Treatment Adherence and Incidence of Coronary Heart Disease in Type 2 Diabetes Mellitus Patients

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Abstract
Previous studies showed that uncontrolled blood sugar and long-term use of several types of antidiabetic could increase the risk of coronary heart disease (CHD). This study aimed to compare the incidence of CHD in type 2 diabetes mellitus (T2DM) patients showing treatment adherence and non-adherence behavior over four years. This was a retrospective cohort study with data sets obtained from the Bogor Cohort Study of Non-Communicable Disease Risk Factors. All study subjects were not diagnosed with CHD at the beginning of the study. The sample was divided into two groups: one had adhered to treatment from health centers and followed the treatment instructions (adherent group), while the other had not followed the treatment instructions (non-adherent group). Of 5,690 subjects, 276 were eligible for this study (84 in the adherent and 192 in the non-adherent group). The incidence of CHD in the non-adherent group was 2.3% higher than in the adherent group (p-value = 0.564) and had a 1.7 times greater risk of developing CHD, but not statistically significant (adjusted HR = 1.739; 95% CI = 0.673-4.490). The non-adherent T2DM patients had a greater risk of developing CHD than adherent T2DM patients.

Keywords: coronary heart disease, diabetes mellitus, treatment adherence

Introduction
Coronary heart disease (CHD) is the leading cause of death in diabetes.¹ Diabetes mellitus (DM) is associated with a two to four-fold increased risk of death from heart disease, and more than 70% of patients with DM aged more than 65 years will die from some form of heart disease or stroke.² This is because insulin resistance, a hallmark of type 2 diabetes mellitus (T2DM), is associated with a group of metabolic and biochemical disorders, including hyperglycemia, hypertension, atherogenic dyslipidemia, inflammation, endothelial dysfunction, and impaired fibrinolysis.¹ The type 1 diabetes mellitus (T1DM) and T2DM lead to increased atherosclerotic cardiovascular disease (ASCVD) incidence. There is strong evidence to suggest a greater risk of ASCVD in dysglycemic conditions. In addition, an 11%-16% increase in the incidence of cardiovascular disease has been reported for every 1% increase in HbA1c.³

On the other hand, the incidence of CHD is also associated with the drugs used to treat T2DM. Li, et al.,⁴ conducted an 11-year observation of 4,902 women with diabetes with an average age of 68. They found that long-term use of sulfonylureas was significantly associated with a higher risk of developing CHD.⁴ Another study comparing the safety of monotherapy with sulfonylureas and metformin concluded that most male patients who started treatment of diabetes mellitus with sulfonylureas had a higher risk of heart failure and death from cardiovascular disease compared to those who began treatment with metformin.⁵ According to a study by Herman, excessive use of insulin could be a predisposing factor for inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure, and arrhythmias. This study supported the findings of a large-scale evaluation showing that insulin therapy had a poorer short- and long-term safety profile than many other antidiabetic therapies.⁶

Based on the data above, both uncontrolled blood sugar and long-term use of several types of antidiabetic drugs have the potential to increase the risk of CHD.³-⁶ This can be a severe problem for patients with diabetes mellitus because both treatment and no treatment can increase the risk of CHD. Adherence to treatment and the right choice of antidiabetic drugs will protect patients from possible complications. Population-based scientific research and long-term observations related to the adherent and non-adherent behavior of patients with dia-

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Received: October 31 2021
Accepted: January 31, 2022
Published: May 31 2022

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betes mellitus related to CHD in middle-income countries such as Indonesia are still very limited. The Non-Communicable Disease Risk Factors in Bogor (the Penyakit Tidak Menular/PTM Bogor Cohort Study) was a population-based study managed by the National Institute of Health Research and Development, Ministry of Health of the Republic of Indonesia. This study was conducted as an initial study to assess the treatment adherence behavior of T2DM patients and to assess whether there was a difference in the risk of coronary heart disease after four years of observation.

Method

This study was conducted as part of a long-term prospective cohort study by the National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia Cohort Study of Non-Communicable Disease Risk Factors (the PTM Bogor Cohort Study), in five subdistricts of Bogor City, West Java Province, over the period of 2011 to 2018. This study used a retrospective cohort design because the study was conducted in 2019, while the study data was taken from 2011 to 2018..Initial observations in the study were determined when patients were diagnosed with diabetes mellitus and free from a CHD diagnosis at baseline, and had a complete blood count. The diagnostic criteria for T2DM were based on the American Diabetic Association (ADA) criteria and local criteria by Perkumpulan Endokrinologi Indonesia (PERKENI). These were based on fasting blood glucose (FBG) levels of ≥126 mg/dL or post-prandial blood glucose (PPBG) ≥200 mg/dL and/or classical symptoms. The patients were divided into two groups; one group had adhered to the treatment prescribed by health centers and had followed the treatment instructions (adherent group), while the other had not followed the treatment instructions (non-adherent group). They were then observed over four years to observe the differences in the incidence of coronary heart disease. If there was a change in treatment behavior, from adherence to non-adherence, or vice versa, then the patient was dropped from the study. In addition, patients who did not have complete blood tests in the fourth year or were considered absent (loss to follow-up) were also excluded.

