Kesmas

Volume 17
Issue 2 *May*

Article 3

5-31-2022

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

Ahmad Sahlan Baniu
Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia, alanlowus@gmail.com

Rani Sauriasari
Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia, rani@farmasi.ui.ac.id

Woro Riyadina
National Institute of Health Research and Development, Ministry of Health of the Republic of Indonesia, Jakarta, Indonesia, w.riyadina02@gmail.com

Pradana Soewondo
Division of Endocrinology, Department of Internal Medicine, Dr. Cipto Mangunkusumo National Referral Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia; Metabolic, Cardiovascular, and Aging Cluster, The Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, soewondops@yahoo.com

Recommended Citation

Baniu AS , Sauriasari R , Riyadina W , et al. Treatment Adherence and Incidence of Coronary Heart Disease in Type 2 Diabetes Mellitus Patients. *Kesmas*. 2022; 17(2): 98-104
DOI: 10.21109/kesmas.v17i2.5453
Available at: https://scholarhub.ui.ac.id/kesmas/vol17/iss2/3

Baniu, *et al. Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal)*. 2022; 17 (2): 98-104
DOI: 10.21109/kesmas.v17i2.5453

Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal)

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

Ahmad Sahlan Baniu[1], Rani Sauriasari[1]*, Woro Riyadina[2], Pradana Soewondo[3,4]

[1]Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia, [2]National Institute of Health Research and Development, Ministry of Health of the Republic of Indonesia, Jakarta, Indonesia, [3]Division of Endocrinology, Department of Internal Medicine, Dr. Cipto Mangunkusumo National Referral Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, [4]Metabolic, Cardiovascular, and Aging Cluster, The Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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-

***Correspondence**:* *Rani Sauriasari, Faculty of Pharmacy, Universitas Indonesia, Kampus Baru UI Depok 16424, Indonesia, E-mail: rani@farmasi.ui.ac.id, Phone: +62 821-1425-2811*

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

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.[7]

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).[8,9] 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.[10] 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.

$$n = \frac{\left\{ z_{1-\alpha/2}\sqrt{2P(1-P)} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{(P_1-P_2)^2}$$

Notes:
α = The standard value of the normal distribution, set at 5%
Z1-α/2 = The same value, with a significant degree of 1.96
Z1-β = The same value as the desired power of 0.84
P = (p1+p2)/2
p2 = The proportion of T2DM patients who do not take diabetes medication and were diagnosed with CHD = 0.5812,[12]
p1 = The proportion of T2DM patients who take diabetes medication and diagnosed with CHD was calculated by estimating the difference considered significant between the proportion of diabetic patients taking medication and those not taking it, set at 30%.
p1 = p2-(30% x 0.58) = 0.406,[13]
n = After calculation, the result obtained was n = 128.2678, rounded up to 130

Formula 1. Sample Size Estimation,[11]

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 Formula 1.[11] The minimum sample size for each group was 130, meaning that as there were two groups, the minimum study sample size was 260.

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 (30.4%) 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

