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Research Article

Antidiabetic and Antihypertensive Therapy Intensification on Clinical Outcomes and ASCVD Risk

Intensifikasi Terapi Antidiabetes dan Antihipertensi Terhadap Outcome Klinis dan Resiko ASCVD

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and hypertension are highly prevalent comorbidities that contribute significantly to the increase of cardiovascular complications, including Atherosclerotic Cardiovascular Disease (ASCVD). Therapy intensification is one of the important strategies to reduce disease progression and improve clinical outcomes; however, its clinical effectiveness remains inconsistent. This retrospective cohort study aimed to evaluate the impact of intensifying antidiabetic and antihypertensive therapy on clinical outcomes and its association with ASCVD status among 179 outpatients with T2DM and/or hypertension, with and without ASCVD, treated at hospitals in Yogyakarta from January to December 2024. Primary outcomes included achieving blood pressure target and glycemic control parameters (fasting plasma glucose and HbA1c). Logistic regression analysis was performed to evaluate associations between therapy intensification, treatment target attainment, and ASCVD status. The results showed that intensification of antidiabetic therapy was not significantly associated with achieving glycemic targets or ASCVD status (p > 0.05). In contrast, antihypertensive therapy intensification was significantly associated with blood pressure control (p=0.008, OR=6.322, 95%CI:1.604-24.916) and ASCVD status (p=0.006, OR=18.66, 95% CI:2.30-151.06). These findings highlight the importance of intensifying antihypertensive therapy in improving clinical outcomes and potentially improving cardiovascular risk control.

Keywords: Medication Adjustment, Glycemic Control, Blood Pressure Control, Target Attainment, Cardiovascular Disease

ABSTRAK

Diabetes mellitus tipe 2 (DMT2) dan hipertensi merupakan dua komorbid dengan prevalensi tinggi yang secara sinergis dapat meningkatkan resiko komplikasi kardiovaskuler, termasuk Atherosclerotic Cardiovascular Disease (ASCVD). Intensifikasi terapi merupakan salah satu strategi untuk memperlambat progresivitas penyakit dan memperbaiki outcome terapi, namun efektivitas strategi ini masih bervariasi. Penelitian kohort retrospektif ini bertujuan untuk menganalisis pengaruh intensifikasi terapi antidiabetes dan antihipertensi terhadap ketercapaian outcome glikemik (GDP, HbA1c), dan tekanan darah, serta menilai hubungannya dengan status ASCVD pada pasien DMT2 dan/atau hipertensi di kota Yogyakarta. Data yang digunakan adalah rekam medis pasien rawat jalan pada periode Januari-Desember 2024. Penelitian melibatkan 179 pasien yang memenuhi kriteria inklusi dan eksklusi. Analisis data dilakukan menggunakan regresi logistik, dengan hasil menunjukkan bahwa variasi intensifikasi terapi antidiabetes tidak berhubungan signifikan dengan ketercapaian outcome glikemik (HbA1c dan GDP) maupun status ASCVD (p>0,05). Sebaliknya, intensifikasi terapi antihipertensi berhubungan signifikan dengan ketercapaian outcome tekanan darah dengan nilai signifikansi 0,008, OR=6,322 (95%CI:1,604-24,916), dan status ASCVD dengan nilai signifikansi 0,006; OR = 18,66; (95% CI = 2,30–151,06). Temuan ini menegaskan bahwa intensifikasi terapi antihipertensi berperan penting dalam ketercapaian target tekanan darah, dan berpotensi meningkatkan kontrol resiko kardiovaskuler.

