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BLOOD PRESSURE MANAGEMENT AND FACTORS AFFECTING ADHERENCE TO ANTIHYPERTENSIVE MEDICATIONS IN THE UNITED ARAB EMIRATES

Akshaya Srikanth Bhagavathula

This dissertation is submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Under the Supervision of Professor Elhadi Husein Aburawi

December 2021

Declaration of Original Work

I, Akshaya Srikanth Bhagavathula, the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this dissertation entitled "*Blood Pressure Management and Factors Affecting Adherence to Antihypertensive Medications in the United Arab Emirates*", hereby, solemnly declare that this dissertation is my own original research work that has been done and prepared by me under the supervision of Professor. Elhadi Husein Aburawi, in the College of Medicine and Health Sciences at UAEU. This work has not previously formed the basis for the award of any academic degree, diploma or a similar title at this or any other university. Any materials borrowed from other sources (whether published or unpublished) and relied upon or included in my dissertation have been properly cited and acknowledged in accordance with appropriate academic conventions. I further declare that there is no potential conflict of interest with respect to the research, data collection, authorship, presentation and/or publication of this dissertation.

Student's Signature:  Date: 19/12/2021

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Advisory Committee

1) Advisor: Prof. Elhadi Husein Aburawi

Title: Professor

Department of Pediatrics

College of Medicine and Health Sciences

2) Co-advisor: Prof. Syed Mahboob Shah

Title: Professor

Public Health Institute

College of Medicine and Health Sciences

Approval of the Doctorate Dissertation

This Doctorate Dissertation is approved by the following Examining Committee Members:

1) Advisor (Committee Chair): Prof. Elhadi H. Aburawi
   Title: Professor
   Department of Pediatrics
   College of Medicine and Health Sciences
   Signature _____ Date 19/12/2021

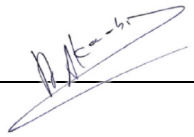
2) Member: Dr. Javaid Nauman
   Title: Associate Professor
   Public Health Institute
   College of Medicine and Health Sciences
   Signature _____ Date 19/12/2021

3) Member: Dr. Amal Akour
   Title: Associated Professor
   Department of Pharmacology & Therapeutics
   College of Medicine and Health Sciences
   Signature _____ Date 19/12/2021

4) Member (External Examiner): Dr. Petru Liuba
   Title: Associate Professor
   Department of Pediatric Cardiology
   Institution: Lund University, Sweden
   Signature _____ Date 19/12/2021

This Doctorate Dissertation is accepted by:

Acting Dean of the College of Medicine and Health Sciences: Professor Juma Alkaabi

Signature  Date 25/01/2022

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Abstract

Hypertension is a significant public health problem worldwide and is a major modifiable risk factor for cardiovascular disease. The dynamics of guidelines-recommended blood pressure (BP) control and adherence to antihypertensive medications in incident hypertensives remain unclear. This dissertation aims to assess guidelines-recommended BP management, adherence to antihypertensive medications, and factors associated with poor BP control among newly diagnosed hypertensive patients in the UAE. A retrospective chart review of 5308 newly treated hypertensives across emirate of Abu Dhabi, UAE, in 2017 was conducted. These patients were diagnosed by the treating physician according to ambulatory (ABPM), or home-based BP monitoring (HBPM) were considered. After collecting data regarding basic details and BP measurements, patients were followed up for six months. Changes in the BP, adherence to antihypertensive treatment within the first six months of treatment initiation, and factors associated with achieving target BP and medication adherence were assessed. Patients who did not reach BP targets despite taking three or more antihypertensive medications were defined as treatment-resistant hypertension (TRH). The mean BP was 133.9 ± 72.9 mmHg at baseline and 132.7 ± 72.5 mmHg at six months. Among the sample, only 31.7% of the patients aged ≤40 years, 37.5% with a body-mass index (BMI) of ≥ 25 kg/m^2, 45.4% smokers, and 37.5% patients with diabetes reached the BP target (<130/80 mmHg). Patients with lower BMI and those treated in secondary care settings were more likely to achieve BP targets. The overall adherence to antihypertensive treatment was 42%. Male gender, secondary care settings, and diabetes were associated with adherence. Among 189 patients using three or more antihypertensive medications, only 34% (n =64) were adherent to the treatment, and only 13.7% (n =26) reached the BP target. The prevalence of TRH was 20.1%. To the best of our knowledge, this is the first work in the UAE to investigate longitudinal BP control and medication adherence in a large community cohort of patients with incident hypertension. The findings provide contemporary evidence on guidelines-recommended BP management and adherence to treatment among newly treated hypertensive patients. BP control and adherence to antihypertensive therapy were suboptimal in the UAE. Moreover, TRH in this population is relatively very high and requires urgent public health attention.

Keywords: Blood pressure, control, cardiovascular, guidelines, goals, hypertension, medication adherence, treatment-resistant hypertension, United Arab Emirates.

Title and Abstract (in Arabic)

الإدارة السريرية لضغط الدم والعوامل التي تؤثر على الالتزام بالأدوية الخافضة للضغط في دولة الإمارات العربية المتحدة

الملخص

يعد ارتفاع ضغط الدم مشكلة صحية عامة وكبيرة في جميع أنحاء العالم وهو العامل الرئيسي الأخطر لأمراض القلب والأوعية الدموية وهو قابل للتعديل (المعالجة). لا تزال ديناميكيات التحكم في ضغط الدم الموصى بها من الإرشادات والالتزام بالأدوية الخافضة للضغط في حالة ارتفاع ضغط الدم غير واضحة. *الأهداف:* تهدف هذه الرسالة إلى تقييم الإدارة السريرية لضغط الدم، والالتزام بالأدوية الخافضة للضغط، والعوامل المرتبطة بضعف التحكم في ضغط الدم لدى مرضى ارتفاع ضغط الدم الذين تم تشخيصهم حديثًا في الإمارات العربية المتحدة. تمت مراجعة الرسم البياني بأثر رجعي لـ 5308 مريض من مرضى ارتفاع ضغط الدم الذين عولجوا حديثًا في جميع أنحاء إمارة أبو ظبي، الإمارات العربية المتحدة، في عام 2017. بعد جمع البيانات المتعلقة بالتفاصيل الأساسية وقياسات ضغط الدم، تمت متابعة المرضى لمدة ستة أشهر. تم تقييم التغييرات في ضغط الدم، ومدى الالتزام بالعلاج الخافض للضغط خلال الأشهر الستة الأولى من بدء العلاج، والعوامل المرتبطة بتحقيق ضغط الدم المستهدف. تم تعريف المرضى الذين لم يصلوا إلى ضغط الدم المستهدف على الرغم من تناول ثلاثة أو أكثر من الأدوية الخافضة للضغط على أنهم ذوي ضغط الدم المرتفع المقاوم للعلاج. كان متوسط ضغط الدم هو: 133.9±72.9مم زئبق في بداية الدراسة و 132.7 ± 72.5 مم زئبق بعد ستة أشهر. وصل 31.7٪ فقط من المرضى المستهدفين الذين تقل أعمارهم عن 40 عامًا، و(37.5٪) مؤشر كتلة جسمهم 25 كجم /م2 و(45.4٪) من المدخنين و(37.5٪) من مرضى السكري إلى ضغط الدم المستهدف (< 80/130 مم زئبق). وكان من الأرجح أن يحقق المرضى الذين يعانون من انخفاض مؤشر كتلة الجسم والذين عولجوا في أماكن الرعاية الثانوية ضغط الدم المستهدف. كان معدل الالتزام العام بالعلاج الخافض للضغط هو 42٪. يرتبط بجنس الذكور، وإعدادات الرعاية الثانوية، ومرض السكري بالالتزام. من بين 189 مريضًا يستخدمون ثلاثة أو أكثر من الأدوية الخافضة للضغط، كان 34٪ منهم فقط (عدد = 64) ملتزمًا بالعلاج، ووصل 13.7٪ منهم فقط (عدد = 26) إلى ضغط الدم المستهدف. كان معدل انتشار ضغط الدم المرتفع المقاوم للعلاج في المرضى هو 20.1٪. *المساهمات الكبيرة:* على حد علمنا هذا هو العمل الاستقصائي الأول في دولة الإمارات العربية المتحدة للاستقصاء في مدى السيطرة على ضغط الدم والالتزام بالأدوية في مجموعة كبيرة من المرضى المصابين بارتفاع ضغط الدم الحديث. تقدم النتائج أدلة معاصرة على الإدارة السريرية لضغط الدم والالتزام بالعلاج بين مرضى ارتفاع ضغط الدم المعالجين حديثًا. تبين أن التحكم في ضغط الدم والالتزام بالعلاج الخافض للضغط دون المستوى الأمثل في الإمارات العربية المتحدة. علاوة على ذلك فإن ارتفاع ضغط الدم المقاوم للعلاج في هذه الفئة من السكان مرتفع نسبيًا ويتطلب اهتمامًا عاجلاً من الصحة العامة.

مفاهيم البحث الرئيسية: ضغط الدم، السيطرة، القلب والأوعية الدموية، المبادئ التوجيهية، الأهداف، ارتفاع ضغط الدم، الالتزام بالأدوية، ارتفاع ضغط الدم المقاوم للعلاج، الإمارات العربية المتحدة.

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My acknowledgment cannot be complete if I don't extend my gratitude to my life partner Dr. Almas for her endearing support over the last three years. I would like to thank my parents, my siblings, and many others that I could not mention due to limited space.

Dedication

To my beloved parents and family

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List of Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACC	American College of Cardiology
ACEi	Angiotensin-Convertase Enzyme inhibitors
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AME	Apparent Mineralocorticoid Excess
AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
ARB	Angiotensin-Receptor Blockers
ASCVD	Atherosclerotic Cardiovascular disease
BMI	Body Mass Index
BP	Blood Pressure
CCB	Calcium-Channel Blockers
CI	Confidence Interval
CNS	Central Nervous System
CV	Cardiovascular
CVD	Cardiovascular Disease
DALY	Disability-Adjusted Life Years
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DU	Diuretics
EMR	Electronic Medical Records
ESC	European Society of Cardiology

ESH	European Society of Hypertension
FIN	Financial Identification Number
GBD	Global Burden Disease
GRA	Glucocorticoid-Remediable Aldosteronism
Gulf RACE	Gulf Registry of Acute Coronary Events
GCC	Gulf Cooperation Council
HbA1c	Glycated Hemoglobin
HBPM	Home-based Blood Pressure Monitoring
ISH	International Society of Hypertension
JNC7	Joint National Committee 7
MMAS	Morisky Medication Adherence Scale
MMM	May Measurement Month
MRN	Medical Record Number
NCD	Non-Communicable Diseases
NCD-RisC	NCD Risk Factor Collaboration
NESH	National Committee for Hypertension Screening, Detection, Intervention, and Follow-up Program
NICE	The National Institute for Health and Care Excellence
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OBPM	Office-based Blood Pressure Monitoring
OR	Odds Ratio
PDC	Proportion of Days Covered
PRH	Pseudo-Resistant Hypertension
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PURE	Prospective Urban Rural Epidemiology
RCT	Randomized-Controlled Trial
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEHA	Abu Dhabi Health Services
SPSS	Statistical Program for Social Sciences
TRH	Treatment-Resistant Hypertension
UAE	United Arab Emirates
UI	Uncertainty Interval
UK	United Kingdom
USA	United States of America
USPSTF	The United States Preventive Services Task Force
WHO	World Health Organization

Chapter 1: Introduction

1.1 Overview of hypertension

Hypertension or high blood pressure (BP) is defined as persistent BP of greater than or equal to 140/90 mmHg during the resting stage of the heart. In 2003, the Seventh Report of Joint National Committee (JNC7) defined hypertension as a chronic elevation of resting systolic blood pressure (SBP) above the threshold value of 120/80 mmHg and/or receiving therapy for the indication of BP lowering (1). Maintaining optimal BP is of crucial importance for the perfusion of vital organs, such as the brain, heart, and kidneys. Delivering oxygen through blood flow is of greater immediate importance for adequate functioning of these vital organs. BP reacts to changes in the physiological environment in the body to maintain organ perfusion in a wide variety of ways via the sympathetic nervous system, renin–angiotensin–aldosterone system, and alteration of plasma volume. In 1896, first Riva-Rocci and then Korotkoff developed the cuff sphygmomanometer for measuring BP (2,3).

Hypertension is a disorder of circulatory regulation, and the etiology of hypertension was first described by Page et al. in 1949 (4). BP regulation entails a series of complex interactions with the kidney, vascular endothelium, the central nervous system, peripheral nervous system, and adrenal and pituitary glands. Various pathophysiological factors could lead to hypertension, and the etiological mechanism of each of these is depicted in Figure 1 (extracted from Carretero et al. (5)).

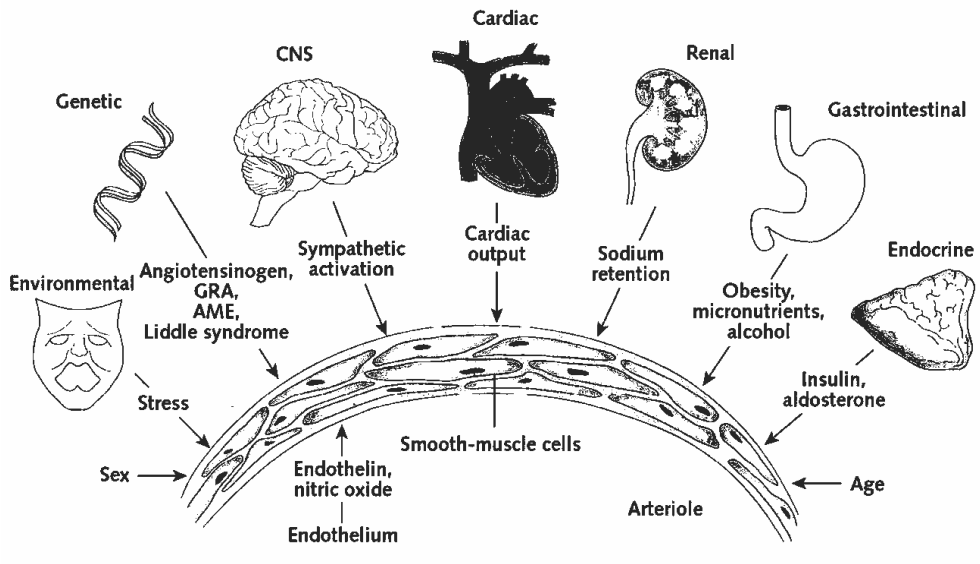

Figure 1: Pathophysiological mechanism of hypertension. AME – apparent mineralocorticoid excess; GRA – glucocorticoid-remediable aldosteronism; CNS – central nervous system.

In 2003, Oparil et al. (6) described the potential pathophysiological causes of hypertension, and they can be summarized as:

1. Long-term high sodium intake, perhaps coupled with inadequate dietary intake of potassium and calcium.
2. Overproduction of sodium-retaining hormones and vasoconstrictors.
3. Deficiencies of vasodilators, such as prostacyclin, nitric oxide, the natriuretic peptides, and/or a variety of other vasodilator peptides (e.g., the angiotensin peptide, calcitonin gene-related peptide, substance P, and/or adrenomedullin).
4. Alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, vascular tone and altered cellular ion transport.
5. Increased sympathetic nervous system activity, perhaps from heightened exposure or response to psychosocial stress.

6. Increased or inappropriate renin secretion with resultant increased production of angiotensin II and aldosterone.
7. Alterations in expression of the kallikrein–kinin system.
8. Diabetes mellitus, insulin resistance, being obese or overweight, and increased activity of related vascular growth factors.
9. Abnormalities of resistance vessels, including selective lesions in the renal microvasculature.

Although several factors contribute to the pathogenesis and maintenance of BP elevation, renal mechanisms play a vital role in renal salt absorption and water retention. Several interacting pathways such as an increase in natriuretic peptides, vascular remodeling, and sympathetic nervous system activity play major roles in increasing BP and mediating target organ damage.

1.1.1 Screening and diagnosis of hypertension

1.1.1.1 Screening

The auscultatory BP measurements by means of sphygmomanometer described by Riva-Rocci is used for oscillometric BP measurement and is the standard measurement method for detecting peripheral BP. A well-calibrated sphygmomanometer should be used to measure BP and is routinely used in patient screening, manual sphygmomanometer is more accurate than the automated electronic measurement. The electronic devices are also used for self-measurement for home screening and follow up. BP is calculated from the mean of the systolic and diastolic jerks.

Each individual from the age of three years or above is recommended to have their BP monitored by a healthcare professional at least once a year (7–9). Screening asymptomatic adults for hypertension can benefit in early detection and delayed progression of the disease. In 2007, The United States Preventive Services Task Force (USPSTF) established guidelines for the screening of high BP in adults (7) and reaffirmed the recommendations in 2015 (8). The USPSTF recommendations are summarized in Table 1.

Table 1: Screening of high BP in adults

Population	Adults aged ≥ 18 years without known hypertension.
Recommendation	Screening for high BP: To obtain BP measurements outside the clinical setting for diagnostic confirmation.
Risk assessment	Individuals at increased risk for high BP are those who have high-normal BP (130–139/85–89 mmHg), those who are overweight or obese, and the African–American population.
Screening tests	Office measurement of BP is usually done with a manual or automated sphygmomanometer. The mean of two BP measurements to be taken while the patient is seated by allowing five minutes or more between entry into the office and BP measurement, using an appropriately sized arm cuff and by placing the patient's arm at the level of his or her right atrium. Furthermore, multiple measurements over time are shown to have a better positive predictive value than a single measurement. Ambulatory and home BP monitoring should be used to confirm a diagnosis of hypertension after initial screening.
Screening interval	Adults aged ≥ 40 years or above and individuals at increased risk for high BP should be screened annually. Adults aged 18 to 39 years with normal BP (lower than 130/85 mmHg) who do not have other risk factors should be rescreened every three to five years.

1.1.1.2 Diagnosis

Casual BP measurements can barely estimate the daily vascular load. Measurement of BP is an exclusive method that can confirm the diagnosis of hypertension. Correct measurement of BP and interpretation of results are essential in the diagnosis of hypertension. It is important to note that measuring BP at two to three cycles is not sufficient to confirm the diagnosis. White-coat hypertension (BP readings that are consistently elevated in the doctor's office or clinic) and masked hypertension (BP readings that are consistently elevated in out-of-clinic environments but normal in the clinic) are other types of hypertensions that lead to underdiagnosis of the patient condition.

According to the evidence-based guidelines, there is a grading of hypertension according to the BP levels (9–15). The summary of recently updated American, European, United Kingdom (UK), and other international guidelines recommended BP thresholds for the diagnosis and BP control according to age are presented in Table 2. These guidelines recommend maintaining a BP of 120–130 and less than 80 mmHg in all patients to prevent the complications associated with high BP.

Table 2: Classification of hypertension and BP targets according to the international guidelines

	ACC/AHA 2017 (9)	ESC/ESH 2018 (11)	NICE guideline 2019 (10)	ISH 2020 (15)
Normal BP	SBP <120 mmHg and DBP < 80 mmHg	SBP 120–129 mmHg and/or DBP 80–84 mmHg	SBP <140 and/or DBP < 90 mmHg	SBP <130 mmHg and/or DBP < 85 mmHg
Elevated BP	SBP 120–129 mmHg and DBP < 80 mmHg	SBP 130–139 and/or DBP 85–89		SBP 130–139 mmHg and/or DBP 85–89 mmHg
Stage 1 hypertension	SBP 130–139 mmHg or DBP 80–89 mmHg	SBP 140–159 mmHg and/or DBP 90–99 mmHg	SBP 140–159 mmHg and/or DBP 90–99 mmHg	SBP 140/159 mmHg and/or DBP 90–99 mmHg
Stage 2 hypertension	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	SBP 160–179 mmHg and/or DBP 100-109 mmHg	SBP 160–179 mmHg and/or DBP 100–120 mmHg	SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg
Hypertension crises	SBP > 180 and/or DBP >120	SBP ≥180 mmHg and/or DBP ≥110 mmHg	SBP ≥ 180 mmHg and/or DBP ≥120 mmHg	-
BP targets (age)				
18–64	< 130/80 mmHg	130/80 mmHg (18–65 years)	< 140/90 mmHg (18–80 years)	< 130/80 mmHg
65–80	< 140/80 mmHg	< 140/80 mmHg (> 65 years)		< 140/90 mmHg
> 80	< 140/80 mmHg	-	< 150/90 mmHg	-

SBP: systolic blood pressure; DBP: diastolic blood pressure; ACC/AHA: American College of Cardiology/American Heart Association; ESC/ESH: European Society of Cardiology/European Society of Hypertension; NICE: The National Institute for Health and Care Excellence; ISH: International Society of Hypertension.

Current clinical guidelines from the United States of America (USA) (9,16), UK (10), Europe (11), Canada (12), Australia (13), Japan (14), and the International Society of Hypertension (ISH) (15) recommend using ambulatory BP monitoring (ABPM) to confirm the diagnosis of hypertension in people with suspected hypertension. These guidelines highlighted two class I recommendations: (a) The diagnosis of hypertension should be based on repeated clinical BP measurements on more than a single visit, except when hypertension is severe; (b) ABPM or home-based

BP monitoring (HBPM) is recommended to confirm the diagnosis of hypertension, the effects of hypertension treatment, and identify the possible cause of side-effects such as symptomatic hypotension.

Because of the benefits of multiple measurements, absence of observer bias, and lack of white-coat effect, ABPM is more accurate than in-clinic measurements and HBPM in diagnosing hypertension (17). The utilization of ABPM is expected to reduce unnecessary treatment in people who do not have true hypertension. Furthermore, measurements obtained through ABPM and HBPM are lower by approximately 5 to 10 mmHg than routine office measures. ABPM readings are lower at night, and the physiologic nocturnal BP "dip" aggregates and compromises the local vascular supply in some patients. This loss of dip is a dominant predictor of cardiovascular disease (CVD) risk, particularly the risk of thrombotic stroke (18). It is worth noting that the diagnosis of hypertension does not automatically entail drug therapy for the patient; this decision depends on the clinician's judgment.

