# **Systematic Review**

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# Patients with a previous stroke attack who suffer from blood pressure control or regulation in Saudi Arabia

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#### **ABSTRACT**

This study aims to discuss the blood pressure (BP) control with patients who suffer from a previous stroke or transient ischemic attack (TIA) in Saudi Arabia, to discuss the risk factors and to examine antihypertensive medication-dosing. The most recent office-based BP reading was compared with the BP <140/90 mmHg objective of the National Institute for Health and Care Excellence (NICE) (NG136) and European Society of Hypertension or European Society of Cardiology (ESH/ESC 2013) study participants. By benchmarking prescription doses for each drug with the World Health Organization-defined daily dosing (WHO-DDD) guidelines, optimal anti-hypertensive medication dosing was calculated. In 10 procedures, we found 328 patients with a prior stroke or TIA. When assessed against the ESH/ESC and NICE guidelines (63.1 percent, n=207), blood pressure was controlled in nearly two-thirds of patients. Of those with BP 140/90 (n=116), just under half (n=44, 47.3 percent) were sufficiently dosed relative to the WHO-DDD guidelines in all anti-hypertensive medicines. To conclude, in at least one-third of patients with a prior stroke or TIA, blood pressure regulation remains sub-optimal. Half of these patients were able to respond to an elevation of the antihypertensive dose. Further analysis is needed to see how best to control blood pressure in primary care patients with a previous stroke or TIA, since the majority of hypertension consultations take place in this setting.

Keywords: Blood pressure control, Previous stroke, Transient ischemic attack, Primary care, Saudi Arabia

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#### INTRODUCTION

Stroke has a profound effect on the lives of people, with personal, social and economic implications for the individual and their families that are often devastating. The cost of stroke was calculated at Euro (EUR) 45 billion in the European Union (EU) in 2015, accounting for an overall mortality rate of 17 percent within the EU, making it the second most common cause of death. Recurrent strokes result in increased disability and mortality rates, but despite this, an examination of the availability of secondary post-stroke or transient ischemic attack (TIA) prevention interventions across Europe has demonstrated substantial deficiencies in specialist care, monitoring and treatment services, the European stroke action plan (ESAP) defined goals for stroke treatment growth. In their action plan, the study identified six areas, one of which is secondary prevention and structured follow-up. With recurrent stroke, the 5-year risk of recurrent stroke is calculated at 9.5 percent, frequently resulting in more debilitating results.<sup>1</sup>

Risk factors such as smoking, hyperlipidemia, obesity, diabetes, atrial fibrillation, sedentary lifestyle, elevated body mass index and hypertension management have the ability to decrease repeat events by up to 80% of these, researchers have shown that the most important modifiable risk factor in stroke is hypertension. The risk increases by approximately one third for every 10 mmHg rise in systolic blood pressure during recurrent stroke.<sup>2</sup>

In Europe, adequate blood pressure (BP) regulation levels are reached in fewer than 60 percent of countries in a secondary stroke prevention survey. In this data, figures from Ireland were included. There were drawbacks to this research. However, authors did not have access to primary data from the registry and many of the responses were estimated, causing unintended biases to be possible. A recent paper published in the Lancet found that, based on a study of national representative surveys in 12 high-income nations, Ireland, Finland and Spain have the lowest levels of knowledge, care and regulation of BP in their populations.<sup>3</sup>

Multi-faceted explanations for sub-optimal BP control include patient, physician variables (including clinical inertia), lifestyle problems and hypertension resistant to treatment. However, a recent study considering pseudoresistance in high-risk cardiovascular patients suggests that treatment resistant hypertension may be less prevalent than expected, with half of the patients in this study prescribed sub-optimal doses of their anti-hypertensive medications. <sup>4-6</sup>

In Saudi Arabia, health-care services have come a long way. Starting with the establishment of the first department of public health in Mecca by a royal decree in 1925 and the Ministry of Health (MOH) in 1950. In 2017, Saudi Arabia had a total of 487 hospitals providing 72,981 beds, around 2, 2 beds per 1000 inhabitants in the

Kingdom. The Health Ministry is responsible for the public health services. Health care services are also provided by a number of semi-independent bodies, the private sector and nongovernmental organizations. The MOH provides 60% of health services while the private sector provides 23% and 17% is provided by other government health sectors.

