DISCUSSION
In spite of controlling for conventional risk factors of CAD, complications in type 2 diabetes mellitus still remain high. Reaven initially proposed that CAD complications could be predicted by measurement of insulin resistance and subsequently many researchers have identified the primary role of insulin resistance in development of coronary artery disease (12). Most of the studies focused on pathogenesis and occurrence of the disease without referring to severity of the disease. But it is the severe disease that alters long term outcome.

At present a lot of importance had been given in understanding the role of non-traditional risk factors for CAD in type 2 diabetes mellitus, particularly hyperinsulinemia and insulin resistance. Thus present study was focused to find out the relation between insulin resistance and severity of coronary artery disease along with other conventional risk factors for CAD in type 2 diabetes mellitus.

**Correlation of Insulin resistance with Severity of Coronary Artery Disease**

Insulin resistance has known to be linked with an occurrence of coronary artery disease in diabetic patients, but correlation with respect to severity of the disease was not studied. In this present study, correlation between insulin resistance (HOMA-IR) and angiographic severity of coronary artery disease in 290 consecutive type 2 diabetic patients who underwent coronary angiogram for the evaluation of clinical suspected coronary artery disease were studied.

The observation from present study showed that there is a positive linear correlation between insulin resistance and severity of CAD which is found to be statistically significant. Further, after adjustment for potential confounder’s in multivariate linear regression model, the HOMA-IR was significantly associated with angiographic severity of CAD in type 2 diabetes mellitus.

Diabetic patients have premature onset of coronary artery disease and the involved vessels show severe disease. In this study, the median duration of diabetes was just 5.5 (2.75-10). Development of CAD appears to be multifactorial and known conventional risk factors explains for about 25% of the disease. The other components of metabolic syndrome did not correlate well with angiographic severity of the disease, in spite of being associated with CAD. Even after being associated with the disease, presence of strong significant positive linear correlation noticed in this study, strengthens the possibility of cause-effect relationship.
This study emphasizes an important role of insulin resistance in the pathogenesis of diabetic vascular disease. A large number of data also reveals that insulin resistance plays a key role in atherosclerosis (371). It is closely related with an increased risk of CAD (372). An impaired insulin signaling in endothelial cells, is considered as an important mechanism for the development cardiovascular disease (372). The endothelial dysfunction, which develops due to the impairment in insulin signaling, results in an accelerated atherosclerosis together with the proinflammatory state induced by insulin resistance (372). Although insulin resistance is known to be a part of the metabolic syndrome, the other clinical markers like BMI and truncal obesity has decreased sensitivity and specificity in recognizing insulin resistance (371).

Insulin resistance is the only component of the metabolic syndrome that is shown to be relatively consistent in type 2 diabetes mellitus. All the other conventional risk factors change over a period of time (15). The insulin resistance as measured by HOMA-IR method has been indicated to be generally steady in type 2 diabetes mellitus, even after many years of conventional treatment for type 2 diabetes mellitus as shown in U.K Prospective Diabetes Study (UKPDS). Whereas even with or without treatment, changes in all the other biochemical risk factors and anthropometric measurements are being observed over the period of time (16). The steady nature of insulin resistance is very well demonstrated in the U.K. Prospective Diabetes study (UKPDS), where insulin sensitivity, the reciprocal of insulin resistance remained constant with 62, 60 and 62% at 0, 1 and 6 years, in over six years of conventional treatment for type 2 diabetes (17). This unique evolution of insulin resistance and its significant association with angiographic severity CAD might help to identify the individuals who are might be at risk from the beginning itself.

**Importance of threshold duration in type 2 diabetes mellitus: Role of Insulin resistance/Hyperinsulinemia**

The profile and complications of the CAD are not uniform among the diabetic population (163). Studies have shown that the spectra of CAD differ with respect to different time intervals of type 2 diabetes mellitus (163). Even in the United Kingdom Prospective Diabetes study risk engine, events less than four years were not considered while forming the risk score (163).
Thus in this present study an evaluation of an angiographic patterns of the coronary artery disease in the diabetics with less than five years, 5-10 years and more than 10 years of duration was carried out. A significant structural changes in the coronary arteries in the patients with more than five years of type 2 diabetes mellitus was noticed.

Earlier studies suggested that the diabetic patients had poor collaterals formation (373), however later studies have shown that collateral formation is independent of diabetes mellitus and depends on the degree of the coronary artery stenosis (374). In this study, it is observed that presence of coronary collaterals is directly proportional to the severity of the CAD. Thus the presence of collaterals was seen only in more than five years of diabetes as SYNTAX score was high in this group compared to non-diabetes and less than five years of diabetes.

