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Research Article

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Incidence and prognosis of apparent-treatment resistant hypertension: a multi-state analysis using real world evidence

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ABSTRACT

Background: There is limited evidence regarding the incidence and prognosis of apparent resistant hypertension (aRHT) in hypertensive patients. This study aimed to estimate the incidence of aRHT and assess the risk of cardiovascular and kidney complications in patients with aRHT compared to those without aRHT, using a multi-state analysis.
Methods: This retrospective cohort study utilized real-world data from hypertensive patients treated at Ramathibodi Hospital, Bangkok, Thailand, between January 2010 and June 2024. aRHT was defined as having uncontrolled blood pressure (BP), while using ≥ 3 antihypertensive medications or having controlled BP with using ≥ 4 antihypertensive medications. The outcomes of interest were cardiovascular and kidney complications including coronary artery disease (CAD), stroke, heart failure (HF), and chronic kidney disease (CKD), and all-cause mortality. A multi-state analysis was applied to estimate the risk of disease progression from hypertension without complications to aRHT, CAD, stroke, HF, CKD, and all-cause death. Kaplan-Meier estimates with a clock-reset approach were used to calculate transition probabilities for each progression. Multivariate Cox regression analysis was applied to assess the risk factors of aRHT and assess the prognosis of aRHT.
Results: Among 114,364 hypertensive patients, the incidence of aRHT was 2.61 per 100 person-years (95% confidence interval [CI], 2.56–2.65). Results from multivariate Cox regression analysis found that the independent risk factors of aRHT were increasing age, males, obesity, type 2 diabetes mellitus, dyslipidemia, and having cardiovascular and kidney complications including CAD, stroke, CKD, and HF. Regarding the prognosis of aRHT, compared to non-aRHT patients, those with aRHT had significant higher risk of CAD, CKD, HF, and all-cause mortality with hazard ratios (95% CI) of 1.80 (1.56–2.08), 1.93 (1.79–2.08), 4.24 (3.54–5.08), and 2.84 (1.89–4.27), respectively.

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Abbreviations

ACEI, angiotensin converting enzyme; ARB, angiotensin receptor blocker; aRHT, apparent resistant hypertension; BB, beta-blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; DLP, dyslipidemia; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HF, heart failure; HR, hazard ratio; HT, hypertension; ICD, international classification of diseases; LDL-C, low density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; RHT, resistant hypertension; RW, real-world; SBP, systolic blood pressure; SGLT2, sodium-glucose transport 2; T2DM, type 2 diabetes mellitus.

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Competing interest

The authors declare that they have no competing interests.

Availability of data and materials

Data used for analysis in this study will be available upon request.

Ethics approval and consent to participate

The study protocol was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA.MURA 2024/498 and COA. MURA 2021/512). Informed consent was not obtained because this study was a retrospective cohort using existing data from the hospital database.

Consent for publication

Not applicable.

Conclusions: The risk of aRHT was higher in hypertensive patients with cardiovascular and kidney complications compared to those without. Patients with aRHT had a worse prognosis than hypertensive patients without aRHT, as evidenced by higher risks of CAD, CKD, HF, and all-cause death.

Keywords: Resistant hypertension; Incidence; Cardiovascular diseases; Chronic kidney disease; Multi-state analysis

INTRODUCTION

Hypertension (HT) is the most common chronic disease and a significant risk factor for coronary artery disease (CAD), stroke, heart failure (HF), and chronic kidney disease (CKD), which are the leading causes of disability and premature deaths worldwide [1]. In Thailand, the sixth National Health Examination Survey conducted in 2019 revealed that 25.4% of Thai adults had HT, of which, 4.3%, 4.2%, and 13.1% developed CAD, stroke, and CKD, respectively [2]. Blood pressure (BP) control is a crucial factor that significantly reduces the risk of these complications in hypertensive patients [3]. However, a significant proportion of treated hypertensive patients fail to achieve long-term BP control [4].

Resistant HT (RHT) is defined as uncontrolled BP despite treatment with 3 or more different antihypertensive medications at their maximum tolerated doses [5]. RHT is a significant contributor to uncontrolled BP in HT patients. The prevalence of RHT varies geographically; global prevalence is estimated at 14.7%, with higher rates reported in Southeast Asia (15.7%), the Western Pacific (19.2%), and the Eastern Mediterranean (20.3%) [6]. While several studies have examined RHT prevalence, data on incidence and prognosis, particularly in Asian populations, remain limited.

Studies in Western populations have shown that RHT is associated with increased risk of end-organ damage compared to non-RHT patients, including carotid intima-media thickening, retinopathy, left ventricular hypertrophy, HF, myocardial infarction, stroke, and CKD [7-9]. Conversely, RHT is highly prevalent among patients with cardiovascular disease (CVD) and CKD [10,11] suggesting that the relationship between RHT and these cardiorenal outcomes may be bidirectional.

Evidence on the bidirectional relationship pathways between RHT and long-term cardiovascular-kidney complications is limited, especially in real-world (RW) clinical settings. Therefore, this retrospective cohort study using RW data from Thailand aimed to evaluate these bidirectional pathways by 1) estimating the incidence of RHT among hypertensive patients with and without such complications, and 2) comparing the risks of cardiovascular–kidney complications—including CAD, stroke, HF, and CKD—between patients with RHT and those without RHT using multistate modelling. However, diagnosing true RHT requires ruling out the white-coat effect and nonadherence to antihypertensive medication. Therefore, in this study, RHT refers to apparent RHT (aRHT), which includes patients whose uncontrolled BP may be influenced by factors such as medication nonadherence, suboptimal treatment regimens, or the white-coat effect [5]. These findings will inform the management of RHT and aid in developing improved treatment strategies specifically within the Thai healthcare context.

Authors' contributions

Conceptualization: Anothaisintawee T, Thakkinstian A, Teza H, McKay GJ, Attia J; Data curation: Teza H, Thakkinstian A, Boonmanunt S, Pattanateepapon A; Formal analysis: Anothaisintawee T, Teza H, Limpijankit T, Tansawet A, Thakkinstian A; Investigation: Anothaisintawee T, Teza H, Limpijankit T, Tansawet A, Thakkinstian A; Validation: Teza H, Thakkinstian A, Boonmanunt S, Pattanateepapon A; Writing - original draft: Anothaisintawee T, Teza H; Writing - review & editing: Boonmanunt S, Limpijankit T, Tansawet A, Pattanateepapon A, McKay GJ, Attia J, Thakkinstian A.

