocardial infarction (16%). In the recently published epidemiological analysis of the UKPDS study,<sup>14</sup> a variation of hemoglobin A<sub>1c</sub> from 5.5% to 11% was associated with a doubling of the risk of myocardial infarction, but a tenfold increase in the rate of microvascular events (retinopathy, renal disease and neuropathy) (Figure 5). Thus, glycemia in type 2 diabetes is associated with an increase in the risk of CHD but the slope of the relationship is much smaller

**Figure 5: MI and microvascular endpoints. Incidence by mean hemoglobin A<sub>1c</sub> concentration.**<sup>14</sup>



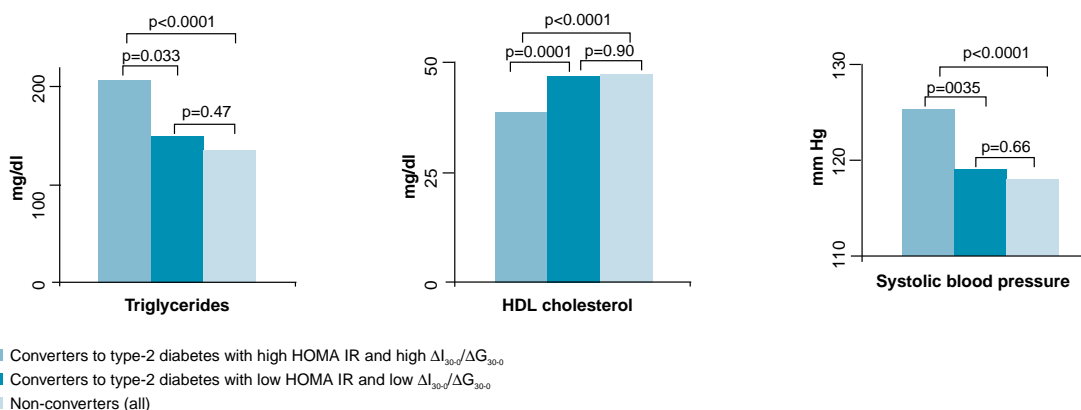
for myocardial infarction than for microvascular events and it is unlikely that even perfect control of glycemia in type 2 diabetes will fully eliminate the excess risk of CHD in type 2 diabetes.

### The prediabetic state

One possible reason for the relatively modest relationship between glycemia and CHD in type 2 diabetes may be the existence of an atherogenic prediabetic state. Several studies have in fact confirmed the existence of such a prediabetic state. In the San Antonio Heart Study,<sup>15</sup> subjects with normal glucose tolerance who later developed type 2 diabetes had higher triglyceride and insulin levels and lower

HDL-cholesterol levels than subjects who had normal glucose tolerance but did not later develop type 2 diabetes. In a more recent analysis from the San Antonio Heart Study,<sup>16</sup> converters to overt diabetes had significantly higher BMI, waist circumference, triglyceride concentration, and blood pressure and lower HDL-cholesterol at baseline than non-converters. Atherogenic changes in converters were markedly attenuated (and no longer significant) after adjustment for the homeostasis model assessment of insulin resistance (HOMA IR, a surrogate for insulin resistance); in contrast, the differences in risk factors between converters and non-converters increased after adjustment for the ratio of early insulin increment to early glucose increment during an oral glucose tolerance test (a surrogate for insulin secretion). We also compared converters who had a predominant decrease in insulin secretion (high HOMA IR and high insulin secretory components) (n=56) and converters who had a predominant decrease in insulin secretion (low HOMA IR and low insulin secretory components) (n=31) with non-converters (n=1539). Only the converters who were insulin resistant had higher blood pressure and triglyceride levels and lower HDL cholesterol levels than non-converters (Figure 6) This data suggests that atherogenic changes in the prediabetic state are mainly seen in insulin-resistant subjects and that strategies to

**Figure 6: Mean levels of cardiovascular risk factors by insulin resistance (HOMA IR), insulin secretion (“ $\Delta I_{30-0}/\Delta G_{30-0}$ ” surrogate for insulin secretion).**<sup>16</sup>



prevent type 2 diabetes might focus on insulin-sensitizing interventions rather than interventions that increase insulin secretion because of potential effects on cardiovascular risk.

### Are cardiovascular risk factor interventions equally effective in diabetic and non-diabetic subjects?

Studies that have examined the effects of lipid alterations, whether with statins or fibrates; blood pressure reducers; beta-blockers; angiotensin-converting enzyme inhibitors; or aspirin; have shown that these interventions are generally as effective in relative risk reduction in diabetic subjects as in non-diabetic subjects. Since the absolute risk of CHD is greater in type 2 diabetic subjects than in non-diabetic subjects, the actual therapeutic benefit per 1000 patients treated would be larger in type 2 diabetes than in non-diabetics. The effectiveness of lipid intervention in diabetes can be seen in the 4S study,<sup>17</sup> CARE<sup>18</sup> and VA-HIT;<sup>19</sup> for blood pressure reduction, it can be seen in the HOT study reference<sup>20</sup> and the UKPDS.<sup>21</sup>

### Conclusion

We have shown in this review that type 2 diabetic subjects have a risk of cardiovascular disease approximately the same as those with prevalent CHD. It is unlikely that perfect control of type 2 diabetes may completely eliminate the excess risk of CHD. Therefore, other interventions to reduce CHD such as aggressive control of CHD risk factors as well as the prevention of type 2 diabetes (especially with the use of insulin sensitizing therapy) may be necessary in reducing the risk of CHD in type 2 diabetes.

Practicing physicians should consider intensive lifestyle interventions in subjects at high risk for type 2 diabetes (ie, those with impaired glucose tolerance). In addition, the use of anti-hypertensive agents that may increase resistance (beta-blockers and thiazides) should probably be avoided in subjects with impaired glucose tolerance.

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