1.1.2 Epidemiology of hypertension

1.1.2.1 Worldwide

Hypertension is a serious medical condition, and an estimated 1.3 billion people worldwide have hypertension (19). It is one of the most prevalent causes of premature death worldwide. The Framingham Heart Study in 1961 was one of the first epidemiological studies to report the prevalence of hypertension and its consequences in a longitudinal cohort (20).

One of the global targets concerning noncommunicable diseases is to decrease the prevalence of hypertension by 25% by 2025 (21,22). The findings of the Global

Burden of Disease (GBD) study, 2015, revealed that exposure to hypertension accounted for 10.7 million deaths (33.2% of deaths attributed to all risk factors) and contributed to nearly 212 million global disability-adjusted life years (DALYs) (23). Furthermore, uncontrolled hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) has increased substantially from 605 to 978 million from 1980 to 2010 (24). This has resulted in high BP moving up from the fourth-ranked risk factor for burden of disease in 1990 to the leading risk factor in 2010 (25). In a comparative risk assessment of 84 risk factors in 195 regions from 1999 to 2017, hypertension ranked at the topmost position for global disease burden, accounting for 10.4 million (95% uncertainty interval [UI]: 9.39–11.5 million) deaths and 218 million (95% UI: 198–237 million) DALYs (26). Understanding the burden of global hypertension, the 2017 ACC/AHA BP guidelines in adults have lowered the threshold for early diagnosis of hypertension from 140/90 mmHg to 130/80 mmHg (9). In accordance with the revised guidelines, it is estimated that the prevalence of hypertension for patients 20–44 years of age is 30% in men and 19% in women and for 65–74 years of age is 77% for men and 75% for women (9).

1.1.2.2 Hypertension in the UAE

The first incidence of hypertension in the UAE among its citizens was reported by Salahudeen et al. in 1987 (27) (prevalence data unavailable). The prevalence of hypertension between 1989 and 1992 was reported by Musaiger et al. in 1994 (28). The overall increased prevalence of hypertension was 20%, ranging from 14.3% in 1989 to 11.9% in 1992 and was higher in the UAE nationals (12.6%) than non-UAE nationals (8.1%). Soon after, in 1995, el Mugamer et al. estimated the prevalence of hypertension among Bedouin Emirati tribes in the UAE (29). In this study, the

prevalence of hypertension among 322 participants was 19% (n = 61), and a quarter (n = 80) had an SBP >140 mmHg. In 1998, the prevalence of hypertension was 23.9% (29). Until this period, epidemiological evidence of hypertension in the UAE was limited.

In 1998, the Ministry of Health (MoH) undertook the initiative to conduct the first National Epidemiological Study to examine the extent of hypertension among UAE citizens (NESH). A National Committee for Hypertension Screening, Detection, Intervention, and Follow-up Program (NESH-UAE) was formed. The study was conducted in different emirates (Sharjah, Abu Dhabi, and Al Ain), and the preliminary findings were reported in 1999 (30). In the NESH-UAE study, hypertension was defined as SBP >140 mmHg or DBP > 90 mmHg or reported treatment with one or more antihypertensive medications for controlling BP. Of 3,150 participants surveyed, hypertension among UAE nationals was 36.6% (95% confidence interval [CI]: 34.9 to 38.3). Higher prevalence was identified in females: 53%, 95% CI: 50.1 to 55.8 versus 47% males, 95% CI: 44.1 to 47; on treatment 41% (95% CI: 38.1 to 43.8), and only 19% (95% CI: 16.8 to 21.3) had their BP under control (30). An interesting finding of this study was that a quarter of the participants (n = 289) fell within the younger population (< 40 years age) (25%, 95% CI: 22.6 to 27.6).

A matched case-control survey investigating the relationship between hypertension and lifestyle factors was conducted between 2001 and 2002 on 426 hypertensive adults aged 20–65 years in Al Ain city, UAE (31). Among hypertensive patients, the mean SBP was found to be 141.9 ± 17.1 (SD: standard deviation), and DBP was 92.7 ± 9.8 than controls (SBP 116.8 ± 8.7 and DBP 75.7 ± 6.2). Hypertension was higher in men, aged 40–49 years, illiterates, and those with low income. This study also identified a strong association between obesity, medium/higher income, history

of diabetes, and low physical activity as significant risk factors for hypertension in the UAE.

In the last two decades, several researchers have actively investigated the epidemiology of high BP across different populations in the UAE. Most of these studies are community-based, cross-sectional studies (32–38), investigating the prevalence, awareness, and treatment (34,35), among youth (36,37), lifestyle behaviors (39), underdiagnosis, and undertreatment of hypertension (40) and an association between hypertension and other comorbidities (36,41). Since the initial recognition of hypertension in the UAE, the epidemiology of high BP has been a leading determinant of mortality and morbidity. The temporal trend of hypertension prevalence according to the NCD Risk Factor Collaboration data (42) is presented in Figure 2.

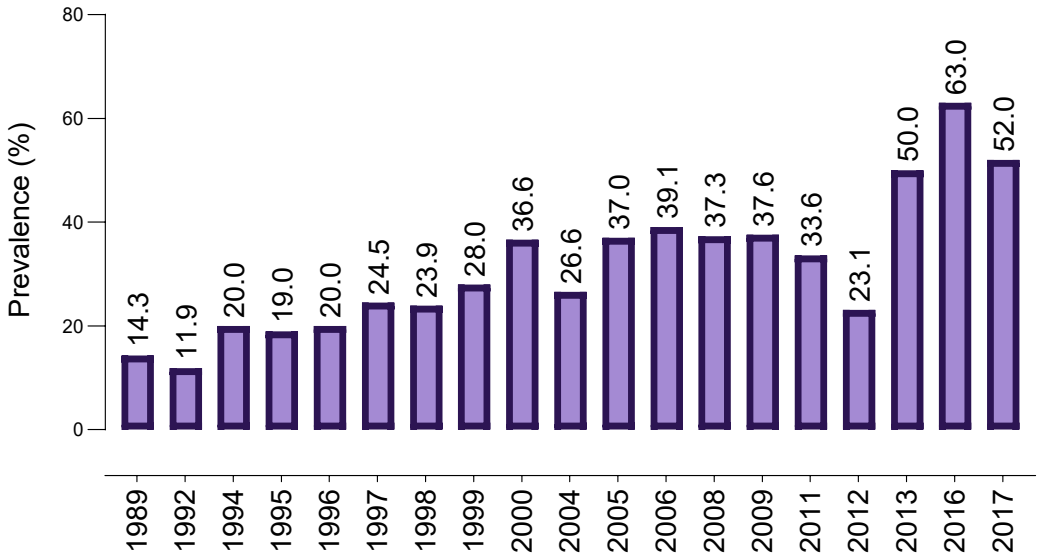

Figure 2: Temporal trend of hypertension across various populations in the UAE

1.1.3 Complications of hypertension

High BP is strongly and directly related to vascular and overall mortality in middle and old age. Higher BP affects structural and functional changes in the

vasculature and heart. With each six-mmHg increase in DBP, the risk of morbidity and mortality is doubled (43).

Better control of hypertension prevents morbidity and mortality. Each 10-mmHg reduction in SBP is associated with a decreased risk of cerebrovascular disease by approximately 35% (44). Cardiovascular complications are a major cause of morbidity and mortality in primary hypertension. Left ventricular hypertrophy through systolic or diastolic dysfunction is associated with heart failure, myocardial ischemia, ventricular arrhythmias, and sudden death. It is also a major predisposing cause of ischemic and hemorrhagic stroke. The incidence of subsequent cognitive decline, dementia, and Alzheimer's disease are higher in hypertensive patients than non-hypertensive patients. Chronic hypertension causes injury in vascular, glomerular, and tubulointerstitial compartments within the kidney and accounts for around 25% of end-stage kidney disease. Complications associated with hypertension are encapsulated in Table 3.

Table 3: Complications of hypertension in premature morbidity and mortality

End-organ	Complications
Brain	Thrombotic stroke
	Ischemic stroke
	Embolic stroke
	Hemorrhagic stroke
Heart	Angina pectoris
	Coronary artery disease
	Congestive heart failure
	Left ventricular diastolic dysfunction
Kidney	Renal arterial disease
	End-stage renal disease
	Embolic renal disease
	Diastolic renal disease
Other emergencies	Aortic aneurysm
	Malignant hypertension
	Pheochromocytoma
	Eclampsia in women

Hypertension increases the risk of premature cardiovascular disease (CVD) and often coexists with other risk factors, such as being obese or overweight, unhealthy diet, and physical inactivity. A meta-analysis on hypertension of over one-million adults across all age groups revealed that for every 20 mmHg increase in SBP and 10 mmHg increase in DBP, the risk of death from CVD or stroke doubles (45).

1.1.4 Risk factors for high blood pressure

Although the etiology of hypertension remains obscure, several risk factors are strongly and independently associated with it. The onset of hypertension usually occurs between 25 and 50 years of age. Factors that exacerbate this condition include age, race, obesity, family history of hypertension, malnutrition, increased salt intake, excess alcohol consumption, cigarette smoking, sleep apnea, unhealthy eating habits, physical inactivity, polycythemia, excess use of nonsteroidal anti-inflammatory drugs (NSAIDs), and low potassium intake. Some of the most crucial risk factors that lead to an increased incidence of hypertension are discussed in Table 4.

Table 4: Potential risk factors for hypertension

Age	Advanced age is associated with increased SBP and an increased incidence of hypertension.
Family history	Hypertension is two times more common in subjects with a family history of hypertension.
Race	Hypertension is more common, more severe, and occurs earlier among black people and those of African descent.
High sodium diet	Sodium intake > 3 g/day increases the risk of hypertension.
Excess alcohol consumption	Excess alcohol intake is associated with the development of hypertension.
Physical inactivity	Physical inactivity increases the risk of hypertension
Cigarette smoking	Smoking raises BP by increasing plasma norepinephrine. The synergetic effect of smoking and hypertension on cardiovascular risk has been well documented
Obesity	Obesity and excess weight are major risk factors for hypertension and are determinants for high BP. They are associated with an increased risk of intravascular volume expansion and elevated cardiac output.
Stress	High levels of stress can lead to a dramatic increase in BP. However, the relationship between stress and hypertension is not well established
NSAIDs	Ibuprofen, naproxen, diclofenac, piroxicam, and celecoxib can cause masked hypertension, worsening of existing hypertension, or the development of hypertension. NSAIDs' use increases in BP by average of 5 mmHg and causes damage to the kidneys, heart failure, and stroke.

Hypertension is the most important modifiable risk factor for premature CVD, being more common than other major risk factors such as cigarette smoking, diabetes, and dyslipidemia (46). A combination of more than one risk factor with hypertension aggravates the risk of adverse cardiovascular and cerebrovascular events (24). A BP of 120–129/80–84 mmHg was found to be associated with a hazard ratio of 1.1 to 1.5 for cardiovascular events, and 130–139/85–89 mmHg with a hazard ratio of 1.5 to 2.0 (47). Excessive BP on the artery walls can damage the blood vessels and lead to organ damage. Uncontrolled BP can lead to stroke, myocardial infarction, heart failure, aneurysm, kidney damage, metabolic syndrome, vision loss, and dementia.

1.1.5 Medication adherence

The World Health Organization (WHO) defined medication adherence as "the extent to which a person's behavior corresponds with agreed recommendations from a health care provider" (48). Medication adherence in chronic illness is a challenging task, and the WHO estimated that approximately 50% of the patients are non-adherent to chronic medications (48). Hypertension is a disease with few symptoms, which makes medication adherence even more challenging (49). A 2015 cross-sectional study that investigated the level of medication adherence to antihypertensive drugs in the UAE, demonstrated that adherence to antihypertensive medications was lower than 50% in the newly diagnosed hypertensive patients (50). A decline in medication adherence over time has shown to increase the risk of stroke, myocardial infarction, and heart failure. Low medication adherence in hypertension is associated with young age, male sex, and mild-to-moderate BP elevation (51). There is compelling evidence that high adherence to antihypertensive treatment results in reduction of cardiovascular risk (52). For example, being adherent to antihypertensive treatment results in 10% lower risk for coronary artery disease (53), 11% lower risk for heart failure (54), and 22% lower risk for cerebrovascular disease (55). Apparent low medication adherence is a common cause of uncontrolled BP.

1.1.6 Hypertension control

Although numerous effective drugs and drug classes are available to control BP, the control rates are suboptimal (56). Several international studies have reported the global and regional variations in hypertension control (32,56–58). While between 48% and 65% of treated patients are well controlled in North America and Europe (57), control rates in the Middle East and South Asia are lower than 20% (32). This

rate is only the tip of the iceberg. Findings from the Prospective Urban Rural Epidemiology (PURE) study conducted on 17 countries, including the UAE, confirmed that the overall hypertension control in the Middle East population was 19% and, in the UAE, it was only 14% (34). The NESH-UAE 1998 study demonstrated the BP control among hypertension treated population was 45% (30). As illustrated by several surveys in the UAE, about three-fourth of patients whose BP values are consistently above goal levels do not have medication started, and for those on antihypertensive medications, the BP control was between 26% to 41% (32,34).

In contrast with the USA, Europe, UK, and Canada, there are limited contemporary data of treatment inertia and the control of BP after the treatment initiation in the UAE population. This is surprising since CVD remains the primary cause of death in the UAE, the mean age of patients with CVD in the UAE is 50 years. There is a general agreement that the absence of BP control reflects the burden of uncontrolled hypertension, and their BP values exhibit the recommended targets of the above-mentioned guidelines. Years of research have clarified that hypertensive individuals who fail to control the BP (therapeutic inertia) and are less adherent to prescribed lifestyle and antihypertensive medications, have a low rate of BP control and ultimately increase their risk of confronting adverse events. Thus, faster BP control at the early stage of hypertension provides cardiovascular protection, and better adherence to prescribed medications can help achieve target BP values. Therefore, improving BP control is of fundamental importance for cardiovascular prevention worldwide.

1.1.7 Treatment-resistant hypertension

In 2018, the AHA defined resistant hypertension or treatment-resistant hypertension (TRH) as BP that remains above goal despite the patient adhering to the maximum tolerated doses of three different antihypertensive medication classes, one ideally being a diuretic (59). The latest ESC/ESH guidelines defined TRH as office BP goal (> 130/80 mmHg or > 140/80 mmHg) despite being treated with at least three antihypertensive drugs, including angiotensin-convertase enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs), a calcium channel blocker (CCB), and a diuretic (DU) medication (11). Thus, assessing the adherence to prescribed therapy is a critical aspect of understanding the success or failure of hypertension management during their early hypertension stage. Moreover, patients with TRH are potential high-risk subsets and at high risk for adverse CV events. Unfortunately, the epidemiological evidence of TRT has been poorly characterized in the literature. Prevalence estimates suggest anywhere from 3% to 30% of the patients require three or more medication to achieve their BP control (60), and around 12% to 18% of the hypertensive population have TRH (61,62). Most of the TRH studies are from western countries and lack longitudinal BP data. However, the epidemiological evidence of TRH in the Middle East is yet to be explored.

1.2 Statement of problem

Hypertension is a significant public health problem worldwide and is recognized as a major modifiable risk factor for CVD (24). It is estimated that over 10 million deaths occur every year due to high BP (23). A 20 mm-Hg increase in SBP and/or a 10 mm-Hg increase in DBP is associated with an increased two-fold risk of death from stroke, heart disease, and other vascular diseases (45). BP reading can vary

to a great extent; a single elevated BP reading is not sufficient to establish the diagnosis of hypertension. Guidelines recommend using ABPM or HBPM at different time intervals to confirm the diagnosis of hypertension (9–16). Nevertheless, BP-lowering treatment is important as it delays the progression of the disease and can reduce the risk of CVD. A three-month delay in the treatment of hypertension in high-risk patients is associated with a two-fold increase in CV morbidity and mortality (45). A systematic review and meta-analysis on adherence to antihypertensive drugs highlighted that nearly half of newly diagnosed hypertensive patients are non-adherent to their medications (63). Non-adherence to antihypertensive medications is identified as the most prominent cause of uncontrolled BP and adverse outcomes (63,64).

The UAE is undergoing rapid and complex demographic and epidemiological transition (65). With a population of 9.27 million, the age-standardized hypertension prevalence was 33% in 2019 (32); less than half (47%) of them were on treatment, and the control group comprised only 19% (66). However, most of the research has focused on awareness, prevalence, treatment, and control of hypertension at the community level (32–35,58). For instance, Shah et al. conducted a cross-sectional questionnaire-based study on South Asian male expatriates seeking employment in Al Ain city (35). They concluded that a high proportion of these immigrants had high BP. More recently, the May Measurement Month (MMM) screening program in the community focused on mass screening and improved awareness regarding high BP in the UAE (66). Moreover, studies investigating the level of medication adherence to antihypertensive drugs in the UAE are very limited, and a 2015 study reported suboptimal (50%) medication adherence to antihypertensive medications (50).

Most of the literature involving studies conducted in the UAE is cross-sectional (33–38,66), and the majority of the studies do not include the representative

population. These factors limit our ability to understand the trajectories of hypertension from diagnosis, treatment modalities, extent of BP control, complications, adherence to antihypertensive medications, and adverse outcomes. Research in the UAE has primarily focused on identifying the determinants for BP control (41), associations with CVD risk factors (39,67–73), such as diabetes (31,39,67–70), obesity (69,71–73), lifestyle factors (39) among immigrant workers (35,72), local population (73), and workers (67). However, these existing studies do not sufficiently examine the achievement of BP goals and trajectories of hypertension among the UAE population. This is important because antecedent hypertensive patients are at a higher risk of developing acute myocardial infarction (AMI). The INTERHEART study reported a hypertension prevalence ranging from 31% to 59% across 52 countries that includes six Arabian Gulf countries (74). In the Gulf Registry of Acute Coronary Events (Gulf RACE), of 8,169 patients with acute coronary syndrome (ACS), nearly half (49.4%) were reported to have hypertension (75). The authors concluded that hypertension is associated with a higher risk profile for increased mortality (12.7%) in ACS patients and increased risk for development of heart failure (19.7%). Furthermore, the UAE-ACS study on 1,842 patients from four tertiary care hospitals identified that around over one-third (34.6%) of young ACS patients (mean age 50.8 ± 10 years) had hypertension and highlighted hypertension as an important modifiable risk factor causing premature CVD in the UAE population (76).

Despite extensive knowledge about ways to prevent and treat hypertension, taking control of BP to improve quality of life has been put under the spotlight and is currently suboptimal due to inadequacies in prevention and diagnosis. In 2016, the LANCET took an initiative to form a commission on hypertension for identifying key

actions to improve the management of BP and investigate the deleterious consequences of high BP in the younger population (77). In general, hypertension is a chronic disease, and its control demands patient self-management, which includes monitoring BP levels, taking medications, and maintaining a healthy lifestyle. Adherence to antihypertensive medications is pivotal for the therapeutic success of BP control, reduction in treatment cost, and the subsequent improvement in quality of life and clinical outcomes (78). In 2015, a cross-sectional study in Ajman assessed medication adherence to antihypertensive medications using the Morisky Medication Adherence Scale (MMAS-4). The study identified that nearly half (45.6%) of the patients with hypertension were non-adherent to medications, but most of the included population was in the older age group (> 60 years) (50). Moreover, no studies have investigated the prevalence or incidence of TRH in the Middle East. There is a scarcity of published data regarding the status of hypertension in clinically confirmed patients in outpatient settings in Abu Dhabi, UAE. A comprehensive assessment of clinical aspects in a representative sample could help us to understand the dynamics of hypertension in the UAE population.

1.3 Literature review

Epidemiological evidence on opportunistic screening for hypertension in the general population and BP control among those treated patients is essential to provide the baseline monitoring and inform the development of new strategies for improving hypertension control in the UAE. Although previous reviews in the Middle East focused on investigating the prevalence of hypertension and its risk factors in the Arabian population, they did not incorporate most of the studies conducted on the UAE population (79,80). Thus, a comprehensive review of the studies conducted in the UAE

is required to understand the hypertension prevalence in apparently healthy adult subjects and identify the level of BP control among those treated.

This literature review is divided into three parts. The first part elaborates the prevalence of hypertension. The second part illustrates the control of hypertension in the UAE adult population. This part also focuses on the global prevalence and incidence of resistant hypertension in treated hypertensive population. The third and the last part presents the level of adherence to antihypertensive medications in the UAE and Middle East countries.

1.3.1 Methodology of the review

A comprehensive systematic search was conducted on PubMed/MEDLINE, Web of Science, Embase (Ovid® interface), and Google Scholar databases to identify population-based studies.

- Prevalence of hypertension in the UAE from January 1, 1995 to May 31, 2021.
- Blood pressure control in the UAE: January 1, 1995 to May 31, 2021.
- Adherence to antihypertensive medications in the Middle East: January 1, 1998, to May 31, 2021.
- Global prevalence of TRH in treated hypertensive population: January 1, 2010, to May 31, 2021.

A combination of Boolean operations such as AND, OR, and NOT in combination with Medical Subject Headings (MeSH) truncation (*) with text words were used to search titles and abstracts. All the identified articles were screened and studies fulfilling the eligibility criteria were considered for a full-text review.

1.3.2 Prevalence of hypertension in the UAE

1.3.2.1 Eligibility criteria

Population-based prospective studies conducted on apparently healthy adult subjects living in the UAE and defined hypertension using the guideline-recommended BP cut-off ≥130/80 mmHg or ≥140/90 mmHg were considered. Studies provided estimates of the prevalence of hypertension by screening the general population. Multi-country studies were included if data on the prevalence of hypertension in the UAE could be distinctly extracted. Only peer-reviewed full-length research articles published in the English language were considered.