METHODS

This retrospective cohort study analyzed data from a master HT cohort [12], comprising patients treated at Ramathibodi Hospital between 2010 and 2024. Hypertensive patients were identified using international classification of diseases (ICD)-10 codes (i.e., I10, I11, I12, I13, I15). In addition, hypertensive patients were identified from antihypertensive medication use, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers (BBs), diuretics, alpha-1 antagonists, hydralazine, and minoxidil. The cohort was updated every 4 months for follow-up data and every 6 months to identify new HT cases through June 2024.

Data linkage was performed using unique hospital numbers, and patients were categorized into 3 groups: those diagnosed with HT based on ICD-10 codes only, those diagnosed using both ICD-10 codes and antihypertensive medication use, and those diagnosed based on medication use only. However, some antihypertensive medications are commonly prescribed for other conditions, such as BBs for hyperthyroidism, ACEIs and ARBs for HF, and alpha-1 antagonists for benign prostatic hyperplasia. Therefore, patients who were prescribed only one of these medications for an alternative indication, such as hyperthyroidism, were excluded from the study. In addition, individuals diagnosed with HT during 2005–2010 who had developed complications before the study's initiation were excluded from the study.

The study protocol was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA.MURA 2024/498 and COA. MURA 2021/512). Informed consent was not obtained because this study was a retrospective cohort using existing data from the hospital database.

Study participants

Patients were eligible for this study if they met the following criteria: they were 18 years or older, newly diagnosed with HT between January 2010 and June 2024, had no cardiovascular or kidney complications prior to or at the time of their HT diagnosis, and were prescribed at least one anti-hypertensive medication. Patients were excluded if they had less than 2 follow-up visits after being prescribed antihypertensive medications. The flow chart of patient identification is presented in **Fig. 1**.

Data collection

Demographic data (i.e., age, sex, and reimbursement scheme), physical examination (i.e., body mass index [BMI], systolic BP [SBP] and diastolic BP [DBP]), underlying diseases (i.e., diabetes mellitus [DM], dyslipidemia [DLP], and hyperthyroidism), laboratory values (i.e., fasting plasma glucose, total cholesterol, high density lipoprotein cholesterol [HDL-C], low density lipoprotein cholesterol [LDL-C], serum triglyceride, and serum creatinine), and drug prescriptions (i.e., anti-hypertensive medications, and statins) were retrieved to form the master HT cohort since the date of initiation of anti-hypertensive medications (i.e., index date) to the date of last follow-up visit. Demographic and physical examinations were retrieved from electronic medical records and hospital information systems. BP was measured using a standardized clinic-based automated BP cuff after patients had rested for at least 15 minutes. All BP values were obtained from the hospital information system. BMI was calculated by dividing body weight in kilograms (kg) by height in meter^2 (m^2). The underlying diseases were identified by ICD-10 codes. Medical prescriptions (including dose, frequency/ day, and number of prescriptions) were retrieved from the computerized provider order

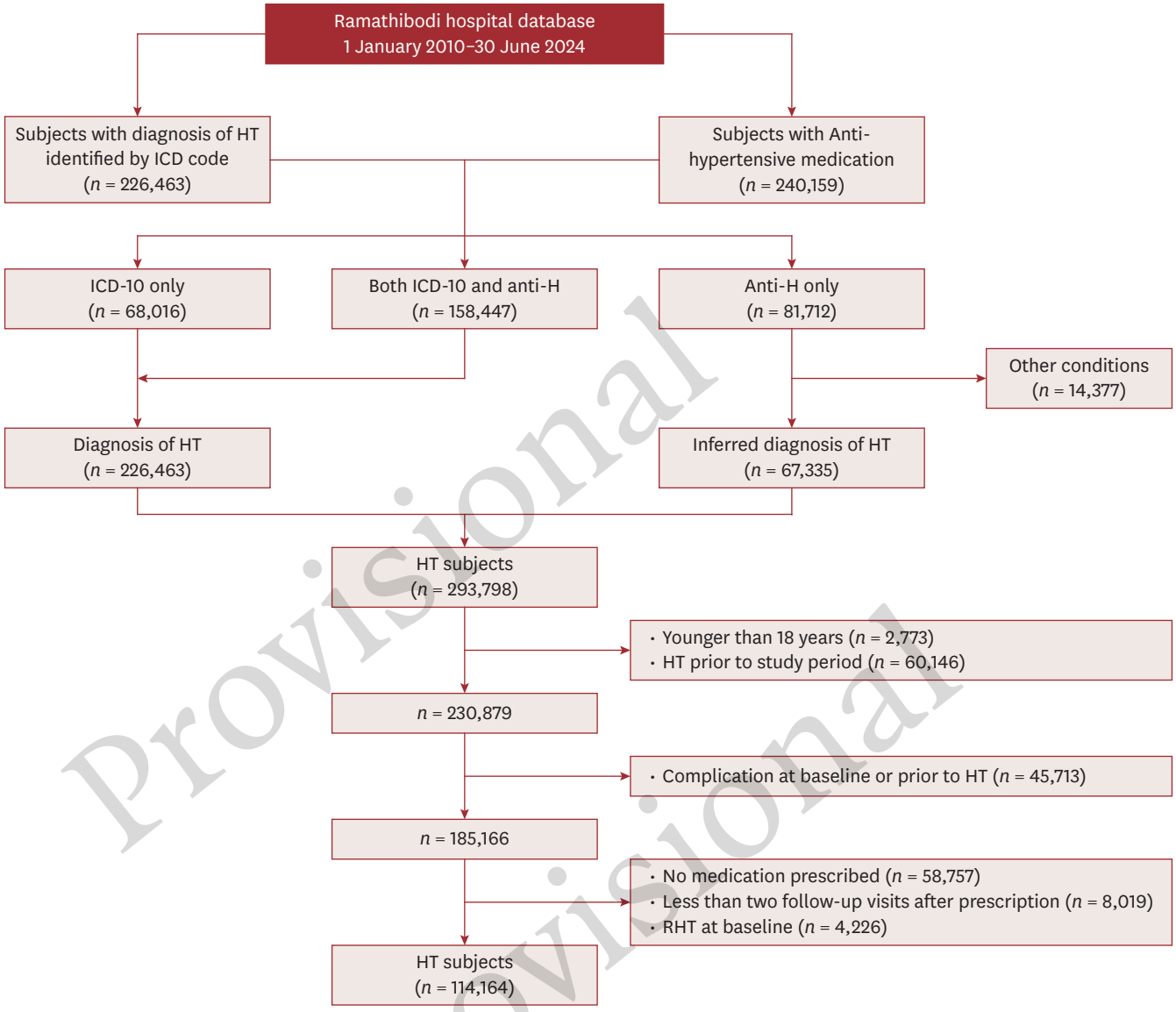

Fig. 1. Flow chart of study participants.
HT, hypertension; ICD, international classification of diseases; RHT, resistant hypertension.

entry system and billing databases according to generic/original trade names, Thai Medical Terminology, and in-house codes. Laboratory data were retrieved from the hospital laboratory information system based on logical observation identifier names and codes.

