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Research Article

The Effect of Medication Adherence and Controlled HbA1c on Blood Pressure and ASCVD Risk in Patients with Hypertension and Type 2 Diabetes Mellitus: A Multicenter Study in Primary Health Care

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ABSTRACT

Hypertension and type 2 diabetes mellitus (T2DM) significantly increase the risk of cardiovascular complications. The effects of medication adherence and glycemic control have been studied extensively, in part, on blood pressure or atherosclerotic cardiovascular disease (ASCVD) risk. The purpose of this study was to analyze the effect of medication adherence and controlled HbA1c levels on blood pressure and ASCVD risk among patients with hypertension and T2DM. An observational study was conducted with a cross-sectional design to analyze the medical records data. Data were extracted from the medical records of patients diagnosed with T2DM and hypertension as comorbid at DIY primary health care (PHC). Adherence was measured quantitatively using the Medication Possession Ratio (MPR) and qualitatively using the Medication Adherence Rating Scale-5 (MARS-5). The ASCVD risk was assessed using the Framingham Risk Score. We performed chi-square and multivariate logistic analyses to analyze the relationships between variables. A total of 720 respondents were recruited and participated in our study, but only 127 fulfilled the inclusion criteria. The uncontrolled blood pressure and high-risk ASCVD were 34.6% and 84.3%, respectively. The MPR was significantly higher in the controlled blood pressure group (p-value = 0.04), but not in the MARS-5 parameters (p-value 0.98). Females tended to have high-risk ASCVD (p-value 0.01). The study could not detect a significant association between adherence and controlled HbA1c to uncontrolled blood pressure and high-risk ASCVD, neither in the bivariate analysis nor after adjusting for some variables (p-value > 0.05). **Conclusion**: Controlled HbA1c level and adherence were not significantly associated with uncontrolled blood pressure or high-risk ASCVD.

INTRODUCTION

Hypertension and type 2 diabetes mellitus (T2DM) are two of the most prevalent chronic conditions worldwide and often coexist, significantly increasing the risk of cardiovascular complications and mortality (Petrie *et al*., 2018). The global prevalence of hypertension is estimated to be 31.1%, affecting 1.39 billion adults (Mills *et al*., 2020), while diabetes affects approximately 537 million adults globally, with T2DM accounting for 90-95% of all cases (Webber, 2013). The co-occurrence of these conditions, often referred to as "diabetic hypertension," presents a complex challenge for healthcare providers, particularly in primary care settings, where the majority of these patients are managed (Long & Dagogo-Jack, 2011).

Effective management of hypertension and T2DM is crucial for reducing the risk of atherosclerotic cardiovascular disease (ASCVD), which remains the driving cause of morbidity and mortality among these patients (Einarson *et al*., 2018). Current American Diabetes Association (ADA) guidelines emphasize the importance of blood pressure control, glycemic management, and comprehensive cardiovascular risk reduction strategies (ADA, 2021; Whelton *et al*., 2018). However, achieving optimal control in real-world clinical practice remains challenging, with factors, such as medication adherence, playing a critical role (Vrijens *et al*., 2017).

According to the World Health Organization (WHO), medication adherence is a key determinant of treatment success in patients with chronic disease (WHO, 2003). Destitute adherence to antihypertensive and antidiabetic medications is related with suboptimal blood pressure and glycemic control, expanded healthcare costs, and higher rates of cardiovascular events and mortality (Krass *et al*., 2015; Mazzaglia *et al*., 2009). Despite its significance, adherence rates for hypertension and T2DM remain suboptimal, with estimates ranging from 50% to 80% (Polonsky & Henry, 2016).

Glycated hemoglobin (HbA1c) is the gold standard for assessing long-term glycemic control in patients with T2DM (ADA, 2021). Many studies have demonstrated that maintaining HbA1c levels within the target range reduces the chance of microvascular and macrovascular complications (Stratton *et al*., 2000). However, the interplay between HbA1c control, blood pressure management, and ASCVD risk in patients with both hypertension and T2DM is complex and not fully elucidated, particularly in diverse primary-care populations (Ferrannini & Cushman, 2012).