The sampling technique used in the PTM Bogor Cohort Study was dynamic sampling, while this study used purposive sampling techniques. The baseline data was taken from the 2011/2012 and 2013/2014 datasets, and the final data after follow-up was taken from the 2015/2016 and 2017/2018 datasets. The diagnosis of T2DM was made by doctors from the PTM Bogor Cohort Study Team based on the patient’s blood examination results. The diagnosis of CHD was determined from the results of an electrocardiogram (ECG) and verified by three cardiologists.

Calculation of the sample size based on the Adequacy of Sample Size Determination in Health Studies World Health Organization (WHO) guidelines to test the hypotheses related to the two different populations was as in the following formula. The minimum sample size for each group was 130, meaning that there were two groups, the minimum study sample size was 260. The sample size was determined using the Chi-square Test. The authors determined the criteria for the increasing or non-increasing changes based on the average change in each clinical characteristic. This study assessed the relative risk (RR), and the data analysis used Cox regression. In general, Cox regression is used for survival analysis and can produce HR (Hazard Ratio) values. In Cox regression analysis, if the time required for the outcome to occur is the same, the HR value is the same as the RR value.

Formula 1. Sample Size Estimation

\[ n = \left( \frac{z_{1-\alpha/2} \sqrt{2p(1-p)} + z_{1-\beta} \sqrt{p_1(1-p_1) + p_2(1-p_2)}}{\Delta} \right)^2 \]

Notes:
- \( \alpha = \) The standard value of the normal distribution, set at 5%
- \( Z_{1-\alpha/2} = \) The same value, with a significant degree of 1.96
- \( Z_{1-\beta} = \) The same value as the desired power of 0.84
- \( p = (p_1 + p_2)/2 \)
- \( p_1 = \) The proportion of T2DM patients who take diabetes medication and were diagnosed with CHD = 0.3812
- \( p_2 = \) The proportion of T2DM patients who do not take diabetes medication and were diagnosed with CHD

The outcome data in the study were divided into two categories, increasing and not increasing, and analyzed using the Chi-square Test. The authors determined the criteria for the increasing or non-increasing changes based on the average change in each clinical characteristic. This study assessed the relative risk (RR), and the data analysis used Cox regression. In general, Cox regression is used for survival analysis and can produce HR (Hazard Ratio) values. In Cox regression analysis, if the time required for the outcome to occur is the same, the HR value is the same as the RR value.

Result

This study is part of the PTM Bogor Cohort Study by the National Institute of Health Research and Development, Ministry of Health of the Republic of Indonesia. The sampling technique used was dynamic sampling. The PTM Bogor Cohort Study patients were monitored for clinical parameters every two years. Authors took patient data from observations over four years to observe differences in the incidence of CHD in diabetic patients with adherent and non-adherent behavior related to treatment. Out of 5,690 subjects, 541 were eligible at the baseline. After four years of observation, 276 eligible patients remained, consisting of 84 subjects who had adhered to treatment (50.4%) and 192 (69.6%) who had not and were therefore untreated (Figure 1). Characteristics of the T2DM patients are presented in Table 1.
The main factors that cause CHD were divided into two groups, the ones that can be controlled (modifiable risk) and ones that cannot be controlled (non-modifiable risk). Controllable risk factors included hypertension, high blood cholesterol levels, smoking, diabetes, obesity, lack of physical activity, unhealthy diet, and stress. Factors that could not be controlled were age (aging could increase risk), sex (men were generally at greater risk of coronary artery disease), family history, and race.14

The study subjects were mostly women (73.8% in the adherent group and 72.4% in the non-adherent group). The majority of whom were under the age of 60 years with an elementary education level. There was no significant difference between any of the baseline characteristics concerning the adherent and non-adherent groups (p-value>0.05), which means that all the T2DM patients had similar characteristics. The proportion of patients with smoking and non-smoking habits was almost the same. Smoking habit data was only taken in the 4th year to show smoking habits, so it could not be continued until a multivariate analysis was conducted. Data on the physical activity of T2DM patients showed almost the same number of patients who were quite active and less active.