Outcomes of interest

Outcomes of interest were aRHT, cardiovascular-kidney complications of HT, and all-cause death. Patients were classified as having aRHT if their BP remained uncontrolled (SBP/DBP > 140/90 mmHg) despite using 3 or more antihypertensive medications from different classes or if their BP was controlled (SBP/DBP < 140/90 mmHg) but required the use of 4 or more antihypertensive medications from different classes [13].

Cardiovascular-kidney complications of HT included CAD, stroke, HF, and CKD. Patients were diagnosed with CKD if their estimated glomerular filtration rate (eGFR) was less

than 60 mL/min/1.73 m^2 on 2 consecutive occasions, at least 90 days apart, or having ICD-10 for CKD (i.e., N18, and N19) or ICD-9 codes for renal replacement therapy. The eGFR (mL/min/1.73 m^2) was calculated using the CKD Epidemiology Collaboration equations [14]. CAD was identified using ICD-10 (i.e., I20, I21, I22, I23, I24, I25) and ICD-9 codes and procedure codes for percutaneous coronary intervention, coronary artery bypass graft surgery ('00.4,' '00.66,' '17.55,' '36.0,' '36.1,' '36.31,' '36.99'). Additionally, CAD was identified using troponin levels in conjunction with electrocardiogram (ECG) findings. CAD was diagnosed when the troponin-T level exceeded 14 ng/mL, and there were positive ECG findings occurring within 2 weeks before or after the troponin test. Stroke was identified using ICD-10 codes for ischemic stroke (i.e., I63, I64) and hemorrhagic stroke (i.e., I60, I61, I62, I69). HF was confirmed based on an ejection fraction of less than 50% as measured by an echocardiogram and/or the ICD-10 code of I50.

All-cause death was defined as death from any cause and was verified using hospital death certificates.

Statistical analysis

A multi-state model was applied to analyze disease progression from initial complication-free state, incorporating transient states (i.e., aRHT, CAD, stroke, HF, CKD) and an absorbing state (i.e., all-cause mortality) (**Fig. 2**). The model included 31 possible transitions: 6 transitions from the initial complication-free state (state 1) to either an intermediate

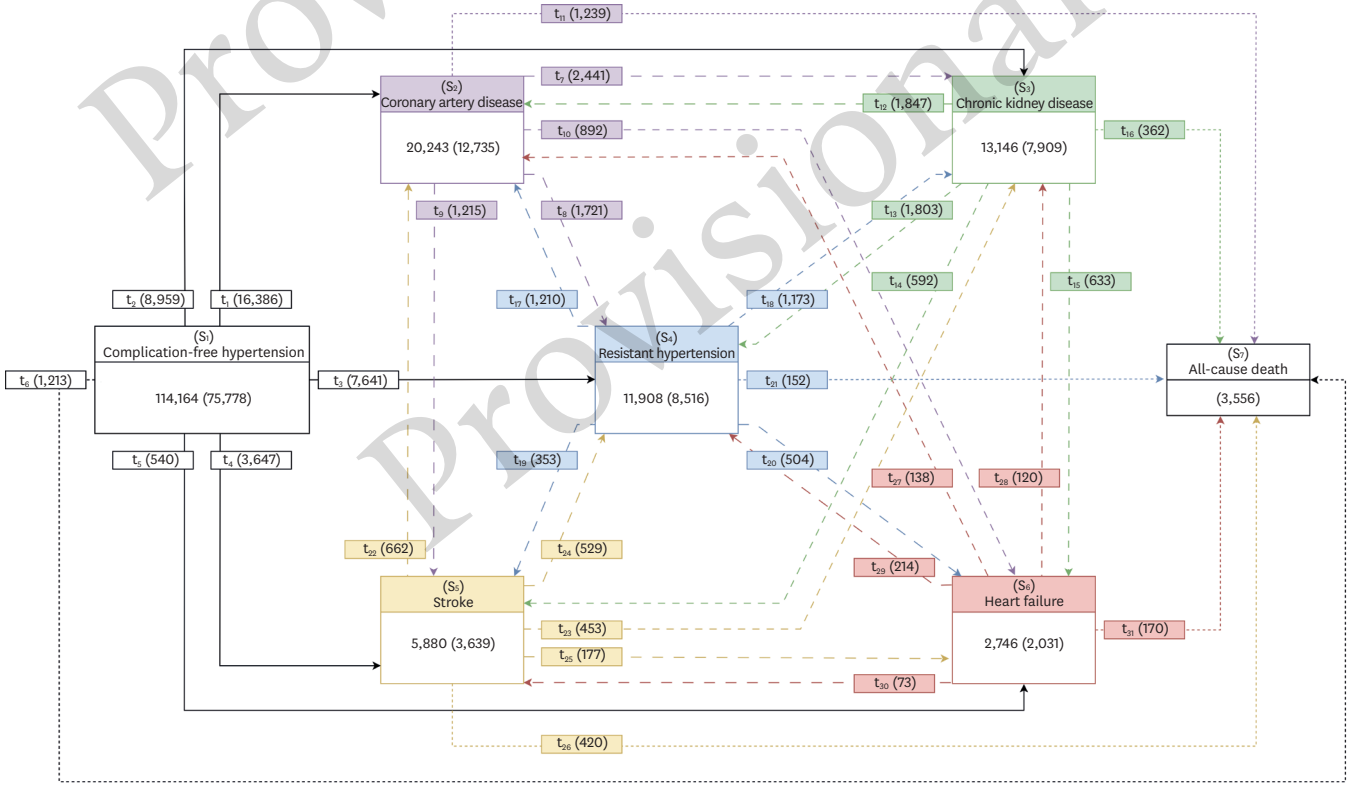

Fig. 2. A Multistate model of disease progression among hypertensive patients. There are 7 states (S_1–S_7) with a total of 31 possible transitions. The numbers in brackets along each transition indicate the number of patients who moved from the state at the tail of the arrow to the state at the head of the arrow. For example, in transition t1, 16,386 patients progressed from complication-free hypertension (tail state) to coronary artery disease (head state). The numbers in brackets within each state denote the number of patients who remained in that state without transition, while the numbers outside the brackets represent the total number of patients who occupied that state at any point during follow-up.

state (states 2–6) or directly to the absorbing state (state 7), and 25 transitions between the intermediate states or from these states to death.