A national study in Indonesia reported a high prevalence of hypertension, as well as T2DM prevalence. The number of hypertension and T2DM cases increase significantly year by year. The Yogyakarta Province has one of the highest prevalence of T2DM, even higher than the national prevalence of T2DM. The prevalence of hypertension in Yogyakarta (DIY) is slightly lower than the national, but it is still a significant health concern (Kemenkes RI, 2018). The hypertension comorbidities among patients with T2DM are closely monitored to reduce complications and mortality. Accordingly, public health sectors should give more attention to those conditions and work toward finding solutions.

However, Indonesia faced several challenges in the management of hypertension and T2DM. A study revealed that less than 10% of hypertensive patients could get controlled blood pressure. Meanwhile, only 30.8% of patients with T2DM achieved HbA1c <7% (Hussain *et al*., 2016). Several factors may contribute to poor controlled blood pressure either HbA1c, such as low medication adherence, lack of health literacy, and limited healthcare providers (Soewondo *et al*., 2013).

Some studies have observed the effect of medication adherence, as well as controlled glycemic, on blood pressure and/or ASCVD outcomes, separately (Khatib *et al*., 2014). Yet, the combination of adherence and glycemic control in comprehensive studies to detect their effects on blood pressure and ASCVD outcomes remains understudied. Therefore, this multicenter study conducted research in several primary health care centers in order to provide a broader perspective on the association of those factors in real-world clinical settings. The findings can be applied to the strategic therapeutic management of T2DM and hypertension to reduce ASCVD risk. Accordingly, the study aimed to analyze the effect of medication adherence and controlled HbA1c on blood pressure and ASCVD risk among T2DM patients with hypertension comorbidity.

METHODS

This was an observational analysis with a cross-sectional design. Data were extracted from the medical records of patients diagnosed with type 2 diabetes mellitus (T2DM) and hypertension as comorbid at DIY primary health care (PHC) centers.

Inclusion criteria were: aged 30-75 years; receiving and collecting routine prescription drugs at least three times during the study period (January 1, 2023–April 30, 2024); having data on antihypertensive drugs received, visit dates, weight, height, and latest blood pressure; possessing recent HbA1C laboratory data (within the last 6 months); and willingness to complete a questionnaire with informed consent. HbA1C levels were used as a key indicator of glycemic control, reflecting the average blood glucose levels over the previous 2-3 month. Exclusion criteria encompassed patients using antihypertensive drugs for non-cardiovascular indications and those with a history of ASCVD (including cerebrovascular accidents, transient ischemic attacks, coronary artery disease, carotid artery disease, peripheral vascular disease, positive exercise tolerance tests, typical angina,

congestive heart failure, and myocardial infarction or ischemic heart disease) were excluded (Zibaeenejad *et al*., 2022).

An ideal therapy adherence measurement method should be low-cost, user-friendly, easily performable, reliable, flexible, and practical. However, as each measurement has limitations, it is advisable to employ multiple adherence measures to obtain results that closely reflect reality. In this study, patient adherence was assessed using the Medication Possession Ratio (MPR) and Medication Adherence Rating Scale-5 (MARS-5). The MPR was calculated as the percentage of days the patient possessed the medication, derived from the ratio of the actual number of days the medication was supplied to the number of days in the study period, plus the days supplied in the last prescription (Suhadi *et al*., 2017). Patients with an average MPR value ≥80% were categorized as adherent, whereas those with an MPR <80% were considered non-adherent. The MARS-5 questionnaire consists of five questions which be designed to measure patients' medication adherence, qualitatively. The MARS-5 questionnaire assess patients' understanding of their attitudes towards prescribed medications. The questionnaire of MARS-5 has been translated into the Indonesian language. The Cronbach's alpha value of Indonesian MARS-5 was 0.80315, which indicated it is acceptable to be applied as a reliable tool (Firdiawan *et al*., 2021).