In this current study a significant increase in the mean SYNTAX score, vessel score and coronary collateral grade was observed between five to 10 years of diabetic duration when compared to less than five years of diabetes. Whereas, the difference in the mean SYNTAX score, vessel score, coronary collateral grade both in the non-diabetics and less than five years of diabetes, five to 10 years and more than 10 years of diabetes was not significant. The observation from the present study indicates that, the coronary profile between the non-diabetic group and the less than five years of diabetes could be similar and a chronic severe structural narrowing of coronary artery takes place in five to 10 years of type 2 diabetes mellitus. Beyond 10 years we visually noticed a plateau trend with no further morphological changes in the coronary arteries.

In this present study a significant difference in the urine microalbumin is observed in more than 10 years of diabetes. Even though the microvascular changes are set in at initial stages of diabetes their progression is significant only after10 years as pointed by our result. But the macrovascular changes are time dependent getting established between 5-10 years of diabetes.

The prevalence of microvascular complications increases with the duration of the diabetes (375). A recent study has showed that the incidence of microvascular outcomes is higher after 10 years of type 2 diabetes mellitus and keeps on progressing whereas the cardiovascular complications seems to be appearing before 10 years of diabetes (376). Type 2 diabetes mellitus with more than five years of duration had severe and complex vascular disease compared to less than five years of diabetes.
Since a severe vascular changes were observed in more than 5 years of type 2 diabetes mellitus, subsequently the factors responsible for these changes were determined. An evaluation of insulin resistance along with other conventional risk factors of CAD was carried out to determine the factors contributing for these structural changes on coronary arteries in more than 5 years of type 2 diabetes mellitus.

In the present study we observed that, the correlation of HOMA-IR with severity of CAD remained moderate in less than 5 years of type 2 diabetes \[r = 0.327\ 95\%\ CI\ (0.17-0.47),\ p = 0.02\] and a strong correlation was seen in more than 5 years of type 2 diabetes \[r = 0.605\ 95\%\ CI\ (0.50-0.70),\ p < 0.001\]. The other conventional risk factors of CAD were not correlated well with severity of CAD. The multivariate linear regression analysis after adjusting for sex and other conventional risk factors of CAD showed that insulin resistance was significantly associated with severity of CAD in more than 5 years of type 2 diabetes \[\beta = 0.659\ (95\%\ CI:0.12-0.24),\ p < 0.001\].

Evidence from larger clinical trials such as ACCORD, ADVACNE, VADT and ORIGIN showed that aggressive glycemic control did not show any cardiovascular benefit for type 2 diabetes mellitus (157, 166, 377, 378). Most of these studies aimed to achieve HbA1c levels of 6.5% to 6% which resulted in increased weight, mortality and risk of hypoglycemia in type 2 diabetic subjects, without any reduction in macrovascular complications (157, 166, 377, 378). Even in LOOK AHEAD study which aimed to reduce cardiovascular complications by life style intervention did not derive any significant macrovascular benefit in type 2 diabetes mellitus (158).

The majority of study population involved in these trials had longer duration of diabetes and preexisting CAD. In VADT, ACCORD and ADVACNCE the mean duration of diabetes was 11.5, 10 and 8 years respectively, with 40%, 35% and 32 % of enrolled patients, respectively, having the history of preexisting CAD (157, 166, 378). Even in LOOKD AHEAD trial half the study population had duration of diabetes more than 5 years with high burden of cardiovascular disease at the baseline (158). Thus all these long term trails failed to derive any form of significant cardiovascular benefit in type 2 diabetes mellitus.

In our study we observed that subjects with more than 5 years of type 2 diabetes mellitus were characterized by severe, long segment, multi-vessel CAD when compared to less than 5 years
of type 2 diabetes mellitus. Hyperinsulinemia/insulin resistance brings about both functional and structural changes in the blood vessels. Functional changes are mediated through nitric oxide by receptor mediated resistance (379). But the structural changes occur by proatherogenic response mediated by MAP kinase pathway which is not affected by insulin resistance (379). The continuous action of hyperinsulinemia through the MAP kinase pathway results in a significant structural change over a period of time (379).

Type 2 diabetes mellitus with more than 5 years of duration have quantitative and qualitative, severe vascular disease compared to less than 5 years of diabetes. The peak effect of hyperinsulinemia and insulin resistance probably appears at 4 to 5 years of diabetes mellitus and thus possibility of developing a significant vascular changes might occur after 5 years of diabetes.

