Implications
The clinical Implications emerging out from this study

Stage Specific Treatment

Treatment for type 2 diabetes mellitus appears to be stage specific. Several clinical trials have been carried out to find out the effect of intensive treatment of hyperglycemia on cardiovascular risk reduction in type 2 diabetes mellitus, but many of these trials have yielded conflicting results.

In the United Kingdom Prospective Diabetes Study (UKPDS), in newly diagnosed type 2 diabetic patients, long-term cardiovascular benefit was seen in those who received intensive treatment for hyperglycemia in comparison to those who received conventional treatment. Inspite of similar glycemic control between the groups that were observed during the subsequent years of observational follow up, the cardiovascular benefit was persevered in those who received aggressive treatment with in 5 years of diabetes (55).

However, similar observations were not seen in other three substantial clinical trials that were performed in patients with type 2 diabetes mellitus. In the Veterans Affairs Diabetes Trial (VADT), no cardiovascular benefit was seen in elderly patients with a mean duration of diabetes of about 10 years, when subjected to an aggressive glycemic control regimen (157).

The results obtained from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial were also similar, which aimed to achieve an HbA1c of 6.5% through aggressive treatment (378). In contrast, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the stricter intensive treatment which aimed to bring down HbA1c levels below 6% in type 2 diabetic patients, resulted in increased weight, mortality and risk of hypoglycemia in the subjects, without any significant reduction in macrovascular events (166).

Even in Action for Health in Diabetes (LOOK AHEAD) trial, intense life style intervention did not favor the cardiovascular benefit in patients with type 2 diabetes mellitus (158). Majority of the study population had high burden of cardiovascular disease at the baseline itself and were with long standing diabetes. Half the study population had diabetes for more than 5 years wherein significant cardiovascular changes might already have occurred. Preventive strategies should be initiated earlier to have full benefit and it is likely that patients with shorter duration
of diabetes and those without preexisting cardiovascular diseases might have benefited by the aggressive life style modification.

The recent Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial was aimed to evaluate whether stricter glucose control with long - acting insulin showed any positive or negative effect on the risk of cardiovascular disease (377). According to the results of the recent ORIGIN trial, strict control of blood sugar levels has not improved cardiovascular outcomes.

In the ORIGIN trial, 12,537 subjects with a mean age of 63 years with cardiovascular risk factors and impaired fasting glucose or with impaired glucose tolerance or type 2 diabetes mellitus were studied. They were designated to obtain either insulin glargine or standard care for diabetes, which included metformin and n – 3 fatty acids or placebo. The target fasting plasma glucose achieved was 95 mg/dL for the insulin glargine group and 123 mg/dL for standard care patients. At the end of the study at 6.2 years, it was noted that although fasting plasma glucose levels and A1C levels were lower in the group taking insulin glargine, there was no significant difference in mortality, microvascular event or results of any interventions in both groups. The study basically showed no significant benefits or harm with respect to cardiovascular effects with long - acting insulin or standard care.

**Insulin Provisioning vs. Restrictive strategies:**

The results from these trials show that aggressive glucose reduction treatment initiated in patients with less than 5 years of diabetes and before significant vascular changes have occurred, have better cardiovascular benefits. Since insulin resistance/hyperinsulinemia is likely to be a major contributor for the cardiovascular changes, Insulin provisioning treatment strategy is less likely to be effective compared to insulin restricting strategies. This was very well demonstrated in UKPDS, wherein metformin resulted in substantial reduction of more than 30% cardiovascular risk (165). Sulfonylurea and insulin were associated with around 15% risk reduction which was statistically not significant (55).
HOMA-IR/ Hyperinsulinemia as a “Risk Stratification Tool”

