In the May 2010 issue of the *Journal of the Chinese Medical Association*, Chuang et al\(^1\) reported their investigation of whether diabetic patients without prior heart disease have a similar risk of cardiovascular (CV) mortality as heart disease patients without diabetes mellitus (DM), and whether the presence of hypertension or metabolic syndrome enhances CV mortality risk in the DM patients identified from a community-based, homogeneous population of Chinese. Their study followed 11,058 Chinese aged $\geq 30$ years on Kinmen island for a median of 15 years, and the results revealed that DM subjects without heart disease had a similar risk of CV mortality as heart disease subjects without DM in this population. Among the 827 DM subjects without heart disease identified at baseline surveys, the presence of hypertension but not metabolic syndrome substantially increased CV mortality risk. The study provides further evidence in a Chinese population that is similar to previous reports in other populations. Haffner et al\(^2\) examined the 7-year incidence of fatal and nonfatal myocardial infarction (MI) of 1,373 nondiabetic and 1,059 diabetic subjects to determine whether patients with DM who have not had MI should be treated as aggressively for CV risk factors as patients who have had MIs. The data suggest that diabetic patients without previous MI have as high a risk of MI as nondiabetic patients with previous MI. The Prospective Cardiovascular Münster Study\(^3\) showed that rates of MI over a 4-year follow-up period in a group of middle-aged men were increased by nearly 3 times in people with DM compared to people without DM. When DM and hypertension occurred together, the incidence of MI was 8-fold greater than in subjects without any risk factors. If dyslipidemia was also present, a further 2-fold increase in risk was observed. These data confirm both the independent risk associated with DM and the synergistic interaction that DM has with other common risk factors for coronary heart disease.

So, there are 2 major questions regarding DM and CV risk. First, whether or not routine screening for coronary artery disease identifies patients with type 2 DM as being at high cardiac risk, and whether it affects their cardiac outcomes. Second, whether or not improved glycemic control in DM patients reduces their CV risk and mortality. Type 2 DM is also widely recognized as a CV risk equivalent, and CVD is often asymptomatic in these patients until the onset of MI or sudden cardiac death. The current standard of care for type 2 DM emphasizes reduction of CV risk factors.\(^4\) Although endorsed by some professional organizations, screening of patients with type 2 DM and no symptoms of coronary artery disease remains highly controversial in the absence of prospective outcome studies supporting its utility. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study is a randomized controlled trial in which participants were randomly assigned either to be systematically screened with stress myocardial perfusion imaging or not be screened.\(^5\) The aim of DIAD was to test the hypothesis that systematic screening would identify higher-risk individuals and beneficially affect their risk of MI or cardiac death. Overall, cardiac event rates in this population were much lower than anticipated. Within this population of patients with asymptomatic type 2 DM, the use of myocardial perfusion imaging screening had no discernable effect on subsequent cardiac events. The results also showed that significant myocardial perfusion imaging abnormalities on screening were associated with a greater incidence of cardiac events, although the positive predictive value of such abnormalities was low and events also occurred in participants with normal screening tests. In this contemporary study population of patients with DM, the
cardiac event rates were low and were not significantly reduced by myocardial perfusion imaging screening for myocardial ischemia over 4.8 years.

Epidemiologic evidence strongly indicates that DM is a major risk factor for CVD. Clinical trials have shown that intensive glucose control reduces the risk of microvascular complications among patients with type 2 DM, but its effect on CVD, including coronary heart disease, stroke and peripheral arterial disease, is uncertain. However, during 2008, 3 large randomized controlled trials reported conflicting results.\(^6\)\(^--\)\(^8\) Although ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial) found no effect of intensive glucose control on major CV events, ACCORD (Action to Control Cardiovascular Disease in Diabetes) identified an increased risk of death from CV causes and total mortality associated with intensive glucose control.\(^6\) The ACCORD trial was stopped prematurely because of an excess overall mortality among the DM patients who were randomized to the intensive glycemic control treatment arm.\(^6\) These patients attained an A1C concentration of 6.0% when compared to the standard glycemic control arm in which the target was to attain a concentration of A1C between 7.0% and 7.9%. Even though there was a non-statistically significant 10% reduction in the primary composite outcome of nonfatal MI, stroke or CV death, the trial was stopped because of the increased overall mortality. The specific cause of the increased mortality with intensive glycemic control is not presently known but was apparently not due to any specific therapy (including rosiglitazone) or to hypoglycemia-related events. The results of the ACCORD, ADVANCE and VADT trials do not suggest that intensive glycemic control is associated with a reduction in CV events, at least with the treatments used in these studies and the length of the follow-up periods.

So, is there no benefit of intensive blood glucose control on CVD in DM patients? Ray et al\(^9\) undertook a meta-analysis of randomized controlled trials to determine whether or not intensive glycemic control is beneficial. Their data suggested that intensive compared with standard glycemic control significantly reduces CV events without an increased risk of death. Kelly et al,\(^10\) who reviewed 5 large trials, found that compared with conventional control, intensive glucose control reduced the risk of CVD but not of CV death or all-cause mortality, and increased the risk of severe hypoglycemia. As the American Diabetes Association has noted, it is likely that the increase in mortality in ACCORD was related to the overall treatment strategies for intensifying glycemic control in the study population, not the achieved A1C per se.\(^4\) The ADVANCE study achieved a median A1C in its intensive arm similar to that in the ACCORD study, with no increased mortality hazard. Thus, the ACCORD mortality findings do not imply that patients with type 2 DM who can easily achieve or maintain low A1C levels with lifestyle modifications with or without pharmacotherapy are at risk and need to increase their A1C. We can find the nadir part of the observational glycemia–CVD risk curves in these 3 trials with the A1C levels in the median of the intensive arms (6.4–6.9%). Importantly, their results should not be extrapolated to imply that there would be no CV benefit of glycemic control from very poor (e.g. A1C > 9%) to good (e.g. A1C < 7%).

In my view, DM is associated with a marked increase in the risk of CVD, and multiple modifiable risk factors for CVD are present in diabetic patients, including hyperglycemia, hypertension and dyslipidemia. A multifactorial intervention, with therapies directed toward modifying lifestyle, reducing total cholesterol, lowering blood pressure, and improving glycemic control, may have a dramatic benefit in diabetic patients, and be better than an approach that is specifically targeted to only 1 CV risk factor.

References