In the present study, the mean SYNTAX score was 13.27 ± 8.93 in less than 5 years of diabetes and 17.50 ± 11.79 in more than 5 years of diabetes (p = 0.003). The mean HOMA-IR was 2.77 ± 0.91 in less than 5 years of type 2 diabetes and 3.40 ± 1.62 in more than 5 years of type 2 diabetes (p = 0.01) respectively. It has been observed that individuals with high SYNTAX score do better with coronary artery bypass graft (CABG) than percutaneous coronary interventions (PCI) (380). A 4-year follow-up study showed that SYNTAX score of 15 or more had a better outcome in CABG than PCI (381). Since in our study, the subjects with more than 5 years are presented with severe and complex CAD, it is likely that patients with more than 5 years of diabetes might be candidates for CABG and patients with less than five years of diabetes duration might be suitable candidates for angioplasty for coronary revascularization.

This study confirms that the extent and the degree of the CAD are similar both in non-diabetics and diabetes with less than five years. They are often present with discrete lesions, less severe disease and involvement of single vessel. However, the structural changes in the coronary arteries were observed in more than five years of diabetes with diffused, long segment and multi vessel stenosis, a characteristic feature of a typical diabetic coronary artery disease.

Numerous studies have shown that insulin resistance has key role in every phase atherosclerosis and is closely linked to increased cardiovascular risk. But the strength of association between the two with respect to duration of diabetes mellitus has not been studied. This strong temporal association observed form our study, along with dose effect response as
manifested by very strong correlation co-efficient suggests, insulin resistance is not just a mere
association but important independent risk factor for diabetic macrovascular disease.

Individual variations are seen in diabetes complications but this study showed that, variations
with respect to the specific time intervals needs to be considered. There appears to be a
threshold period of five to 10 years, beyond which the CAD appears. Since there is strong
association and possible biological explanation, targeting insulin resistance as a therapeutic
modality might be crucial.

The microvascular benefits can be seen even in the longer duration of diabetes but
macrovascular benefits are restricted to the initial five years of type 2 diabetes mellitus. Thus
the window of opportunity for targeting the cardiovascular complications in type 2 diabetes
mellitus is restricted to 0 to 5 years of diabetes, beyond 5 years complications are severe.
Patients with high HOMA-IR should be managed aggressively.

Even the previous UKPDS studies have shown that intense therapeutic interventions have
reduced the macrovascular complications in less than five years of diabetes (382). Thus in
general the diabetic population intense therapeutic interventions are to be considered within
five years to reduce the cardiovascular complications.

**Hyperinsulinemia/Insulin resistance, as a predictor of Complex and Severe CAD
(SYNTAX Score > 22)**

Although hyperinsulinemia is identified as a possible risk factor for cardiovascular mortality
and morbidity, but at what level it is at risk is not very well defined. Angiographically measured
SYNTAX score of more than 22 is considered to be severe CAD (365, 366). Most of these
patients are not suitable candidates for angioplasty. Since a good correlation between HOMA
IR and SYNTAX score is already established in this study, hence we further explored the
possibility of determining the cut off value of HOMA IR/insulin which would reliably predict
SYNTAX score of more than 22 and thus identify severe CAD.

In this regard, present study identifies hyperinsulinemia > 20 µIU/ml, HOMA-IR > 3.4 and
duration of diabetes > 5 years which are independently associated with angiographically
determined severe and complex CAD. In this present study, a clear risk of
hyperinsulinemia/insulin resistance appears to be at a threshold level of 20 µIU/ml and
HOMA-IR 3.4, beyond which it has a very high odds ratio towards a severe and complex CAD. It is not just hyperinsulinemia, but hyperinsulinemia beyond a threshold seems to be associated with very high severe and complex disease. The high odds ratio for the severe disease was observed even after adjusting for other conventional risk factors.

The threshold level for insulin has been very well demonstrated in this study. Hyperinsulinemia is a part of type 2 diabetes mellitus, anything above normal range for insulin is commonly seen in type 2 diabetes mellitus, and until it reaches certain high levels they do not have major risk for developing severe disease. In this study, it is observed that, the risk for predicting severe and complex CAD was heightened beyond an insulin level of 20 µIU/ml, and below the threshold the risk for developing severe and complex CAD was substantially low.

It has been shown that, the development of insulin resistance is found to be distinct in type 2 diabetes mellitus. Since the exposure is constant, this allowed to calculate the odds ratio based on case-control study design and thereby enabling to assess the impact of risk factors on severe coronary artery disease.

The molecular basis by which hyperinsulinemia and insulin resistance leads to severe CAD has been elucidated. During insulin resistance, the metabolic action of insulin is altered while the mitogenic action would be still progressing (379). In other words, the phosphatidylinositol (PI) 3-kinase pathway is inhibited and MAPK pathway is still intact. The basal insulin functions are intact but pulsatile action of insulin is impaired. Based on findings from this present study, it is speculated that the MAPK pathway might be activated beyond threshold level of insulin, which leads to fibrotic and proliferative changes in the vasculature, and that threshold levels for insulin may be beyond 20 µIU/ml.

