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### Hubungan Antara Penggunaan Antihipertensi dan Tekanan Darah Tidak Terkontrol Pada Penyakit Ginjal Kronik Dengan Hemodialisis Rutin

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**ABSTRAK:** Hipertensi pada pasien penyakit ginjal kronik (PGK) stadium akhir yang menjalani hemodialisis (HD) merupakan kondisi yang sulit dikendalikan. Penelitian ini bertujuan untuk mengetahui hubungan antara jumlah obat antihipertensi yang dikonsumsi dan penggunaan obat antihipertensi yang terdialisis terhadap tekanan darah yang tidak terkontrol pada pasien PGK yang menjalani hemodialisis. Metode pengambilan sampel yang digunakan adalah consecutive sampling dalam desain penelitian kohort retrospektif. Pengumpulan data penelitian dilakukan pada bulan Juli 2023 di Rumah Sakit Umum Daerah Temanggung. Kriteria inklusi dalam penelitian ini adalah pasien PGK yang menjalani hemodialisis rutin dua kali seminggu, berusia  $\geq 18$  tahun, serta dengan atau tanpa penyakit penyerta. Data dikumpulkan melalui rekam medis dan wawancara dengan subjek penelitian. Sebanyak 52 subjek penelitian terdiri atas 48 pasien dengan luaran klinis berupa tekanan darah pradialisis yang tidak terkontrol dan 4 pasien dengan tekanan darah pradialisis yang terkontrol. Jumlah obat antihipertensi yang digunakan berhubungan secara signifikan dengan tekanan darah pradialisis yang tidak terkontrol pada pasien PGK yang menjalani hemodialisis dan menggunakan obat antihipertensi (nilai  $p = 0,033$ ). Sebaliknya, penggunaan obat antihipertensi yang terdialisis tidak menunjukkan hubungan dengan tekanan darah pradialisis yang tidak terkontrol pada pasien PGK yang menjalani hemodialisis dan menggunakan obat antihipertensi (nilai  $p = 0,115$ ).

**Kata kunci:** Penyakit Ginjal Kronik, Hemodialisis, Antihipertensi

### The Relationship Between Antihypertensive Use And Uncontrolled Blood Pressure In Chronic Kidney Disease With Routine Hemodialysis

**ABSTRACT:** Hypertension in end-stage chronic kidney disease (CKD) patients undergoing HD is difficult to control. The aim of the study was to determine the relationship between the number of antihypertensive medications taken and the use of dialyzed antihypertensive medications on uncontrolled blood pressure in CKD patients on hemodialysis. Consecutive sampling was employed in a retrospective cohort study. Data collection for the study took place in July 2023 at Temanggung Regional Hospital. The inclusion criteria in this study were CKD patients who undergoing routine hemodialysis twice a week, aged  $\geq 18$  years, and without or with comorbidities. Medical records and interviews with research participants were used to gather data. Forty-eight patients with clinical outcomes of uncontrolled predialysis blood pressure and four patients with regulated predialysis blood pressure made up the 52 research subjects. The number of antihypertensive drugs used is significantly associated with uncontrolled predialysis blood pressure in CKD patients with hemodialysis using antihypertensives ( $p$ -value 0,033). The use of dialyzed antihypertensive drugs is not associated with uncontrolled predialysis blood pressure in CKD patients on hemodialysis using antihypertensives ( $p$ -value 0,115).

**Keyword:** Chronic Kidney Disease; Hemodialysis; Antihypertension

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## Introduction

Hypertension is highly prevalent among patients with end-stage chronic kidney disease (CKD) undergoing hemodialysis (HD), affecting approximately 80–85% of adults<sup>1</sup>. The coexistence of CKD and hypertension substantially elevates the risk of cardiovascular complications, which remain the leading cause of morbidity and mortality in this population<sup>2</sup>. In Indonesia, cardiovascular disease accounted for 42% of deaths among HD patients in 2018, while another 31% of deaths were attributed to unknown causes, likely due to occurrences outside healthcare facilities<sup>3</sup>.

Interventions aimed at lowering blood pressure may mitigate cardiovascular risk among individuals with chronic kidney disease (CKD). Nevertheless, hypertension in patients with end-stage CKD undergoing hemodialysis (HD) remains challenging to diagnose and exceedingly difficult to manage<sup>4,5</sup>. Therefore, evaluating the determinants of uncontrolled blood pressure in CKD patients receiving routine HD is essential, as it serves as a critical indicator for assessing therapeutic effectiveness and the overall quality of care provided to hemodialysis-dependent CKD patients. The aim of this study was to determine the relationship between the number of antihypertensive drugs used and the use of dialyzed antihypertensive drugs on uncontrolled blood pressure in chronic kidney patients on hemodialysis who use antihypertensives.