Controlled HbA1c level was defined as <7% based on data from the medical records. Our study defined uncontrolled blood pressure while systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg. The 10-years risk of ASCVD was estimated through Framingham Risk Score-Body Mass Index (FRS-BMI). An Excel-based tool of FRS-BMI is available at the Framingham Heart Study website (https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/). Several variables, such as age, sex, BMI, systolic blood pressure, antihypertensive treatment status, smoking behavior, and diabetes diagnosis, are used to assess ASCVD risk through FRS-BMI. Patients who was receiving more than five medicines were categorized as a polypharmacy.

A univariate analysis was applied to analyze the distribution of respondents' characteristics, the chi-square test assessed the relationship between variables, and multivariate logistics analyzed the proportion adjusted for age and gender (model 1), and adjusted for BMI, lipid profiles, and polypharmacy (model 2). Subgroup analysis was performed by combining HbA1c and adherence factors. Significant results were p-value < 0.05, based on 2 sided testing.

Research permission was obtained from the Ethics Commission of the University of Yogyakarta (0244.3/FIKES/PI/XII/2023). The written informed consent form was signed by all of the participants who were recruited in this study.

RESULTS AND DISCUSSION

A total of 720 respondents participated in our study. We excluded 593 respondents because of incomplete HbA1c and lipid profile data. A total of 127 respondents were included in all data calculations, but only 107 respondents completed the MARS-5 questionnaire. All respondents' characteristic data were grouped according to blood pressure and ASCVD risk, as shown in Table 1. The prevalence of uncontrolled blood pressure and high-risk ASCVD was 34.6% and 84.3%, respectively. Overall, women were predominant in all groups. The mean BMI in all groups could be classified as obese (BMI > 25 kg/m^2). The MPR was higher in the controlled blood pressure group (p-value = 0.04), but not in the MARS-5 parameters (p-value 0.98).

Compared to males with high-risk ASCVD, females were more likely to have high-risk ASCVD (52.0% vs. 32.3%, p-value 0.01). The mean age of the patients was significantly different between the groups (p-value < 0.05). No significant differences were observed in BMI, glycemic profiles, lipid profiles, adherence indicators, or polypharmacy related to ASCVD risk.

Table 2 shows the subgroup analysis of HbA1c and adherence, either according to MPR or MARS-5, compared to uncontrolled blood pressure, high-risk ASCVD, MPR, and MARS-5, which are presented as odds ratios (OR) with confidence intervals (CI) and p-value. Controlled HbA1c levels and adherence were used as references. There was no significant association even in the uncontrolled HbA1c group that did not adhere to either uncontrolled blood pressure or high-risk ASCVD (p-value >0.05).

As shown in Table 3, the adjustment for age and sex (model 1) and the addition of BMI, lipid profiles, and polypharmacy (model 2) did not significantly improve the risk of uncontrolled blood pressure and high-risk ASCVD in any of the four groups compared to the bivariate analysis. The patterns were observed in the overall group (e.g. OR (95%CI) among "controlled HbA1c and adhere" vs "uncontrolled HbA1c and not adhere" to uncontrolled blood pressure based on MPR,

Table 1. Respondents demographic and clinical characteristic according to blood pressure and ASCVD risk

Characteristics	Blood Pressure			ASCVD risk		
	Controlled (n=90)	Uncontrolled (n=37)	*p* value	Low-intermediate risk (n=20)	High risk (n=107)	*p* value
Gender (n,%)						
Male	28 (22.1)	13 (10.2)	0.66	0 (0)	41 (32.3)	0.01*
Female	62 (48.8)	24 (18.9)		20 (15.7)	66 (52.0)	
Age (years old)	60.27±5.46	60.35±4.85	0.94	53.45±5.95	61.57±4.03	0.00*
BMI (kg/m^2)	25.54±5.52	25.70±4.75	0.88	27.20±5.47	25.29±5.22	0.14
FBG (mg/dL)	147.93±63.41	147.97±47.21	0.99	153.65±65.70	146.88±57.90	0.64
HbA1c (%)	7.68±2.05	7.80±1.86	0.78	7.89±2.09	7.69±1.98	0.68
LDL-c (mg/dL)	138.56±34.75	129.78±28.84	0.18	138.85±27.75	135.47±34.29	0.68
HDL-c (mg/dL)	46.77±10.32	47.73±8.97	0.62	48.30±7.83	46.81±10.28	0.54
Total cholesterol (mg/dL)	154.04±86.57	165.65±92.19	0.96	212.65±31.82	207.16±39.44	0.56
Triglycerides (mg/dL)	154.04±86.57	165.65±92.19	0.50	150.75±65.75	158.67±91.80	0.71
MPR (%)	83.12±20.22	75.00±19.74	0.04*	78.90±17.99	81.10±20.81	0.66
MARS-5	22.19±2.26	22.21±1.24	0.98	22.29±1.90	22.18±2.52	0.89
Polypharmacy (n,%)						
Yes	14 (11.0)	3 (2.4)	0.26	2 (1.6)	15 (11.8)	0.63
No	76 (59.8)	34 (26.8)		18 (14.2)	92 (72.4)	