Table 1 shows the differences in the changes in clinical parameters after four years of observation, including changes in systolic blood pressure, diastolic blood pressure, PPBG, total cholesterol, low density lipoprotein.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Adherent (n = 84)</th>
<th>Non-Adherent (n = 192)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>22 (26.2)</td>
<td>53 (27.6)</td>
<td>0.924a</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>62 (73.8)</td>
<td>139 (72.4)</td>
<td></td>
</tr>
<tr>
<td>Age in the 4th year</td>
<td>&lt;60 years</td>
<td>48 (57.1)</td>
<td>122 (63.5)</td>
<td>0.384a</td>
</tr>
<tr>
<td></td>
<td>≥60 years</td>
<td>36 (42.9)</td>
<td>70 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Education level in the 4th year</td>
<td>Further education</td>
<td>29 (34.5)</td>
<td>80 (41.7)</td>
<td>0.526a</td>
</tr>
<tr>
<td></td>
<td>Elementary education</td>
<td>55 (65.5)</td>
<td>112 (58.3)</td>
<td></td>
</tr>
<tr>
<td>Employment in the 4th year</td>
<td>Employed</td>
<td>79 (94.0)</td>
<td>187 (97.4)</td>
<td>0.308a</td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>5 (6.0)</td>
<td>5 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Smoking status in the 4th year</td>
<td>Do not smoke</td>
<td>36 (42.9)</td>
<td>99 (51.6)</td>
<td>0.185b</td>
</tr>
<tr>
<td></td>
<td>Smoked at some time</td>
<td>10 (11.9)</td>
<td>12 (6.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoker</td>
<td>38 (45.2)</td>
<td>81 (42.2)</td>
<td></td>
</tr>
<tr>
<td>Physical activity in the 4th year</td>
<td>Moderately active (METs)</td>
<td>41 (48.8)</td>
<td>97 (50.3)</td>
<td>0.896a</td>
</tr>
<tr>
<td></td>
<td>Less active (METs)</td>
<td>43 (51.2)</td>
<td>95 (49.5)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP changes</td>
<td>Increased</td>
<td>15 (17.9)</td>
<td>44 (22.9)</td>
<td>0.433a</td>
</tr>
<tr>
<td></td>
<td>No Increase</td>
<td>69 (82.1)</td>
<td>148 (77.1)</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP changes</td>
<td>Increased (&gt;14.98 mmHg)</td>
<td>8 (9.5)</td>
<td>36 (18.8)</td>
<td>0.080a</td>
</tr>
<tr>
<td></td>
<td>No Increase (14.98 mmHg)</td>
<td>76 (90.5)</td>
<td>156 (81.3)</td>
<td></td>
</tr>
<tr>
<td>PPBG change</td>
<td>Increased</td>
<td>16 (19)</td>
<td>25 (13)</td>
<td>0.266a</td>
</tr>
<tr>
<td></td>
<td>No Increase</td>
<td>68 (81)</td>
<td>167 (87)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol change</td>
<td>Increased</td>
<td>19 (22.6)</td>
<td>41 (21.4)</td>
<td>0.940a</td>
</tr>
<tr>
<td></td>
<td>No Increase</td>
<td>65 (77.4)</td>
<td>151 (78.6)</td>
<td></td>
</tr>
<tr>
<td>LDL changes</td>
<td>Increased</td>
<td>18 (21.4)</td>
<td>33 (17.2)</td>
<td>0.505a</td>
</tr>
<tr>
<td></td>
<td>No Increase</td>
<td>66 (78.6)</td>
<td>159 (82.8)</td>
<td></td>
</tr>
<tr>
<td>HDL Change</td>
<td>Increased</td>
<td>22 (26.2)</td>
<td>39 (20.3)</td>
<td>0.355a</td>
</tr>
<tr>
<td></td>
<td>No Increase</td>
<td>62 (73.8)</td>
<td>153 (79.7)</td>
<td></td>
</tr>
<tr>
<td>BMI Change</td>
<td>Increased</td>
<td>19 (22.6)</td>
<td>56 (29.2)</td>
<td>0.328a</td>
</tr>
<tr>
<td></td>
<td>No Increase</td>
<td>65 (77.4)</td>
<td>136 (70.8)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: the above data is expressed in amount (n) and percentage (%) terms, BP = Blood Pressure, PPBG = Post-Prandial Blood Glucose, LDL = Low Density Lipoprotein, HDL = High Density Lipoprotein, BMI = Body Mass Index.
(LDL), high density lipoprotein (HDL), body mass index (BMI), and hypertension in each group. There was no significant difference in the proportion of patients who had experienced changes in the clinical parameters in the two groups. Prior to the final multivariate analysis, the author performed a bivariate analysis to compare the proportion of adherents and non-adherents in relation to the incidence of CHD after four years of observation.