Time from the index date (first antihypertensive prescription in complication-free state) to each transient (i.e., aRHT, CAD, CKD, stroke, HF) or death state was calculated, whichever occurred first. For patients experiencing subsequent transitions, the time from one transient state to another transient or absorbing state was also calculated. Patients without events were censored on June 30, 2024. If a patient was lost to follow-up, censoring occurred on the date of their last recorded visit.

Kaplan-Meier estimates with a clock-reset approach were used to calculate transition probabilities for each transition. The probabilities of having cardiovascular-kidney complications were compared between patients who did and did not develop aRHT using multivariate Cox proportional hazards models. Co-variables (e.g., age, sex, BMI, history of DM, statin use, and eGFR) with *P*-value less than 0.1 from univariate Cox regression analysis, were considered in multivariate Cox regression analysis to assess the independent association between aRHT and the risks of cardiovascular-kidney complications. All analyses were performed using the lifelines package (version 0.30.0) [15] and Python (version 3.12.8) [16] in Visual Studio Code (version 1.96.4) [17].

RESULTS

The process for identifying and forming the HT cohort is illustrated in **Fig. 1**. In summary, 230,879 adult patients were diagnosed with HT between January 2010 and June 2024. Exclusion criteria were as follows: pre-existing complications prior to HT diagnosis (n = 45,713), lack of anti-hypertensive medication at diagnosis (n = 58,757), fewer than 2 follow-up visits after initiating anti-hypertensive treatment (n = 8,019), and a diagnosis of aRHT at the time of initial HT diagnosis (n = 4,226). Finally, 114,364 patients were included in this cohort study, contributing a total of 502,249 person-years. The median follow-up time (interquartile range [IQR]) was 2.36 years (1.01–4.97).

Baseline characteristics of the study participants are summarized in **Table 1**. The mean age and BMI were 59.8 ± 15.2 years and 26.5 ± 5.3 kg/m^2, respectively; 60.5% were females. The Civil Servant Medical Benefits Scheme covered 42.4% of participants. Prevalence of type 2 DM (T2DM), DLP, and hyperthyroidism were 23.7%, 45.2% and 5.2%, respectively. Initial anti-hypertensive medication use was most frequent for CCBs (44%), followed by renin-angiotensin-aldosterone system (RAAS) inhibitors (37.3%), BBs (25.4%), diuretics (6.53%), and mineralocorticoid receptor antagonists (MRAs; 0.73%). Only 1.4% of patients with type DM received sodium-glucose transport 2 (SGLT2) inhibitors. Mean ± standard deviation

Table 1. Baseline characteristics of study's participants

Factors	Participants (N = 114,164)
Demographic data	
Age (yrs)	59.79 ± 15.15
< 60	52,317 (45.83)
≥ 60	61,847 (54.17)
Sex	
Females	69,061 (60.49)
Males	45,103 (39.51)

(continued to the next page)

Table 1. (Continued) Baseline characteristics of study's participants

Factors	Participants (*N* = 114,164)
Reimbursement	
Civil Servant Medical Benefits Scheme	48,371 (42.37)
Social Security Scheme	5,598 (4.90)
Universal Health Coverage	15,760 (13.80)
Others	44,435 (38.93)
Physical examination	
Body mass index (kg/m^2)	26.51 ± 5.34
< 23	18,629 (16.32)
23–27.5	30,121 (26.38)
≥ 27.5	27,700 (24.26)
Systolic blood pressure (mmHg)	152 (137–163)
Diastolic blood pressure (mmHg)	86.15 ± 10.78
Underlying diseases	
Diabetes mellitus	
Yes	27,071 (23.71)
No	87,093 (76.29)
Hyperthyroidism	
Yes	5,975 (5.23)
No	108,189 (94.77)
Dyslipidemia	
Yes	51,542 (45.15)
No	62,622 (54.85)
Anti-hypertensive medications at baseline	
Renin-angiotensin system inhibitor	
Yes	37,365 (32.73)
No	76,799 (67.27)
Beta blockers	
Yes	29,023 (25.42)
No	85,141 (74.58)
Calcium channel blockers	
Yes	50,275 (44.04)
No	63,889 (55.96)
Diuretics	
Yes	7,456 (6.53)
No	106,708 (93.47)
Mineralocorticoid receptor antagonists	
Yes	113,328 (99.27)
No	836 (0.73)
Initial medication count	
None	0
Monotherapy	90,351 (79.14)
Combination therapy	23,813 (20.86)
Other medications	
Statins	
Yes	49,808 (43.63)
No	64,356 (56.37)
SGLT2i in patients with diabetes mellitus	
Yes	368 (1.36)
No	26,703 (98.64)
Laboratory	
Fasting plasma glucose	106 (95–131)
Total cholesterol (mg/dL)	193.74 ± 48.16
High density lipoprotein cholesterol (mg/dL)	53.06 ± 14.01
Low density lipoprotein cholesterol (mg/dL)	119.26 ± 37.83
Triglyceride (mg/dL)	118 (87–163)
Serum creatinine	0.81 (0.68–1.00)
eGFR (mL/min/1.73 m^2)	85.59 ± 18.08

Values are presented as mean ± standard deviation or median (interquartile range) or number (%).
SGLT2i, sodium glucose transport 2 inhibitor; eGFR, estimated glomerular filtration rate.

LDL-C, HDL-C, and eGFR levels were 119.3 ± 37.8 mg/dL, 53.1 ± 14.0 mg/dL, and 85.6 ± 18.1 mL/min/1.73 m^2, respectively.

Incidence of aRHT

A total of 11,908 out of 114,364 patients subsequently developed aRHT, with an incidence rate of 2.61 per 100 person-years (95% confidence interval [CI], 2.56–2.65) (**Fig. 2**). **Table 2** and **Fig. 3** present the 5- and 10-year transition probabilities of developing aRHT from the initial states of being complication-free, CAD, stroke, HF, and CKD. Among HT patients who were initially complication-free, the probabilities of developing aRHT were 9.63% (95% CI, 9.39–9.88) at 5 years and 15.19% (95% CI, 14.80–15.59) at 10 years. These probabilities were lower than those observed in HT patients with existing cardiovascular and renal complications. Among patients with complications, the highest 5-year cumulative risk of developing aRHT was observed in those with HF (38.0%; 95% CI, 32.4–44.22), followed by CKD (20.96%; 95% CI, 19.98–21.98), stroke (16.98%; 95% CI, 15.49–18.59), and CAD (16.57%; 95% CI, 15.74–17.44) (**Table 2**).