## Methods

The design of this research is an observational study with a retrospective cohort design. Data collection for the study took place in July 2023 at Temanggung Regional Hospital. This research has been approved by the FKMK UGM ethics committee with number KE/FK/1191/EC/2023.

The population of this study were all patients with chronic kidney disease on routine hemodialysis, who met the inclusion criteria by looking at medical record data using a data collection sheet. Inclusion criteria include: all

patients diagnosed with stage 4-5 chronic kidney disease who routinely undergo routine hemodialysis 2 times per week, have undergone hemodialysis for at least 3 months, aged  $\geq 18$  years, patients with or without comorbidities, and willing to take part in the study with sign informed consent.

The instrument used in the research was medical record data from Temanggung Regional Hospital patients. The tool used in the research was a data collection sheet in the form of a data sheet about CKD patients on hemodialysis. Data that will be taken include: medical record number, patient name, date of birth (age), gender, diagnosis, accompanying/ comorbid diseases, predialysis blood pressure, data about the antihypertensive drug used (name of antihypertensive drug, drug dosage, form antihypertensive drug preparations, medication data, patient weight data (predialysis and postdialysis body weight) and laboratory data (predialysis and postdialysis urea). Data was also collected by interviewing patients to obtain the information on the time of use (before or after hemodialysis) of antihypertensive drugs on the day of hemodialysis.

Characteristics of each group of dependent variables include age which is presented in the form of an average and gender which is presented in terms of the number of patients and percentages. Bivariate analysis was carried out to see the relationship between variables, namely the independent variable (the number of antihypertensive drugs used and the use of dialyzed antihypertensives) and the dependent variable (predialysis blood pressure). The blood pressure data used is the average predialysis blood pressure on the 1st to 8th hemodialysis. Bivariate analysis was carried out using Fisher's Exact Test.

## Result

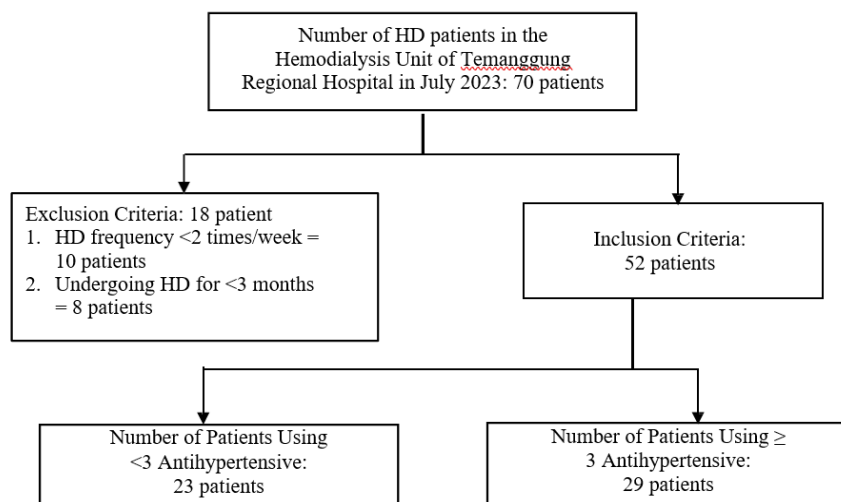
During July 2023, 70 patients, were found undergoing routine hemodialysis at the Hemodialysis Unit of Temanggung Regional General Hospital. Fifty-two patients met the inclusion criteria, while 18 patients met the exclusion criteria. Of the exclusion criteria, 10 patients underwent hemodialysis less than twice

a week, and 8 patients underwent routine hemodialysis less than 3 months. Of the 52 patients who met the inclusion criteria, they were divided into two groups: those receiving <3 antihypertensive medications (23 patients) and those receiving  $\geq 3$  antihypertensive medications (29 patients), it can be seen in Figure 1.