The main finding of the study was that there was a higher incidence of CHD in the non-adherent group (9.4%) than in the adherent group (7.1%), but not at a significant level (p-value = 0.564) (Table 2). In addition, the adherent group had a non-CHD level of 92.9%, higher than the non-adherent group, whose level was 90.6%. This shows that the non-adherent group had a 2.3% greater proportion of CHD compared to the adherent group and had a 1.3 times greater chance of developing CHD.

The analysis of the determining confounding variables was based on the delta HR value. If the HR delta is greater than 10%, it will be considered a confounding variable in the final analysis. There are variables with HR values above 10%, which is the LDL change variable. The selection of confounding variables was also made based on a theoretical study of the variables most likely to influence the relationship between the independent and dependent variables. Changes in physical activity became a variable that was selected as a confounding variable. In addition, because CHD is a degenerative disease in which age and sex are modifiable risk factors, sex and age were added as control variables.

**Discussion**

This retrospective cohort study aimed to assess the effect of treatment non-adherence on the incidence of CHD in T2DM patients in Indonesia during a 4-year follow-up period. The main finding of the study was that the non-adherent group had a 2.3% greater level of CHD than the adherent group and a 1.3 times greater chance of developing CHD. One reason for this is that the main purpose of using antidiabetic drugs is to lower blood sugar levels. Kaaffah, et al. conducted a study of T2DM patients in the PTM Bogor Cohort Study, which showed that T2DM adherent group patients could make a three-fold reduction in their PPBG levels compared to the non-adherent group. In the non-adherent group, the risk of hyperglycemia was one of the causes of the accelerated ASCVD observed in patients with diabetes mellitus. Insulin resistance and insulin deficiency in the non-adherent group could also cause hyperglycemia, which could increase the production of reactive oxygen species (ROS), protein kinase C, and free fatty acids, which in turn could increase the production of inflammatory mediators such as tumor necrosis factor (TNF)-α and interleukin-1, allowing the formation of atherosclerosis, which would develop into CHD. Blood sugar control was essential for the patients in the T2DM PTM Bogor Cohort Study to prevent the occurrence of CHD. This situation was in

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Variable</th>
<th>Category</th>
<th>HR</th>
<th>p-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherent behavior</td>
<td>Non-Adherent</td>
<td>1.312</td>
<td>0.564</td>
<td>0.321–3.306</td>
<td></td>
</tr>
<tr>
<td>Adherent (Ref)</td>
<td>Non-Adherent</td>
<td>1.739</td>
<td>0.253</td>
<td>0.673–4.490</td>
<td></td>
</tr>
</tbody>
</table>

Notes: HR = Hazard Ratio, CI = Confidence Interval, LDL = Low Density Lipoprotein, *p-value<0.05
acCORDANCE WITH A PREVIOUS META-ANALYSIS STUDY IN THE AMERICAN HEART JOURNAL, WHICH ANALYZED EIGHT RANDOMIZED CONTROL TRIALS OF 1,800 PATIENTS WITH T1DM, AND SIX RANDOMIZED CONTROL TRIALS OF 4,472 T2DM PATIENTS, CONCLUDING THAT EFFORTS TO IMPROVE GLYCEMIC CONTROL COULD REDUCE MACROVASCULAR EVENTS, INCLUDING BOTH T1DM AND T2DM.16

This study showed that the non-adherent group had a 1.7 times greater risk of developing CHD than the adherent group after controlling for changes in LDL and physical activity, which means that the adherent group tended to have some protection against the incidence of CHD, even not statistically significant. A study conducted by Fung, et al.,17 involving 3,400 patient pairs, aimed to evaluate the effect of metformin monotherapy on all-cause mortality and cardiovascular disease. The conclusion of the study showed that T2DM patients who started metformin monotherapy showed improvements in many clinical parameters and reductions in all-cause mortality and CVD incidence compared to lifestyle modification alone. Li, et al.,4 stated that the use of sulfonylurea antidiabetic drugs could lead to a higher risk of CHD and cardiovascular death compared to metformin. Gliclazide and glimepiride are associated with a lower risk of all-cause and cardiovascular death compared with glibenclamide.18 In addition, high daily insulin use in patients with T2DM is associated with an increased risk of cardiovascular events.19 This shows that the type of antidiabetics used by patients is an essential variable in establishing the specific cause of CHD incidence associated with antidiabetics. This study was unable to analyze this because of the unavailability of drug data.