Kata Kunci: Penyesuaian Terapi, Kontrol Glukosa Darah, Kontrol Tekanan Darah, Ketercapaian Target Terapi, Penyakit Kardiovaskuler

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) and hypertension are global health problems that frequently coexist. The two conditions are considered comorbidities that contribute significantly to increased risk of cardiovascular complications, including atherosclerotic cardiovascular disease (ASCVD) (Moke et al., 2023). In Indonesia, the prevalence of T2DM increased to 10.6% in 2021, up from 5.1% in 2011, and hypertension affects approximately 40% of the Indonesian population as of 2019 (IDF Diabetes Atlas, 2021; World Health Organization., 2023). In Yogyakarta, the prevalence of diabetes, as diagnosed by physicians, is reported at 2.9%, while hypertension affects 12.3% of the population (RISKESDAS, 2023).

Many clinical guidelines have been developed and updated regularly to manage and optimize these two conditions, but evidence shows that many patients still fail to achieve their treatment targets. Research conducted in Gianyar, Bali, indicated that 64.83% of patients did not reach glycemic targets (Kurnianta et al., 2021). Meanwhile, a study conducted in Kalideres reported that 72% of T2DM patients had uncontrolled blood glucose levels, with 76.4% also presenting with hypertension (Axel et al., 2023).

The coexistence of these two conditions is particularly harmful due to their shared and synergistic pathophysiological mechanisms, which accelerate vascular dysfunction and substantially increases risk of life-threatening cardiovascular disease, including coronary artery disease, cerebrovascular disease, renal failure, and congestive heart failure (Moke et al., 2023; Petrie et al., 2018). Therefore, effective management of both conditions is essential to achieve optimal glycemic and blood pressure control.

Intensification through dose escalation or the addition of new medications has been recommended to slow disease progression and reduce cardiovascular risk. Previous studies have demonstrated that the active intensification of antidiabetic and antihypertensive therapies enhances optimized glycemic control and contributes to the prevention of recurrent stroke (Kim et al., 2021; Rodriguez et al., 2024).

The decision to intensify therapy requires careful consideration. Concerns about adverse effects, such as hypoglycemia, hypotension, drug interactions, increased treatment costs, and low adherence, can be a barrier to adopting intensification strategies, particularly among elderly patients, patients presenting multimorbidity, or those receiving polypharmacy (Wong et al., 2022).

Despite these findings, real-world evidence evaluating the impact of antidiabetic and antihypertensive therapy intensification on clinical target attainment remains limited, particularly in Indonesian clinical practice. The variability in previous studies and the limited evidence on patients with and without ASCVD in Yogyakarta suggest that further research is warranted. Therefore, this study aimed to evaluate the effect of intensifying antidiabetic and antihypertensive therapies on clinical outcomes, including blood pressure, fasting plasma glucose, HbA1c, and ASCVD status, in real-world hospital settings in Yogyakarta. HbA1c was selected as the gold standard indicator of long-term glycemic control, while fasting plasma glucose represents a short-term control measure commonly available in daily clinical practice. Blood pressure was included as the primary outcome of hypertension.

II. METHOD

A. Study Design

This study employed a retrospective cohort study and was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, at the Public Health and Nursing

Universitas Gadjah Mada - Dr. Sardjito General Hospital (KE/FK/1807/EC).

B. Population and Sampling

The study was conducted as a multicenter retrospective cohort study, the study population consisting of outpatients diagnosed with type 2 diabetes mellitus (T2DM) and/or hypertension at three hospitals in Yogyakarta from January to December 2024. The hospitals were selected purposively based on the availability of medical records, the diversity of patient populations, and their classification as type-B referral hospitals. A total sampling was applied, enrolling all patients who met eligibility criteria.

The inclusion criteria were age ≥ 40 years, confirmed diagnosis of T2DM and/or hypertension, clinical follow-up at least three times in different months, received oral/injectable antidiabetic therapy and/or antihypertensive therapy, and had complete medical records, including historical therapy, clinical parameters, and ASCVD status.

Exclusion criteria included pregnant or breastfeeding women, those who received antidiabetic or antihypertensive therapy for non-cardiovascular indications, had incomplete medical records, admission to the emergency department or inpatient ward during the study period, or received injectable medications that could influence blood pressure.