1.3.2.2 Exclusion criteria

- Studies where standard methods for measurement of hypertension were not clearly described. Studies conducted on diseased populations (other than hypertensives), hospitalized patients, children, and pregnant women were excluded.
- Editorials, correspondence, conference proceedings, abstracts, non-human studies, interventional studies, hospital-based studies, and expert reviews were excluded.
- Studies with unclear outcome measures, articles with missing or insufficient data were excluded.
- The updated Preferred Reporting Items for Systematic reviews and Meta-analysis 2020 (PRISMA) guideline was used to identified records, screening of titles and abstracts accompanied by evaluation of eligibility of full texts for final inclusion (81).

1.3.2.3 Overview of the included studies

A total of 1,038 articles from initial searches were retrieved in various databases. After removing 176 duplicates and 998 irrelevant titles, 50 studies were found eligible for a full-text review. Amongst these, 35 were excluded with reasons: 16 studies were conducted on diseased patients, eight studies did not provide the outcome of interest estimates, three were reviews, one study was conducted on children, and seven did not meet the inclusion criteria. Finally, 15 studies conducted between January 1, 1995 to May 31, 2021, were included in the review (29,30,32–34,38,58,66,72,82–87). Figure 3 illustrates the methodology for identification of pertinent studies.

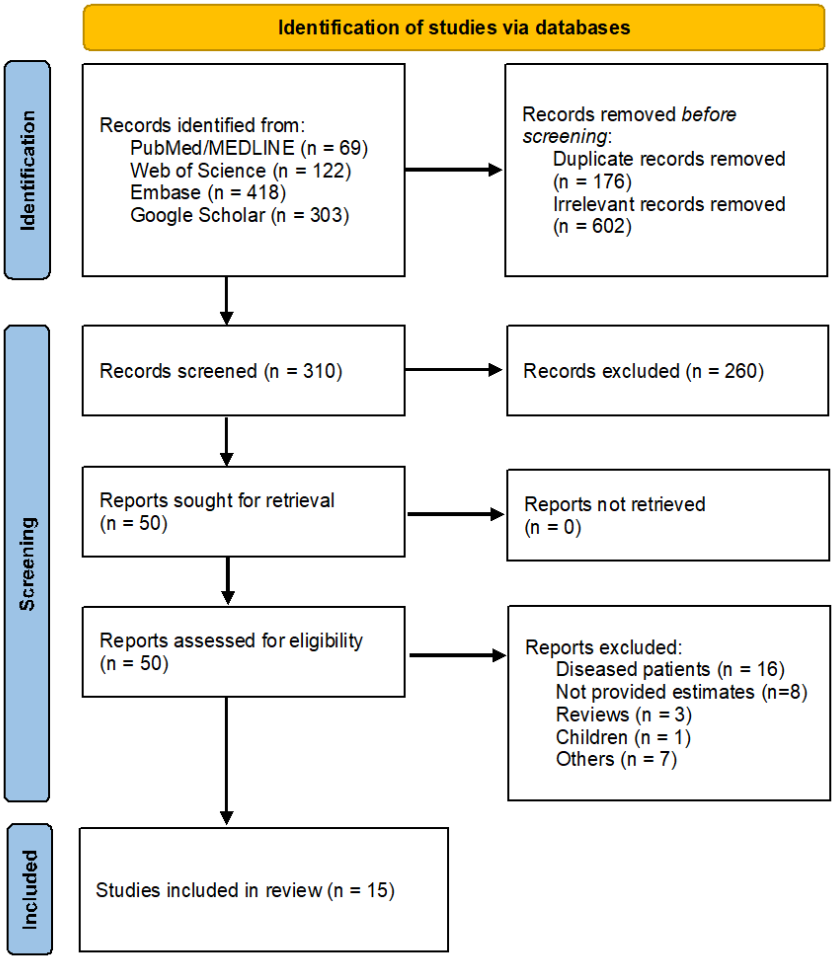

Figure 3: PRISMA 2020 flow diagram for literature search

1.3.2.4 Characteristics of included studies

The included studies comprised a total of 139,907 participants (63.5% male) from Abu Dhabi (n = 5, 33.3%), Dubai (n = 5, 33.3%), one from Ras Al Khaimah (n = 1, 6.6%), and four studies were conducted on different emirates (26.6%). All the studies were cross-sectional and predominantly conducted on the general public (n = 13, 86.6%). In addition, the majority of the studies were conducted in community settings (73.3%), and the overall mean age was 37.2 ± 11.3 years. These characteristics are summarized in Table 5.

Table 5: Characteristics of included studies (n = 15)

Author (year)	Location	Study design	Setting	Population	Sample size	Mean age (years)
Yusufali et al. (2020)	Seven emirates	CS	Health centers	General public	31,316	36.8±11.4
Hussain et al. (2019)	Dubai	CS	Household	General public	3,289	-
Alzaabi et al. (2019)	Abu Dhabi, Al Ain, and Sharjah	CS	Medical examination centers	Men	33,327	21.6
Yusufali et al. (2019)	Seven emirates	CS	Community	General public	6,193	38.2±13.1
Yusufali et al. (2017)	Dubai	CS	Community	General public	917	49.5±10.3
Al Faisal et al. (2017)	Dubai	CS	Community	General public	3,716	-
Shah et al. (2015)	Al Ain	CS	Community	South Asian Immigrants	1,375	34
Yusufali et al. (2015)	Dubai	CS	Community, hospital	General public	4,128	38.4±11.4
Quraishi et al. (2013)	Ras Al Khaimah	CS	Kerala market	General public	74	-
Baynouna et al. (2013)	Al Ain	CS	Community	General public	817	-
Chow et al. (2013)	Dubai	CS	Community	General public	918	49.1±10.2
Hajat et al. (2012)	Abu Dhabi	CS	Community	General public	50,138	36.8±14.3
Al-Sarraj et al. (2010)	Al Ain	CS	Hospital	UAE citizens	227	31.2±8.9
El-Shahat et al. (1999)	Abu Dhabi, Al Ain, Sharjah	CS	Community	General public	3150	-
El Mugamer et al. (1995)	Abu Dhabi	CS	Community	General public	322	-

CS: cross-sectional

1.3.2.5 Prevalence of hypertension

All the 15 studies used automatic and/or manual sphygmomanometer to record the BP in the population surveyed and defined hypertension as BP ≥ 140/90 mmHg, except Hussain et al.'s study, which applied a cut-off of > 130/80 mmHg (82). Studies estimated the prevalence of hypertension in the UAE, ranging from 9% (83) to 52% (34,58,87). In Abu Dhabi, studies estimated the prevalence of hypertension was between 21% (41) to 52% (87), and 24% (84) to 52% (34) in Dubai. Only one study was conducted on a small sample size (n = 74) visiting the Kerala market in Ras Al Khaimah (85) and reported that half of the population studied had elevated BP (≥ 140/90 mmHg). Furthermore, four studies were multi-regional studies in which two studies included populations from seven emirates (32,66) and the other two conducted on the general public from Abu Dhabi, Al Ain, and Sharjah (30,83). Multi-regional studies reported a prevalence ranging from 9% (83) and 37% (30). However, Shah et al. (35) and Alzaabi et al. (83) included only the male population attending medication examination centers. Further details are succinctly encapsulated in Table 6.

Table 6: Prevalence of hypertension in the UAE from 1995 to 2021

Author	Year	Screened population	BP device	Evaluation criteria (BP reading)	Prevalence (%)
Yusufali et al. (61)	2020	31,316	Automated /Manual	≥140/90 mmHg	19.9
Hussain et al. (55)	2019	3,289	Manual	>130/80 mmHg	25.1
Alzaabi et al. (56)	2019	33,327	Manual	≥140/90 mmHg	9.2
Yusufali et al. (39)	2019	6,193	Automated	≥140/90 mmHg	30.2
Yusufali et al. (39)	2019	917	Automated	≥140/90 mmHg	51.9
Al Faisal et al. (59)	2017	3,716	Manual	≥140/90 mmHg	24.0
Shah SM et al. (62)	2015	1,375	Automated	≥140/90 mmHg	30.5
Yusufali et al. (63)	2015	4,128	Automated	≥140/90 mmHg	30.5
Quraishi et al. (60)	2013	74	Manual	≥140/90 mmHg	50.0
Baynouna et al. (47)	2013	817	Manual	≥140/90 mmHg	20.8
Chow et al. (64)	2013	918	Automated	≥140/90 mmHg	52.0
Hajat et al. (65)	2012	50,138	Automated	≥140/90 mmHg	23.1
Al-Sarraj et al. (58)	2010	227	Automated	≥135/85 mmHg	51.5
El-Shahat et al. (23)	1999	3150	Manual	≥140/90 mmHg	36.6
El Mugamer et al. (22)	1995	322	Manual	≥140/90 mmHg	25.2

1.3.3 Blood pressure control in hypertensive-treated patients in the UAE

Six cross-sectional studies were identified through literature review and reported the BP control among those treated in the UAE (30,32,34,35,38,66), see Table 7.

Table 7: Level of BP control among hypertensives in the UAE

Author	Year	Location	Hypertension	
			Treated	Control
Yusufali et al. (66)	2020	Seven emirates	11,681	7,077 (60.6%)
Yusufali et al. (32)	2019	Seven emirates	3,499	1,420 (40.6%)
Yusufali et al. (34)	2017	Dubai	239	62 (25.9%)
Shah et al. (35)	2015	Al Ain	667	55 (8.2%)
Yusufali et al. (38)	2015	Dubai	600	290 (48.3%)
El-Shahat et al. (30)	1999	Abu Dhabi, Al Ain, Sharjah	334	150 (44.9%)

The overall sample size of the study population ranged from 239 (34) to 11,681 (66). Shah et al. (35) conducted on immigrant men and reported that only 8.2% of those treated had their BP under control. In 2019 and 2020, Yusufali et al. (32,66) screened more than 15,000 hypertensive subjects on treatment as a part of MMM. Findings from the 2020 MMM study indicated that around 60% of those treated had their BP under control. Studies conducted on hypertensive population with diabetes and other comorbidities are highly extensive and beyond the thematic purview of this dissertation.

1.3.4 Comparison of prevalence and control of hypertension in the GCC countries

To benchmark hypertension prevalence and control in the UAE, pooled estimates from the different UAE studies were compared to country-specific estimates

of the NCD-RisC study (57) published in Lancet 2021. NCD-RisC analyzed the data of 1201 nationally representative surveys across 200 countries from 1990 to 2019 across to their income and reported the hypertension prevalence, awareness, treatment, and control. For the review, country-specific data related to prevalence and control in Arabian Gulf countries – Bahrain, Kuwait, Oman, Qatar, and Saudi Arabia were used. The comparison of hypertension prevalence and control in the UAE and five Gulf Cooperation Council (GCC) countries is presented in Figure 4 (57).

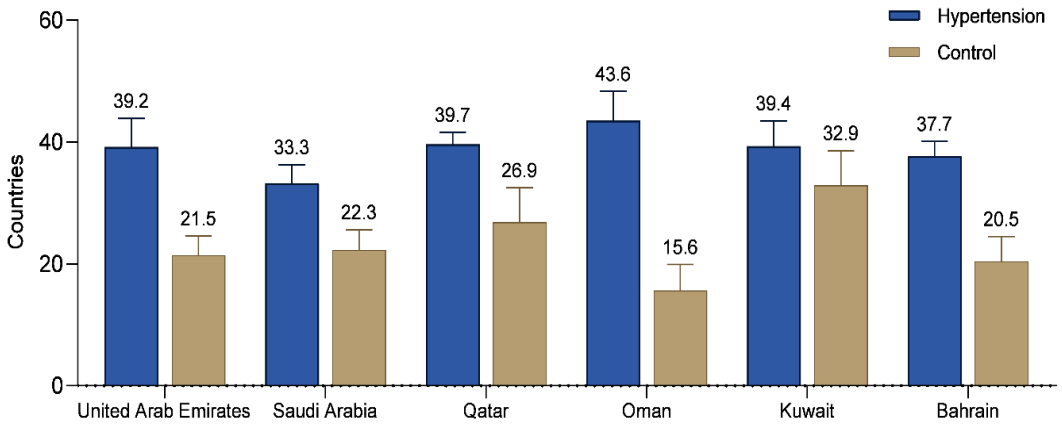

Figure 4: Prevalence and control of hypertension in the UAE and other GCC countries

1.3.5 Adherence to antihypertensive medications in the Middle East

A literature review was conducted by using the PubMed/MEDLINE databases. A manual search was also applied to identify additional articles from the reference lists of key articles. A number of articles were found on adherence to antihypertensive medications in the Middle East but only two in the UAE. No longitudinal studies were found on hypertensive population in the Middle East. The search strategy was based on the terms: adherence, compliance, medication-compliance, medication adherence, and antihypertensive therapy. These keywords were combined using Boolean operators as appropriate. Around 235 articles were identified. After deduplication,

titles and abstracts of 210 studies were screened, and 29 studies were downloaded and reviewed for a full-text review. Finally, 22 articles fulfilled the inclusion criteria. To eliminate search bias, another researcher adopted the same search procedure independently. There was no discrepancy with regard to articles retrieved. The PRISMA 2020 flow diagram for literature search was shown in Figure 5.

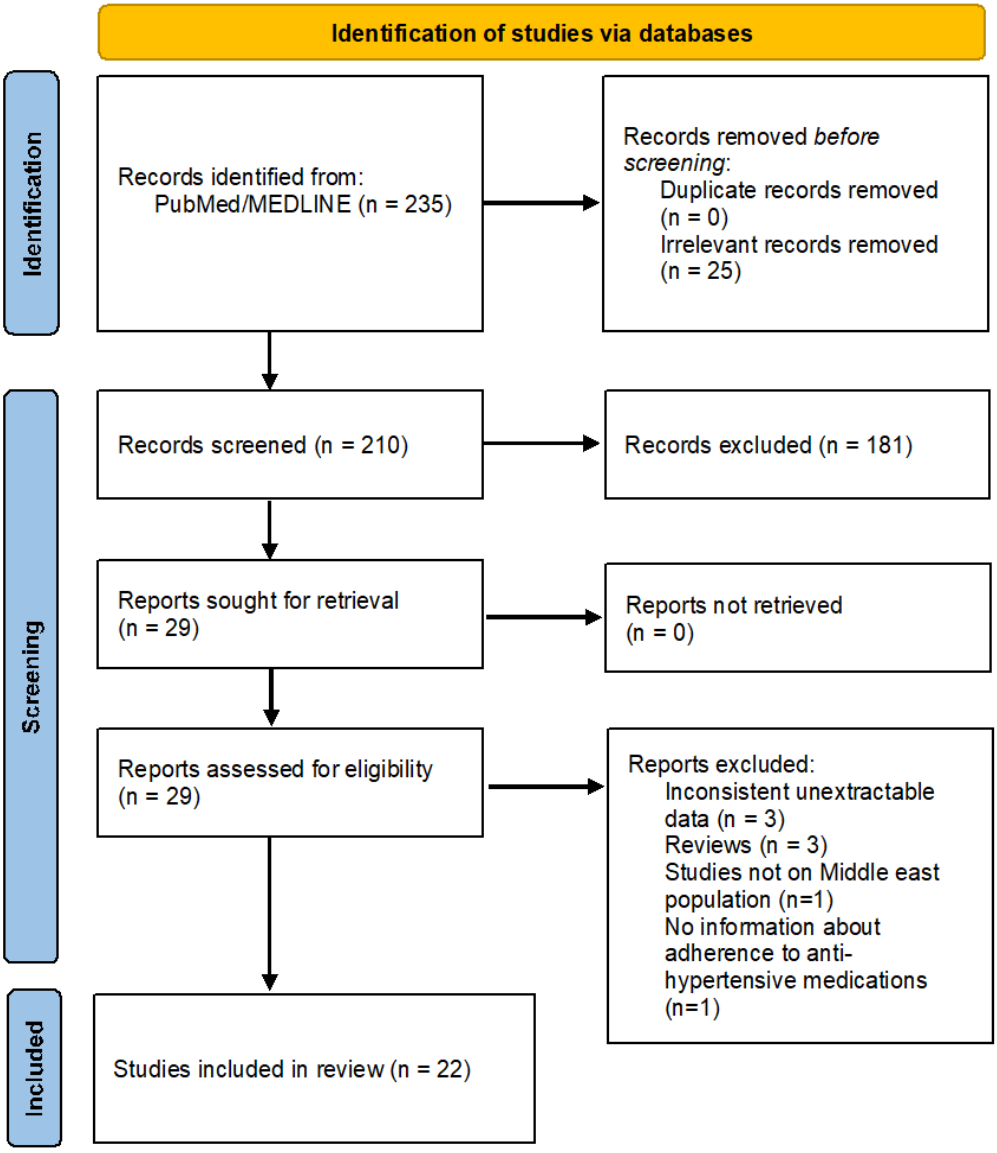

Figure 5: PRISMA 2020 Flow diagram of literature search

Key characteristics and outcomes of the studies investigating the level of adherence to antihypertensive medications conducted in Middle East countries are summarized in Table 8.

Table 8: Non-adherence to antihypertensive medications in the Middle East

Country	Study, Year	Study design	Sample size	Mean age (years)	Assessment method	Non-adherence % (95% CI)
Iran	4	Cross-sectional	1831			57 (42 – 72)
Kamran et al. (88)			671	-	MMAS-4	76 (72 – 79)
Saadat et al. (89)			280	60.3 ± 10	MMAS-8	51 (45 – 57)
Behnood-Rod et al. (90)			280	60.0 ± 10	MMAS-8	50 (44 – 56)
Sadeghi et al. (91)			600	56.4 ± 12.3	MMAS-8	51 (47 – 55)
Iraq	2	Cross-sectional	753			29 (4 – 62)
Al-banna et al. (92)			418	-	Structured questionnaire	12 (9 -15)
Ismael et al. (93)			335	58.7 ± 11.9	MMAS-8	46 (41 – 51)
Jordan	4	Cross-sectional	1116			30.5 (27 – 34)
Al-Jbour et al. (94)			273	69 ± 2.3	MMAS-4	13 (9 – 17)
Al-Daken et al. (95)			192	52.8 ± N/A	Hill-Bone	8 (4 – 12)
Goussous et al. (96)			471	59 ± 11.2	Structured questionnaire	24 (20 – 28)
Abu Khudair et al. (97)			180	-	ARMS	77.2 (70 – 83)
Lebanon	1	Cross-sectional	210			22 (16 – 28)
Mohammad et al. (98)			210	59.3 ± 12.2	Structured questionnaire	22 (17 – 29)
Oman	1	Cross-sectional	45			51 (42 – 72)
Al-Noumani et al. (99)			45	52 ± 14.6	MMAS-8	51 (36 – 66)
Palestine	1	Cross-sectional	450			54 (49 – 59)
Al-Ramahi et al. (100)				59 ± 12.2	MMAS-8	54 (49 – 59)

Table 8: Non-adherence to antihypertensive medications in the Middle East (Continued)

Country	Study, Year	Study design	Sample size	Mean age (years)	Assessment method	Non-adherence % (95% CI)
Saudi Arabia	8	Cross-sectional	1969			60 (55 – 65)
Al-Sowielem et al. (101)			190	50 ± 11.7	Structured questionnaire	66 (59 – 73)
Elbur et al. (102)			144	-	MMAS-4	65 (57 – 63)
Shaik et al. (103)			282	52 ± 12.0	MMAS-8	55 (49 – 61)
Khayyat et al. (104)			204	59 ± 12.2	MMAS-8	54 (46 – 62)
Alotayfi et al. (105)			262	-	Structured questionnaire	67 (62 – 73)
Alqarni et al. (106)			108	-	Structured questionnaire	67 (58 – 76)
Alkhamis et al. (107)			372	53 ± 12.4	Structured questionnaire	49 (44 – 54)
Abdelhalim et al. (108)			402	54.1 ± 10.7	Structured questionnaire	60 (56 – 65)
UAE	2	Cross-sectional	453			49 (45 – 52)
Fahey et al. (109)			203	52. ± N/A	MMAS-4	48 (41 – 55)
Bader et al. (50)			250	44 ± 5.6	MMAS-8	46 (39 – 52)

CI: confidence interval; MMAS: Morisky medication adherence scale; ARMS: adherence to refills and medications scale; UAE: United Arab Emirates

Numerous studies in the Middle East (50,90–110) have explored adherence to antihypertensive treatment. All the studies are cross-sectional, used structured questionnaires or adherence scales, and were published between 1998 (101) and 2019 (107,108). Overall, the level of adherence to antihypertensive medication in the Middle East was suboptimal, and over half of the hypertensive patients in Saudi Arabia (60%), Iran (57%), Palestine (54%), and Oman (51%) were non-adherent to antihypertensive medications. In the UAE, the level of adherence to medication was only 50% (50,109).

1.3.5.1 Focus on the UAE

Two studies were conducted in the UAE (50,109) and assessed the adherence to medications using four-item (109) and eight-item (50) Morisky medication adherence scale (MMAS). The overall medication adherence was only 51% and around half of the hypertensive patients were not adherent to antihypertensive treatment.

In 2006, Fahey et al. (109) conducted a study on 203 patients attending two outpatient health centers in Abu Dhabi, and the medication adherence was assessed using self-reported medication adherence recall in the past three months. Ninety percent were Arabs, and their mean age was 52 years. The median time since the hypertensive treatment was 5.1 years (range: 0.19–27.4 years). Overall, 52% (n = 103) reported adherence to hypertensive medication using the MMAS-8 scale, and the reason for non-adherence from the doctor's point of view was “forgetfulness.”