Risk factors for RHT

For the risk factors associated with aRHT, results from the univariate Cox regression analysis suggested that increasing age, male sex, obesity, history of T2DM and DLP, and the presence of cardiovascular and kidney complications were significantly associated with the risk of aRHT (**Supplementary Table 1**). Findings from the multivariate Cox regression analysis confirmed that these factors were independently associated with the risk of aRHT. Each 1-year increase in age significantly raised the risk of aRHT, with a hazard ratio (HR) of 1.007 (95% CI, 1.006–1.008) (**Table 3**). Males had a 1.11-fold higher risk of aRHT (95% CI, 1.08–1.14) compared to females, while patients with a history of T2DM, and DLP had a 1.28-fold (95% CI, 1.25–1.32) and 1.17 (95% CI, 1.14–1.20) higher risk compared to those without T2DM and DLP. Regarding cardiovascular and kidney complications, the HRs were 2.58 (95% CI, 2.47–2.70) for CAD, 2.02 (95% CI, 1.87–2.17) for stroke, 3.12 (95% CI, 2.98–3.28) for CKD, and 1.96 (95% CI, 1.74–2.21) for HF.

Risk of complications and all-cause mortality between RHT and non-RHT

Overall, 16,386, 8,959, 3,647, and 540 patients developed CAD, CKD, stroke, and HF, respectively, with incidence rates (95% CI) of 4.52 (4.45–4.59), 2.47 (2.42–2.52), 1.01 (0.97–1.04), and 0.15 (0.14–0.16) per 100 person-years (**Fig. 2**). Regarding all-cause mortality, 1,213 patients died during the follow-up period, resulting in a mortality rate of 0.33 (0.32–0.35) per 100 person-years (**Fig. 2**).

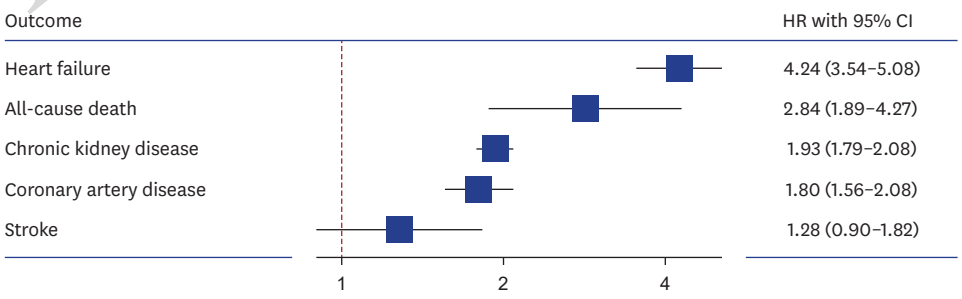

Fig. 3. HR of cardiovascular and kidney complications in patients with apparent resistant hypertension: results from multivariate Cox regression analysis.
HR, hazard ratio; CI, confidence interval.