A total of 229 patients were initially identified, 179 of whom were included in the final analysis, with the three hospitals contributing a comparable proportion of the patients. The patient selection flowchart is presented in Figure 1.

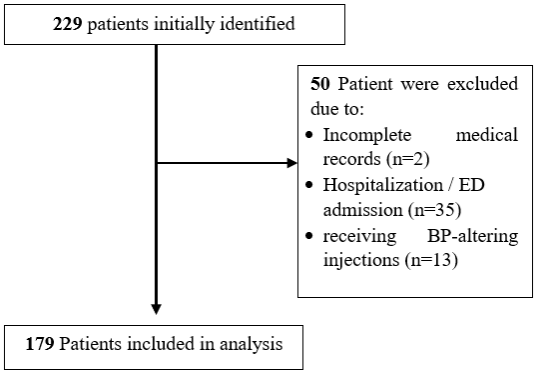


Figure 1. Patient selection flowchart

C. Data Collection

Data were collected retrospectively from medical records, including demographic characteristics (age, sex), clinical history (T2DM, hypertension, ASCVD), clinical parameters (blood pressure), laboratory parameters (fasting plasma glucose [FPG], HbA1c), and medication regimens. ASCVD status was defined as the presence of documented atherosclerotic cardiovascular disease (coronary artery disease, ischemic stroke, transient ischemic attack, or peripheral arterial disease) in patients' medical records.

D. Therapy Intensification

Therapy intensification was analyzed separately for antidiabetic and antihypertensive treatments, allowing patients who received only one therapy or both to be included in the analysis.

Antidiabetic therapy intensification was classified based on observed treatment changes and was not evaluated for appropriateness to the Indonesian guideline. According to Wong *et al*, 2022, changes in treatment regimens were categorized as: intensification therapy (IT, adding of medication, increasing dosage, or combination of both); deintensification (DT, reduction in dosage or discontinuation of medication); combination therapy comprising intensification and deintensification therapies, and no change in therapy (Wong et al., 2022). Antidiabetic intensification was assessed, based on monthly treatment changes over a one-year observation period. Evaluation of antihypertensive therapy was assessed using the intensification therapy (IT) score (Equation 1).

$$\text{IT score} = \frac{Observed\ changes - Expected\ changes}{Number\ of\ visits} \quad \ldots \textbf{(1)}$$

Observed changes refer to actual modifications in antihypertensive therapy, including dose escalation or the addition of an antihypertensive drug. Expected changes represent the number of treatment intensifications indicated by persistently uncontrolled blood pressure during follow-up visits. The IT score was calculated per patient over the one-year observation period.

The IT score ranges from -1 to +1, with a negative value indicating delay or absence of intensification therapy when clinically indicated, a value of 0 indicating timely intensification, and a positive value indicating active or aggressive intensification (Fontil et al., 2022; Kim et al., 2021).

For analytical purposes, antihypertensive intensification therapy was subsequently classified into intensification and non-intensification categories. Patients with an IT score ≥0, indicating having timely or active intensification therapy, were categorized into the intensification group, while those with a score <0, indicating absent or delayed intensification, were classified as the non-intensification group.

E. Clinical Outcome Assessment and Statistical Analysis

Clinical outcomes, including blood pressure, fasting plasma glucose, and HbA1c, were determined based on standardized measurements documented at the latest visit in 2024. ASCVD status was also evaluated as a clinical factor associated with therapy intensification patterns, given

its significant contribution to morbidity and mortality.

Controlled blood pressure was defined as systolic pressure ≤130 mmHg for patients aged < 65 years, and 130−139 mmHg for older patients, with diastolic blood pressure in the range 70-79 mmHg for all age groups. Measurements outside these ranges were classified as uncontrolled (PERKI, 2022).

HbA1c control was defined as HbA1c <7 % for patients aged <65 years and <8.5% for older patients. FPG control was defined by the range 80-130 mg/dL. Values outside these ranges were classified as uncontrolled (PERKENI, 2021).