Several previous studies linking diabetes and cardiovascular events have shown that the duration of diabetes significantly affects cardiovascular events. The Framingham Heart Study conducted a 12-year follow-up of 588 diabetic patients and reported a 1.38-fold higher risk of coronary heart disease and a 1.86-fold higher risk of cardiovascular death for each 10-year increase in diabetes duration.20 In addition, analysis conducted for the British Regional Heart Study showed that only diabetes with a period of more than 10 years equates to the risk of coronary heart disease.21 These two studies showed that it took more than ten years to analyze the relationship between diabetes and CHD. As this study was conducted over less than ten years, this may result in the absence of statistically significant results. However, this study can still be used as an initial description to assess the relationship between the adherent behavior of T2DM patients and CHD incidence.

This study also showed that higher LDL levels could increase CHD risk by 3.5 times. This result is consistent with a study conducted by Ference, et al.,22 which assessed whether the association between LDL and AS-CVD met the criteria for causality by evaluating evidence from genetic studies, prospective epidemiological cohort studies, Delian randomization studies, and randomized trials involving more than 2 million patients and more than 150,000 cardiovascular events. However, the results of this study are consistent with and support a variety of previous clinical and genetic studies that have clearly demonstrated that elevated LDL may increase the risk of ASCVD. In addition, according to Arsana, et al.,23 as well as LDL, an increase in total cholesterol, triglyceride levels, and a decrease in HDL also play an important and related role in the process of atherosclerosis. Besides, this study also showed that increased physical activity lowers the risk of CHD by 78%. This result was reinforced by the study conducted by Setyaji, et al.,24 in 2018 involving 374,506 women and 347,823 men aged over 15. Patients who did not engage in strenuous activity or did less than 80 minutes of exercise per week were found to have a higher prevalence of CHD than those who were much more active (p-value<0.001).24

There are several limitations to this study. It employs a retrospective cohort study design and uses secondary data. The authors could not control the state and quality of the data that enumerators previously collected in the role of interviewers. There are no detailed data on types of antidiabetic drugs or on drug use compliance which could affect the study results. The authors suggest that the National Institute of Health Research and Development of the Ministry of Health of the Republic of Indonesia add questions in the PTM Cohort Bogor Study questionnaire about common drugs consumed by patients. In addition, this preliminary study was conducted over four years and needed to be continued with observations over a more extended period. Given the important findings in this study, the researchers suggested that the Indonesian government needs to focus on improving Indonesian T2DM patients’ adherence to treatment.

Conclusion

In this study, the number of non-adherent T2DM patients was higher than the adherent. After being observed over four years, the adherent and non-adherent groups did not differ significantly in CHD incidence. Changes in LDL and physical activity were selected as confounding variables and significant contributing variables to the incidence of CHD. This is an essential consideration for T2DM patients to control LDL levels, physical activity, and medication adherences to avoid CHD.

Abbreviations

CHD: Coronary Heart Disease; T2DM: Type 2 Diabetes Mellitus; DM: Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; ASCVD: Atherosclerotic Cardiovascular Disease; PTM: Penyakit Tidak Menular; ADA: American Diabetic Association; PERKENI:

Ethics Approval and Consent to Participate
This study has received ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia, with number KET-934/UN2.F1/ETIK/PPM.00.02/2019, and has received approval for data collection through a statement letter number 05081901-044 from the Head of the Data Management Laboratory, the National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia.

Competing Interest
The author declares that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials
This study has received approval for data collection through a statement letter number 05081901-044 from the Head of the Data Management Laboratory, the National Institute of Health Research and Development, Ministry of Health of the Republic of Indonesia.

Authors’ Contribution
ASB conceptualized, designed, and prepared the initial draft and framework, analyzed and interpreted the data. RS and WR conceptualized, designed, determined the methodology, supervised, wrote, reviewed, and edited the manuscript. RS also contributed to funding acquisition. PS conceptualized, designed, and determined the methodology.

Acknowledgment
The authors are grateful to the Ministry of Research and Technology or National Research and Innovation Agency of the Republic of Indonesia for giving financial support through PDUPT Grant No. NKB-064/UN2.RST/HKP.05.00/2021. This paper has been presented at the 16th APRU Multi-Hazards Symposium 2021 hosted by Disaster Risk Reduction Center Universitas Indonesia in collaboration with the Association of Pacific Rim Universities.

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