On the whole, for those who were adherent to antihypertensive treatment, the BP target achievement (JNC VI criteria, 140/90 mmHg or 135/85 mmHg for diabetes) was 52% versus 48% in non-adherent patients. The findings of the study revealed that practical assessment of adherence and drug management would greatly benefit if the physicians incorporated medication assessment in their routine practice.

Bader et al. (50) conducted a cross-sectional study in Ajman, UAE, and assessed the predictors of non-adherence to antihypertensive medications in 250 randomly selected hypertensives attending outpatient clinics. Medication adherence was assessed using the MMAS-4 scale and reported that the level of non-adherence was 45.6%. In this study, 70% of the study participants were expatriates, and the mean age of the study population was 44 ± 5.6 years. In addition, this study reported several

predictors of adherence to antihypertensive medications as sociodemographic, therapy-, patient-, and healthcare-related predictors.

Sociodemographic predictors include males being more likely to be non-adherent to antihypertensive medications ($P = 0.01$) than females and patients with two or more children who were more likely to be non-adherent to antihypertensive treatment than patients with no or a single child ($P = 0.03$).

Disease status and medication-related predictors such as those hypertensive patients with more than one hospital admission had a higher rate of non-adherence to antihypertensive medications ($P = 0.04$). Patients on two or more antihypertensive medications were more likely to be non-adherent ($P = 0.05$). Hypertensive patients who believed that the cost of the medications was high ($P < 0.001$) and used traditional remedies ($P < 0.001$), were strongly associated with non-adherence to antihypertensive therapy.

The patient-related factors, such as forgetfulness, being aware of hypertension complications, and identifying their hypertensive medication, were significantly associated with non-adherence to antihypertensive medications ($P < 0.01$).

Patients who lost their clinic follow-up for more than a month ($P < 0.001$), attended patient counseling sessions ($P < 0.001$), frequently changed physicians ($P = 0.02$), and were already well aware of physician's instructions ($P = 0.01$) were more likely to be non-adherent to antihypertensive medications.

Bader et al.'s (50) study recommended that using adherence questionnaires in hospitals can aid in identifying patients who are non-adherent to antihypertensive medications.

1.3.6 Treatment-resistant hypertension

Comprehensive reviews of the literature on global, regional, and national prevalence and incidence of TRH are already available in the literature (110–112). Judd et al. (110) review published literature and obtained data of TRH in North America and Europe from 1990 to 2010. They combined the data of more than 600,000 hypertensive patients data and reported the prevalence of TRH was 10.1% among individuals treated for hypertension and 7.9% in all hypertensives. In 2014, Achelrod et al. (111) conducted a systematic review and meta-analysis by pooling 20 observational and four randomized controlled trials (RCTs) comprising 961,035 hypertensive population. The pooled prevalence of observational studies was 13.7% (95% CI: 11.2–16.2) and 16.3% (10.6–21.9) in RCTs, respectively. The study also demonstrated no differences in the TRH prevalence in males (15.3%, 95% CI: 12.5–18.1) and 15.6% (95% CI: 13.6–17.6) in females. Most recently, in 2019, Noubiap et al. (112) reviewed all the articles published from 1991 to 2017 and pooled the data of 3.2 million patients with hypertension on antihypertensive drugs globally. This study included 91 studies, and most of the included studies used office blood pressure measurement (OBPM). The pooled prevalence was stratified into three sections and provided pooled prevalence of true-resistant hypertension, apparent TRH, and pseudo-resistant hypertension. The pooled prevalence of apparent TRH was 14.7% (95% CI: 13.1–16.3).

A brief review of epidemiological research conducted on the hypertensive population published between 2010 and May 31, 2021, was summarized in this thesis. Cross-sectional and cohort studies treated for hypertension were considered. Fifty-five articles identified and reported the prevalence of TRH, but there was only one article

in the Middle East – Israel (113). No literature was found regarding TRH in the UAE. A summary of global, regional, and national prevalence of TRH is presented in Table 9.

Table 9: Prevalence of treatment-resistant hypertension from 2010 to May 31, 2020.

Location	Study design	Settings	Male (%)	Mean age	BP measurement	Sample size	TRH cases	Prevalence (95% CI)
Global		-	52.6	60.2	ABPM, HBPM, OBPM	3,528,043	346,707	15 (14 – 16)
Multinational	Prospective	Hospital	61.3	69	OBPM	53530	6790	13 (12 – 13)
Africa		-	53.4	48.2	ABPM, OBPM	9120	1331	13 (8 – 18)
Algeria	Prospective, Retrospective	Hospital	55.4	54.7	ABPM, OBPM	4542	293	11 (10 – 12)
Burkina Faso	Prospective	Unclear	39.7	54.8	ABPM	692	91	13 (11 – 16)
DR.Congo	Retrospective	Hospital	52.1	56	ABPM	636	75	12 (10 – 15)
Ethiopia	Prospective	Hospital	58.9	46.2	OBPM	338	29	9 (6 – 12)
Ghana	Prospective	Hospital	58.8	23.3	OBPM	2912	550	19 (18 – 20)
Asia		-	54.7	60.4	OBPM	127,233	18,678	16 (14 – 19)
China	Retrospective	Hospital	55.8	62.2	OBPM	2011	286	14 (12 – 15)
India	Retrospective	Hospital	62	51.2	OBPM	6262	1170	19 (18 – 20)

Table 9: Prevalence of treatment-resistant hypertension from 2010 to May 31, 2020 (Continued)

Location	Study design	Settings	Male (%)	Mean age	BP measurement	Sample size	TRH cases	Prevalence (95% CI)
Korea	Retrospective	Hospital	53.2	61.1	OBPM	6010	541	10 (8 – 12)
Pakistan	Prospective	Hospital	53.8	61.3	OBPM	687	226	32 (28 – 35)
Sri Lanka	Prospective	Hospital	50.2	61	OBPM	277	53	19 (15 – 24)
Taiwan	Prospective, Retrospective	Hospital, Population	50.3	61	OBPM	112263	16455	15 (14 – 15)
Europe		-	53.3	63.2	ABPM, HBPM, OBPM	1,537,561	125,921	16 (13 – 19)
Multinational	Retrospective	Population	52.6	58.5	ABPM, OBPM	1312	423	32 (30 – 35)
France	Retrospective	Hospital	58	62	HBPM, OBPM	144	8	6 (3 – 11)
Georgia	Retrospective	Hospital	55	66.6	OBPM	1756	268	15 (14 – 17)
Germany	Prospective, Retrospective	Population, Unclear	-	-	ABPM, HBPM	2869	370	13 (12 – 15)
Greece	Prospective, Retrospective	Hospital	44.7	57.8	OBPM	3721	777	18 (17 – 19)

Table 9: Prevalence of treatment-resistant hypertension from 2010 to May 31, 2020 (Continued)

Location	Study design	Settings	Male (%)	Mean age	BP measurement	Sample size	TRH cases	Prevalence (95% CI)
Italy	Prospective, Retrospective	Hospital, Population	70.1	59.2	ABPM, OBPM	2259	361	19 (4 – 33)
Poland	Prospective	Unclear	41	63.6	OBPM	12375	3060	25 (24 – 25)
Spain	Prospective, Retrospective	Hospital, Population	51.5	67.8	ABPM, HBPM, OBPM	130470	15598	10 (8 – 12)
Sweden	Retrospective	Hospital	44	69	OBPM	53090	9185	17 (17 – 18)
UK	Retrospective	Population	-	-	OBPM	1,317,290	92811	7 (7 – 7)
Middle East		-	-	-	OBPM	172432	15104	9 (9 – 9)
Israel	Retrospective	Unclear	-	-	OBPM	172432	15104	9 (9 – 9)
North America		50.0	61.8	HBPM, OBPM	1,627,272	178,748	15 (12 – 19)	-
Multinational	Retrospective	Unclear	56.2	66.3	OBPM	14684	1870	13 (12 – 13)

Table 9: Prevalence of treatment-resistant hypertension from 2010 to May 31, 2020 (Continued)

Location	Study design	Settings	Male (%)	Mean age	BP measurement	Sample size	TRH cases	Prevalence (95% CI)
Canada	Retrospective	Population	49.9	-	OBPM	677	82	12 (10 – 15)
USA	Prospective, Retrospective	Hospital, Population	49.3	61.3	HBPM, OBPM	1611911	176796	15 (12 – 19)
South America			32.5	62	ABPM, HBPM, OBPM	895	135	14 (12 – 17)
Argentina	Retrospective	Hospital	32.5	66.6	HBPM	289	29	10 (7 – 14)
Brazil	Prospective	Hospital	-	57.3	ABPM, OBPM	606	106	17 (15 – 21)

TRH: treatment-resistant hypertension; CI: confidence interval; ABPM: ambulatory blood pressure monitoring; HBPM: home-based blood pressure monitoring; OBPM: office-based blood pressure monitoring.

1.4 Study aims and objectives

1.4.1 Aims

To assess the BP management, adherence to antihypertensive medications, and factors associated with poor BP control in newly diagnosed hypertensive patients in the UAE.

1.4.2 Objectives

1. To assess the changes in the BP within first six months of treatment initiation and compare the achievement of BP targets recommended by the current international guidelines.
2. To identify the factors that are associated with the achievement of BP treatment targets with the recommendations of each of the guidelines: ACC/AHA, ESC/ESH, NICE, and ISH.
3. To assess the level of adherence to antihypertensive treatment and identify the factors associated with adherence to antihypertensive medications.
4. To assess the occurrence of TRH and PRH within the first six months of antihypertensive treatment initiation.

Chapter 2: Methods

2.1 Study design

A retrospective cohort study was conducted by reviewing the medical charts of newly treated hypertensive patients registered in Abu Dhabi Health Services (SEHA) clinics between January 1, 2017 and December 31, 2017, across the Abu Dhabi region, UAE. The chart review was conducted from September 1, 2018, until October 31, 2019.

2.2 Study setting

The study setting includes all healthcare centers and outpatient clinics at different health settings across Abu Dhabi region, under SEHA facilities and providing chronic care to patients with hypertension. SEHA is the largest and main corporate healthcare network in the UAE, which provides comprehensive medical care to five million population. Throughout the Abu Dhabi region, a total of 38 SEHA health clinics are located across primary and secondary care centers and an additional 14 auxiliary clinics are available at tertiary care centers (114).

2.3 Study population

The target population includes the national representative Emirati adult population, newly registered for hypertensive treatment across all the SEHA clinics during the year 2017. Each eligible patient's data were followed for six months using SEHA Cerner database.

2.4 Selection of subjects

The subjects were selected retrospectively and patients with incident hypertension, visiting outpatient health clinics to refill their antihypertensive medications were included.

2.4.1 Inclusion criteria

The inclusion criteria were:

- United Arab Emirates national representative patients.
- Aged ≥18 years.
- Newly diagnosed with hypertension during 2017.
- Registered for hypertension treatment at SEHA facilities.

2.4.2 Exclusion criteria

- Non-UAE nationals.
- Patients with established hypertension and not confirmed by ABPM or HBPM by treating physician.
- Hospitalized hypertension patients.
- Not on antihypertensive medications.
- Not on follow-up for at least one-month treatment.
- Hypertensive patients with a history of antihypertensive medication use or hospitalization due to elevated BP in the past 12 months of the index period.
- Patients with hemoglobinopathy disorders and/or with systemic or malignant disease (needs special consideration).
- Significant renal impairment (plasma creatinine concentration >2.0 mg/L).

2.5 Sample size collection

The minimum number of subjects to include in this study was determined in order to have sufficient statistical power to detect any changes in the BP. The mean SBP in the INTERHEART study was 132.5±11.9 mmHg and DBP was 73.1±9.7 (74). The mean SBP in our study group was 133.8±17.1 mmHg and DBP was 72.3±12.7 mmHg.

- By considering the type-I error (α) of 5% (0.05) (indicating a 5% chance that a significant difference is actually due to chance and may not represent the true difference).
- The probability of type-II error (β) (not detecting a difference when one actually exists).
- Study power as P = 1 − β, with a 20% (0.2) chance that a significant difference may be missed.

Calculated the sample size as per the formula

SBP

$$N = \frac{\sigma^2(z_{1-\beta} + z_{1-\alpha/2})^2}{(\mu_0 - \mu_1)^2}$$

$$N = \frac{(11.9^2(0.84 + 1.96)^2}{(132.5 - 133.8)^2}$$

$$N = 658$$

DBP

$$N = \frac{\sigma^2(z_{1-\beta} + z_{1-\alpha/2})^2}{(\mu_0 - \mu_1)^2}$$

$$N = \frac{(12.7^2(0.84 + 1.96)^2}{(72.3 - 73.1)^2}$$

$$N = 1978$$

Where N= sample size of study population

μ0= mean level of BP in INTERHEART study

μ1= assuming the mean BP in this study

β = probability of type-II error (usually 0.2)

α = probability of type-I error (usually 0.05)

σ = variance of BP in INTERHEART study z = critical Z value for a given α or β

As the data was collected retrospectively, a post-hoc power calculation for correlations and t-tests was performed using G*Power software (115) (Figure 6). First, the effect size of study population in the INTERHEART study was calculated using the formula:

$$\text{Effect size} = \frac{[\text{Mean of the experimental group}] - [\text{Mean of the control group}]}{\text{Standard deviation}}$$

The effect size of the INTERHEART case-control study was 0.1063 (74).

By using the t-test correlation: Point biserial model

Input	Tail(s)	= 1
	Effect size |ρ|	= 0.1063
	α err prob	= 0.05
	Power (1-β err prob)	= 0.95
Output		
	Non-centrality parameter δ	= 3.2933208
	Critical t	= 1.6464643
	Df	= 947
	Total sample size	= 949
	Actual power	= 0.9501298

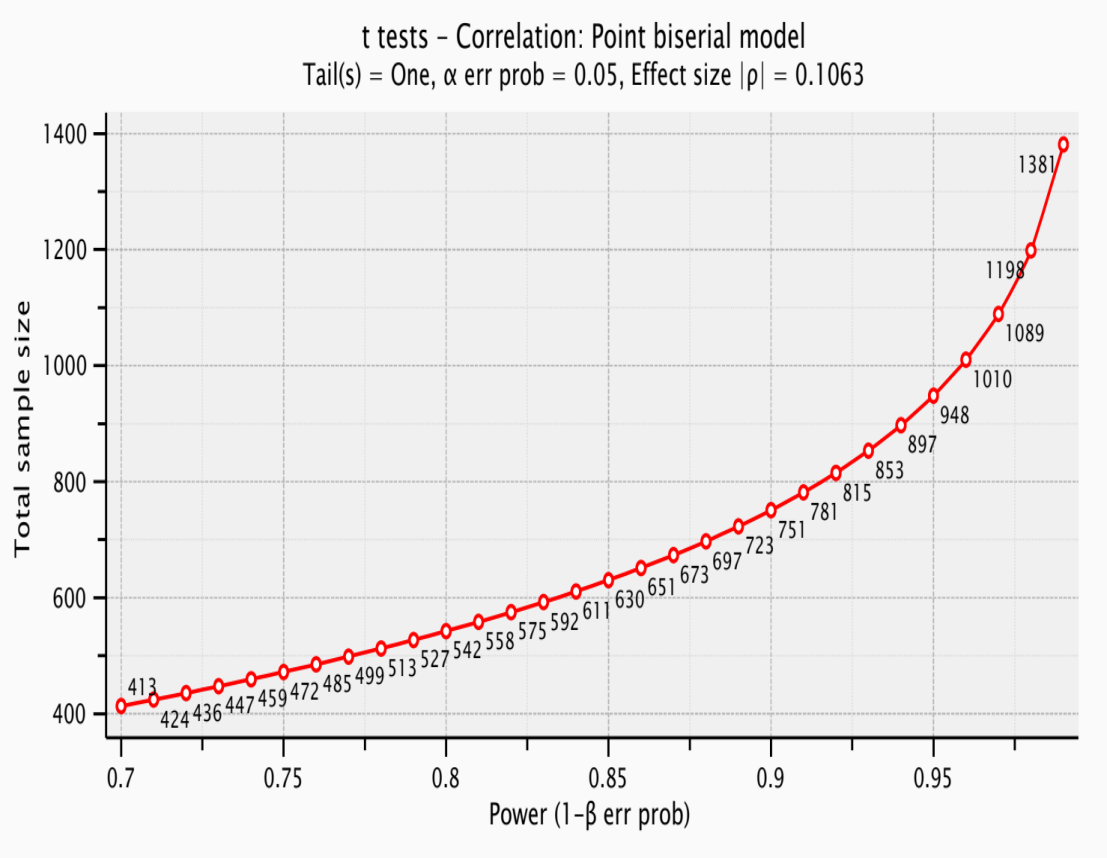

Figure 6: Power sampling method

2.6 Study measurements

The entire data collected at baseline and follow-up are summarized in Table 10.

Table 10: Summary of key data variables includes

Sociodemographic	
Age (years)	Registered clinical setting
Gender (Male/female)	Height (cm)
Weight (kg)	Waist circumference (cm)
Body mass index (kg/m^2)	Smoking status (yes/no)
Past medical and medication history	
Clinical characteristics	
SBP (mmHg)	DBP (mmHg)
Heart rate (beats/minute)	Date of hypertension diagnosis

Table 10: Summary of key data variables includes (Continued)

Diabetes (yes/no)	Type of diabetes (Type 1 and Type 2)
Fasting blood glucose (mmol/l)	Glycated hemoglobin A1c (%)
Dyslipidemia (yes/no)	Serum creatinine (µmmol/L)
List of antihypertensive medications	Diabetic medications
Duration of treatment (days prescribed)	Medication adherence (Proportion of days covered)
Outcome variables	
Changes in the BP	Mortality
Hospitalization	Non-adherence

The proportion of days covered (PDC) is a widely adopted approach used to assess the medication adherence using medication refilling rate (116). The PDC calculation is based on the fill dates and days' supply for each fill of a prescription i.e., the number of days between the first fill of the medication during the measurement period and the end of the measurement period. A PDC threshold level of about 80% is considered adherent to medications and has a reasonable likelihood of achieving the most clinical benefits (116).

2.7 Data collection procedure

The study used the Cerner® health care databases managed by SEHA facilities to obtain the data. These extensive, electronically linked health data pertained to the UAE residents covered by provincial health insurance. The data for the study were collected from the health clinics and included cardiology, endocrinology, and nephrology clinics across SEHA facilities in the UAE. Patient data, including demographics, clinical, and other variables related to the study objective, were collected from the patients' electronic medical records (EMR) in Cerner database. All the collected information was carefully cross-checked with the patients' Financial

Identification Number (FIN) for pharmacy claims linked to the medical record number (MRN) for each patient.

2.8 Ethical considerations

Ethical approval was obtained from the Al Ain Hospital Research Ethics Committee (AAHEC-08-18-103) prior to the initiation of the study. The obtained data were considered anonymous and no personal information was collected.

2.9 Timeline

The study included patients newly diagnosed and registered for hypertension treatment between January 1, 2017 to December 31, 2017 with a follow-up period of six months for each patient. The retrospective data collection was performed from September 1, 2018, until October 31, 2019.

2.10 Data analysis and statistical tests

Statistical analysis was performed using the statistical software package SPSS for Windows version 24 (IBM Corp., Armonk, New York, USA). Baseline characteristics and follow up data for six months are described using summary statistics, and all outcome events were recorded and summarized individually as proportions and 95% CIs. Statistical significance was set as two-sided $P \leq 0.05$.

Objective 1: To assess the changes in the BP within first six months of treatment initiation and to compare the achievement of BP targets recommended by the current international guidelines.

- Categorical variables were presented as frequency and percentages.
- Mean ± standard deviation (SD) was used for continuous variables.

- Changes in the BP parameters from baseline to six-month follow-up across different groups for categorical variables were assessed using chi-square test and ANOVA or Kruskal–Wallis test was used for continuous variables, as appropriate.
- BP measurements were stratified according to the ACC/AHA 2017, ESC/ESH 2018, NICE UK 2019 and ISH 2020 guidelines and the level of BP goal achievement were compared in accordance with these guidelines.
- Data were presented as proportions with 95% CI.

Objective 2: To identify the factors that are associated with the achievement of BP treatment targets according to the guidelines-recommended BP targets, see Table 2.

- BP control at six months is first categorized according to the guideline-recommended BP targets, see Table 2.
- Factors independently associated with the changes in BP in 6-month follow-up were determined using Wilcoxon signed-rank test and Mann-Whitney *U* test or Kruskal-Wallis test, as appropriate.
- Univariate and multivariate logistic regression analysis was performed to identify the factors associated with increasing the likelihood of achieving BP targets according to each guideline.
- Odds ratios (OR) with 95% CI were calculated.

Objective 3: To assess the level of adherence to antihypertensive treatment, its effect on BP control and to identify the factors associated with adherence to antihypertensive medications.

- Adherence to medications was assessed according to PDC (≥80% as adherent and <80% non-adherent).
- Factors independently associated with the changes in BP at six-month follow-up between adherent and nonadherent groups were determined using the Mann-Whitney U test or Kruskal-Wallis test, as appropriate.
- Non-adherence as an outcome measure was used in the regression analysis and defined as PDC <80% at six-months follow-up.
- Covariate that influences adherence such as age, type of health setting, body mass index and smoking were evaluated and used as reference categories.
- Crude and adjusted OR with 95% CI were calculated.

Objective 4: To assess the occurrence of TRH and PRH within the first six months of antihypertensive treatment initiation.

- A decision tree algorithm model was used to determine the occurrence of TRH and PRH in the study cohort.