Data analysis was performed using SPSS, including descriptive statistics to summarize patient characteristics and binary logistic regression analysis to evaluate the association between therapy intensification and clinical target attainment, as well as ASCVD status. Age and sex were included as adjustment variables based on their clinical relevance. A p-value of <0.05 was considered statistically significant.

III. RESULTS AND DISCUSSION

Based on the patient characteristics in Table I, most of the patients with T2DM and hypertension were women (53.1%) aged 40−64 years. This finding is in line with the literature, which states that biological, hormonal, and lifestyle factors can mutually increase the risk of cardiovascular disease in women. Prior studies indicate that during the premenopausal phase, estrogen exerts cardioprotective effects through improved lipid profiles, enhanced insulin sensitivity, and vasodilatation. This protective effect, however, declines significantly after menopause, resulting in an elevated cardiometabolic risk (Colafella & Denton, 2018; Siusiuka et al., 2024).

Table I. Patient characteristics

Patient characteristic	n (%)
Gender	
Female	95 (53.1)
Male	84 (46.9)
Age	
40 – 64 (adult)	114 (63.7)
≥ 65 (older people)	65 (36.3)
ASCVD status	
ASCVD	60 (33.5)
Non-ASCVD	119 (66.5)
Received Therapy	
Antidiabetic	46 (25.7)
Antihypertensive	3 (1.7)
Both Therapies	130 (72.6)
Blood Pressure	
Controlled	70 (39.1)
Uncontrolled	109 (60.9)
Fasting Plasma Glucose	
Controlled	48 (55.2)
Uncontrolled	39 (44.8)
HbA1c	
Controlled	19 (24.1)
Uncontrolled	60 (75.9)

Hypertension risk in women has also been linked to reproductive factors, such as menstrual history, pregnancy complications, and parity (Wang et al.,

2024). In addition, an unhealthy lifestyle with inappropriate dietary habits and physical inactivity may exacerbate the risk of diabetes and hypertension (Colafella & Denton, 2018). Furthermore, in this study, one-third (33.5%) of patients presented a history of ASCVD, underscoring T2DM and hypertension as significant risk factors for cardiovascular complications (Moke et al., 2023; Petrie et al., 2018).

Regarding treatment patterns, most of the patients (72.6%) received a combination of therapies for diabetes and hypertension. However, clinical parameters revealed that 60.9% of patients did not achieve optimal blood pressure control, and 75.9% failed to reach their HbA1c target. These findings suggest that the current therapy may have been suboptimal for achieving glycemic and blood pressure targets. Various factors may contribute to this failure, including low medication adherence, inadequate treatment adjustments, and insufficient familiarity with current treatment guidelines (Rodriguez et al., 2024).

Consistent with this finding, previous studies have verified that medication adherence has a significant impact on glycemic control, HbA1c target attainment, and blood pressure control (Asseggaf & Ulfah, 2022; Ariyanti et al., 2024; Pratiwi et al., 2024). A further study also confirmed that timely intensification by clinicians can significantly improve HbA1c target achievement (Buysman et al., 2018).

Table II. Effect of antidiabetic intensification therapy on glycemic outcome attainment

Category	Glycemic Outcome n (%)			
	Achieved	**Not achieved**	**p-value**	**OR (95% CI)**
HbA1c (n=79)				
Intensification	1 (1.3)	17 (21.5)	0.10	0.15 (0.01-1.45)
Deintensification	3 (3.8)	2 (2.5)	0.19	4.65 (0.46-46.24)
Combination	6 (7.6)	28 (35.4)	0.11	0.33 (0.08-1.26)
No Change	9 (11.4)	13 (16.5)		1.000 (reference)
Total	19 (24.1)	60 (75.9)		
FPG (n=86)				
Intensification	6 (7)	7 (8.1)	0.21	0.41(0.10-1.66)
Deintensification	4 (4.7)	4 (4.7)	0.39	0.49 (0.09-2.48)
Combination	19 (22.1)	18 (20.9)	0.22	0.52 (0.18-1.47)
No Change	19 (22.1)	9 (10.5)		1.000 (reference)
Total	48 (55.8)	38 (44.2)		