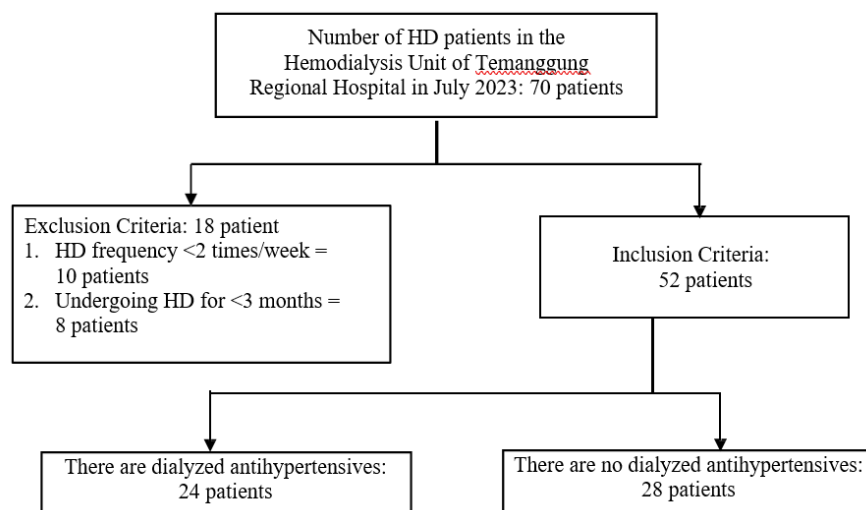
In addition to being divided based on the number of antihypertensive medications used, the 52 patients who met the inclusion criteria were also divided into two groups based on their use of dialyzed antihypertensive medications: those receiving dialyzed

antihypertensive medications and those not receiving dialyzed antihypertensive medications. The flow of determining research subjects based on their use of dialyzed antihypertensive medications, it can be seen in Figure 2.

The use of antihypertensive therapy in chronic kidney disease patients undergoing routine hemodialysis at Temanggung Regional Hospital in July 2023 can be seen in Table 1. The effect of the number of antihypertensive drugs on predialysis blood pressure can be seen in Table 2. The effect of dialysis antihypertensive drug use on predialysis blood pressure can be seen in Table 3.



**Figure 1.** Flowchart for Determining Research Subjects Based on the Number of Antihypertensive Used



**Figure 2.** Flowchart for Determining Research Subjects Based on the Use of Dialyzed Antihypertensive

**Table 1.** Antihypertensive Therapy in CKD Patients Undergoing Routine Hemodialysis at Temanggung Regional Hospital, July 2023

| Antihypertensive Therapy                                      | Number of Patients<br>N (%) |
|---|-----------------------------|
| <b>Monotherapy</b>  |                             |
| Amlodipine  | 3 (6,38)                    |
| Clonidine   | 1 (2,13)                    |
| <b>Combination of 2 Antihypertensives</b>                     |                             |
| Amlodipine + Candesartan                                      | 13 (27,66)                  |
| Bisoprolol + Candesartan                                      | 1 (2,13)                    |
| <b>Combination of 3 Antihypertensives</b>                     |                             |
| Amlodipine + Candesartan + Furosemide                         | 4 (8,51)                    |
| Amlodipine + Candesartan + Diltiazem                          | 4 (8,51)                    |
| Amlodipine + Candesartan + Clonidine                          | 11 (23,40)                  |
| Bisoprolol + Candesartan + Furosemide                         | 1 (2,13)                    |
| Bisoprolol + Candesartan + Nifedipin                          | 1 (2,13)                    |
| Candesartan + Diltiazem + Furosemid                           | 1 (2,13)                    |
| <b>Combination of 4 Antihypertensives</b>                     |                             |
| Amlodipine + Candesartan + Furosemide + Clonidine             | 4 (8,51)                    |
| Amlodipine + Candesartan + Furosemide + Diltiazem             | 2 (4,25)                    |
| <b>Combination of 5 Antihypertensives</b>                     |                             |
| Amlodipin + Candesartan + Furosemide + Clonidine + Bisoprolol | 1 (2,13)                    |
| <b>Total</b>  | 47 (100)                    |

**Table 2.** The Effect of the Number of Antihypertensive Drugs on Predialysis Blood Pressure

| Category                                     | Uncontrolled BP<br>n (%) | Controlled BP<br>n (%) | p Value |
|--|--------------------------|------------------------|---------|
| <b>Number of Antihypertensive Drugs Used</b> |                          |                        |         |
| < 3 Drugs                                    | 19 (82,6)                | 4 (17,4)               | 0.033*  |
| ≥ 3 Drugs                                    | 29 (100)                 | 0 (0)                  |         |

**Note :** BP = Blood Pressure

\* Bivariate analysis was conducted using Fisher's Exact Test, with results considered statistically significant at  $p < 0.05$