Chapter 3: Results

3.1 Study cohort

At first, hypertensive patients comprising 178,335 aged 18-100 years registered for the treatment across SEHA facilities from 2011 to June 2018 were identified. Of these, those who are taking at least one antihypertensive medication from January 1, 2011, until December 31, 2016, were identified. Those newly diagnosed patients and first dispensed of an antihypertensive medication from January 1, 2017, were considered index date. To ensure that selection only included newly-treated individuals, patients for whom one or more prescriptions of hypertensive medications or hospitalization due to hypertension before the index date were excluded. A total of 12,297 patients with incident hypertensive patients and on treatment were identified through ICD-10 code I10 (essential hypertension) as primary diagnoses were considered. Finally, because the purpose of the study was to determine the guidelines-recommended BP management and medication adherence in the UAE nationals, patients with insufficient follow-up data (n = 2143), expatriates (n = 4740), and died (n=106) were excluded. The remaining patients constituted the study cohort. More details are in Figure 7.

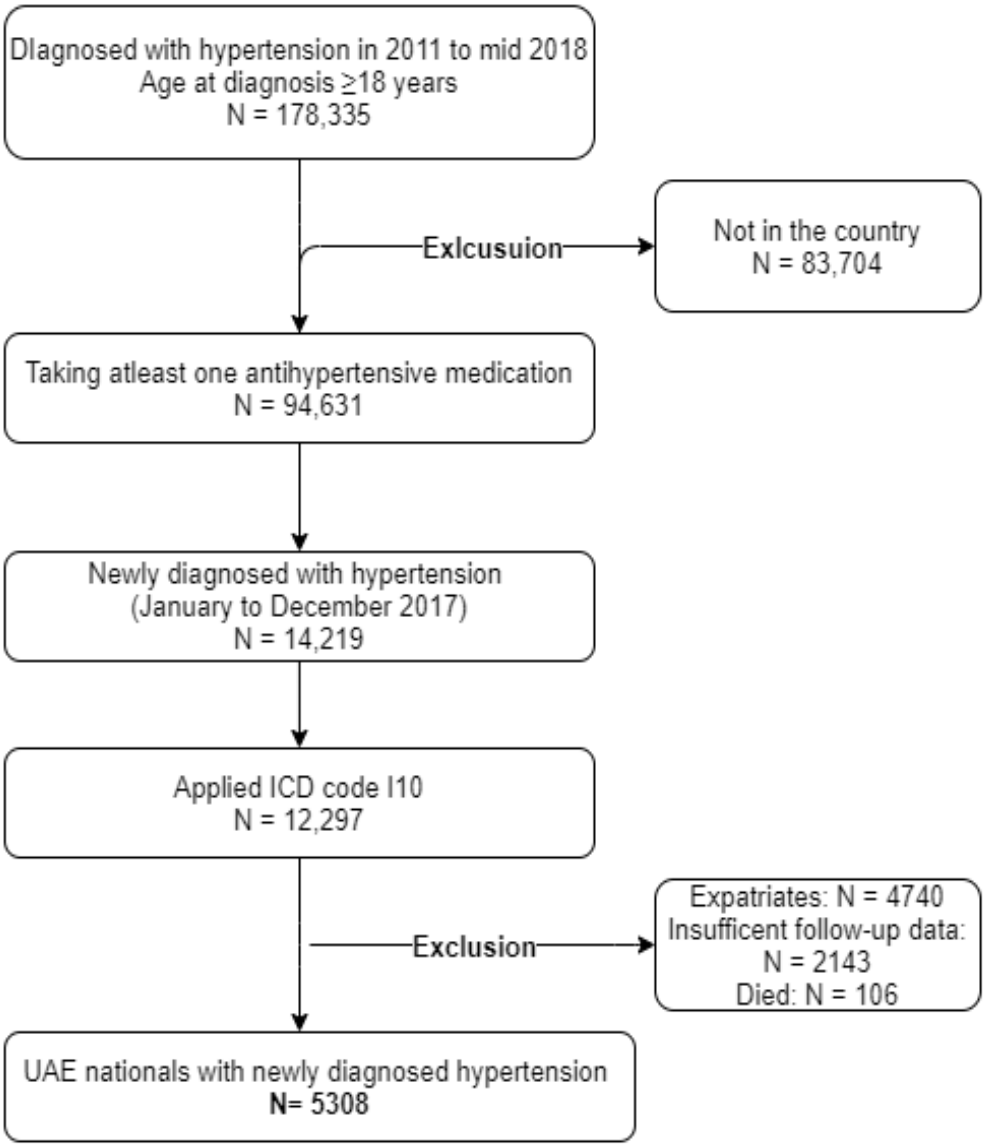

Figure 7: Consort flow diagram of the cohort studies

A total of 5308 patients with incident hypertension were registered across 52 health centers-SEHA facilities in the emirates of Abu Dhabi between January 1, 2017, and December 31, 2017, and had a follow-up data of 6-months. The distribution of subjects stratified by age is shown in Table 11.

Table 11: Distribution of hypertensive subjects by age and gender

Age group (years)	Male	Female	Total
Total	2459 (46.3%)	2849 (53.7%)	5308 (100%)
18 – 40	285 (5.4%)	251 (4.7%)	536 (10.1%)
41 – 50	654 (12.3%)	629 (11.9%)	1283 (24.2%)
51 – 60	969 (18.3%)	1267 (23.9%)	2236 (42.1%)
61 – 75	397 (7.5%)	517 (9.7%)	914 (17.2%)
>75	154 (2.9%)	185 (3.5%)	339 (6.4%)

Although the sample does not represent the whole UAE population, it captured a good proportion of incident hypertensives across Abu Dhabi. The completeness of the data was above 85% for BMI (n = 4588), height (n= 4703), weight (n = 4868). However, data for some clinical parameters, such as HbA1c (n = 4501), serum creatinine (n = 400) and dyslipidemia (n = 2007) data were incomplete. The rest of the data regarding sociodemographics, antihypertensive treatments, and BP parameters were complete.

Overall, the mean age of the study cohort was 53.8 years (SD± 11.5) with a mean BMI of 31.2 (SD± 7.5) kg/m^2. At baseline, the mean SBP was 133.9 ± 17.1 mmHg and DBP was 72.9 ± 12.7 mmHg. The baseline characteristics of the study cohort according to the BP levels are illustrated in Table 12.

Table 12: Characteristics of the study population according to the BP levels at baseline

Characteristics	Total	<120 and <80	120–129 and <80	130–139 or 80–89	≥140 or ≥90	P-value
Number (%)	5,308 (100.0)	958 (18.0)	874 (16.5)	2,099 (39.5)	1,377 (25.9)	
Age, Mean (±SD)	54.8 (±11.5)	55.2 (±11.8)	55.3 (±11.9)	54.5 (±10.9)	54.8 (±12.1)	0.164
Gender, n (%)						0.223
Men	2,459 (46.3)	422 (44.1)	391 (44.7)	996 (47.5)	650 (47.2)	
Women	2,849 (53.7)	536 (55.9)	483 (55.3)	1,103 (52.5)	727 (52.8)	
Health center location, n (%)						0.662
Rural	2,595 (48.9)	479 (50.0)	412 (47.1)	1,027 (48.9)	677 (49.2)	
Urban	2,713 (51.1)	479 (50.0)	462 (52.9)	1,072 (51.1)	700 (50.8)	
Healthcare setting, n (%)						<0.001
Primary	3,189 (60.1)	468 (48.9)	488 (55.8)	1,388 (66.1)	845 (61.4)	
Secondary	795 (15.0)	220 (23.0)	135 (15.4)	243 (11.6)	197 (14.3)	
Tertiary	1,324 (24.9)	270 (28.2)	251 (28.7)	468 (22.3)	335 (24.3)	
Smoking, n (%)						0.955
Smoker	1,883 (35.5)	346 (36.1)	313 (35.8)	740 (35.3)	484 (35.1)	
Nonsmoker	3,425 (64.5)	612 (63.9)	561 (64.2)	1,359 (64.7)	893 (64.9)	
BMI (kg/m^2), Mean (±SD)	31.2 (±7.5)	30.6 (±6.8)	30.6 (±6.3)	31.6 (±8.4)	31.4 (±6.9)	0.001
Missing	720 (13.6)	159 (16.6)	116 (13.3)	236 (11.2)	209 (15.2)	
Diabetes, n (%)						0.590
No	4,437 (83.6)	796 (83.1)	730 (83.5)	1,744 (83.1)	1,167 (84.7)	
Yes	871 (16.4)	162 (16.9)	144 (16.5)	355 (16.9)	210 (15.3)	

BMI: body mass index, SD: standard deviation

At baseline, overall, 26% of the subjects had a BP of ≥140 or ≥90 mmHg, and higher BP was observed in women (52.8%), nonsmokers (64.9%), and the non-DM population (84.7%). However, significant differences in the BP levels were observed according to their BMI and the type of health setting.

At baseline, there were 28.4%, 29.2%, 29.2%, and 24.6% subjects with stage 1 hypertension according to the ACC/AHA, the ESC/ESH, the NICE, and the ISH guidelines, respectively. More details on the distribution of BP according to international guidelines are shown in Figure 8.

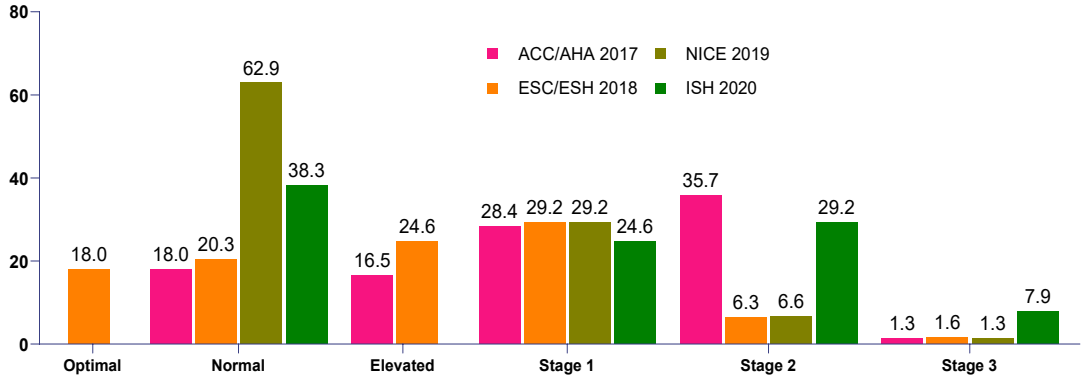

Figure 8: Distribution of BP according to international guidelines at baseline

From the day of diagnosis of hypertension, over 8.7% of newly diagnosed hypertensive patients were hospitalized and 63 (1.2%) patients died within six months due to various medical reasons. Different classes of antihypertensive drugs were prescribed as monotherapy (71.5%) or combination therapy (28.4%). The class of drugs used (missing data 0.3%) are shown in Figure 9.

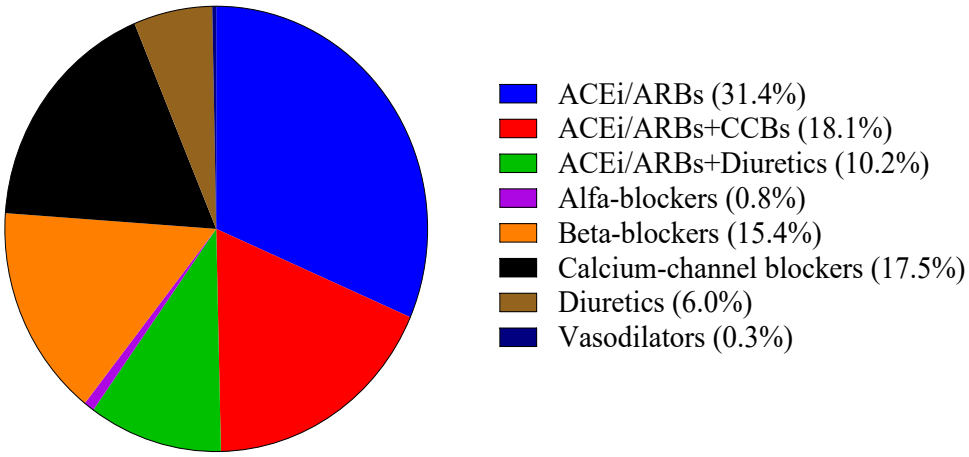

Figure 9: Antihypertensive drug classes prescribed

The majority (77.6%) had taken one antihypertensive medication, whereas 189 (3.6%) patients had taken three or more classes of antihypertensive medications concurrently for at least one month. Higher medication use was significantly associated with old age. The baseline characteristics of the study cohort based on the number of antihypertensive medications given are listed in Table 13.

Table 13: Characteristics of study cohort with number of antihypertensive medications given at baseline

Characteristics	Total (N = 5308)	Number of antihypertensive medications			P-value*
		One	Two	Three	
		4117, 77.6%	1002, 18.9%	189, 3.6%	
Age, Mean ±SD	54.8 ±11.5	54.0 ± 11.5	57.1 ± 11.2	59.3 ± 11.4	<0.001
Gender, n (%)					0.201
Men	2,459 (46.3)	1906 (35.9)	454 (8.6)	99 (1.9)	
Women	2,849 (53.7)	2211 (41.7)	548 (10.3)	90 (1.7)	
Health center location, n(%)					0.970
Rural	2,595 (48.9)	2012 (37.9)	492 (9.3)	91 (1.7)	
Urban	2,713 (51.1)	2105 (39.7)	510 (9.6)	98 (1.8)	
Healthcare setting, n(%)					0.126
Primary	3,189 (60.1)	2494 (47)	582 (11)	113 (2.1)	
Secondary	795 (15.0)	588 (11.1)	176 (3.3)	31 (0.6)	
Tertiary	1,324 (24.9)	1035 (19.5)	244 (4.6)	45 (0.8)	
Smoking, n(%)					0.001
Smoker	1,883 (35.5)	1406 (26.5)	393 (7.4)	84 (1.6)	
Nonsmoker	3,425 (64.5)	2711 (51.1)	609 (11.5)	105 (2.0)	
BMI (kg/m^2), (n = 4583, 86.3%)	31.2 ± 7.4	31.2 ± 7.6	31.0 ± 6.5	31.2 ± 6.9	0.824
<18.5	41 (0.9)	32 (0.7)	8 (0.2)	1 (0)	
18.5–25	631 (11.9)	500 (10.9)	114 (2.5)	17 (0.4)	
25–30	1485 (28)	1148 (25)	280 (6.1)	57 (1.2)	
>30	2483 (45.7)	1889 (41.2)	454 (9.9)	83 (1.8)	
Diabetes, n (%)					0.001
No	4,437 (83.6)	3403 (64.1)	863 (16.3)	171 (3.2)	
Yes	871 (16.4)	714 (13.5)	139 (2.6)	18 (0.3)	
Baseline systolic BP, mmHg	133.9 ± 17.1	134.0 ± 17.1	133.8 ± 17.2	134.4 ± 18.4	0.962
Baseline diastolic BP, mmHg	72.9 ± 12.7	73.1 ± 12.6	72.2 ± 12.9	71.9 ± 12.9	0.061

*chi-square test for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables

3.2 Blood pressure at baseline and at 6-month across the study cohort

At 6-month follow-up, a significantly higher BP reduction was observed in men (SBP: –1.68 mmHg and DBP: –1.15 mmHg) than women (SBP: –0.84 mmHg), and no significant reduction in the DBP (0.22 mmHg) was observed in women. Moreover, a significant reduction in the SBP was observed in the 41-75 years age group, and those aged 61-75 years showed higher SBP difference from baseline (–1.82 mmHg) than other age groups. Those hypertensives treated at primary care settings showed a significant re-duction in the SBP by –2.31 mmHg (P <0.001) and DBP by –2.15 mmHg (P <0.001), with no such reduction in SBP and DBP in those treated at secondary and tertiary care settings, as shown in Table 14.

Table 14: Mean BP at baseline and at 6-month according to the subgroups

Characteristics	Systolic blood pressure		Diastolic blood pressure	
	Baseline	6-months	Baseline	6-months
Overall	133.9 (133.5 – 134.4)	132.7 (132.3 – 133.2)	72.9 (72.6 – 73.3)	72.5 (72.1 – 72.8)
Sex				
Men	133.8 (133.1 – 134.5)	132.1 (131.5 – 132.8)	74.3 (73.8 – 74.8)	73.2 (72.7 – 73.6)
Women	134.1 (133.4 – 134.7)	133.2 (132.6 – 133.8)	71.7 (71.2 – 72.1)	71.9 (71.4 – 72.3)
Age (years)				
18-40	134.7 (133.2 – 136.1)	133.3 (132.5 – 134.1)	75.2 (74.0 – 76.4)	74.5 (73.4 – 75.7)
41-50	133.2 (132.3 – 134.1)	131.8 (130.9 – 132.7)	75.3 (74.6 – 75.9)	74.0 (73.3 – 76.7)
51-60	134.0 (133.3 – 134.7)	133.0 (132.3 – 133.7)	72.6 (72.1 – 73.1)	72.5 (72.0 – 73.0)
61-75	134.5 (133.4 – 135.7)	132.7 (131.6 – 133.8)	71.6 (70.8 – 72.4)	70.8 (70.1 – 71.5)
>75	133.5 (131.6 – 135.5)	132.5 (130.6 – 134.4)	65.8 (64.5 – 67.1)	67.9 (66.6 – 69.3)
Health center location				
Rural	133.9 (133.2 – 134.5)	132.8 (132.1 – 133.4)	73.0 (72.5 – 73.5)	72.5 (72.1 – 73.0)
Urban	134.0 (133.4 – 134.7)	132.7 (132.0 – 133.3)	72.8 (72.3 – 73.0)	72.4 (71.9 – 72.9)

Table 14: Mean BP at baseline and at 6-month according to the subgroups (Continued)

Healthcare setting				
Primary	135.3 (134.8 – 135.9)	133.0 (132.4 – 133.6)	75.6 (75.3 – 76.0)	73.5 (73.1 – 73.9)
Secondary	130.7 (129.5 – 132.0)	131.7 (130.6 – 132.9)	66.5 (65.6 – 67.5)	69.9 (69.0 – 70.8)
Tertiary	132.5 (131.6 – 133.5)	132.5 (131.6 – 133.5)	70.1 (69.4 – 70.9)	71.6 (70.9 – 72.3)
BMI (kg/m^2)				
<18.5	130.3 (124.7 – 135.9)	130.1 (123.5 – 136.7)	65.8 (62.1 – 69.5)	66.6 (61.9 – 71.3)
18.5-25	131.7 (130.3 – 133.0)	131.5 (130.1 – 132.9)	70.6 (69.6 – 71.6)	70.8 (69.8 – 71.7)
25-30	134.0 (133.1 – 134.8)	132.4 (131.6 – 133.2)	73.7 (73.1 – 74.4)	73.0 (72.4 – 73.6)
>30	134.7 (134.0 – 135.4)	133.8 (133.2 – 134.5)	74.1 (73.6 – 74.6)	74.2 (73.5 – 74.7)
Smoking				
Smoker	133.7 (132.9 – 134.5)	132.4 (131.6 – 133.1)	73.0 (72.4 – 73.5)	72.2 (71.7 – 72.8)
Non-smoker	134.1 (133.5 – 134.7)	132.9 (132.3 – 133.5)	72.8 (72.4 – 73.3)	72.6 (72.2 – 73.1)
Diabetes				
Yes	133.1 (131.9 – 134.2)	132.8 (131.6 – 133.9)	73.3 (72.4 – 74.1)	72.5 (71.7 – 73.4)
No	134.1 (133.6 – 134.6)	132.7 (132.2 – 133.2)	72.8 (72.5 – 73.2)	72.5 (72.1 – 72.8)

BMI: body mass index

3.3 Changes in the blood pressure within the first six months of treatment initiation

At 6-month follow-up, the mean SBP was 132.7 ± 16.9 mmHg, and DBP was 72.5 ± 12.4 mmHg. A significant average reduction in SBP of -1.68 mmHg (95% CI: -2.46 – -0.91; $P < 0.001$), and DBP of -1.15 mmHg (95% CI: -1.69 – -0.60; $P < 0.001$) was observed in men. For women, a significant reduction was observed in SBP of -0.84 mmHg (95% CI: -1.57 – -0.12, $P = 0.046$), but not in DBP (0.22 mmHg) (95% CI: -0.29–0.73, $P = 0.795$). Significant changes were observed in the average changes in DBP and SBP between men and women ($P < 0.001$, $P = 0.035$, respectively).

Moreover, significant differences in SBP ($P < 0.001$) and DBP ($P < 0.001$) were observed across healthcare settings. Those hypertensive patients treated at primary care settings showed a significant reduction in the SBP by -2.31 mmHg, (95% CI: -2.99 – -1.63; $P < 0.001$) and DBP by -2.15, (95% CI: -2.60 – -1.70; $P < 0.001$); however, no such differences in SBP were observed for patients treated at secondary and tertiary care settings, as shown in Table 15. Moreover, no significant differences in SBP and DBP were observed between the groups and the healthcare center location, BMI, smoking status and DM status.