Table III. Effect of antihypertensive intensification therapy on blood pressure target attainment

Category	Blood Pressure Outcome n (%)			
	Achieved	**Not achieved**	**p-value**	**OR (95% CI)**
Intensification Therapy	9 (6.8)	3 (2.3)		
No Intensification Therapy	38 (28.6)	83 (62.3)	0.008	6.32 (1.60-24.91)
Total	47 (35.3)	86 (64.7)		

Given the high percentage of patients who failed to meet their glycemic and blood pressure targets, further analysis was conducted to evaluate whether intensified therapy was associated with improved outcomes. After controlling for age and sex, the results of the logistic regression in Table II revealed that none of the antidiabetic intensification patterns were significantly associated with achieving HbA1c or FPG targets (p-value >0.05). These findings differ from those reported by Buysman et al. (2018), who reported that timely intensification therapy improved HbA1c levels (Buysman et al., 2018). Several factors may explain these findings, including a higher baseline HbA1c level, which makes it more challenging to achieve targets (Canivell et al., 2019). Moreover, previous studies have shown that the most significant reduction in HbA1c occurs within the first six months after intensification, with minimal benefit observed at 12 months. This suggests that if patients do not achieve the target during the initial period, they generally remain noncompliant by the end of the observation period. Furthermore, the study also found that medication adherence tends to decline after treatment intensification, which may limit the effectiveness of this approach (Jude et al., 2019, 2020).

In antihypertensive intensification therapy, among the 179 outpatients included in the study, 133 were eligible for the antihypertensive intensification study. The analysis was performed using the IT score, which ranges from -1 to +1. The median IT score was −0.600 (IQR: −0.800 to −0.362), indicating that treatment intensification occurred less frequently than clinically expected during the observation period. Most patients (n=121, 91%) had an IT score <0, suggesting absent or delayed intensification. Only 12 patients (9%) demonstrated an IT score ≥0, reflecting timely or active intensification. Binary logistic regression (Table III) demonstrated a significant association between antihypertensive intensification and blood pressure outcome (p-value = 0.008; OR = 6.32; 95% CI: 1.60-24.91), indicating that patients who received intensification therapy were 6.32-fold more likely to

achieve blood pressure control compared to patients who did not. This result is consistent with a previous study indicating that early intensification therapy, particularly within the first month of diagnosis, results in better blood pressure control over 6−30 months and contributes to better clinical outcomes (Barrett et al., 2025).

Following the evaluation of glycemic and blood pressure outcomes, the association between therapy intensification and ASCVD status was examined due to its significant contribution to morbidity and mortality among patients with T2DM and hypertension. The results in Table IV show that both deintensification and combined therapy categories were significantly associated with ASCVD status, where deintensification had a p-value of 0.049 (OR = 3.453; 95% CI: 1.008−11.828), and combination therapy had a p-value of 0.021 (OR = 2.558; 95% CI: 1.152−5.677). This indicates that patients who received deintensification and combination therapy were approximately 3.4-fold and 2.5-fold, respectively, more likely to have ASCVD status compared to the group with no change in therapy. These findings are consistent with the literature reporting that deintensification therapy is more commonly administered in patients with existing cardiovascular disease, older patients, patients with multimorbidity, and a higher risk of hypoglycemia (Wong et al., 2022).