It is important to realize that even with aggressive risk factor modification certain diabetics not get sufficient cardiovascular benefit as per the ACCORD study. It is possible that these are the individuals who have got a complex and severe disease because of the burden of severe hyperinsulinemia over a period of time.

It is known that risk factor reduction to target levels after optimized therapies does not reduce the risk of developing severe CAD in all diabetic patients. The presence of hyperinsulinemia despite optimized therapies to reduce the atherosclerotic risk factor may be a residual risk
factor. It is evident from this study that individuals with insulin levels $> 20 \, \mu\text{IU/ml}$, HOMA-IR $> 3.4$ are likely to be associated with severe CAD, thus making it possible to identify these high-risk individuals at the beginning itself. In this context, the observations from the present study suggest the possibility of using insulin $> 20 \, \mu\text{IU/ml}$ as an indicator of high risk CAD across the population.

**Manipal Diabetes Coronary Artery Severity Score 2 [MDCASS 2]**

So far majority of risk scores does not predict severity of CAD, they only seems to inform about the risk of developing CAD. Since major therapeutic decisions depend on severity of CAD, i.e. subjects with SYNTAX score of greater than 22 do better with CABG than with PCI.

A simple clinical and biochemical parameter that predicts before-hand the possibility of score above or below 22, would be beneficial for the patient, especially in third world countries. This would allow patients to prepare themselves mentally and financially for a subsequent procedure. Thus in this study we explored the possibility of developing a risk score based on simple clinical parameters that could predict SYNTAX score of less than and more than 22.

In this study, we developed and validated a simple and non-invasive coronary artery severity score which is composed of routinely measured and easily available clinical and laboratory variables which could predict the SYNTAX score of above 22 in patients with type 2 diabetes mellitus. This score named as the Manipal Diabetes Coronary Artery Severity Score 2 (MDCASS 2), was accurate in identifying subjects with a SYNTAX score of above 22.

The development and severity of CAD can also differ, based on duration of diabetes. We have observed that patients with more than 5 years of diabetes have severe CAD when compared to less than 5 years of diabetes. Thus in the current study MDCASS 2 was developed using insulin resistance, fasting insulin and duration of diabetes where all the variables are known to be independently associated with severe CAD. However other conventional risk factors were not associated with severe CAD, hence they were not included in this study model. Gender was also not included in the risk model, as in diabetes, women are especially associated with more severe and diffuse CAD.
The patients with a SYNTAX score above 22, do better with coronary artery bypass graft CABG than with angioplasty (383). Observations from the present study indicates that a score of 8.5, allowed high accuracy for excluding patient with a SYNTAX score above 22, thus effectively identifying patients who might be suitable for angioplasty. Additionally, by using this severity score model developed using variables which are common in routine clinical practice and health examination, SYNTAX score of above 22 could be predicted well in advance, allowing patients to prepare mentally and financially for subsequent procedure.

The biochemical markers that are used to develop severity score are known to be relatively constant despite many years of treatment for type 2 diabetes mellitus. Insulin resistance which is one of the components used in the score has shown to be relatively stable in type 2 diabetes mellitus whereas all the other conventional risk factors changes over a period of time (15-17). We also observed insulin resistance to be associated with severity of CAD. Thus MDCASS 2 would be a relatively reliable tool in identifying SYNTAX score of above 22 in these patients, aiding in appropriate decision for revascularization.

**Low levels of Insulin resistance is associated with No Apparent Coronary Artery Disease in long standing diabetes (diabetic duration > 10 years)**

While the risk scores and HOMA IR >3.4 reliably identified high risk type 2 diabetic patients, the present study explored the possibility of developing markers of low risk type 2 diabetes patients also. Not all diabetic patients are at risk of developing cardiovascular complications. Some patients remain free of CAD despite many years of treatment for diabetes. Identifying factors associated with favorable CAD profile will help us to avoid or reduce the burden medications in such patients.

In this study, we have evaluated the role of insulin resistance along with other clinical markers in type 2 diabetes patients who are angiographically documented with and without CAD, and on treatment for more than 10 years of diabetes, to find out which one these factors would be associated for favorable cardiovascular outcomes in type 2 diabetic patients.

The observation from this present study showed that low levels of HOMA-IR (< 2.5), low levels of microalbumin (< 20mg/L) and females were independently associated with no
apparent CAD, in type 2 diabetic subjects who are on treatment for more than 10 years of duration.