ASCVD: atherosclerosis cardiovascular disease, FBG: fasting blood sugar, LDL-c: low density lipoprotein cholesterol, HDL-c: high density lipoprotein cholesterol, MPR: medication possession ratio, MARS-5: medication adherence rating scale-5; *p value < 0.05.

model 1 was 2.58 (0.91 – 7.34) and model 2 was 2.45 (0.85 – 7.08).

Recent research has yielded intriguing findings regarding the relationship between glycated hemoglobin (HbA1c) control, medication adherence, blood pressure management, and ASCVD risk in patients with diabetes. Contrary to some expectations, studies have suggested that HbA1c control and medication adherence may not always be correlated with improved blood pressure control or reduced ASCVD risk. Therefore, we discussed about the implication of diabetes managements to controlled comorbid conditions, which was included in the link between hypertension and ASCVD.

Several studies have mentioned that better glycemic control could improve controlled blood pressure (Alhassan *et al*., 2022; Cai *et al*., 2019). However, our findings were contrary of those views, even after adjusted for age, gender, BMI, lipid profiles, and polypharmacy. Additionally, one study also did not find any significant association between HbA1c levels and blood pressure control in patients with type 2 diabetes (Khorasani *et al*., 2019). They observed that glycemic control mechanism and regulation of blood pressure is more independent and were affected by various risk factors.

Similarly, medication adherence of T2DM medication which is an important aspect of diabetes management, might not directly affect controlled blood pressure. We noted that various risk factors, including lifestyle, diet, and genetic predisposition might play important roles in blood pressure regulation (Paula *et al*., 2015; Sreedevi *et al*., 2022; Virginia *et al*., 2022). These findings highlight that diabetes management is complex and requires a multifaceted approach. Yet, several studies have proven that good medication adherence leads to better controlled blood pressure (Baiee & Makai, 2022; Rabizadeh *et al*., 2021).

Association between HbA1c, medication adherence, and ASCVD risk has been addressed in this recent investigation, with some remarkable findings. Despite the fact that tight glycemic control is a cornerstone of diabetes

management (Afroz *et al*., 2019), its impact on ASCVD has not been fully studied. A study by the ACCORD Study Group demonstrated that using glucose lowering agents intensively did not significantly reduce major ASCVD (Gerstein *et al.*, 2016). We revealed that stricter controlled HbA1c was not significantly associated with better ASCVD risk outcome. Our findings from the Chi-square tests showed that age and gender were factors contributing to the ASCVD outcome.

A meta-analysis stated that benefit of controlled blood glucose on ASCVD risk were modest. Controlled blood glucose has a small reduction in non-fatal myocardial infarctions, but no significant effect on all-cause mortality or cardiovascular death (Rodríguez-Gutiérrez, 2016). Notably, it is more important to focus on individualizing glycemic targets according to patient characteristics to enhance the therapeutic goals. Individualization of the glycemic target was preferable to reduce ASCVD risk (Westall *et al*., 2022).

Although medication adherence was usually associated with better health outcomes, its relationship with ASCVD risk among T2DM remains complex. A study found that medication adherence could improve glycemic control, but its impact on preventing ASCVD was less pronounced than expected (Kosiborod *et al*., 2018). The authors suggested that other factors such as overall lifestyle modifications and management of comorbidities may play equally important roles in cardiovascular risk reduction.