The combination pattern of intensification and deintensification strategies reflects a more complex clinical condition, where patients with diabetes and ASCVD have a high risk of major cardiovascular events (MACE). In such a high-risk population, current clinical guidelines prioritize the use of cardio-renal protective agents, such as SGLT2 inhibitors or GLP-1RAs (Aristizábal-Colorado et al., 2025). On the other hand, deintensification or simplification therapy is also necessary, especially in conditions of clinical instability such as decreased kidney function, hospitalization conditions, and hypoglycemia (Bahat et al., 2023).

Table IV. Effect of antidiabetic intensification therapy on ASCVD

Category	ASCVD Status n (%)			
	ASCVD	Non ASCVD	p-value	OR (95% CI)
Intensification	6 (3.4)	23 (13.1)	0.944	0.10 (0.34-3.17)
Deintensification	7 (4)	8 (4.5)	0.049	3.45 (1.00-11.82)
Combination	30 (17)	45 (25.6)	0.021	2.56 (1.00-11.82)
No Change	14 (8)	43 (24.4)		1.000 (reference)
Total	57 (3.4)	119 (67.6)		

Table V. Effect of antihypertensive intensification therapy on ASCVD

Category	Blood Pressure Outcome n (%)			
	ASCVD	**Non ASCVD**	**p-value**	**OR (95% CI)**
Intensification Therapy	11 (8.3)	1 (0.8)	0.006	18.66 (2.305-151.06)
No Intensification Therapy	44 (33.1)	77 (57.9)		
Total	55 (41.4)	78 (58.6)		

In addition, the logistic regression analysis presented in Table V demonstrated a significant association between antihypertensive intensification and ASCVD status (p-value = 0.006; OR = 18.66; 95% CI: 2.30−151.05), indicating that patients on intensified therapy were 18.66-fold more likely to have ASCVD status than patients without intensified therapy. The finding aligns with the 2021 ESC Guideline, which recommends more aggressive blood pressure management with stricter targets (<130/80mmHg) for high-risk patients, including those with established ASCVD (Visseren et al., 2021).

Although glycemic and blood pressure control remained inadequate in this study, the results demonstrate the effectiveness of antihypertensive therapy, although adjustments to intensification were rarely made. Antidiabetic therapy was intensified in only 16.5% of patients, and antihypertensive therapy was intensified in only 9%. The low rate of intensification reflects a disparity between actual clinical practice and guideline recommendations, which focus on consistent individualized assessment, timely adjustment, and appropriate treatment evaluation (Davies et al., 2022; PERKENI, 2021; Visseren et al., 2021). The therapeutic pattern observed in this study is in line with previous studies reporting that more than 40% of physicians in the USA did not intensify the therapy of their patients with T2DM despite clear clinical indication (Grant et al., 2009).

A similar observation has been reported in antihypertensive management, where intensification rates were seen in only 6.7−16.8% of clinical visits with uncontrolled blood pressure (Willock et al., 2018). Together, these results illustrate the concept of therapeutic inertia, which refers to the failure or delay to intensify therapy despite clinically unmet targets. Factors that may contribute to this condition, including concerns about medication side effects, treatment costs, patient adherence, long-term complications, clinician knowledge gaps, limited consultation time, and restricted access to medications (Willock et al., 2018; Usherwood, 2024).

This study has limitations, including an imbalance in category distribution, a relatively small sample size, and limited variability of categories and outcomes,

which may affect the strength of the analysis. Therefore, further research is recommended to include a larger and more evenly distributed sample, employing a prospective design with follow-up to evaluate the long-term effects of therapy intensification. Future prospective studies should incorporate assessment of adverse effects to better identify clinical and patient-centered factors that may hinder long-term adherence following intensification therapy.

IV. CONCLUSION

This study demonstrates that intensification of antihypertensive therapy is associated with improved blood pressure control and ASCVD status among patients with T2DM and/or hypertension in real-world clinical settings. In contrast, intensification of antidiabetic therapy was not significantly associated with glycemic target attainment or ASCVD status. These findings highlight the importance of optimizing antihypertensive therapy to improve cardiovascular risk control in clinical practice.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this research.

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