Table 15: Changes in the BP at 6-month follow-up across the study subjects

Characteristics	Change in SBP	P-value*	P-value**	Change in DBP	P-value*	P-value**
Sex			0.035			<0.001
Men	-1.68 (-2.46 to -0.91)	<0.001		-1.15 (-1.69 to -0.60)	<0.001	
Women	-0.84 (-1.57 to -0.12)	0.046		0.22 (-0.29 to 0.73)	0.795	
Age (years)			0.951			0.012
18–40	-0.81 (-2.48 to 0.85)	0.262		-0.72 (-1.96 to 0.52)	0.289	
41–50	-1.39 (-2.46 to -0.32)	0.013		-1.25 (-2.03 to -0.47)	0.002	
51–60	-1.03 (-1.83 to -0.22)	0.006		-0.09 (-0.64 to 0.45)	0.244	
61–75	-1.82 (-3.15 to -0.49)	0.016		-0.81 (-1.74 to 0.11)	0.104	
>75	-1.07 (-3.30 to 1.15)	0.246		2.17 (0.63 to 3.70)	0.027	
Health center location			0.713			0.912
Rural	-1.11 (-1.87 to -0.35)	0.004		-0.46 (-0.99 to 0.06)	0.039	
Urban	-1.35 (-2.09 to -0.61)	<0.001		-0.37 (-0.90 to 0.16)	0.068	
Healthcare setting		<0.001			<0.001	
Primary	-2.31 (-2.99 to -1.63)	<0.001		-2.15 (-2.60 to -1.70)	<0.001	
Secondary	1.01 (-0.36 to 2.37)	0.144		3.38 (2.34 to 4.42)	<0.001	
Tertiary	0.02 (-1.05 to 1.09)	0.877		1.48 (0.69 to 2.28)	<0.001	

Table 15: Changes in the BP at 6-month follow-up across the study subjects (Continued)

Characteristics	Change in SBP	P-value*	P-value**	Change in DBP	P-value*	P-value**
BMI (kg/m^2)			0.277			0.077
<18.5	-0.20 (-7.22 to 6.83)	0.909		0.78 (-3.46 to 5.02)	0.630	
18.5–25	-0.16 (-1.69 to 1.38)	0.646		0.22 (-0.89 to 1.32)	0.401	
26–30	-1.56 (-2.54 to -0.57)	<0.001		-0.74 (-1.42 to -0.05)	0.007	
>30	-0.89 (-1.65 to -0.13)	0.044		0.07 (-0.48 to 0.62)	0.939	
Smoking			0.838			0.259
Smoker	-1.32 (-2.21 to -0.42)	0.004		-0.75 (-1.37 to -0.14)	0.011	
Nonsmoker	-1.19 (-1.85 to -0.53)	<0.001		-0.23 (-0.70 to 0.24)	0.128	
Diabetes			0.124			0.463
Yes	-0.29 (-1.57 to 0.97	0.121		-0.73 (-1.65 to 0.19)		0.119
No	-1.41 (-2.0 to -0.8)	<0.001		-0.35 (-0.76 to -0.05)		0.432

*Wilcoxon signed-rank test, ** Mann-Whitney U test, or Kruskal-Wallis test

3.4 Achievement of blood pressure goals according to international guidelines

The overall BP goal achievements at 6th months were 39.5% (95% CI: 38.2–40.9), 43% (95% CI: 41.6–44.3), 65.7% (95% CI: 64.4–66.9), and 40.9% (95% CI: 39.5–42.3) according to the ACC/AHA, ESC/ESH, NICE, and ISH guidelines, respectively. Figure 10 summarizes the proportion of patients achieving the BP goals recommended by each guideline according to age strata. According to the ACC/AHA guidelines, only 36.3% (95% CI: 34.9–37.7) of the patients aged 18–64 years reached BP goal of <130/80 mmHg and 56.3% (95% CI: 52.9–59.6) of patients aged 65 years or older achieved BP goal of <140/80 mmHg.

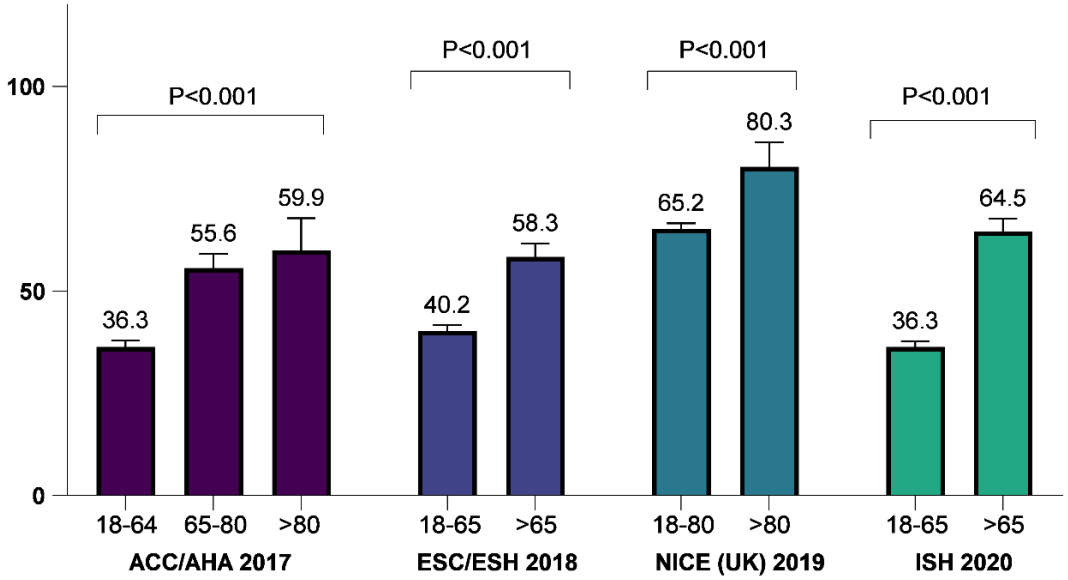

Figure 10: Proportion of hypertensive patients achieving BP goals by age strata at 6-month according to the international guidelines. *Chi-square test; ACC/AHA: American College of Cardiology/American Heart Association; ESC: European Society of Cardiology/European Society of Hypertension; NICE: National Institute of Health Care and Excellence (UK); ISH: International Society of Hypertension.

The achievement of BP goals according to each guideline was stratified by age, smoking status, BMI, and diabetes status, as presented in Table 16. At 6 months, only 31.7% of patients aged ≤40 years achieved the ACC/AHA recommended BP goal. In comparison to the ESC/ESH, the NICE, and the ISH guidelines, among the patients, 45.4% of smokers and 37.5% of those with BMI of ≥25 kg/m^2 achieved the ACC/AHA recommended BP goal (<130/80 mmHg).

Table 16: Percentage of adults who achieved BP goals according to the international guidelines.

Characteristics		Total (%)	ACC/AHA 2017	ESC/ESH 2018	NICE 2019	ISH 2020
Age (years)	≤40	536 (10.1)	31.7 (27.9 - 35.8)	37.1 (33.1 - 41.3)	61.6 (57.4 - 65.6)	31.7 (27.9 - 35.8)
	>40	4,772 (89.9)	40.4 (39.0 - 41.8)	43.4 (42.0 - 44.8)	66.1 (64.8 - 67.4)	41.7 (40.3 - 43.1)
Smoking	Smoker	1883 (35.5)	45.4 (43.2 - 47.7)	47.4 (45.2 - 49.7)	66.7 (64.5 - 68.8)	48.6 (46.3 - 50.9)
	Nonsmoker	3,245 (64.5)	36.3 (34.7 - 37.9)	40.2 (38.5 - 41.8)	65.1 (63.5 - 66.7)	36.3 (34.7 - 37.9)
BMI	<25 kg/m^2	672 (12.6)	44.2 (40.5 - 48.0)	47.5 (43.7 - 51.2)	68.2 (64.5 - 71.6)	44.9 (41.2 - 48.7)
	≥25 kg/m^2	3,910 (73.6)	37.5 (36.0 - 39.1)	40.8 (39.3 - 42.4)	65.2 (63.7 - 66.7)	38.8 (37.3 - 40.3)
BMI	<30 kg/m^2	2,156 (47.1)	41.5 (39.4 - 43.6)	44.9 (42.9 - 47.1)	67.9 (65.9 - 69.8)	42.8 (40.7 - 44.9)
	≥30 kg/m^2	2,426 (52.9)	35.9 (34.0 - 37.8)	39.0 (37.1 - 41.0)	63.6 (61.7 - 65.5)	36.9 (35.0 - 38.9)
Diabetes	No	4,437 (83.6)	39.9 (38.5 - 41.4)	43.2 (41.8 - 44.7)	66.2 (64.8 - 67.6)	41.3 (39.8 - 42.7)
	Yes	871 (16.4)	37.5 (34.4 - 40.8)	40.2 (37.0 - 43.5)	62.9 (59.7 - 66.1)	37.5 (34.4 - 40.8)

ACC/AHA: American College of Cardiology/American Heart Association; ESC/ESH: European Society of Cardiology/European Society of Hypertension; NICE: National Institute for Health and Care Excellence hypertension in adult guidelines; ISH: International Society of Hypertension; BMI: body mass index.

3.5 Factors associated with the achievement of guidelines-recommended BP targets

The factors that are significantly associated with each guideline-recommended BP goal attainment in hypertensive patients are shown in Table 17. The unadjusted logistic regression analysis indicated that a normal BMI of <25 kg/m^2 is a significant predictor of attaining ACC/AHA recommended BP goals (OR: 1.32, 95% CI: 1.12–1.55). Similar findings were observed with the ESC/ESH (OR: 1.31; 95% CI: 1.11–1.54) and ISH (OR: 1.29; 95% CI: 1.09–1.52) recommended goals. On the contrary, ESC/ESH and NICE recommended goals were associated with secondary care settings (OR: 1.23; 95% CI: 1.03–1.47, and OR: 1.26; 95% CI: 1.04–1.52).

After adjusting for multiple covariates, the guidelines-recommended BP goal was more likely to be achieved by those who maintained normal BMI and were treated in secondary healthcare settings. Briefly, those with BMI of <25 kg/m^2 were associated with BP targets achievement recommended by the ACC/AHA (OR: 1.26, 95% CI: 1.07–1.49), the ESC/ESH (OR: 1.27, 95% CI: 1.08–1.50), and the ISH guidelines (OR: 1.22, 95% CI: 1.03–1.44). More details are shown in Table 17.

Table 17: Factors associated with the achievement of each guideline-recommended BP goals

Variable	Odds ratio (95% confidence interval)							
	ACC/AHA 2017		ESC/ESH 2018		NICE 2019		ISH 2020	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Age								
<65 years	0.44 (0.38-0.51)	0.47 (0.39-0.58)	0.54 (0.46-0.62)	0.59 (0.48-0.73)	0.92 (0.79-1.07)	1.04 (0.84-1.28)	0.33 (0.28-0.39)	0.34 (0.28-0.42)
≥65 years	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Sex								
Men	1.06 (0.95-1.18)	0.99 (0.88-1.12)	1.04 (0.93-1.16)	0.97 (0.86-1.10)	1.00 (0.89-1.12)	0.95 (0.84-1.07)	1.06 (0.95-1.18)	1.00 (0.88-1.12)
Women	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Health center location								
Rural	1.02 (0.91-1.13)	0.93 (0.80-1.08)	1.04 (0.93-1.16)	0.96 (0.82-1.11)	1.07 (0.95-1.19)	0.97 (0.83-1.13)	1.01 (0.90-1.12)	0.92 (0.79-1.07)
Urban	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Healthcare setting								
Primary	0.96 (0.84-1.10)	1.09 (0.92-1.30)	0.99 (0.87-1.13)	1.12 (0.95-1.32)	1.05 (0.92-1.20)	1.15 (0.97-1.37)	0.96 (0.84-1.09)	1.11 (0.94-1.32)
Secondary	1.19 (0.99-1.42)	1.31 (1.03-1.66)*	1.23 (1.03-1.47)*	1.32 (1.05-1.67)*	1.26 (1.04-1.52)*	1.41 (1.11-1.81)**	1.18 (0.99-1.42)	1.34 (1.05-1.70)*
Tertiary	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Smoking status								
Nonsmoker	0.69 (0.61-0.77)	0.97 (0.83-1.13)	0.74 (0.66-0.83)	0.95 (0.82-1.11)	0.93 (0.83-1.05)	0.93 (0.80-1.09)	0.60 (0.54-0.68)	0.97 (0.83-1.13)
Smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Table 17: Factors associated with the achievement of each guideline-recommended BP goals (Continued)

Variable	Odds ratio (95% confidence interval)							
	ACC/AHA 2017		ESC/ESH 2018		NICE 2019		ISH 2020	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
BMI (kg/m^2)								
<25	1.32 (1.12-1.55)**	1.26 (1.07-1.49)**	1.31 (1.11-1.54)**	1.27 (1.08-1.50)**	1.14 (0.96-1.36)	1.14 (0.96-1.37)	1.29 (1.09-1.52)**	1.22 (1.03-1.44)*
≥25	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Diabetes								
Yes	0.90 (0.78-1.05)	1.07 (0.90-1.26)	0.88 (0.76-1.02)	1.00 (0.85-1.17)	0.87 (0.75-1.01)	0.90 (0.76-1.07)	0.85 (0.74-0.99)	1.07 (0.90-1.26)
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

*p≤0.05, **p≤0.01, significant factors that increase the likelihood to achieve guidelines-recommended BP goals are bolded. ACC/AHA: American College of Cardiology/American Heart Association; ESC/ESH: European Society of Cardiology/European Society of Hypertension; NICE: National Institute for Health and Care Excellence hypertension in adult guidelines; ISH: International Society of Hypertension. Adjusted for age, type of health center, BMI, smoking.

3.6 Level of adherence to antihypertensive treatment

After six months of treatment initiation, adherence to antihypertensive medication was found to be 42%. A significantly higher adherence was found among the patients taking one medication (42.8%) than those taking three or more medications (34%). The level of adherence to the number of antihypertensive drugs used was stratified by gender, age, type of healthcare setting, smoking status, BMI, and DM status, as presented in Table 18. Overall, medication adherence was higher among patients younger than 40 years (67.9%), those with DM (53.6%), those who were treated at secondary care settings (49.1%), nonsmokers (47.8%), and those who had a normal BMI of <25 kg/m^2 (47.1%). However, significant differences in medication adherence were observed by gender, health center location, type of settings, and DM status.

Table 18: Adherence to antihypertensive medication across subgroups at 6-months

Characteristics	Overall adherence	Number of antihypertensive medications			P-value
		One	Two	Three or more	
	n = 2223, (41.9%)	1764 (42.8%)	395, (39.4%)	189, (33.9%)	0.011
Gender					
Men	1032 (42%)	821 (43.1)	180 (39.5)	31 (31.3)	0.211
Women	1191 (41.8%)	943 (42.7)	215 (39.2)	33 (36.7)	0.037
Age (years)					
18–40	364 (67.9%)	326 (68.2)	37 (63.9)	1(-)	0.696
41–50	726 (56.6)	603 (57)	103 (57.2)	20 (44.1)	0.246
51–60	799 (35.7)	609 (36)	163 (34.9)	27 (35.5)	0.912
61–75	222 (24.3)	154 (23.2)	59 (28.4)	9 (20.9)	0.280
>75	112 (33)	72 (32)	33 (36.7)	7 (29.2)	0.668
Health center location					
Rural	1080 (41.6)	850 (42.2)	201 (40.9)	29 (31.9)	0.135
Urban	1143 (42.1)	914 (43.4)	194 (38)	35 (35.7)	0.037

Table 18: Adherence to antihypertensive medication across subgroups at 6-months (Continued)

Characteristics	Overall adherence	Number of antihypertensive medications			P-value
		One	Two	Three or more	
	n = 2223, (41.9%)	1764 (42.8%)	395, (39.4%)	189, (33.9%)	
Healthcare setting					
Primary	1280 (40.1)	1024 (41.1)	213 (36.6)	43 (38.1)	0.127
Secondary	390 (49.1)	296 (50.3)	86 (48.9)	8 (25.8)	0.029
Tertiary	553 (41.8)	444 (42.9)	96 (39.3)	13 (28.9)	0.122
Smoking					
Smoker	587 (31.2)	442 (31.4)	125 (31.8)	20 (23.8)	0.067
Non-smoker	1636 (47.8)	1322 (48.8)	270 (44.3)	44 (41.9)	0.326
Body mass index (kg/m^2)					
18.5–25	297 (47.1)	238 (47.6)	53 (46.5)	6 (35.3)	0.601
25–30	588 (39.6)	462 (40.2)	109 (38.9)	17 (29.8)	0.282
>30	916 (37.8)	733 (38.8)	153 (33.7)	30 (36.1)	0.125
Diabetes					
No	1756 (39.6)	1378 (40.5)	326 (37.8)	52 (30.4)	0.015
Yes	467 (53.6)	386 (54.1)	69 (49.6)	12 (66.7)	0.337

* chi-square test

3.7 Changes in the blood pressure at 6-months according to their medication adherence

In analyzing BP changes at six-month follow-up, a significant mean reduction in the SBP of 4.5 mmHg (95% CI: -5.4 – -3.77). and DBP of 6.0 mmHg (95% CI: -6.5 – -5.4) was observed among those who were adherent to antihypertensive treatment compared to the nonadherent patients (SBP: 1.15, 95% CI: 0.50 – 1.79, DBP: 3.57, 95% CI: 3.14 – 4.04) ($P < 0.001$ for SBP and $P < 0.001$ for DBP). Likewise, when comparing BP changes among patients adherent to medications at 6-month follow-up, a significant higher SBP reduction was observed in men than women (– 5.6 mmHg versus – 3.5 mmHg; $P = 0.024$), and in patients with BMI of >30 kg/m^2 (– 4.4 mmHg; $P = 0.003$), as shown in Figure 11. Moreover, significant ($P \leq 0.001$) differences in DBP were observed across age, sex, and BMI; however, no such differences in SBP and DBP were observed in patients with or without DM.

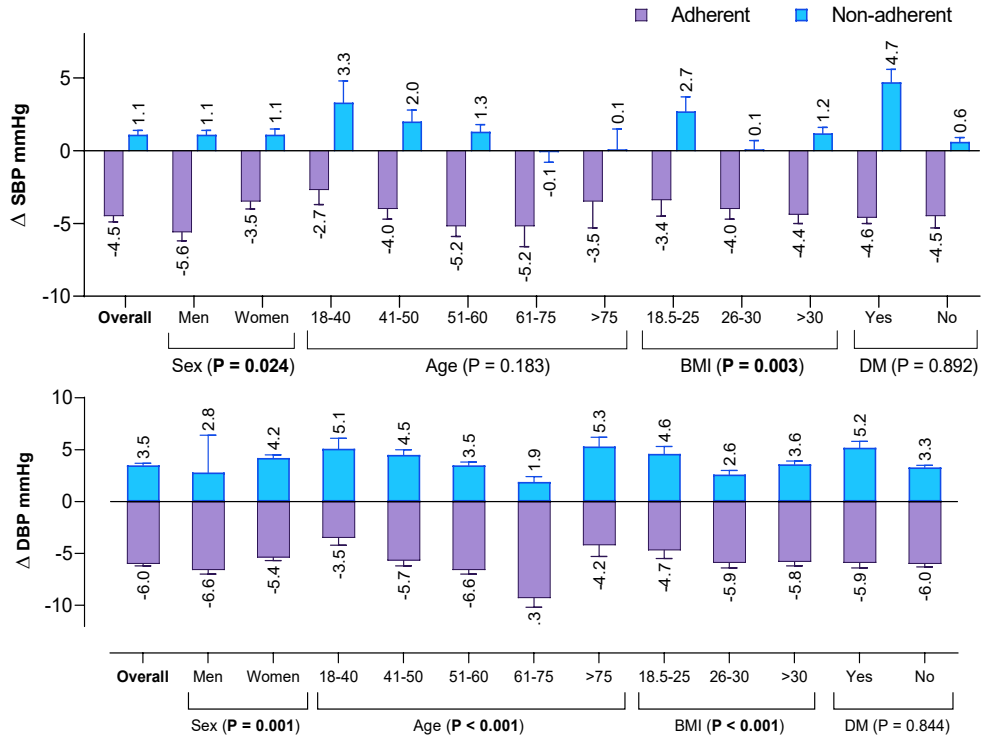

Figure 11: Mean changes in the BP from baseline to 6–months in the subjects according to their adherence status. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; DM: diabetes mellitus.

As shown in Figure 12, optimal adherence was observed in middle-aged categories (51-60 years) for all the different classes of antihypertensive drugs. Moreover, younger age (18–40 years) and older age (>60 years) had low adherence to antihypertensive therapies irrespective of the number of medications prescribed.

Among these newly diagnosed disease, the overall medication adherence was higher in 51 – 60 years age group, particularly combination therapy of ARBs or ACEi with DU (45% and 44.4%), and ACEi with CCBs (44.4%). In contrast, adherence to ACEi in the 40 to 50 year age group was higher (40.1%) and it gradually decreased as the age increase with the adherence being at 29.9% and 13% in the 51-60 years and >60 years age group, respectively. Medication adherence to three or more antihypertensive medication was higher in 51 – 60 year age group (42.2%) than 41 – 50 years (31.3%), 61 – 75 years (14.1%) and > 75 years (10.9%).