Although HbA1c control and medication adherence remain important aspects of diabetes management, their relationships with blood pressure control and cardiovascular risk are more complex than previously thought. Therefore, a patient-centered approach that addresses multiple risk factors simultaneously is likely to yield the best outcomes in managing diabetes and its cardiovascular complications.

Table 2. Subgroup analysis: The association between interaction of controlled HbA1c and adherence to uncontrolled blood pressure and high risk ASCVD

Characteristics	Uncontrolled Blood Pressure		High Risk ASCVD	
	p value	OR (95%CI)	*p* value	OR (95%CI)
MPR				
Controlled HbA1c and adhere		1.00 (reference)		1.00 (reference)
Controlled HbA1c and not adhere	0.28	1.96 (0.58 – 6.63)	0.27	3.37 (0.37 – 29.19)
Uncontrolled HbA1c and adhere	0.62	1.30 (0.46 – 3.65)	0.49	1.58 (0.43 – 5.75)
Uncontrolled HbA1c and not adhere	0.09	2.40 (0.87 – 6.60)	0.53	0.69 (0.22 – 2.16)
MARS-5				
Controlled HbA1c and adhere		1.00 (reference)		1.00 (reference)
Controlled HbA1c and not adhere	0.64	1.50 (0.28 – 8.09)	0.91	0.87 (0.09 – 0.84)
Uncontrolled HbA1c and adhere	0.42	2.67 (0.25 – 28.44)	N.A	NA
Uncontrolled HbA1c and not adhere	0.28	2.48 (0.47 – 13.02)	0.54	0.54 (0.06 – 4.89)

ASCVD: atherosclerotic cardiovascular disease, CI: confidence interval, MARS-5: medication adherence rating scale-5, MPR: medication possession ratio, OR: odds ratio.

Table 3. Multivariate analysis

Characteristics	Uncontrolled Blood Pressure		High Risk ASCVD	
	AOR[1]	AOR[2]	AOR[1]	AOR[2]
MPR				
Controlled HbA1c and adhere	1.00 (reference)		1.00 (reference)	
Controlled HbA1c and not adhere	2.07 (0.60 – 7.08)	2.23 (0.62 – 8.02)	2.51 (0.24 – 26.21)	3.17 (0.35 – 25.59)
Uncontrolled HbA1c and adhere	1.37 (0.48 – 3.94)	1.13 (0.35 – 3.67)	4.26 (0.69 – 26.22)	1.60 (0.37 – 6.87)
Uncontrolled HbA1c and not adhere	2.58 (0.91 – 7.34)	2.45 (0.85 – 7.08)	2.29 (0.37 – 14.09)	0.65 (0.20-2.13)
MARS-5				
Controlled HbA1c and adhere	1.00 (reference)		1.00 (reference)	
Controlled HbA1c and not adhere	1.51 (0.28 – 8.18)	1.75 (0.30 – 10.22)	1.53 (0.11 – 21.94)	0.78 (0.06 – 11.18)
Uncontrolled HbA1c and adhere	2.64 (0.24 – 28.60)	2.80 (0.20 – 39.63)	NA	NA
Uncontrolled HbA1c and not adhere	2.54 (0.46 – 13.88)	2.68 (0.48 – 15.05)	3.32 (0.22 – 51.25)	0.49 (0.04 – 6.37)

AOR: adjusted odds ratio; [1]adjusted for age, gender; [2]adjusted for BMI, lipid profile, polypharmacy.

Our study had major limitations. Practical constraints such as a high proportion of missing data caused many respondents to be excluded. Since we performed a multicenter study of public health centers and involved a number of physicians, it was difficult to control the therapeutic regimen and/or standard therapeutic guidelines. Therefore, our results may differ slightly from those of previous studies.

CONCLUSIONS

Based on the research results, controlled HbA1c levels and adherence did not show any significant association with uncontrolled blood pressure or high-risk ASCVD. Other factors that may affect blood pressure and ASCVD should be investigated further.

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CONFLICT OF INTEREST

The authors declare there's no conflict of interest.

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