The main objective of this study was to identify the prevalence of sub-optimal regulation of blood pressure in a cross-sectional population of primary care patients with a prior stroke/TIA. Secondly, we wanted to explore the features of this cohort-searching for correlations that could predict inadequate regulation of BP and, thirdly, we wanted to test the dosing schedules of anti-hypertensive drugs in these patients. This is the first research, to our knowledge, exploring these problems in primary care.<sup>7</sup>

#### **METHODS**

General practices in the education and research network of university students have been invited to participate via email. Of the 14 responding practices, ten were chosen as they were from the university within 2 hours of travel, had the opportunity to host the researcher and used electronic health care records. A number of practice sizes (small, medium, large) and forms (urban, rural, mixed, teaching and non-teaching) were included in the 10 practices that took parts.<sup>8</sup>

In September 2020, data collection was performed. Qualified patients were classified in their discharge summaries from specialists as those patients who were coded for stroke or TIA or those who were not coded but had a stroke or TIA diagnosed in a hospital. These cases were categorized as either ischemic, hemorrhagic, TIA or unexplained stroke. If more than one of these incidents occurred in patients, they were graded based on their most serious case. The type of each stroke, where this was not possible or uncertainty occurred, was usually classified by disease coding, hospital discharge summaries and specialist reports were reviewed to explain the diagnosis.<sup>9</sup>

The use of ambulatory blood pressure monitoring (ABPM) to identify cases of white coat hypertension (normal 24 hours ABPM, with elevated manual office BP reading) has been studied, especially in those with sub-optimal BP control. Average day time readings >134/84 mmHg meant sub-optimal regulation of BP.

The optimum use of anti-hypertensive medication doses was calculated by benchmarking prescribed anti-hypertensive drug doses against the World Health Organization-defined daily dosing (WHO-DDD) schedule for each individual prescribed drug. We used this as a surrogate for the adequacy of dosing to be examined. The WHO-DDD is the presumed average maintenance dose per day for a drug used in adults for its primary indication followed a slightly different approach, analyzing the number of patients taking diuretics apart for each drug, at

least half of the maximum dose. Here we present both approaches. When all prescription medications were at or above these levels, patients were considered to be properly dosed. 10-12

For all patient characteristics, graphical summaries were generated to distinguish any abnormalities or possible outliers. Summary statistics were developed that were appropriate (i.e. mean, standard deviation and medians) for the explanatory variable in question. Independent t-tests were used to compare the mean of the different quantitative variables between regulated (<140/90 mmHg)

and uncontrolled (140/90 mmHg) groups and to similarly compare factors for the two-sample proportion comparison (chi-square test). Chi-squared tests were also used to evaluate if there was a substantial difference between the predicted frequencies for monitored (<140/90 mmHg) and uncontrolled (140/90 mmHg) patients in different categories. To model the relationship between the (log) odds of BP control (<140/90 mmHg) and explanatory variables of interest, binary logistic regression was used. In Statistical package for social sciences (SPSS) -version 26, all statistical analysis (IBM, 2018) took place.<sup>13</sup>

**Table 1: General practice characteristics.** 

Involved in post graduate GP Practice size					Practice location	Practice type training	
Single handed	(n=2)	Urban	(n=2)	<1000 patients	(n=5)	Yes	(n=3)
2-3 GPs	(n=6)	Rural	(n=4)	1000-2000 patients	(n=3)	No	(n=7)
> 3 GPs	(n=1)	Mixed	(n=4)	>2000 patients	(n=2)		

Table 2: Patient characteristics by blood pressure.

