CRITICAL APPRAISAL

OVERVIEW OF THE STUDY:

INTRODUCTION:

This study was conducted by Toshio Hayashi et al in 2011. According to this study, elderly patients who are suffering from type from type 2 Diabetes Mellitus are more prone to the increased risk of occurrence of IHD and CVA. Diabetes can seriously jeopardize the life span of an individual up to significant extent. Thus the major concern of investigators was the identification and establishment of association between these risk factors and rate of mortality in the elderly patients suffering from diabetes.

AIMS AND OBJECTIVES:

Major aim of this study was to disclose the relationship and extent of effect of age, gender, insulin and blood glucose status on the ischemic heart disease (IHD) and stroke (CVA).

MATERIALS AND METHODS:

This study was a nationwide observational cohort study and conducted in Japan. This is also known as Japan – CDM (Japan Cholesterol and Diabetes Mellitus Investigation) and in this study 4014 Japanese individuals with diabetes mellitus were selected. For patient selection, 40 institutions of Japan were taken into consideration. This research was conducted from September 2004 to March 2005. Few patients were excluded from the study according to the inclusion and exclusion criteria designed by the authors. In this study authors have taken precautions to avoid the chances of biases and for the generalization of results. Thus, in this direction a predesigned exclusion criterion was utilized for the patient selection. This criterion has taken following things into consideration: Those patients were excluded from the study who had experienced previous myocardial infarction or cerebrovascular accidents, complications of serious heart disease, serious hepatic or renal disease (liver cirrhosis, renal failure requiring hemodialysis, malignancy,

chronic diseases with the chances of poor prognosis and the recommendation of treating physician.

In this prospective multicentre longitudinal cohort study, 4014 patients were admitted. To avoid any gender discrimination appropriate ratio of females and males has been taken into account. Out of 4014 patients, 1936 women and 2078 men were included in this study. Mean age of all participants were 67.4 ± 9.5 years, range of their age was 35-83 years and median of their ages was 70.4 years. For effective analysis of results follow up period was also planned by the authors. Rate of one year follow up was 98.2% and second year follow up rate was 92.3%.Primary and secondary endpoints were also pre decided. Primary endpoints considered were the occurrence of CVA and IHD. Secondary endpoints were considered as those cases of sudden death which did not involve myocardial infarction, transient ischemic attack, subarachnoid hemorrhage and all-cause mortality.

To avoid any legal controversy informed consent was already taken by every participant. For the evaluation of plasma lipid levels, blood glucose levels and HbA1C levels blood samples were taken from the participants during the same month each year. In this study diagnostic criteria for T2D of the American diabetes association and guidelines of the Japan Atherosclerosis Society, which state that LDL values should be less than 120 mg/dL and HDL values should be higher than 40 mg/dL in diabetic individuals were used.

STATISTICAL ANALYSIS:

Statistical analysis was performed using JMP (version 7, SAS Institute Inc., Cary, NC) and results were presented in the form of means ± SD (standard deviation). Categorical comparison of data was performed using chi-square test and Fisher's exact test. Mann-Whitney U test was used to test the differences in the means of continuous measurements. A univariate logistic regression analysis and multiple logistic regression analysis were utilized to identify risk factors related to the increased incidence of IHD and CVA. Furthermore, to confirm the relationship between IHD, CVA and different variables stepwise regression analysis test was performed.

To establish the association between age and glycemic control participants were divided into following groups:

1) NF: Patients under 70 years of age with fair glycemic control (n = 870)

2) NP: patients under70 years of age with poor glycemic control (n = 1,072);

3) OF: patients over 70 years of age with fair glycemic control (n = 923)

4) OP: patients over 70 years of age with poor glycemic control (n = 1,149).

Again they were divided into 4 groups based on the gender and hemoglobin A1C levels ($\leq$ 7.0and > 7.0%). These groups are:

1) MF: Male patients with glycemic control (n = 1063)

2) MP: males with poor glycemic control (n = 950)

3) FF: females with fair glycemic control (n = 859)

4) FP: females with poor glycemic control (n = 1,142).

RESULTS AND DISCUSSION:

Results of this study concluded that 152 cerebrovascular episodes and total 17 deaths occurred in the study duration of 2 years. Rate of the occurrence of IHD and CVA was 7.9and 7 .2 per 1000 person – years, respectively. Further results are as follows:

Results of multiple regression analysis which are useful in examining the association between risk of IHD and clinical variables for all 4 groups divided by age and glucose control: In patients aged 70 years or younger, according to univariate analysis higher systolic blood pressure, higher LDLC and lower HDL - C were the main risk factors associated with IHD. Further details by the multiple regression analysis indicated that only systolic blood pressure is significantly associated with risk. In Patients of more than 70 years age, lower diastolic blood pressure was associated with IHD risk among patients in the OF group. In OP group insulin usage was associated with IHD risk.