Several studies have demonstrated that, the long term cardiovascular complications in type 2 diabetes mellitus could be predicted by the measure of insulin resistance (10, 12), and subsequently we have shown that, an increased level of insulin resistance is significantly associated with severity of CAD in type 2 diabetes mellitus even after adjusting for known risk factors. In this study, a decreased level of HOMA-IR is independently associated with favorable CAD profile in long standing diabetic population.

Since insulin resistance predicts long term cardiovascular complications, its unique evolution might help to identify the individuals with high HOMA-IR from the beginning itself. Thus in clinical practice it important to look for insulin resistance who are at high risk of developing complications.

Gender is said to be one of the known risk factor that is associated with cardiovascular disease. However, in diabetes the protection against the females for CAD is negated. The diabetic females are at higher risk for developing severe CAD when compared to males. The mean HOMA-IR in type 2 diabetic females and males without CAD was found to be 2.73 ± 0.68 and 2.11 ± 0.59 repetitively. Vonbank et al has demonstrated that insulin resistance in females is not associated with angiographically determined CAD it is only related to metabolic syndrome (384). The observation from the present study showed that females are having HOMA-IR value greater than 2.5. Inspite of high HOMA-IR values the type 2 diabetic females did not have significant CAD which was documented by cororary angiography. The findings of our study in relation gender is in line with an earlier observation by Vonbank et al.

Microalbuminuria is a well-established risk factor for CAD is known to be associated with coronary endothelial dysfunction. The prospective studies have shown that the an elevated levels of microalbumin is significantly correlated with coronary endothelial dysfunction in type 2 diabetes mellitus (385). However, the findings from longitudinal and cross sectional studies have shown that, insulin resistance is independently associated with development of microalbuminuria in type 2 diabetes mellitus (386, 387).
Since insulin resistance develop much before an onset of type 2 diabetes mellitus, it is likely that an increased level of insulin resistance contribute towards the development of microalbuminuria in type 2 diabetes mellitus which results in coronary endothelial dysfunction. In our study the mean microalbumin levels in subjects with HOMA-IR less than 2.5 was found to be 18.62 ± 11.28. Thus lower levels of microalbuminuria was found to be associated with favorable CAD profile in long standing diabetes.

The findings from kim et al, showed that a positive coronary remodelling was observed in individuals with HOMA-IR > 2.5 when compared to those with HOMA –IR < 2.5 (120). In this study by kim et al. Intravascular Ultrasound (IVUS) was used for the investigation of coronary artery remodelling (120). The observations from this present study are in lines with the results derived by kim et al. Thus individuals with high HOMA-IR (HOMA-IR > 2.5) are at increased for developing future cardiovascular events.

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). Since low levels of HOMA-IR is associated with no apparent CAD in long standing diabetes, the subjects with low IR may be managed conservatively without subjecting them for aggressive medications. However, this needs to be confirmed through a long term study.

**Hyperinsulinemia beyond a threshold as a predictor of Major Adverse Cardiac Events [MACE] at one year after Coronary Angiogram**

A substantial reduction in cardiovascular mortality and morbidity has been achieved in general population which is attributed to an improvement in treatment for cardiovascular risk factors and disease. However, the same magnitude of benefit has not been demonstrated in type 2 diabetes mellitus and the factors that are responsible for these new cardiovascular events have not been fully elucidated in this population.

Our study reveals that, an insulin level beyond a threshold of 20 µIU/ml is a significant predictor of new adverse cardiac events at one year in type 2 diabetic subjects, even adjusting for other potential risk factors.
In prospective study by UKPDS group it was observed no relation was found between insulin resistance and incidence of fatal or non-fatal MI, stroke and cardiovascular disease in a newly diagnosed type 2 diabetes population. They further concluded that insulin resistance is not a risk factor for cardiovascular disease (388). However, in this study group most of them did not have high insulin resistance. HOMA-IR was measured in an entire different population and insulin was not taken into consideration. It may be too early for the changes to been seen. Insulin resistance was measured shortly after diagnosis of diabetes, it is possible that insulin resistance stabilize after several years of diabetes and hence no correlation was observed, whereas in Verona diabetes study, it was demonstrated that insulin resistance was associated with the risk of cardiovascular disease in type 2 diabetes mellitus (10). The insulin resistance was measured at a mean time of 9.3 years after diagnosis of diabetes. This study is in line with the present study, where it is observed that hyperinsulinemia/insulin resistance was subsequently associated with adverse cardiac events at one year in type 2 diabetes mellitus.