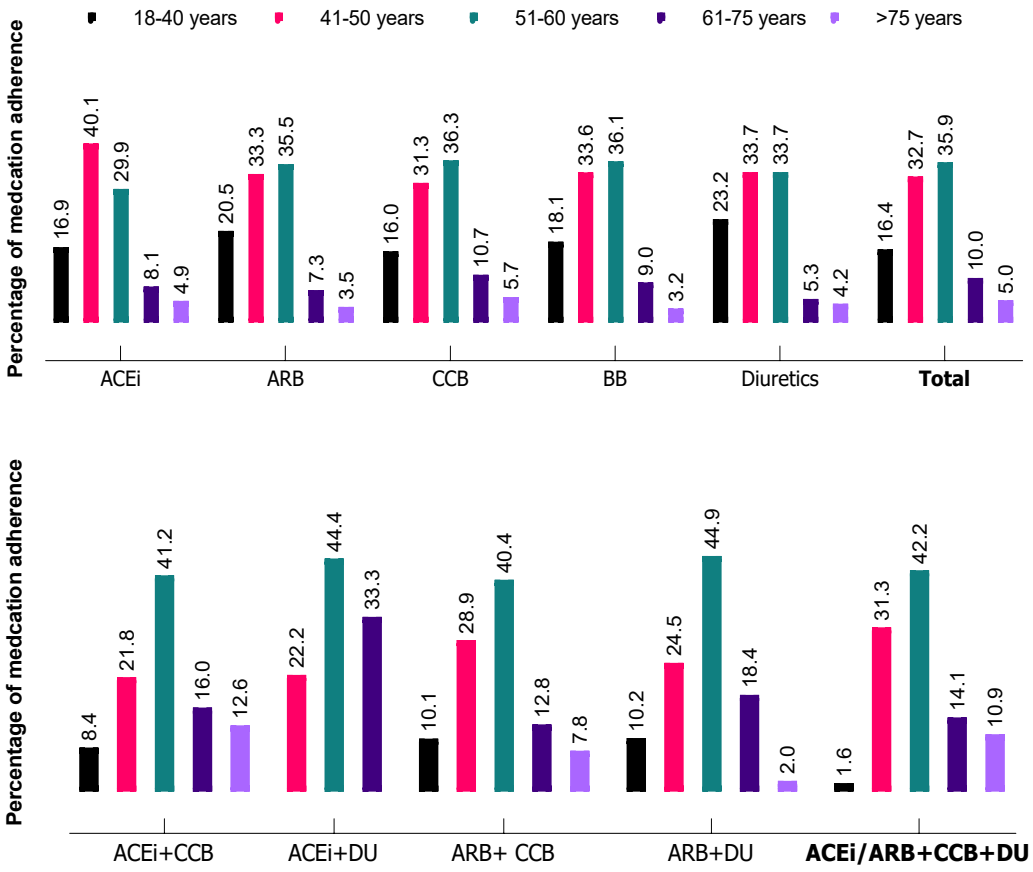

Figure 12: Medication adherence to different classes of drugs during the first 6-months of antihypertensive treatment initiation. ACEi: angiotensin-convertase enzyme inhibitor, ARB: angiotensin-receptor blockers, CCB: calcium channel blockers, BB: beta-blockers, DU: diuretics.

3.8 Factors associated with adherence to antihypertensive medications

Factors significantly associated with the number of medications and adherence to antihypertensive drugs are shown in Table 19. The unadjusted logistic regression analysis indicated that treatment at secondary care settings (OR: 1.35, 95% CI: 1.10 – 1.65), nonsmokers (OR: 2.07, 95% CI: 1.83 – 2.37), and patients with DM (OR: 1.73, 95% CI: 1.47–2.03) were significant predictors of adherence when only one antihypertensive drug was taken. Similar findings were observed when two medications were taken (except in secondary care setting). On the contrary,

nonsmokers (OR: 2.30, 95% CI: 1.22–4.35) and patients with DM (OR: 4.57, 95% CI: 1.63–12.85) were associated with adherence to three or more antihypertensive drugs.

Table 19: Factors associated with adherence to antihypertensive medications

Variables	One medication		Two medications		Three medications	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Age	0.94 (0.93-0.95)**	0.93 (0.92-.0.94)**	0.96 (0.94-0.97)**	0.95 (0.93-0.96)**	0.96 (0.93-0.99)**	0.96 (0.92-1.01)
Sex						
Men	0.98 (0.86-1.11)	1.20 (1.04-1.39)**	0.98 (0.76-1.26)	0.95 (0.71-1.27)	1.27 (0.69-2.32)	1.54 (0.75-3.17)
Women	1	1	1	1	1	1
Health center location						
Rural	0.95 (0.84-1.07)	0.87 (0.73-1.04)	1.12 (0.87-1.45)	0.91 (0.63-1.30)	0.82 (0.46-1.54)	0.62 (0.26-1.50)
Urban	1	1	1	1	1	1
Healthcare setting						
Primary	0.92 (0.80-1.07)	0.92 (0.78-1.09)	0.89 (0.65-1.21)	0.89 (0.62-1.27)	1.51 (0.71-3.19)	1.57 (0.66-3.73)
Secondary	1.35 (1.10-1.65)**	1.45 (1.15-1.84)**	1.47 (0.99-2.18)	1.49 (0.95-2.35)	0.85 (0.30-2.40)	0.77 (0.23-2.55)
Tertiary	1	1	1	1	1	1
Smoking status						
Nonsmoker	2.07 (1.83-2.37)**	1.12 (0.95-1.33)	1.70 (1.30-2.22)**	1.07 (0.76-1.52)	2.30 (1.22-4.35)**	1.55 (0.62-3.82)
Smoker	1	1	1	1	1	1
BMI (kg/m^2)	0.99 (0.98-0.99)**	0.98 (0.97-0.99)**	0.97 (0.95-0.99)**	0.96 (0.94-0.98)**	1.02 (0.97-1.07)	1.02 (0.97-1.07)
Diabetes						
Yes	1.73 (1.47-2.03)**	1.27 (1.06-1.53)**	1.62 (1.13-2.32)**	1.15 (0.76-1.73)	4.57 (1.63-12.85)**	3.61 (1.11-11.72)*
No	1	1	1	1	1	1

Adjusted for age, type of health center, BMI, smoking

After adjusting for multiple covariates, an increase in age and BMI was associated with a gradual decrease in odds to adherence to one and two antihypertensive medications. Among the patients receiving monotherapy, men (OR:

1.20, 95% CI: 1.04–1.39), patients treated at secondary care setting (OR:1.45, 95% CI: 1.15–1.84), and DM patients (OR: 1.27, 95% CI: 1.06–1.53) were more likely to be adherent to monotherapy. Furthermore, DM patients were 3.6 times more likely to adhere to three or more antihypertensive medications (OR: 3.61, 95% CI: 1.11–11.72).

3.9 Occurrence of treatment-resistant hypertension and pseudo-resistant hypertension

The mean SBP in patients with TRH was higher in those aged ≥ 65 years (151.0 ± 8.2 mmHg) than those aged <65 years (146.5 ± 13.8 mmHg). For PRH patients, the mean SBP and DBP were much higher in the older population aged ≥65 years than in younger patients (<65 years). More details are in Table 20.

Table 20: Age-stratified mean BP of hypertensive patients with treatment-resistant hypertension and pseudo-resistant hypertension

	<65 years		≥ 65 years	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
TRH	146.5 ± 13.8 mmHg	91.0 ± 9.7 mmHg	151.0 ± 8.2 mmHg	101.0 ± 4.9 mmHg
PRH	144.2 ± 11.6 mmHg	92.3 ± 5.8 mmHg	159.5 ± 10.8 mmHg	99.4 ± 8.0 mmHg

Among a total of 189 patients taking three or more classes of antihypertensive medications for at least one month, 64 (33.8%) patients were adherent, and 125 (66.2%) were nonadherent to therapy. Among the patients adherent to medications, 28 (14.8%, 95% CI: 10.0 – 20.7) patients aged <65 years did not reach the BP target of 130/80, and ten patients (5.3%, 95% CI: 2.5 – 9.5) aged ≥65 years had BP above 140/80. The overall prevalence of TRH was 20.1% (95% CI: 14.6 – 26.5). On the contrary, 125 patients were nonadherent to antihypertensive treatment, 21 (11.1%, 95% CI: 7 – 16) and 25 (13.2%, 95% CI: 8.7 – 18.9) patients did not reach the BP target of 130/80, and 140/80, respectively. These patients were classified as PRH

(24.4%, 95% CI: 18.4 – 31.1) caused by poor medication adherence. Figure 13 presents the 5308 patients in detail based on their baseline BP, follow-up at 6-month, and subsequent TRH and PRH status.

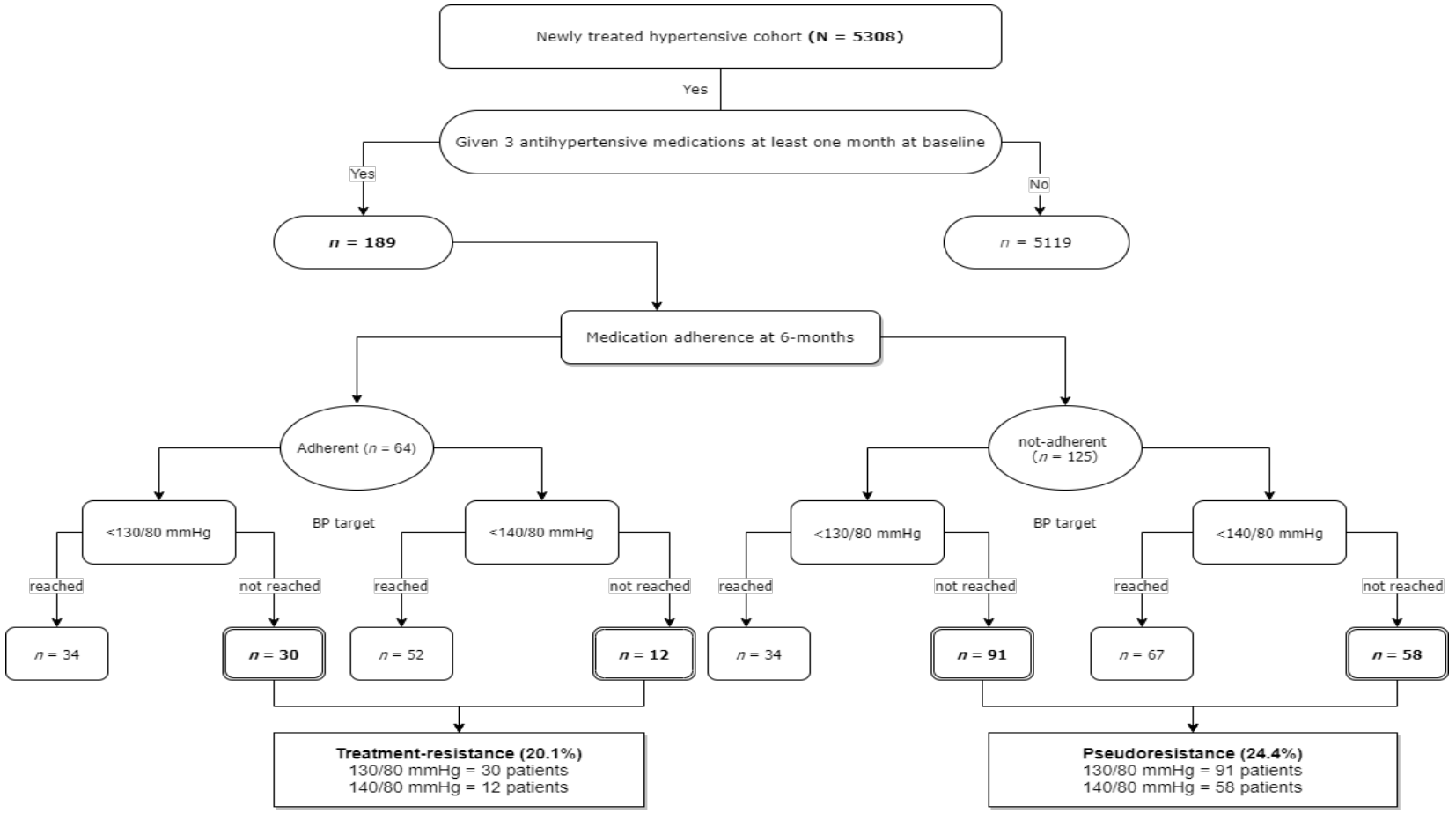

Figure 13: Flowchart of study population taking ≥3 medications for at least one month and prevalence of treatment-resistant hypertension

Chapter 4: Discussion

4.1 Overview

The overall purpose of this thesis was to better understand the BP management, adherence to antihypertensive therapy, and factors potentially influencing BP control in the newly diagnosed hypertensive cohort within the first six months of treatment initiation. A retrospective chart review was applied to identify the target population and address the specific objectives of the thesis. As a starting point, a comprehensive literature search was conducted to identify the existing epidemiological evidence on the burden of hypertension and medication adherence across different healthcare settings in the UAE. Based on the gaps identified in the review, consecutive studies were performed to investigate changes in the BP and achievement of guidelines-recommended targets for BP. Following this, associated factors that could increase the likelihood of reaching age-specific BP targets recommended by ACC/AHA 2017, ESC/ESH 2018, NICE 2019, and ISH 2020 guidelines were examined. The level of medication adherence to different classes of drugs during the first six months of antihypertensive treatment initiation and its effect on BP control was assessed. The author also evaluated the extent of TRH and PRH among a subset of patients who did not reach BP goals despite being treated with three or more antihypertensive medications.

Several clinical trials and meta-analyses have demonstrated that maintaining SBP of 120 mmHg, and DBP of 80 mmHg has several benefits in reducing the risk associated with CVD, cerebrovascular, and renal complications significantly (117–121). Numerous efficacious medications are currently available for treating hypertension. However, nonadherence to antihypertensive treatment is among the

major causative factors for uncontrolled hypertension (63,122–124). Therefore, recent clinical guidelines have evolved to recommend lower BP thresholds combined with lifestyle changes and adherence to antihypertensive drug therapy (9–11,15). Each guideline aimed to improve the diagnosis and control of hypertension by redefining the optimal systolic/diastolic BP targets for treatment in line with the most recent evidence. They also strongly emphasized the importance of medication adherence to improve BP control (9,11,15). However, differences in these guidelines may influence the diagnosis and treatment targets worldwide, including Arabian countries, where most physicians follow various international guidelines. Currently, there is a lack of data on BP management and control in the UAE and GCC countries, with only a few community-based cross-sectional surveys focusing on this topic (described in literature review section 1.4.4). Therefore, this dissertation has envisioned providing novel insights into BP management, medication adherence, and factors potentially influencing BP control after treatment initiation.

4.2 Summary of the key findings

- The overall reduction in the SBP and DBP within 6-months of follow-up was only -1.23 mmHg and -0.4 mmHg respectively.
- A higher reduction in the SBP was observed in overweight (-1.56 mmHg), men (-1.68 mmHg), those aged 61–75 years (-1.82 mmHg), and treated at primary care settings (-2.31 mmHg).
- Men (-1.15 mmHg), those aged 41–50 years of age (-1.25 mmHg), and those treated at primary care settings (-2.15 mmHg) showed a higher reduction in the DBP.

- Guidelines-recommended BP goal achievement was suboptimal, at 39.5%, 43%, 65.6%, and 40.8% according to the ACC/AHA, the ESC/ESH, the NICE, and the ISH guidelines, respectively.
- The attainment of guidelines-recommended BP targets (<130/80 mmHg) among younger patients (≤40 years), smokers, overweight and obese, and among patients with diabetes was dramatically low.
- Those who had a normal BMI and were treated at secondary care settings were more likely to achieve guideline-recommended BP targets.
- The overall adherence to antihypertensive medications was only 42%. Higher adherence was found among the patients on monotherapy (42.8%) than those taking two (39.4%) and ≥3 medications (34%).
- At 6-month, a significant reduction in BP was observed in patients adherent to medications (systolic: – 4.5 mmHg and diastolic: – 5.9 mmHg) than those who were nonadherent to antihypertensive therapy (SBP increased by 1.15 mmHg and DBP by 3.59 mmHg).
- Among the patients who were adherent to medications, higher SBP reduction was observed in men than women (– 5.6 mmHg versus – 3.5 mmHg), and in patients with BMI of >30 kg/m^2 (– 4.4 mmHg)
- A higher reduction in the DBP was observed in those aged 61–75 years (– 9.3 mmHg), men (– 6.6 mmHg), and overweight and obese (– 5.9 mmHg and – 5.8 mmHg) patients exhibiting good medication adherence.
- A DM diagnosis was associated with higher odds of treatment adherence to monotherapy (OR: 1.27) and three or more antihypertensive drugs (OR: 3.61). Patients treated at secondary care settings (OR: 1.45) and male gender (OR: 1.20) were more likely to be adherent to monotherapy. However, an increase in age (OR:

0.93) and BMI (OR: 0.98) was associated with lower odds of medication adherence.

- The overall prevalence of TRH was 20.1%, with 14.8% and 5.3% in those aged <65 years and ≥65 years, respectively.

4.3 Blood pressure changes from baseline to six-months

The primary analysis of this thesis focused on changes in BP after six months of antihypertensive treatment initiation. Results showed broad difference in SBP (– 1.23 mmHg) and DBP (– 0.4 mmHg) changes in six months. The magnitude of the BP changes in six months varied across the study population based on age, gender, and healthcare settings. To the best of our knowledge, no studies in the UAE or the Middle East have used longitudinal data to date to investigate the BP changes in the Arabian population. Prior studies from the Western countries demonstrated that greater visit-to-visit changes in BP over time were associated with increased risk for CVD events, irrespective of mean BP levels (125,126). A recent SPRINT ancillary study indicated a potential for more significant differences in the mean between trial SBP participants by – 7.3 mmHg (95% CI: – 7.6 mmHg to – 7.1 mmHg) than standard care (–4.6 mmHg, 95% CI: – 4.9 mmHg to – 4.4 mmHg) at one year (127). In addition, the differences between the routine BPs and trial BPs are not consistent over time and also found varied significantly by sex, history of CVD, and clinical sites. This highlights the differences in BP measurement techniques, quality of estimates, and clinical practice between trials and routine clinical practice. However, most of the SPRINT trial participants were older adults (mean age: 68.5 ± 9.1 years) and had a history of CVD (118,126). This limits our ability to generalize or translate these findings to the present

population, who are at the early stage of hypertension, with a mean age of 54.8 ± 11.5 years.

Another interesting finding observed in this thesis was that the mean reduction in SBP was much lower in young adults (<40 years) than in the older population. Recent Coronary Artery Risk Development in Young Adults (CARDIA) study demonstrated that the with mean annual increase in the SBP (per 1.03 mmHg/year) and DBP (per 0.95 mmHg/year) was associated with an increase in CVD events by 55% (HR: 1.55, 95% CI: 1.39 – 1.73) and 43% (HR: 1.43, 95% CI: 1.25 – 1.64), respectively. However, these results may not be generalizable due to differences in the population (African American). Given the implications of the earlier onset of ASCVD among young UAE nationals (<55 years) than in western countries, interventions to control BP and other CVD risk factors should be prioritized to reduce premature CVD events and deaths in the UAE.

4.4 Blood pressure control

Adopting a lower BP threshold for hypertension (≥130/80 mmHg) and stringent target BP goals underlines the importance of early preventive measures and non-pharmacological intervention. Despite this, studies continue to record inadequate BP control (128,129) and show poor physician compliance with such guidelines (130–132). The continental divide of guidelines-recommended BP goals is reflected in the UAE cohort, showing variations in achievement across hypertensive subjects. Applying the ACC/AHA criteria (<130/80 mmHg) to this study population, a substantially lower proportion of patients (39.5%) achieved a consistent BP target varied to the rates of the USA (46.6%) (133), Canada (41.1%) (134), and Spain (25.1%) (135). However, when using the BP targets of the ESC/ESH, NICE, and ISH

criteria, the achievement of BP goal was similar or lower than Italy (66.5%) (136) and the UK (63%) (137), but higher than the 2019 global BP control (13.8%) (56).

The thesis' findings revealed substantially low BP goal achievement recommended by the four different guidelines across hypertensive patients of different age groups. Furthermore, a marginal difference in the achievement of guidelines-recommended BP goals was observed between the groups. These variations were also reflected across all the compared guidelines. Since the underlying reasons for the association between the groups and less improved BP control were unclear, this putative relationship warrants further elucidation. The improved BP control among these patients may be partly explained by the comprehensive promotion of a healthy lifestyle, such as adequate physical activity, low saturated fat intake, low-salt meals, and medical information provided by counselors regarding CVD risks related to hypertension.

Hypertension in young adults is mostly latent and associated with obesity and metabolic syndrome (79). International guidelines have paid more attention to the management of hypertension and CVD risks in older patients (9–11), although the long-term (>10 years) risks are higher in young adults. Also, this study found 31.7% achievement of guidelines-recommended BP goal of 130/80 mmHg in those aged ≤40 years. Thus, improving BP control and the systematic management of cardiometabolic risk factors in younger patients is vital to reduce the burden of atherosclerotic CVD (ASCVD).

The notable finding of this thesis is the overall high rate of BP goal achievement among patients maintaining normal BMI. These patients are more likely to reach guidelines-recommended BP targets (except NICE recommendation). As shown in the guidelines, the first step of intervention in newly diagnosed hypertensive

patients is a lifestyle change (9–11,15). This non-pharmacological approach can induce weight loss. A recent Cochrane review observed that a 4.0 kg reduction in body weight reduces SBP and DBP by 4.5 mmHg and 3.2 mmHg, respectively, and significantly reduces cardiovascular mortality (HR: 0.70, 95% CI: 0.57–0.87) in hypertensive individuals (138). A meta-analysis of 25 randomized controlled trials showed a reduction in BP on average by 1.05/0.92 mmHg for each kilogram of weight loss (139). Regardless of whether BP values are above normal, a healthy diet and lifestyle modifications should be prioritized along with adherence to pharmacological treatment, which could ultimately lower CVD risk in the early stage of hypertension.

In this thesis, about 15% of patients were managed at secondary care settings and were more likely to achieve the BP targets recommended by four different international guidelines. A study conducted by Billups et al. investigated the BP control among 86,512 hypertensive subjects in the USA by applying a BP cutoff of <140/90 mmHg (140). They observed that the patients treated in primary care settings were more likely to control their BP than those treated in specialty settings. The reason for these findings is not clear, and more research is needed to understand the determinants of BP control at an early stage of hypertension.

A significant variation in the SBP and DBP was observed across the study population based on age, gender, and healthcare setting. No authentic data are available from the UAE or the Middle Eastern countries to estimate the BP threshold levels or target BP goal achievement to help reduce the CVD risk in this region, particularly among high-risk patients. The epidemiological evidence on BP control (<140/90 mmHg) among UAE nationals was conducted more than two decades ago (30). Findings on the NESH-UAE conducted in 1998 demonstrated poor BP control among known hypertensive subjects (19%), out of which only 42% were taking

antihypertensive medications (30). Evidence from the meta-analyses showed that lower BP targets, compared to any higher BP target, help reduce the risk of stroke, myocardial infarction, major CV events, and heart failure (59,141–143). The study findings suggest that the optimal BP target for patients with hypertension is still elusive. Thus, these variables should be considered while using the international guidelines for BP control and early CVD management in the UAE.