Table 2. Cumulative transitional probability of each state

Transition	Time (yrs)									
	1	2	3	4	5	6	7	8	9	10
Initial → aRHT	**3.68 (3.36–3.81)**	5.46 (5.30–5.63)	6.82 (6.63–7.01)	8.37 (8.15–8.59)	**9.63 (9.39–9.88)**	10.83 (10.56–11.10)	12.20 (11.90–12.50)	13.31 (12.98–13.64)	14.14 (13.78–14.50)	**15.19 (14.80–15.59)**
CAD → aRHT	**6.39 (5.99–6.83)**	9.30 (8.78–9.86)	12.13 (11.49–12.79)	14.80 (14.05–15.58)	**16.57 (15.74–17.44)**	18.50 (17.57–19.48)	20.39 (19.33–21.50)	21.62 (20.48–22.82)	22.85 (21.60–24.16)	**24.13 (22.74–25.59)**
CKD → aRHT	**7.49 (6.99–8.03)**	11.27 (10.62–11.95)	15.30 (14.52–16.11)	18.24 (17.36–19.15)	**20.96 (19.98–21.98)**	23.46 (22.37–24.60)	26.00 (24.77–27.27)	27.94 (26.60–29.34)	29.44 (27.97–30.96)	**31.34 (29.69–33.05)**
Stroke → aRHT	**7.12 (6.35–7.98)**	10.03 (9.06–11.10)	13.02 (11.84–14.30)	15.11 (13.78–16.56)	**16.98 (15.49–18.59)**	18.36 (16.73–20.13)	20.23 (18.37–22.25)	22.42 (20.24–24.81)	24.08 (21.60–26.80)	**25.37 (22.57–28.45)**
HF → aRHT	**13.55 (11.47–15.98)**	20.88 (17.75–24.48)	26.17 (22.35–30.50)	29.69 (25.33–34.62)	**38.00 (32.40–44.22)**	42.31 (36.02–49.20)	46.82 (39.71–54.53)	49.99 (42.14–58.44)	51.91 (43.55–60.85)	**55.12 (45.36–65.44)**
Initial → CAD	**10.84 (10.65–11.04)**	12.65 (12.44–12.87)	14.05 (13.82–14.29)	15.44 (15.19–15.70)	**16.85 (16.58–17.13)**	18.22 (17.92–18.52)	19.87 (19.54–20.20)	21.37 (21.01–21.73)	22.91 (22.52–23.31)	**24.71 (24.27–25.16)**
aRHT → CAD	**5.57 (5.08–6.11)**	8.87 (8.22–9.56)	11.62 (10.85–12.44)	14.41 (13.53–15.35)	**17.47 (16.46–18.55)**	19.76 (18.63–20.94)	22.71 (21.41–24.08)	25.50 (24.00–27.08)	27.86 (26.14–29.66)	**30.74 (28.64–32.95)**
Stroke → CAD	**10.21 (9.22–11.30)**	14.62 (13.38–15.96)	17.88 (16.45–19.42)	20.52 (18.92–22.23)	**23.67 (21.85–25.62)**	26.71 (24.65–28.91)	30.10 (27.73–32.62)	33.50 (30.77–36.41)	36.63 (33.49–39.97)	**36.63 (33.49–39.97)**
CKD → CAD	**8.75 (8.17–9.36)**	12.44 (11.73–13.18)	16.42 (15.59–17.29)	19.89 (18.94–20.87)	**22.67 (21.62–23.76)**	25.79 (24.61–27.02)	28.97 (27.63–30.36)	32.01 (30.49–33.58)	35.57 (33.82–37.37)	**38.77 (36.78–40.83)**
HF → CAD	**14.31 (11.63–17.53)**	25.37 (20.58–31.03)	29.65 (24.17–36.05)	39.70 (32.81–47.44)	**45.88 (37.95–54.61)**	51.01 (42.05–60.67)	58.07 (47.43–69.11)	58.07 (47.43–69.11)	66.45 (49.56–82.50)	**66.45 (49.56–82.50)**
Initial → CKD	**5.34 (5.22–5.52)**	7.29 (7.11–7.47)	8.66 (8.46–8.87)	9.78 (9.55–10.00)	**10.81 (10.57–11.06)**	11.89 (11.62–12.16)	13.16 (12.86–13.46)	14.37 (14.04–14.70)	15.41 (15.05–15.78)	**16.36 (15.97–16.76)**
aRHT → CKD	**6.32 (5.78–6.90)**	9.82 (9.13–10.56)	12.60 (11.79–13.45)	15.08 (14.18–16.04)	**17.39 (16.38–18.45)**	19.96 (18.82–21.17)	22.49 (21.19–23.85)	24.21 (22.77–25.73)	25.52 (23.93–27.19)	**29.47 (27.24–31.83)**
CAD → CKD	**11.23 (10.71–11.78)**	14.80 (14.17–15.45)	17.39 (16.68–18.13)	19.19 (18.41–19.99)	**20.86 (20.01–21.74)**	22.78 (21.84–23.76)	24.64 (23.57–25.73)	26.04 (24.88–27.24)	27.58 (26.30–28.92)	**29.09 (27.66–30.58)**
Stroke → CKD	**6.36 (5.60–7.22)**	9.54 (8.55–10.65)	12.58 (11.36–13.92)	14.65 (13.27–16.16)	**16.48 (14.94–18.16)**	18.40 (16.65–20.31)	19.54 (17.63–21.62)	20.82 (18.71–23.13)	22.33 (19.91–24.98)	**23.18 (20.55–26.09)**
HF → CKD	**11.30 (8.95–14.21)**	21.96 (16.28–29.24)	26.72 (19.65–35.72)	41.52 (29.56–56.02)	**46.39 (32.61–62.66)**	46.39 (32.61–62.66)	59.16 (40.93–78.19)	59.16 (40.93–78.19)	59.16 (40.93–78.19)	
Initial → Stroke	**2.26 (2.16–2.36)**	2.89 (2.78–3.01)	3.38 (3.25–3.51)	3.85 (3.71–4.00)	**4.23 (4.08–4.39)**	4.71 (4.54–4.89)	5.16 (4.96–5.36)	5.62 (5.41–5.84)	6.02 (5.78–6.23)	**6.60 (6.33–6.88)**
aRHT → Stroke	**1.54 (1.30–1.82)**	2.56 (2.23–2.94)	3.19 (2.80–3.62)	3.92 (3.47–4.43)	**4.64 (4.12–5.23)**	5.13 (4.55–5.77)	6.33 (5.60–7.16)	6.84 (6.03–7.75)	7.93 (6.92–9.09)	**8.74 (7.53–10.12)**
CAD → Stroke	**5.26 (4.92–5.63)**	6.69 (6.27–7.13)	7.86 (7.38–8.37)	8.97 (8.42–9.55)	**10.22 (9.58–10.90)**	10.95 (10.25–11.69)	12.06 (11.26–12.92)	12.71 (11.83–13.66)	13.35 (12.39–14.38)	**14.54 (13.39–15.78)**
CKD → Stroke	**2.64 (2.35–2.96)**	3.73 (3.36–4.13)	4.87 (4.43–5.36)	5.85 (5.34–6.41)	**6.71 (6.13–7.35)**	7.79 (7.11–8.54)	8.84 (8.04–9.72)	9.59 (8.69–10.57)	10.07 (9.09–11.14)	**10.76 (9.63–12.01)**
HF → Stroke	**3.46 (2.52–4.74)**	5.32 (3.88–7.27)	7.59 (5.63–10.20)	9.55 (7.11–12.77)	**10.16 (7.53–13.63)**	12.09 (8.66–16.74)	15.83 (10.52–23.43)	15.83 (10.52–23.43)	22.58 (13.84–35.58)	**22.58 (13.84–35.58)**
Initial → HF	**0.19 (0.16–0.22)**	0.26 (0.23–0.30)	0.36 (0.32–0.41)	0.46 (0.40–0.51)	**0.57 (0.51–0.64)**	0.72 (0.64–0.80)	0.88 (0.79–0.92)	1.04 (0.94–1.16)	1.2 (1.08–1.34)	**1.36 (1.22–1.52)**
aRHT → HF	**1.58 (1.34–1.86)**	2.55 (2.22–2.92)	3.59 (3.18–4.06)	4.79 (4.28–5.35)	**6.24 (5.62–6.93)**	7.67 (6.93–8.49)	8.41 (7.60–9.31)	10.07 (9.06–11.20)	11.91 (10.62–13.34)	**16.57 (14.34–19.11)**
CAD → HF	**2.43 (2.19–2.70)**	3.67 (3.35–4.03)	5.15 (4.73–5.61)	6.84 (6.30–7.41)	**8.22 (7.60–8.90)**	9.97 (9.21–10.80)	11.53 (10.63–12.50)	12.60 (11.60–13.67)	14.34 (13.15–15.61)	**16.14 (14.75–17.65)**
CKD → HF	**3.64 (3.33–3.99)**	4.04 (3.70–4.41)	4.67 (4.29–5.10)	5.34 (4.89–5.82)	**5.84 (5.35–6.37)**	6.60 (6.02–7.23)	7.10 (6.46–7.81)	7.56 (6.83–8.34)	8.07 (7.26–8.97)	**8.18 (7.35–9.11)**

(continued to the next page)

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Table 2. (Continued) Cumulative transitional probability of each state