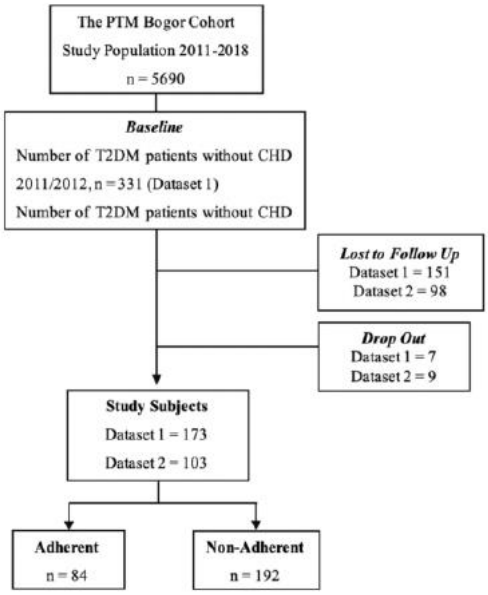

Figure 1. Patients Recruitment Flow

Table 1. Characteristics of the Type 2 Diabetes Mellitus Patients

Variable	Category	Adherent (n = 84)	Non-Adherent (n = 192)	p-value
Sex	Male	22 (26.2)	53 (27.6)	0.924[a]
	Female	62 (73.8)	139 (72.4)	
Age in the 4th year	<60 years	48 (57.1)	122 (63.5)	0.384[a]
	≥60 years	36 (42.9)	70 (36.5)	
Education level in the 4th year	Further education	29 (34.5)	80 (41.7)	0.326[a]
	Elementary education	55 (65.5)	112 (58.3)	
Employment in the 4th year	Employed	79 (94.0)	187 (97.4)	0.308[a]
	Unemployed	5 (6.0)	5 (2.6)	
Smoking status in the 4th year	Do not smoke	36 (42.9)	99 (51.6)	0.185[b]
	Smoked at some time	10 (11.9)	12 (6.3)	
	Smoker	38 (45.2)	81 (42.2)	
Physical activity in the 4th year	Moderately active (METs)	41 (48.8)	97 (50.5)	0.896[a]
	Less active (METs)	43 (51.2)	95 (49.5)	
Systolic BP changes	Increased	15 (17.9)	44 (22.9)	0.433[a]
	No Increase	69 (82.1)	148 (77.1)	
Diastolic BP changes	Increased (>14.98 mmHg)	8 (9.5)	36 (18.8)	0.080[a]
	No Increase (14.98 mmHg)	76 (90.5)	156 (81.3)	
PPBG change	Increased	16 (19)	25 (13)	0.266[a]
	No Increase	68 (81)	167 (87)	
Total cholesterol change	Increased	19 (22.6)	41 (21.4)	0.940[a]
	No Increase	65 (77.4)	151 (78.6)	
LDL changes	Increased	18 (21.4)	33 (17.2)	0.505[a]
	No Increase	66 (78.6)	159 (82.8)	
HDL Change	Increased	22 (26.2)	39 (20.3)	0.355[a]
	No Increase	62 (73.8)	153 (79.7)	
BMI Change	Increased	19 (22.6)	56 (29.2)	0.328[a]
	No Increase	65 (77.4)	136 (70.8)	

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.

Table 2. Effect of Non-Adherent Behavior Compared to Adherent Behavior on the Coronary Heart Disease Incidence

Adherent Behavior	CHD (n = 24)	Non-CHD (n = 252)	p-value	Hazard Ratio	95% CI
Non-Adherent	18 (9.4%)	174 (90.6%)	0.564	1.312	0.521–3.306
Adherent	6 (7.1%)	78 (92.9%)			

Notes: the above data is expressed in amount (n) and percentage (%) terms; CHD = Coronary Heart Disease, CI = Confidence Interval.

Table 3. Effect of Non-Adherent Behavior on the Incidence of Coronary Heart Disease after Confounding Variable Control

Model	Variable	Category	HR	p-value	95% CI
Model 1	Adherent behavior	Non-Adherent	1.312	0.564	0.521–3.306
		Adherent (Ref)			
Model 2	Adherent behavior	Non-Adherent	1.739	0.253	0.673–4.490
		Adherent (Ref)			
	Sex	Male	0.455	0.159	0.152–1.362
		Female (Ref)			
	Age	Increase	0.577	0.182	0.258–1.293
		No Increase (Ref)			
	LDL changes	Increase	3.566	0.007*	1.416–8.976
		No Increase (Ref)			
	Changes in physical activity	Increase	0.220	0.003*	0.081–0.600
		No Increase (Ref)			

Notes: HR = Hazard Ratio, CI = Confidence Interval, LDL = Low Density Lipoprotein, *p-value<0.05

(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,[15] 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.[3] 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

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 ASCVD 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.[22] 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 adherents 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:

Perkumpulan Endokrinologi Indonesia; FBG: Fasting Blood Glucose; PPBG: Post-Prandial Blood Glucose; ECG: Electrocardiogram; WHO: World Health Organization; RR: Relative Risk; HR: Hazard Ratio; BMI: Body Mass Index; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; ROS: Reactive Oxygen Species; TNF: Tumor Necrosis Factor.

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.