Results of multiple regression analysis which are useful in examining the association between risk of CVA and clinical variables for all 4 groups divided by age and glucose control: In

patients aged 70 years or younger higher HbA1C levels are significantly associated with risk of cerebrovascular problems in NF group. In NP group lower HDL- C and longer diabetes duration were associated with risk. In Patients of more than 70 years age, lower HDL-C levels are associated as risk factor in OF and OP group and insulin usage was associated with CVA risk in OF group.

Results of stepwise regression analysis: According to stepwise regression analysis higher systolic blood pressure, lower HDL-C and higher LDL-C were associated with IHD risk in the NF group. Insulin use and age were associated with IHD risk in the OP group. Higher levels of hemoglobin A1C were associated with cerebrovascular risk in the NF group and lower HDL-C and the duration of diabetes were associated with CVA risk in the NP group. Insulin use was associated with CVA risk among patients in the OF group. Lower HDL-C levels tended to be associated with CVA in the OF group and the OP group although these associations were not statistically significant.

Results of association between insulin usage and risk of IHD and CVA diseases: In patients aged 70 years or younger, usage of insulin is associated with decreased chances of occurrence of IHD and CVA diseases but in cases over 70 years insulin tended to have an increased incidence of CVA. In MP group insulin usage was associated with IHD risk and in FP group risk of cerebrovascular problems increase.

Results of multiple regression analysis which are useful in examining the association between risk of IHD and clinical variables for all 4 groups divided by gender and glucose control: In case of male patients, risk of increased IHD is associated with high systolic blood pressure and fair glycemic control. Insulin usage is also associated with IHD risk in males. In case of female patients IHD risk is associated with short diabetic history.

Results of multiple regression analysis which are useful in examining the association between risk of cerebrovascular disease and clinical variables for all 4 groups divided by gender and glucose control: In case of male patients, cerebrovascular problems were not associated with any variables and in case of female patients CVA was associated with short duration of diabetic history. Insulin usage was also associated with this disease in females.

CONCLUSION:

Conclusions of this study indicated that numerous risk factors are associated with the occurrence of CVA and IHD disease. These factors are mainly age, gender and glycemic control status of the patients. Among the diabetics of elderly age, insulin usage is associated with the prevention of IHD but on the other hand it mediates the occurrence of CVA in patients. Several investigations have been conducted in this context and results of those previous investigations including this one suggests that the insulin should be used for the diabetes control but its level should be in control to prevent the chances of CVA in elderly patients.

Analysis:

To evaluate the success of this study and to prepare the effective background for the future researches this study has been critically analyzed successfully to gather both positive and negative information in this context.

Authors have drawn the attention towards a well stated and valid research question which is mainly concerned with the health of elderly diabetic patients. This research question effectively evaluates the impact of health related problems and their risk factors. It determines the magnitude of problem in a significant manner and also proposes the effective interventions for the better treatment therapies.

Type of study selected for this research is appropriate in the given context. This is a prospective longitudinal cohort type of study and it suites according to the structure of research in an appropriate manner.

To avoid any bias related to sample size and gender discrimination author selected a large sample size and ratio of males and females in this study is appropriate. A predesigned inclusion and exclusion criteria were also used in this study to avoid any confounding factors and for the generalization of the results.

Measurement of outcomes has been performed by the standard statistical tests and different other tests (already described above) have been used to identify and establish the association between risk factors and IHD as well as CVA. All relevant outcomes have been assessed and there is no measurement error in this study.

To avoid any sort of confounding bias authors have taken all factors into consideration. Sampling method used in this study was randomized. Double blinding was used in the method of sample collection. This study was conducted throughout Japan and numerous (approximately 40) institutions were involved in this research work. Selection bias was not present in this study. Thus there were no chances of bias in external validity.

To avoid chances of bias in internal validity, subjects were assigned to different groups according to the requirements. All participants were divided into total 8 groups for ease in the measurement of risk factors. Out of 8 groups 4 groups were divided according to the age and glycemic status and rest 4 groups were divided according to the gender and glycemic status. Follow up period was also specified for all participants. One-year and two-year follow-up rates were 98.2% and 92.3%, respectively.

Results of this study were significant both in the clinical and social manner. These results and different findings of this study prepared the background for the future researches for the sake of elderly diabetic patients.

This study was completely ethical and any legal, social or unethical controversy was not related to this research work.

Important conclusion drawn by the author established the significant relation of various factors like age, gender, glycemic control and insulin with the occurrence of ischemic heart disease (IHD) and stroke (CVA).

Although author have taken necessary steps to prevent bias and for the generalization of results of this study yet few limitations are also associated with this work. Treatment of diabetes in this study was based on the data recorded at the time of enrollment. All patients were followed for 2 years, and authors did not find a successful way of analyzing the detailed mechanisms underlying insulin therapy as the risk factor of IHD and CVA.

Further studies should be conducted in this context to overcome the barriers and pitfalls of this study and to explore different methods by which adverse effects of insulin can be controlled without affecting its beneficial outcomes on the glycemic status.