4.5 Medication adherence

In clinical practice, nonadherence is a common cause of antihypertensive treatment failure and treatment resistance. In this study, out of the 5308 patients with incident hypertension who started on hypertension treatment, adherence to antihypertensive medications was found among 42% of the patients. A recent meta-analysis reported that the overall nonadherence to antihypertensive medications was 48% for the Asian population (95% CI: 41 – 54%) and 41% for the Middle Eastern population (95% CI: 30 – 52) (123). Current estimates on the prevalence of adherence to antihypertensive medication in the Middle East are based on cross-sectional studies and self-reported questionnaires. The reported proportion of medication adherence to antihypertensive therapy in this study (42%) is in concordance with adherence rates reported in Arabian Gulf countries, including Saudi Arabia (40%) (108), Oman (49%) (99), and two studies in the UAE (52% and 54%) (50,109). This study has the advantage of accounting for longitudinal BP control and medication adherence using detailed pharmacy information among a large, community cohort of patients with incident hypertension.

Another important finding of this thesis is the evaluation of the BP changes among patients adherent to antihypertensive treatment compared to the nonadherent

patients. Focusing on BP changes is important to understand the implications of medication adherence on BP control in incident hypertensive patients. Analysis of BP changes indicated that patients adherent to treatment had a significant reduction in BP than those nonadherent to antihypertensive therapy (Figure 11). This numeric difference in BP indicates a clinically meaningful effect of adherence on BP control. Thus, monitoring medication adherence on each visit can be used as a therapeutic tool and significantly improve BP control. Educating patients regarding positive changes in diet and lifestyle in standard care coupled with improved adherence to antihypertensive medication can have an absolute improvement in BP control.

4.6 Treatment-resistant hypertension

Nonadherence to antihypertensive medications is among the most common reasons for uncontrolled blood pressure and a significant cause of TRH. The degree of nonadherence to medications and prevalence of TRH remains unknown in the Arabian population. Guidelines defined TRH as the patients who did not reach BP targets despite taking three or more antihypertensive medications for at least one month (11,59). In general, patients adherent to ≥3 classes of antihypertensive medications but not reaching the BP goals are called TRH. A similar scenario in nonadherent patients is considered pseudo-resistant hypertension (PRH) (111). Thus, medication adherence plays a significant role in defining antihypertensive treatment failure and treatment resistance. However, most studies could not rule out PRH caused by nonadherence to drug therapy and distinguish true TRH from PRH (111). Therefore, knowledge regarding medication adherence after initiation of therapy, TRH among the patients adherent to antihypertensive medications, and PRH caused by poor adherence is essential to improve hypertension management.

Patients with TRH have a poor prognosis and a higher risk of end-organ damage, heart failure, cardiovascular events, and premature death (11,59,144). Few studies described the prevalence of TRH in incident hypertensive patients (62,111,145), and a meta-analysis by Noubiap et al. reported the pooled prevalence of TRH of 14.7% (95% CI: 13.1 – 16.3) and PRH of 10.3% (95% CI: 6.0 – 15.5) (112). Based on the present study, one in every five incident hypertensive patients taking three or more antihypertensive medications will continue to meet TRH criteria over follow-up. In addition, the thesis also showed that one in every four patients who were not adherent to hypertensive treatment had PRH. According to the guidelines-recommended BP targets for different age groups, the prevalence of TRH among patients aged 18-64 years was 14.8% and 5.3% in patients aged 65 years or older. Our overall estimates of TRH (20.1%) are higher than global prevalence (14.7%) (112,146), but lower than Europe (32%), Pakistan (32%) (147), and Poland 25% (148). The discrepancy is significant, and the variation might be due to the differences in study design, target population, definitions used, and failure to exclude suboptimal adherence, a common cause of apparent TRH. A recent randomized trial on smartphone app intervention showed improved patient adherence and BP control in patients with uncontrolled hypertension (149).

4.7 Association between BP goals and medication adherence with selected baseline characteristics

Several factors at the patient level might be associated with guideline-recommended BP goal attainment and adherence to antihypertensive therapy. These factors may include age, sex, BMI, healthcare settings, smoking status, and diabetes. Some researchers have hypothesized that guidelines-recommended BP control may be strongly affected by gender (150), worsen with urbanization (151), and obesity (152). Moreover, other studies have shown that variations in the healthcare setting (140,153)

and underlying CVD risk factors, such as smoking and DM, strongly influence target BP goal attainment (9,15).

Adequate number and dose of prescribed BP medications and medication adherence contribute to hypertension control in treated patients. Studies have shown less than 50% adherence to antihypertensive therapy in the first year of treatment initiation (63,64). The increase in the number of antihypertensive drugs, older age, and family history of CVD are some of the specific factors associated with good adherence (154,155). However, studies examining the factors affecting adherence to antihypertensive medications in the UAE are limited (50). This thesis briefly examined the relationship between baseline characteristics and target BP goal attainment and adherence to antihypertensive therapy.

Findings from this thesis identified seven factors significantly and independently associated with guidelines-recommended BP goal attainment and medication adherence to antihypertensive therapy, including older age. This finding contradicts prior studies that indicated that older age was associated with better medication adherence (155,156). In contrast, those who had a normal BMI and were treated at secondary care settings were more likely to achieve guideline-recommended BP targets. In addition, about 15% of patients were managed at secondary care settings and were more likely to achieve the BP targets recommended by four different international guidelines (9–11,15). As shown in the guidelines, the first step of intervention in newly diagnosed hypertensive patients is a lifestyle change (9–11,15). Therefore, non-pharmacological approaches such as weight reduction can help achieve BP control and reduce CVD risk. Another approach to improve patient outcomes is through the patients' medical records examination to quickly identify their risk factors and tailor interventions for those who are not at their goals.

The notable finding of this study is that hypertensives treated at secondary care settings are shown to be associated with guidelines-recommended BP achievement and better adherence. This study observed that the patients treated in secondary care settings were more likely to control their BP than those treated in primary and tertiary care settings. Several studies have observed adherence to antihypertensive treatment among hypertensive patients treated at primary care but lack consistency (157–159). A recent study from Pakistan demonstrated significant variations in the medication adherence to hypertensives treated at primary (23.8%), secondary (38.9%), and tertiary care settings (43.6%) (157). The plausible reasons for this in the secondary care settings are specialty clinic settings for chronic disease, and physicians spend more time with patients explaining the importance of BP control and improved medication adherence.

Individuals with DM were found to have a significantly lower risk of nonadherence to antihypertensive treatment. This finding is similar to other studies that showed hypertensive patients with DM were more likely to adhere to medications (155,160). This suggests that patients with concomitate comorbid conditions might be more aware of having higher disease risk and thus exhibit better medication adherence.

4.8 Strengths and limitations

This dissertation described the extent of guidelines-recommended BP control and medication adherence among the Emirati population across 54 health facilities in the emirates of Abu Dhabi, UAE. This is the first study conducted among a nationally representative sample of hypertensive patients in the UAE after the 1998 NESH-UAE study. Therefore, our findings could reasonably compare the public health implications of each guideline in the UAE population. Furthermore, it is essentially the first

longitudinal study conducted among the incident hypertensive population and described BP changes and adherence to antihypertensive therapy after treatment initiation. Multiple clinical factors along with BP management as well as medication adherence were analyzed, and the prevalence of TRH and PRH was estimated in a large newly treated hypertensive cohort. The relatively large sample size and consecutive data of both BP parameters and pharmacy refilling information permitted robust analyses of less common but important outcomes, such as TRH and PRH. However, like many epidemiological studies conducted on hypertension with methodological limitations, this work encountered some limitations that need to be considered in interpreting the results. This section will discuss the methodological strengths and limitations of this work.

4.8.1 Study design

One of the main strengths of this thesis is the amount of data used to estimate BP management and medication adherence. Cohort studies – either prospective or retrospective design – are among the most powerful observational study designs to answer various research questions reliably (161). These designs have high accuracy and efficiency as their respective main advantage. In prospective cohort design, where exposure is assessed at baseline, each subject is followed in time to study disease or mortality development. In contrast, in a retrospective design, eligible subjects are identified, a cohort is composed, and exposures are assessed at baseline. After that, the subsequent event occurrence or death is studied during the historical observational period. However, prospective design is expensive and time-consuming because of a usually extended follow-up, due to which it also suffers from loss-of-follow-up. Vice versa, retrospective design is a very time-efficient and elegant way of answering new

questions with existing data (162). In the UAE, EMR records BP measured at the SEHA clinics and provided a complete picture of hypertension in the population than the coded health information collected at acute hospital discharges. Thus, a retrospective chart review is appropriate to capture the incident hypertensives with follow-up data to answer the research hypothesis. Furthermore, the sample size was determined by using statistical power sampling to approve or reject the working hypothesis and avoid random errors in the results of the research work.

4.8.2 Internal and external validity

Although cohort studies have a lower risk of presenting bias than ecological, case-control, cross-sectional, or prevalence studies, they are not free from bias. In general, observational studies are evaluated in terms of both internal and external validity. Internal validity refers to the strength of the inferences from the study. That is, did the "exposure" cause a difference in the outcome. The importance of assessing internal validity is whether observed changes can be attributed to exposure and not to other plausible causes. It is determined by a series of factors that can lead to systematic errors. The bias can occur at any stage of research, such as sample selection, data collection, or analysis. Whereas external validity is the ability to generalize study results to a more universal population (163). Factors that allowed for the validity of the thesis are discussed below.

a. Selection bias

Selection bias is a systematic error that occurs if the selection of the exposed or unexposed subjects in a retrospective study is somehow related to the outcome of interest. Since a retrospective cohort study starts after all subjects have been exposed to the disease, they would generally know their exposure and outcome status. In

general, selection bias is a problem when the study subjects are not a truly representative population and might cause differences in the associations between exposure and outcomes. Selection bias can occur in many ways, such as the loss-to-follow-up, healthy-worker bias, and non-response bias (164).

In this research, selection bias was minimized by including a representative sample of the population from primary, secondary, and tertiary care health centers across emirates of Abu Dhabi. The Emirati population has full health insurance coverage and has a unique EMR and FIN number that helps capture the accurate information of each patient during the follow-up. Furthermore, all the subjects met the inclusion criteria and had sufficient exposure during the study period, and outcomes data were considered.

b. Information bias

Information bias is another systematic error that could originate from the erroneous collection of information, instruments used to assess the outcomes, or loss-to-follow-up. In the retrospective design, data is collected from existing records. There could be missing data due to poor registration quality or missing variables that are important to assess the outcomes. To minimize the information bias in this research work, the author considered the variables above 85% of completeness. Data of some clinical parameters, such as HbA1c (n = 4501), serum creatinine (n = 400), and lipid parameters (n = 2007), were incomplete and were excluded from the analyses. Moreover, all the data were extracted at a similar time to capture appropriate and consistent information.

To further reduce misclassification bias, all the data were collected from the medical records using ICD-10 coding following physician confirmed cases of incident hypertension by ABPM or HBPM and initiated antihypertensive treatment. However,

EMR records also face erroneous and missing data, which might affect the inferences of research. To circumvent this issue, specific sociodemographic and clinical variables measuring similar observations were collected from the EMR.

c. Confounding

Confounders are the variables associated with the exposure and health outcomes but not necessarily a cause of the event or outcome. The importance of confounding is that it suggests an association that does not exist or masks a true association. Confounding commonly occurs in observational studies and poorly designed RCTs. The most common confounders in the epidemiological survey are age and gender. In the cohort design, people are not randomly assigned to exposed and unexposed groups. It is difficult to maintain both groups by certain variables, such as age, sex, or other confounders. The authors considered important confounders observed from previous studies and applied statistical adjustment techniques to overcome bias and minimize confounders. Furthermore, all regression models were adjusted for commonly interfering factors, such as age, BMI, smoking, and type of healthcare center. However, residual confounding cannot be ruled out.

4.8.3 Limitations

The study has some limitations. First, the present study relied on automated office BP measurements and pharmacy refill information from an electronic medical record; however, this method for determining hypertension and medication adherence has been widely applied in previous studies (165–167). Second, due to the study's retrospective nature, it cannot obtain complete information regarding some of the factors associated with guidelines-recommended BP targets achievement, including medication-taking behavior, patient-physician interactions, physical activity, and

some cardiometabolic risk factors, and diet, to control hypertension. Third, we did not have data on patients with white-coat hypertension or masked hypertension. Fourth, our data were collected from 2017–2018 across SEHA health facilities in the emirate of Abu Dhabi, the largest emirate in the UAE, which may not represent the entire UAE. Fifth, we did not account for optimal dosage of medications or the use of fixed-dose combination therapy; however, medication use and dosage in the present study represent real-world management choices. Sixth, Previous studies have indicated that ABPM may provide more accurate estimates of TRH and be more prognostic than routinely used office-based BP measurement (168,169). Moreover, office-based BP measurements are routinely used in the management of hypertension. Due to the study's retrospective nature, we could not distinguish the white-coat effects on apparent TRH, which might present a chance of misclassification as some patients may use additional medications and be treated at private health facilities. Penultimately, although the adherence was poor, we did not investigate the potential causes and barriers to antihypertensive medication adherence. Lastly, it is hard to define the response to treatment within six months of treatment initiation and needs more emphasis to define TRH in the incident hypertensive population.

4.9 Implications for future research

One of the main strengths of this research is the amount of data used to explore the perspectives of hypertension in the UAE. This research has provided a valuable platform for future investigations around hypertension epidemiology and management in the UAE by laying a foundation for intensifying prevention efforts in the high-risk population.

There was a lack of information on other important variables, such as the family history of CVD, physical activities, dietary intake, and prescribing patterns. Hence, a more comprehensive assessment of hypertension and its determinants among the UAE population is needed to account for the impact of these factors on BP control. Moreover, there is a dearth of evidence on the epidemiology of hypertension among the Arabian Gulf population. Also, the driving force behind hypertension prevalence remains largely unknown, even though CVD risk factors are highly pertinent in these countries.

None of the studies from the Middle East have used ABPM or HBPM to assess hypertension, even though guidelines recommended ABPM as a gold-standard method for diagnosing hypertension. Moreover, no longitudinal studies are conducted to evaluate the changes in the BP over time. Thus, more studies assessing hypertension using prospective longitudinal studies are needed to ascertain the actual status of hypertension in the Arabian samples. Finally, there is a need for studies to investigate trajectories and future outcomes in the young population.

Chapter 5: Conclusions

In conclusion to this dissertation, BP control was suboptimal across the study population, and more than half (58%) of the patients were nonadherent to the treatment. This research identified variations in the BP goals according to the ACC/AHA vs. the ESC/ESH, NICE, and ISH guidelines in the UAE population. The overall average reduction in BP within six months was only 1.23 (SBP) and 0.40 (DBP) mmHg. Patients who were adherent to an antihypertensive therapy reported a significant BP reduction at a 6-month follow-up. About one in every five patients taking three or more antihypertensive medications continued to meet the criteria for TRH.

The dissertation found that hypertensive patients with normal BMI and those who are treated at secondary care settings are more likely to reach guidelines-recommended BP targets. Age and BMI were among the independent risk factors for medication adherence.

These findings support the need for more extraordinary efforts toward improving medication adherence and BP control during the early stages of hypertension. BP control efforts should also prioritize improving cardiometabolic goals and lifestyle changes at an early stage of hypertension. Further studies are needed to determine the causes of nonadherence to antihypertensive treatment and the prognosis of patients with TRH.

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List of Publications

1. Bhagavathula AS, Shah SM, Aburawi EH. Medication adherence and treatment-resistant hypertension in newly treated hypertensive patients in the United Arab Emirates. Journal of Clinical Medicine 2021; 10: 5036. Doi: 10.3390/jcm10215036. PMID: 34768553 Link: https://www.mdpi.com/2077-0383/10/21/5036/pdf
2. Bhagavathula AS, Shah SM, Aburawi EH. Prevalence, awareness, treatment, and control of hypertension in the UAE: A systematic review and meta-analysis. International Journal of Environmental Research and Public Health 2021; 18(23): 12693. Doi: PMID: 34886421 Link: https://www.mdpi.com/1660-4601/18/23/12693/pdf
3. Bhagavathula AS, Shah SM, Suliman A, Oulhaj A, Aburawi EH. Hypertension control and guidelines-recommended target blood pressure goal achievement at an early stage of hypertension in the UAE. Journal of Clinical Medicine 2022; 11(1): 47. Doi: 10.3390/jcm11010047. PMID: 35011789 Link: https://www.mdpi.com/2077-0383/11/1/47/pdf

Appendix

Appendix A: List of hospitals and data collection

Hospital	Number	Percent	Location	Settings
AA Al Ain Hospital	347	6.5	Urban	Tertiary
AA Behavioral Science	5	.1	Urban	Secondary
AH Bahia HC	133	2.5	Rural	Primary
AH Bani Yas HC	264	5.0	Rural	Primary
AH Bateen HC	229	4.3	Urban	Primary
AH Falah HC	46	.9	Rural	Primary
AH Faqah HC	12	.2	Rural	Primary
AH Hayar Health Center	29	.5	Rural	Primary
AH Hili Health Center	175	3.3	Urban	Primary
AH Jahli HC	189	3.6	Urban	Primary
AH Khalifa City A HC	150	2.8	Rural	Primary
AH Khatem Health Center	15	.3	Rural	Primary
AH Khazna Health Center	11	.2	Rural	Primary
AH Madinat Mohamed Bin Zayed HC	73	1.4	Rural	Primary
AH Maqam Health Center	105	2.0	Rural	Primary
AH Maqtaa HC	59	1.1	Rural	Primary
AH Mezyad Health Center	198	3.7	Rural	Primary
AH Mushrif Children's Specialty Center	27	.5	Urban	Primary
AH Muwaeji HC	74	1.4	Urban	Primary
AH Nahda HC	57	1.1	Rural	Primary
AH Naima HC	84	1.6	Urban	Primary
AH Niyadat Health Center	51	1.0	Urban	Primary
AH Oud Al Touba HC	302	5.7	Rural	Primary

Hospital	Number	Percent	Location	Settings
AH Quaa Health Center	86	1.6	Urban	Primary
AH Remah Health Center	19	.4	Rural	Primary
AH Rowdha HC	52	1.0	Urban	Primary
AH Samha HC	43	.8	Rural	Primary
AH Shamkha HC	67	1.3	Rural	Primary
AH Shwaib Health Center	14	.3	Rural	Primary
AH Sweihan Health Center	16	.3	Rural	Primary
AH Towayya HC	101	1.9	Urban	Primary
AH Yahar Health Center	116	2.2	Rural	Primary
AH Zafrana HC	160	3.0	Urban	Primary
AH Zhaker Health Center	35	.7	Rural	Primary
GH Al Dhafra FMC	78	1.5	Rural	Primary
GH DL Delma Hospital	31	.6	Rural	Secondary
GH GY Gayathy Hospital	47	.9	Rural	Secondary
GH LW Liwa Hospital	29	.5	Rural	Secondary
GH MI Mirfa Hospital	45	.8	Rural	Secondary
GH MZ Madinat Zayed Hospital	74	1.4	Urban	Secondary
GH SA Silla Hospital	44	.8	Rural	Secondary
MQ Al Mafraq	418	7.9	Rural	Secondary
RH Al Rahba	102	1.9	Rural	Secondary
SK Diabetic Center	82	1.5	Urban	Primary
SK Sheikh Khalifa Medical City	284	5.4	Urban	Tertiary
TW Tawam Hospital	678	12.8	Urban	Tertiary
TWVIP	15	.3	Urban	Tertiary
TWWG Al Wagan Hospital	37	.7	Rural	Primary
Total	5308	100.0		

Appendix B: Ethical approval letter

مستشفى العين
AL AIN HOSPITAL

AAH Research Ethics Committee

TO: Prof. Abdullah Shehab; a.shehab@uaeu.ac.ae
Associate Professor & Consultant Cardiovascular Medicine
College of Medicine and Health Sciences, UAEU

CC: AAH Research Ethics Governance Committee

Date: 12th August 2018

RE: **Proposed Research Study:** *Hypertension Registry Study*

Ref: *AAHEC-08-18-103*

On behalf of the Al Ain Hospital Research and Ethics Governance Committee, I am pleased to confirm a favorable ethical opinion for the above research on the basis described in the application form and supporting documentation.

The favorable opinion is given provided that you comply as per the context set out in your research study.

You are hereby advised to commence your research study at Al Ain Hospital. In keeping with our policy, the AAH Research and Ethics Governance Committee is kindly requesting you to report any ethical concerns/considerations that may arise during the course of your research, in a timely manner.

Annual Reports plus terminal reports are necessary and the Committee would appreciate receiving copies of abstracts and publications should they arise.

The REC approval is only valid for two years (24 months from the date of the approval letter issued) however it should be renewed yearly for the continuation of the approval. Two (2) months before expiry of the validity period, the Continuing Review Form should be submitted to REC. Late submissions may not be processed in time, and you are not allowed to continue the study without approval.

The Committee is wishing you a success for this project.

Respectfully yours,

Dr. Ghanem Ali Mohd Al Hassani
Deputy Chief Medical Officer (A)
Al Ain Hospital

Dr. Ghanem Ali Al Hassani
Chairman, AAH Research Ethics Committee
Acting Deputy Chief Medical Officer
Al Ain Hospital

P.O. Box 1006, Al Ain
Tel: +971 3 763 5888
Fax: +971 3 763 4322
www.alain-hospital.com

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