Transition	Time (yrs)									
	1	2	3	4	5	6	7	8	9	10
Stroke → HF	**1.75 (1.39–2.20)**	2.84 (2.32–3.46)	3.92 (3.26–4.71)	4.80 (4.01–5.73)	**5.84 (4.89–6.96)**	6.48 (4.43–7.74)	7.25 (6.04–8.70)	7.95 (6.55–9.63)	9.68 (7.76–12.05)	**11.75 (9.16–15.01)**
Initial → Death	**0.98 (0.91–1.04)**	1.17 (1.10–1.24)	1.27 (1.19–1.35)	1.37 (1.29–1.46)	**1.44 (1.35–1.53)**	1.51 (1.42–1.61)	1.59 (1.50–1.70)	1.66 (1.56–1.78)	1.77 (1.65–1.89)	**1.84 (1.71–1.96)**
aRHT → Death	**0.76 (0.60–0.97)**	1.32 (1.09–1.60)	1.57 (1.31–1.88)	1.77 (1.48–2.11)	**1.93 (1.62–2.30)**	2.09 (1.75–2.50)	2.19 (1.83–2.63)	2.50 (2.05–3.05)	2.61 (2.12–3.22)	**3.45 (2.54–4.67)**
CAD → Death	**6.08 (5.72–6.47)**	7.36 (6.94–7.81)	7.96 (7.51–8.44)	8.44 (7.96–8.95)	**8.95 (8.43–9.51)**	9.24 (8.69–9.83)	9.83 (9.20–10.50)	10.05 (9.39–10.76)	10.26 (9.56–11.01)	**10.75 (9.94–11.62)**
CKD → Death	**1.90 (1.65–2.18)**	2.63 (2.32–2.97)	3.19 (2.84–3.58)	3.59 (3.21–4.02)	**4.04 (3.61–4.52)**	4.47 (3.98–5.02)	4.77 (4.23–5.37)	5.11 (4.50–5.79)	5.39 (4.72–6.16)	**5.81 (5.01–6.73)**
Stroke → Death	**6.85 (6.18–7.59)**	7.68 (6.94–8.49)	8.50 (7.69–9.40)	9.01 (8.14–9.98)	**9.73 (8.75–10.80)**	10.04 (9.31–11.62)	10.73 (9.56–12.03)	11.43 (10.06–12.99)	11.76 (10.27–13.46)	**11.76 (10.27–13.46)**
HF → Death	**6.88 (5.85–8.09)**	8.93 (7.47–10.65)	9.96 (8.25–12.00)	11.46 (9.33–14.04)	**12.90 (10.35–16.03)**	16.32 (12.52–21.13)	17.74 (13.31–23.43)	17.74 (13.31–23.43)	20.79 (14.31–29.65)	**20.79 (14.31–29.65)**

Values are presented as cumulative transitional probabilities (95% confidence intervals).
Values in bold are cumulative transitional probabilities at 1, 5, and 10 years with their 95% confidence intervals.
CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; aRHT, apparent resistant hypertension.

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Table 3. Risk factors of apparent resistant hypertension: results from multivariate Cox regression analysis

Factors	Hazard ratio	95% Confidence interval
Age	1.007	1.006–1.008
Sex		
Females	1	-
Males	1.11	1.08–1.14
Body mass index (kg/m^2)		
< 23	1	-
23–27.5	1.02	0.99–1.05
> 27.5	1.22	1.18–1.25
Type 2 diabetes mellitus		
No	1	-
Yes	1.28	1.25–1.32
Dyslipidemia		
No	1	-
Yes	1.17	1.14–1.20
Cardiorenal complications		
Coronary artery disease		
No	1	-
Yes	2.58	2.47–2.70
Chronic kidney disease		
No	1	-
Yes	3.12	2.98–3.28
Stroke		
No	1	-
Yes	2.02	1.87–2.17
Heart failure		
No	1	-
Yes	1.96	1.74–2.21

Compared to non-aRHT patients, those with aRHT had a higher 5-year cumulative risk of CAD (17.5% vs. 16.9%), CKD (17.4% vs. 10.8%), stroke (4.6% vs. 4.2%), HF (6.2% vs. 0.6%), and all-cause death (1.9% vs. 1.4%) (**Table 2** and **Supplementary Fig. 1**). Similarly, results from univariate Cox regression found the significant higher risks of CAD, CKD, stroke, HF, and all-cause mortality in patients with aRHT than those without aRHT (**Supplementary Table 2**).

After adjusting for co-variables in multivariate analysis, aRHT remained independently associated with CAD (HR, 1.80; 95% CI, 1.56–2.08), CKD (HR, 1.93; 95% CI, 1.79–2.08), HF (HR, 4.24; 95% CI, 3.54–5.08), and all-cause mortality (HR, 2.84; 95% CI, 1.89–4.27) but not with stroke (**Fig. 3** and **Supplementary Table 3**).

For the subgroup analysis among patients with T2DM, the results were generally consistent with those of the full cohort (**Supplementary Tables 4** and **5**). aRHT remained independently associated with an increased risk of CAD (adjusted HR, 1.34; 95% CI, 1.11–1.62), CKD (adjusted HR, 1.40; 95% CI, 1.28–1.52), and HF (adjusted HR, 1.17; 95% CI, 1.05–1.32), but not stroke (adjusted HR, 1.00; 95% CI, 0.90–1.12). However, unlike in the overall cohort, aRHT was not significantly associated with all-cause mortality. Additionally, the use of SGLT2 inhibitors was not significantly associated with a reduced risk of all-cause mortality or cardiovascular–kidney complications among hypertensive patients with T2DM (**Supplementary Tables 4** and **5**).

DISCUSSION

Based on our RW cohort, the incidence rate of aRHT was 2.61 per 100 person-years. The risk of developing aRHT was significantly higher in patients with cardiovascular or kidney complications compared to those without. Additionally, patients with aRHT had a worse prognosis, with significantly higher risks of CAD, CKD, HF, and all-cause mortality compared to non-aRHT patients. Notably, the risk of developing HF was approximately 4.24 times greater, and the risk of CKD was 1.93 times greater in aRHT patients compared to non-aRHT patients.

To our knowledge, only 3 studies from the UK and US—2 cohort studies [18,19] and an analysis of data from 2 previous randomized controlled trials (RCTs), SPRINT and ACCORD-BP [20]—have reported on the incidence of aRHT. The incidence rates of aRHT reported in the 2 cohort studies were 0.7 and 1.20 per 100 person-years, which are lower than the incidence estimates in our study (2.61 per 100 person-years). Given the previous cohort studies also used RW data and the same aRHT definition, the differences observed may be attributed to variations in study populations given their patient cohorts were sourced from primary care settings, in contrast to the tertiary care setting in our study.

In contrast, the RHT incidence reported in pooled RCTs data [20] was substantially higher than our estimate (i.e., 30.3 vs. 2.6 per 100 person-years, respectively).

This substantial difference may be attributed to the lower BP threshold used to define RHT in the RCTs (i.e., > 130/80 mmHg as per the updated 2018 American Heart Association) compared to our study (> 140/90 mmHg). Applying the > 140/90 mmHg threshold to the RCT data reduced the estimated RHT incidence to 9.7 per 100 person-years. Moreover, the SPRINT and ACCORD-BP trials focused on high-risk CVD patients (e.g., T2DM with HbA1c ≥ 7.5% or those with existing CVD), whereas our study included a broader range of hypertensive patients initially free of complications. However, the risk factors for aRHT identified in our study are consistent with previous evidence, highlighting male sex, obesity, a history of DM, and reduced eGFR as significant risk factors for aRHT [19,21,22].