It has been observed that the risk for cardiac events in type 2 diabetic patients with no previous history of CAD, is the same as seen in subjects with a prior myocardial infarction (1). However, subsequent studies have challenged this notion and showed that diabetes status may not be a CAD equivalent in all conditions (399). Diabetes is not a homogenous disease. Risk of developing severe cardiovascular disease varies across the spectrum of diabetic patients. Similar observations have been noted for the management of dyslipidemia and hypertension wherein aggressive treatment is reserved for those with higher cardiac risk profile (400). But such an approach has not evolved in the management of diabetes although American Diabetes Association has suggested such an approach in its recent guideline (401). In a computer model evaluation, patients with high cardiovascular risk derived significant benefit from aggressive treatment whereas those with lower risk levels had net negative effect on their Quality Adjusted Life Years suggesting overall harm in low risk patients (14). Unfortunately, markers to identify these risk categories have not yet been developed in diabetes. Hypertension and dyslipidemia have not provided sufficient risk stratification capabilities. We feel that insulin resistance/hyperinsulinemia is likely to yield this vital information in risk stratifying patients with diabetes. It is possible that patients with type 2 diabetes and HOMA IR>3.4 or Insulin > 20 µIU/ ml are likely to develop severe CAD by about 5 years and should be very aggressively treated from the time of diagnosis. After 5-10 years, such an aggressive approach might not be required since structural changes would already have occurred in the vessels. This is in line with the observations of ACCORD which showed higher cardiac mortality with aggressive glycemic control in those with longer duration of diabetes (166).

Further, insulin level above 20 µIU/ml could predict adverse cardiac events in type 2 diabetic patients even after undergoing coronary angiogram, and thus making it possible to identify individuals who are likely to develop complications and are needed to follow up meticulously with aggressive medical management.

On the other hand, diabetics with HOMA IR <2.5 are likely to be free of significant CAD for a long duration and hence can be spared of the burden of aggressive medications. Measurement of HOMA IR/fasting insulin to stratify risk may become a major step in selecting patients for
aggressive treatment and thus be an important biomarker for individualizing treatment in diabetes.

Based on the previous studies and our observations, the individualization of treatment for type 2 diabetes mellitus may be done as follows, for the prevention/management of macrovascular complications.

**Stage of Prediabetes:**

Aggressive life style modification; Those with HOMA-IR > 3.4/ fasting insulin > 20 µIU/ml need to be evaluated thoroughly for risk factors of CAD and managed aggressively.

**Stage of early type 2 diabetes mellitus (Duration of diabetes 5-10 years)**

In subjects with HOMA-IR > 3.4/fasting insulin > 20 µIU/ml, aggressive risk management and insulin restricting strategies like metformin would be appropriate. In those with HOMA-IR < 2.5, the risk of macrovascular complications is less and hence, aggressive medications may be avoided.

**Stage of established CAD (More than 10 years of diabetes)**

Treatment is mainly “palliative”, since irreversible macrovascular changes have occurred. Aggressive glycemic control is not advisable.

**The Utility of Manipal Diabetes Coronary Artery Severity Score 2 [MDCASS 2]**

The utility of this present score would be beneficial for the patient, especially in third world countries which would allow patients to prepare themselves mentally and financially beforehand for a subsequent procedure. However, this needs to be confirmed on a longitudinal basis. Since the parameters used in the construction of risk score are known to remain constant in type 2 diabetes mellitus, it is possible that the risk score could be used in the initial stage of diabetes itself, enabling to identify individuals who are likely to develop severe disease. This could help clinicians to manage individuals aggressively from the early stages itself. Large trials should take into consideration the IR/Insulin level as a measure of severity and balance it in their arms of the study.
Insulin resistance/Hyperinsulinemia – beyond a marker

Insulin resistance is likely to emerge as a potential target for treatment in the future. So far IR has been studied extensively as a risk factor only. Molecular studies have shown that Insulin resistance might be contributing to structural and functional changes in the vasculature. While glycemic control has yielded significant control over microvascular events, macrovascular complications have not yet been fully controlled. Newer modalities of treatments should focus on managing insulin resistance rather than targeting glycemic end points. Specifically, minimizing the mitogenic and proinflammatory action of insulin through MAP kinase pathway is likely to yield better cardiovascular protection.