References

1. Carnethon MR, Biggs ML, Barzilay J, Kuller LH, Mozaffarian D, Mukamal K, et al. Diabetes and coronary heart disease as risk factors for mortality in older adults. Am J Emerg Med. 2010; 123 (6): 556.e1-556.e9.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update. Circulation. 2014; 129 (3): e28–292.
3. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Atherosclerotic cardiovascular disease and heart failure in type 2 diabetes – mechanisms, management, and clinical considerations. Circulation. 2016; 133 (24): 2459–502.
4. Li Y, Hu Y, Ley SH, Rajpathak S, Hu FB. Sulfonylurea use and incident cardiovascular disease among patients with type 2 diabetes: prospective cohort study among women. Diabetes Care. 2014; 37 (11): 3106–13.
5. Roumie CL, Greevy RA, Grijalva CG, Hung AM, Liu X, Murff HJ, et al. Association between intensification of metformin treatment with insulin versus sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. JAMA. 2014; 311 (22): 2288–96.
6. Herman ME, O'Keefe JH, Bell DSH, Schwartz SS. Insulin therapy increases cardiovascular risk in type 2 diabetes. Prog Pediatr Cardiol. 2017; 60 (3): 422–34.
7. Euser AM, Zoccali C, Jager KJ, Dekker FW. Cohort studies: prospective versus retrospective. NEC. 2009; 113 (3): c214–7.
8. American Association Diabetes. Classification and diagnosis of diabetes: standards of medical care in diabetes. Diabetes Care. 2021; 44 (Supplement 1): S15–33.
9. Soelistijo, Soebagijo Adi, Lindarto D, Decroli E, Permana H, Sucipta KW, Kusnadi Y, et al. Pedoman pengelolaan dan pencegahan diabetes melitus tipe 2 dewasa di Indonesia 2019. PB. PERKENI; 2019.
10. Robinson RS. Purposive Sampling. In: Michalos AC, editor. Encyclopedia of quality of life and well-being research. Dordrecht: Springer Netherlands. 2014, p. 5243–5.
11. Lemeshow S, World Health Organization, editors. Adequacy of sample size in health studies. Chichester. New York : New York, NY, USA: Published on behalf of the World Health Organization by Wiley; Distributed in the U.S.A., Canada, and Japan by Liss. 1990, p. 239.
12. Husni H, Lapau B, Hardhana B. Hubungan dislipidemia dan diabetes mellitus dengan kejadian penyakit jantung koroner di RSUD Ulin Banjarmasin. CNJ: Caring Nursing Journal. 2018; 2 (2): 66–9.
13. Dahlan S. Seri 2 besar sampel dalam penelitian kedokteran dan kesehatan. Jakarta: Epidemiologi Indonesia; 2019.
14. Hajar R. Risk factors for coronary artery disease: historical perspectives. Heart Views. 2017; 18 (3): 109–14.
15. Kaaffah S. Evaluasi perilaku berobat terhadap penurunan parameter glikemik penderita diabetes melitus tipe 2: studi kohor Bogor. [Master's Thesis]. Depok (ID): Universitas Indonesia; 2019.
16. Stettler C, Allemann S, Jüni P, Cull CA, Holman RR, Egger M, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. American Heart Journal. 2006; 152 (1): 27–38.
17. Fung CSC, Wan EYF, Wong CKH, Jiao F, Chan AKC. Effect of metformin monotherapy on cardiovascular diseases and mortality: a retrospective cohort study on Chinese type 2 diabetes mellitus patients. Cardiovascular Diabetology. 2015; 14 (1): 137.
18. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. The Lancet Diabetes & Endocrinology. 2015; 3 (1): 43–51.
19. Stoekenbroek RM, Rensing KL, Moens SJB, Nieuwdorp M, DeVries JH, Zwinderman AH, et al. High daily insulin exposure in patients with type 2 diabetes is associated with increased risk of cardiovascular events. Atherosclerosis. 2015; 240 (2): 318–23.

20. Fox CS, Sullivan L, D'Agostino RB, Wilson PWF. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham heart study. Diabetes Care. 2004; 27 (3): 704–8.
21. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. Arch Intern Med. 2011; 171 (5).
22. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. European Heart Journal. 2017; 38 (32): 2459–72.
23. Arsana PM, Rosandi R, Manaf A, Budhiarta A, Permana H, Sucipta KW, et al. Panduan pengelolaan dislipidemia di Indonesia - 2015. Jakarta: PB. PERKENI; 2015.
24. Setyaji DY, Prabandari YS, Gunawan IMA. Aktivitas fisik dengan penyakit jantung koroner di Indonesia. Jurnal Gizi Klinik Indonesia. 2018; 14 (3): 115–21.