Several large prospective studies have shown that hyperinsulinemia is associated with new cardiac events in general population (107,115, 389). In a prospective study, fasting immune reactive insulin levels beyond 20 µIU/ml was independently associated with an incidence of CAD in insulin treated diabetic cohort (108). The subjects with insulin levels greater than 20 µIU/ml had an adjusted 5 to 6 fold increased risk for developing CAD (108). Further, in a cross-sectional study it was observed that an insulin levels > 20 µIU/ml was independently associated with angiographically determined CAD (110).

The findings derived from our study are in relation to an earlier studies, and shows that insulin > 20 µIU/ml is not only associated with incidence of CAD, but also predicts adverse cardiac events at one year in type 2 diabetes mellitus. Our study provides an additional support for these observations. The threshold level for insulin has been very well demonstrated in our study. In our study, it is observed that the risk for predicting MACE was heighten by two to four fold beyond an insulin level of 20 µIU/ml, and below the threshold the risk for developing new cardiac events were lowered.

Inspite of undergoing successful coronary interventions the risk of developing new adverse cardiac events still remain high in type 2 diabetes mellitus. Prospective studies in type 2 diabetic population have shown that, it is the severity of the disease and the type of coronary
interventions that are mainly associated with the adverse cardiac outcomes in this population (390, 391).

The Medicine, Angioplasty or Surgery Study (MASS) on multivessel CAD showed that, the different treatment strategies did not influence the cardiac outcomes in type 2 diabetes mellitus during the first year follow-up (392). A five-year follow-up study in type 2 diabetic patients with the single vessel coronary stenting has shown that, the risk of adverse event is high in type 2 diabetes mellitus, which is irrespective of its severity of the disease (393). Further the risk of repeat revascularization was high only in the first year after single lesion stenting, but they were at increased risk for other clinical events including cardiac death and non-fatal MI over next four years (393).

In a subgroup analysis of FREEDOM trial, in type 2 diabetes mellitus with multi vessel CAD, it was observed that the rate of MACE was higher in insulin provisioning treatment group than in those who were restricted for insulin treatment, even after adjusting for clinical demographics, severity of the disease and revascularization treatment (390). Further, no significant difference was seen in the magnitude of PCI or CABG benefit in type 2 diabetic patients with insulin treatment group (390).

However, majority of these studies did not identify the sub-group who might be at high risk for developing future complications. It appears that these are the individuals who might be having an insulin levels greater than 20 µIU/ml and hence did not derive significant benefit even after successful revascularization procedures.

The findings from the present study shows that, an overall MACE rate in subjects with type 2 diabetes mellitus (24.04%) was higher in comparison to non-diabetes (12%). This concurs well with previous long term trials such as SYNTAX, CARDia, BARI 2D and FREEDOM (160-163). In a similar observation by Lourenço et al, the MACE rate in diabetic population following acute coronary syndrome (ACS) at one year was found to be 20.4%, where blood sugar levels > 130.5mg/dl was an independent predictor for MACE (164). But sub-group analysis based on sugar levels was not studied.

Interestingly in this study, the subgroup analysis based on threshold level for insulin levels showed that, MACE rate was significantly higher in those with Insulin > 20 µIU/ml [42.4 %
Discussion

when compared to insulin < 20 µIU/ml [10.2% (12)] (p < 0.001). The MACE rate in those with insulin < 20 µIU/ml [10.2% (12)] and non-diabetics [12% (9)] (p = 0.676) were found to be almost similar. This finding highlights that the type 2 diabetes is not a homogenous population, not all patients with type 2 diabetes mellitus and CAD would be at risk for developing adverse cardiac events, only particular sub-group appears to be at an increased risk for MACE. These are the individuals who are needed to be followed-up meticulously.

In this study, basal 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 regularly with aggressive medical management. Insulin levels up to 20 µIU/ml does not appear to produce complications in diabetics, and they seems behave as non-diabetics who may be spared with intense therapeutic management and follow-up.

Till now hyperinsulinemia was associated with occurrence of CAD, but findings from this study showed that it has a major implications in terms of cardiovascular outcomes. In clinical practice this threshold value is a practical tool. It helps to identify high risk groups and intensify management efforts. Treatment strategies for managing CAD, which include drugs which inhibit vascular remodeling, dual anti-platelet therapy, revascularization procedures etc. may be more useful in this subset.

**Importance of Threshold Level**

Hyperinsulinemia is a part of type 2 diabetes mellitus, anything above normal range for insulin is commonly seen in type 2 diabetes mellitus, and until it reaches certain high levels they do not seem to have risk for developing CAD complications.

In this present study, the threshold concept of insulin has been demonstrated. It is observed that, the risk for predicting severe and complex CAD and MACE was heightened beyond an insulin level of 20 µIU/ml [Figure 11 and 15], and below the threshold the risk for developing severe and complex CAD (SYNTAX score > 22) and adverse cardiac events were comparable to non-diabetics.