Several previous studies have found that RHT is more prevalent in patients with comorbidities such as CAD, stroke, HF, and CKD [19,22-24]. The findings from our study align with these observations, showing that the cumulative risks of aRHT were higher in hypertensive patients who developed complications, particularly those with HF and CKD, than in hypertensive patients without complications. In our study, the 5-year cumulative risk of aRHT in patients with HF and CKD was approximately 2 and 1.3 times higher, respectively, compared to patients with CVD, including CAD and stroke. Additionally, the 5-year cumulative risk of aRHT in patients with HF and CKD was about 3 and 2 times higher, respectively, than in hypertensive patients without complications. The possible underlying mechanism that plays a major role in the bidirectional relationship between HF, CKD, and RHT is the overactivation of the RAAS [25]; patients with HF and CKD often experience chronic RAAS overactivation [26,27] leading to increased vasoconstriction, enhanced salt and water retention, raised arterial stiffness, and vascular remodeling, and elevated BP. In turn, high BP increases afterload, causing left ventricular dysfunction and exacerbating HF. Moreover, HT worsens CKD by increasing glomerular pressure and accelerating nephron loss. Together, these factors create a vicious cycle that perpetuates and worsens outcomes for HF, CKD, and RHT.

Our findings confirm the vicious cycle hypothesis involving HF, CKD, and RHT. Patients with aRHT were found to have a significantly higher risk of developing HF and CKD compared to patients without aRHT. The HRs of HF and CKD in patients with aRHT were approximately 4.24 times and 1.93 times higher, respectively than those in hypertensive patients without aRHT. Our findings align with those of previous studies. A cohort study involving more than 200,000 patients reported that the elevated risk of developing CKD was the primary driver for the increased rates of CVD events in patients with RHT compared to those without [19]. Another study conducted in > 400,000 patients similarly reported that the relative risks of CKD and HF in patients with RHT were higher than the relative risk of CAD, compared to patients without RHT [8]. These findings highlight the importance of early identification of RHT, particularly among patients with CKD and HF, who are at substantially higher risk of developing RHT. In addition, the observed bidirectional relationship between RHT and cardiovascular–kidney complications underscore the need for timely adjustment of antihypertensive therapy and the avoidance of treatment inertia to prevent the progression of related complications, ultimately improving long-term cardiovascular and renal outcomes in patients with RHT. In addition, the bidirectional relationship and vicious cycle involving HF, CKD, and RHT highlight the critical role of RAAS overactivation as an underlying mechanism of RHT.

Consequently, treatments targeting RAAS overactivation are essential for lowering BP and reducing the risk of target organ damage in patients with RHT. Findings from a systematic review and network meta-analysis of RCTs indicate that among the available pharmacological therapies (e.g., chlorthalidone, indapamide, BBs, and endothelin receptor antagonists), MRAs, such as spironolactone, demonstrated the highest efficacy in reducing office and 24-hour ambulatory SBP in patients with RHT [28,29]. However, evidence on the effectiveness of MRAs in reducing the risk of target organ damage, compared to other medications, remains limited. Therefore, future RCTs and studies utilizing RW data are needed to evaluate the effectiveness of MRAs in lowering the risk of target organ damage, such as HF and CKD.

In our study, patients with aRHT had a higher risk of stroke compared with hypertensive patients without aRHT; however, this association did not reach statistical significance after multivariable adjustment. This finding is inconsistent with the findings from previous studies that reported a significantly increased risk of stroke among patients with aRHT. Notably, some prior studies also demonstrated that the risk of stroke was not significantly different in individuals with controlled RHT compared with those with non-RHT, suggesting that the underlying BP level—rather than the classification of aRHT itself—may play a more important role in determining stroke risk. These observations imply that the association between aRHT and stroke may be largely mediated by the degree of BP control. Therefore, further studies are required to disentangle the direct effect of aRHT on stroke risk from the indirect effect mediated through BP levels.

First, this study presents the initial estimate of aRHT incidence in Thailand, providing valuable insights, which may be applicable to similar Asian contexts. Second, we utilized a large RW cohort of approximately 110,000 newly diagnosed hypertensive patients who were initially free of complications. This allowed us to employ multi-state modeling to comprehensively analyze aRHT risk and disease progression pathways. Third, the study compared the risk of target organ damage—including CAD, stroke, HF, and CKD—between aRHT and non-aRHT patients, while also exploring the bidirectional relationship between aRHT and hypertensive complications.

Our study has several limitations. First, we relied on BP measurements taken at clinic, which may have led to the inclusion of patients with white-coat HT, potentially overestimating the incidence of RHT. Second, we lacked data on medication adherence, which could also contribute to overestimating RHT incidence. However, it is estimated that only 10% of pseudo-RHT is due to these factors [19]. In addition, the definition of aRHT in our study relied on 2 criteria, including one based on the use of ≥ 4 antihypertensive medications regardless of BP levels. This definition does not rely on the methods of BP measurements and is therefore less affected by the limitations of BP assessment methods. Third, the use of fixed covariates in our multi-state model may have introduced bias in the effect estimates, as covariate status can change over time. Future analyses should address this limitation by incorporating time-varying covariates to improve accuracy.

Lastly, since our study relied on data from a single institution, the generalizability of our findings is limited compared with multicenter or multi-ethnic cohort studies. Future research utilizing data from multiple centers is necessary to more accurately reflect the true incidence and prognosis of RHT in Thailand.

CONCLUSIONS

The results of our study indicate that the risk of aRHT was higher in HT patients who developed cardiovascular and kidney complications compared to those without complications. Patients with aRHT had a worse prognosis than those without aRHT, particularly for development of CKD and HF, possibly due to the role of RAAS overactivation. These findings emphasize the importance of implementing targeted management strategies to reduce the risk of aRHT and improve patient outcomes.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Risk factors of apparent resistant hypertension: results from univariate Cox regression analysis

Supplementary Table 2
Associated factors of cardiovascular and renal complications among hypertensive patients: results from univariate Cox regression analysis

Supplementary Table 3
Independent associated factors of cardiovascular and renal complications among hypertensive patients: results from multivariated Cox regression analysis

Supplementary Table 4
Associated factors of cardiovascular and renal complications among hypertensive patients with diabetes mellitus: results from univariate Cox regression analysis

Supplementary Table 5
Independent associated factors of cardiovascular and renal complications among hypertensive patients with diabetes mellitus: results from multivariate Cox regression analysis

Supplementary Fig. 1

Transition probability from initial and apparent RHT states to cardiovascular and kidney outcomes.

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