**Table 3.** The Effect of Dialysis Antihypertensive Drug Use on Predialysis Blood Pressure

| Category   | Uncontrolled BP<br>n (%) | Controlled BP<br>n (%) | p Value |
|--|--------------------------|------------------------|---------|
| <b>Use of Antihypertensive Drugs During Dialysis</b> |                          |                        |         |
| There is no dialyzed antihypertensive                | 24 (85,7)                | 4 (14,3)               | 0.115   |
| There is dialyzed antihypertensive                   | 24 (100)                 | 0 (0)                  |         |

**Note :** BP = Blood Pressure

## Discussion

Based on study results, the most common combination was two antihypertensives: amlodipine and candesartan (27.66%), followed by three antihypertensives: amlodipine, candesartan, and clonidine (23.40%). In the analysis of antihypertensive medication usage, patients prescribed fewer than three agents exhibited uncontrolled predialysis blood pressure in 19 cases (82.6%) and controlled levels in 4 cases (17.4%). Conversely, all patients receiving more than three antihypertensive agents ( $n = 29$ ; 100%) demonstrated uncontrolled predialysis blood pressure. Bivariate analysis using Fisher's exact test indicated a statistically significant association between the number of antihypertensive medications and predialysis blood pressure outcomes ( $p = 0.033$ ). As the  $p$ -value was less than 0.05, this finding confirms a significant difference in predialysis blood pressure between patients taking fewer than three medications and those taking more than three. These findings are consistent with previous cross-sectional research reporting that a greater number of antihypertensive agents correlates with elevated blood pressure ( $p = 0.002$ )<sup>6</sup>. It is therefore essential that the escalation in pharmacological therapy be accompanied by intensified non-pharmacological interventions. An excessive reliance on multiple antihypertensive medications may perpetuate a cycle of difficulty achieving optimal dry weight, potential fluid overload, and consequently, persistent hypertension<sup>7</sup>.

In this study, a total of 24 patients received dialyzed antihypertensive medications, consisting of 7 patients treated with diltiazem and 17 patients treated with clonidine. In the analysis of dialyzed antihypertensive drug use, all patients who received these medications ( $n = 24$ ; 100%) exhibited uncontrolled predialysis blood pressure (BP). Among patients who did not receive dialyzed antihypertensive medications, 24 patients (85.7%) had uncontrolled predialysis BP, while 4 patients (14.3%) had controlled predialysis BP. Bivariate analysis using Fisher's Exact Test yielded a  $p$ -value of 0.115 for the clinical outcome of predialysis BP. Since the  $p$ -value was greater

than 0.05, there was no statistically significant difference in predialysis BP between patients who received dialyzed antihypertensive medications and those who did not.

According to pharmacokinetic data, clonidine is removed by hemodialysis at approximately 5%, while diltiazem is removed at about 30%<sup>8,9</sup>. However, the results of this study indicate a potential association between the use of dialyzed antihypertensive medications and predialysis blood pressure (BP). A limitation of this study lies in the incomplete documentation within patient medication records, which did not specify the timing of antihypertensive administration. Consequently, it was not possible to verify patient-reported medication use or determine whether diltiazem and clonidine were taken before or after hemodialysis sessions. This uncertainty suggests that some patients may have taken dialyzed antihypertensive agents prior to dialysis, potentially influencing their predialysis BP measurements.

Hemodialysis patients frequently exhibit elevations in blood pressure between treatment sessions, and the administration of antihypertensive agents following dialysis may contribute to post-dialytic blood pressure increases. Moreover, the post-dialysis use of these medications may predispose patients to intradialytic hypertension, which is characterized by a rise in blood pressure occurring during or upon completion of the dialysis procedure<sup>10</sup>. The absence of a statistically significant difference in predialysis BP between the groups may also be attributed to non-adherence to prescribed antihypertensive regimens on dialysis days. Medication non-adherence is known to contribute to uncontrolled BP among hemodialysis patients<sup>11</sup>. In this study, two patients with uncontrolled predialysis BP reported not taking their antihypertensive medications on dialysis days to avoid intradialytic hypotension, while one patient admitted to irregular medication use due to treatment fatigue after prolonged therapy. Another limitation of this study is the lack of patient or caregiver interviews regarding

whether clinicians and pharmacists provided appropriate education on antihypertensive medication use. This gap may have influenced patients' understanding and adherence to therapy, thereby affecting BP control outcomes.

## Conclucions

The number of antihypertensive drugs used is significantly associated with uncontrolled predialysis blood pressure in CKD patients with hemodialysis using antihypertensives (p-value 0,033). The use of dialyzed antihypertensive drugs is not associated with uncontrolled predialysis blood pressure in CKD patients on hemodialysis using antihypertensives (p-value 0,115).

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