The complications encountered in type 2 diabetes mellitus seems to be associated with the threshold level of basal insulin. At normal physiological level of insulin, the metabolic
functions are mediated through phosphatidylinositol (PI) 3-kinase pathway, on the contrary the mitogenic action of insulin is mediated through mitogen-activated protein kinases (MAPK) pathway. In the case of insulin resistance, the phosphatidylinositol (PI) 3-kinase pathway is inhibited, while the MAPK pathway continues to function.

Based on the observations from this present study, it is proposed that the MAPK pathway might be activated beyond threshold level of insulin, which leads to fibrotic and proliferative changes in the vasculature, and that threshold levels for insulin may be beyond 20 µIU/ml. Insulin provisioning treatment strategy is less likely to be effective in subjects with insulin > 20 µIU/ml compared to insulin restricting strategies.

**Gender and Coronary Artery Disease in Type 2 diabetes Mellitus**

It has been observed that diabetic women are at higher risk of developing cardiovascular disease and adverse cardiac outcomes. Examinations of coronary angiogram shows severe coronary atherosclerosis in diabetic women when compared to diabetic men (76).

The Framingham study found that, incidence of cardiovascular disease was found to be three fold higher in women with type 2 diabetes mellitus (78). Subsequent study in a Finnish population with type 2 diabetes mellitus had reported that, incidence of coronary artery disease is 8 to 11 fold higher in women with type 2 diabetes mellitus (317). In a recent meta-analysis 44% greater relative risk of an incidence of CAD has been reported in women vs. men with diabetes (394).

However, conflicting results has also been reported, where gender did not show any significant difference in terms of cardiovascular risk. The CAD risk is equivalent in both the sexes in the presence of type 2 diabetes mellitus even after adjusting for potential cardiovascular risk factors (79, 395, 396).

The findings from this present study shows that, risk of severe CAD is same in both men and women with type 2 diabetes mellitus. The severity of CAD in male vs. female as measured by Gensini, SYNTAX and extent score was found to be the same. There was no significant difference between the median Gensini [34 (13, 58) vs. 30 (6, 50), p = 0.119], SYNTAX [12 (7, 21) vs. 11 (3, 18), p = 0.114] and extent score [20 (9.27, 34.29) vs. 18.93 (6.59, 32.02), p = 0.112] in diabetic men and women respectively.
Similar observation was also seen in our study with respect to adverse cardiac outcome at one year after coronary angiogram. The rate of adverse cardiac events were found to be same in both males and females with MACE rate of 24.6% and 22.7 % \( (p = 0.763) \) respectively.

The mean HOMA-IR among males and females \( (3.06 \pm 1.4 \text{ vs } 3.07 \pm 1.2, \ p = 0.821) \) were found to be similar. The fasting insulin levels also appeared to be same in both diabetic males and females \( (20.10 \pm 7.0 \text{ vs } 19.93 \pm 6.4, \ p = 0.792) \) respectively. Since HOMA-IR/hyperinsulinemia is same in both males and females, the loss of protection females had when they develop type diabetes mellitus appears to be explained by component of insulin resistance/ hyperinsulinemia.

Overall in this present study, sub group analysis based on gender, did not show any significant difference in terms of severity of CAD and adverse cardiac outcomes. The risk of cardiovascular compilations were found to be same in both men and women with type 2 diabetes mellitus. The similar CAD risk observed in this study could be attributable to small number of female study participants.

**Insulin Resistance vs. Insulin levels (Hyperinsulinemia)**

The Homeostasis model assessment of Insulin resistance (HOMA-IR) is a simple, less invasive and inexpensive popular technique used for the measurement of insulin resistance (135). The HOMA-IR has shown to correlate well with euglycemic glucose clamp technique which is a gold standard method for the measurement of insulin resistance (137). Inspite of good correlation with euglycemic clamp technique, the use of HOMA model is restricted by certain limitations.

The insulin resistance measured by HOMA is basically an ethnic specific. It would not be possible to compare HOMA-IR across different population and genetic background. A lot of clarity is needed in reporting HOMA values (137). Thus result reported in this study would be specific to only a particular subset of population which cannot be applicable to all.

However, in this study fasting insulin levels were also associated with severity of CAD and predicted adverse cardiac outcome at one after coronary angiogram. The fasting insulin levels have shown to correlate well with insulin resistance as measured by euglycemic clamp
technique (397). It is thus justifiable to use fasting insulin levels as a measure of insulin resistance in the epidemiological studies.

It is hypothesized that it is the elevated basal insulin levels that causes insulin resistance state in an individual. Hyperinsulinemia seems to be a driver for insulin resistance. Several in vitro and in vivo studies have demonstrated that basal insulin level beyond a threshold leads to generalized insulin resistance (398). In an in vitro study, where mice transfected with extra copies of human insulin gene showed a two threefold increase in basal insulin secretion. The hyperinsulinemia induced the resistance by desensitization of insulin receptor due to an elevated triglyceride levels and hyperinsulinemia (398).

Similar results were observed with in vivo studies, where administration of high doses of insulin have confirmed basal hyperinsulinemia leading to insulin resistance (398). An acute rise in insulin is stimulatory, but continuous rise in insulin levels desensitizes the target cells through various mechanisms, including effects at the level of the insulin receptor and at several sites beyond the receptor leading to generalized insulin resistance. Thus, hyperinsulinemia is a leading factor in the induction of insulin resistance.

It is thus better to compare insulin levels than the HOMA-IR. In this context, our observations suggest the possibility of using insulin as an indicator of high risk CAD across different population.
Key findings observed from this present study in relation to other studies

- It is known that insulin resistance/hyperinsulinemia develops much before the development of type 2 diabetes mellitus and is associated with occurrence and pathogenesis of CAD. But in this present study, it is observed that insulin resistance/hyperinsulinemia is much more than an initiation factor for CAD. It is strongly correlated and associated with severity of CAD.

- Type 2 Diabetes Mellitus is said to be coronary artery equivalent. But not all the patients with type 2 diabetes mellitus develop macrovascular complications. Only a particular subgroup of patients are at risk of developing cardiovascular complications. Identifying these high risk group is important. In this study, it was observed that individuals with HOMA-IR > 3.4 and insulin > 20 µIU/ml are the ones who appear to be at risk of developing severe and complex CAD. Those with HOMA-IR < 2.5 did not have significant CAD. Thus type 2 diabetes is not a homogenous disease.

- Similarly, it was observed that only particular sub group of type 2 diabetic patients were at risk of developing adverse cardiac events at one year after undergoing coronary angiogram. Insulin > 20 µIU/ml was significantly associated with adverse cardiac outcome in these cohort. These are the individuals who are needed to be followed-up meticulously.

- It is not just mere hyperinsulinemia/insulin resistance is a possible risk factor for cardiovascular mortality and morbidity in type 2 diabetes mellitus. In this study, a clear risk of hyperinsulinemia/insulin resistance appears to be at a threshold level of 20 µIU/ml and HOMA-IR 3.4 for cardiovascular complications.

- The macrovascular complications seems to develop much earlier in type 2 diabetes when compared to microvascular complications. There appears to be a specific time frame for the development of CAD in type 2 diabetes mellitus. The findings from the study showed that the severity of CAD is known to be time specific. A severe cardiovascular complications was seen between 5 to 10 years of type 2 diabetes mellitus, whereas mild to moderate CAD was observed in less than 5 years of type2 diabetes mellitus. Beyond ten years severity of the disease appears to be constant where irreplaceable damage has already occurred. Thus the window of opportunity of initiating optimal therapeutic strategy is
restricted under 5 years of type 2 diabetes mellitus. The peak effect of insulin resistance/hyperinsulinemia is likely set up after 5 years of diabetic duration resulting in malignant CAD in more than 5 years of type 2 diabetes mellitus.

- Only the meta-analysis of large clinical trials have shown the cardiovascular benefit in type 2 diabetes mellitus. However, individual clinical trials have shown that near glycemic control and control of other conventional risk factors has not reduced the macrovascular complications in type 2 diabetes mellitus. The presence of hyperinsulinemia/insulin resistance appears to be a residual risk factor.

- Intense medical therapy initiated during an early stages of type 2 diabetes mellitus seems to be beneficial in reducing cardiovascular complications. Optimal medical therapy is an appropriate initial strategy in type 2 diabetic patients with mild to moderate coronary artery disease. The same magnitude of benefit is not seen in type 2 diabetic patients with severe coronary artery disease. Thus identification of these high risk individuals at an earlier stages of type 2 diabetes mellitus is important.

- The recent guidelines from American Diabetes Association have suggested an individualized treatment strategies should be implicated based on patient characteristics and perceived risk and benefits towards management type 2 diabetes mellitus. However, the present day equation based assessment of CV risks is not sufficient to individualize the treatment for type 2 diabetes mellitus. The hyperinsulinemia/insulin resistance likely to play a key role individualizing the treatment for type 2 diabetes mellitus. The unique evolution of insulin resistance helps to identify the high risk individuals who are susceptible for developing severe CAD from the beginning itself.