Variables	BP < 140/90	BP ≥ 140/90	No BP recorded	Total	% of Total	
variables	N (%)	N (%)	N (%)	•		
Total	207 (63.1)	116 (35.4)	5 (1.5)	328	_	
Female	71 (34.3)	50 (43.1)	3 (60)	124	37.8	
Male	136 (65.7)	66 (56.9)	2 (40)	204	62.2	
Average age (SD)	72.8 (12.3)	74 (10.5)	70.8 (8.8)	73.3 (11)	_	
Stroke subtype						
Ischemic	57 (27.5)	38 (32.8)	1 (20)	96	29.3	
Hemorrhagic	21 (10.2)	10 (8.6)	1 (20)	32	9.8	
TIA	84 (40.6)	50 (43.1)	1 (20)	135	41.2	
Unknown	45 (21.7)	18 (15.5)	2 (40)	65	19.8	
GMS Status						
Full medical card	152 (73.4)	93 (80.2)	5 (100)	250	76.2	
Doctor visit card	26 (12.6)	12 (10.3)	0 (0)	38	11.6	
Private patient	29 (14)	11 (9.5)	0 (0)	40	12.2	
Multimorbidity						
Diabetes	32 (15.5)	19 (16.4)	0 (0)	51	15.5	
CKD	44 (21.3)	29 (25)	1 (20)	74	22.6	
Diabetes and CKD	13 (6.3)	6 (5.2)	0 (0)	19	4.9	
Total cholesterol >4.5	50 (17.6) <sup>a</sup>	37 (13) <sup>a</sup>	2 (0.7) <sup>a</sup>	89 <sup>a</sup>	31.3ª	
LDL 2.5	54 (19.8) <sup>a</sup>	35 (12.8) <sup>a</sup>	$0 (0)^{a}$	89 <sup>a</sup>	32.6 <sup>a</sup>	
Drugs prescribed		•	•	•		
Aspirin	95 (45.9)	64 (55.2)	2 (40)	161	49.1	
Clopidogrel	37 (17.9)	19 (16.4)	0 (0)	6	17.1	
Statin	154 (74.4)	89 (76.7)	3 (60)	246	75	
Warfarin	44 (21.3)	12 (10.3)	0 (0)	56	17.1	
DOAC	14 (6.8)	8 (6.9)	0 (0)	22	6.7	
ABPM ever	95 (45.9)	64 (55.2)	0 (0)	159	48.5	

aTotal cholesterol and LDL assessed in a subset of patients. Total cholesterol (n=284), LDL (n=273)

Table 3: Antihypertensive dosing by blood
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Variables	BP <140/90 (n=207) N (%)	BP ≥140/90 (n=116) N (%)	No BP recorded (n=5) N (%)	Total (n=328) N (%)			
0 antihypertensives prescribed	51 (24.6)	22 (19)	2 (40)	73 (22.3)			
1 antihypertensive prescribed	65 (31.4)	31 (26.7)	1 (20)	97 (29.6)			
Detailed analysis of antihypertensives prescribed							
Patient on ≥1 antihypertensive	n=156	n=93	n=3	n=252a			
Adequate dose (WHO)	73 (46.8)	49 (52.7)	1 (33.3)	123 (48.8)			
Inadequate dose (WHO)	83 (53.2)	44 (47.3)	2 (66.6)	129 (51.2)			
Adequate dose (Egan)	105 (67.3)	71 (76.3)	1 (33.3)	177 (70.2)			
Inadequate dose (Egan)	51 (32.7)	22 (23.7)	2 (66.6)	75 (29.8)			

<sup>&</sup>lt;sup>a</sup>Antihypertensive dose not recorded for one patient.

With 328 patients reported as having a prior stroke or TIA, ten procedures were involved. The features of patients are listed in table 2. 62.2% of the surveyed population (n=328) are male and 37.8% are female. 29.3 percent ischemic stroke, 9.8 percent hemorrhagic stroke and 41.2 percent TIA were included in the stroke subtype, with 19.8 percent unknown or not registered. For free GP services, 87.8 percent were registered with PCRS. Among this cohort of patients, multimorbidity is a common feature; 15.5 percent had diabetes, 22.6 percent had Chronic kidney disease (CKD), and 4.9 percent had both diabetes and CKD.<sup>14</sup>

Independent t-tests have been used to compare the mean of different quantitative variables (age, renal function parameters, ambulatory blood pressure, lipids) between regulated (<140/90 mmHg) and uncontrolled (<140/90 mmHg) classes. In order to compare factors (gender, PCRS status, co-morbidity and sub-optimal BP control (about 140/90 mmHg), a two-sample comparison of proportions (or chi-square test) was also done. There were no statistically significant variations shown between the groups.<sup>15</sup>

Chi-squared tests were also used to assess if there was a substantial difference between the predicted frequencies and the observed frequencies in different categories in managed patients (<140/90 mmHg) versus uncontrolled patients (?? 140/90 mmHg) and no significant differences in sex, subtype stroke, GMS status and comorbidity were observed. To model the association between the (log) odds of BP control and explanatory variables of interest, binary logistic regression was used. There were no predictors found for sub-optimal BP.

For 252 patients who were prescribed antihypertensive drugs, comprehensive drug dosing data were available (Table 3). For those with BP  $\geq$ 140/90 mmHg, 44 (47.3%) patients and 22 (23.7%) patients were inadequately dosed, in each of their medications, according to WHO-DDD guidelines respectively. Of the 116 patients who had uncontrolled BP ??140/90 mmHg, 23 did not take any antihypertensive drug and 31 took a single drug.  $^{16-18}$ 

For 64 (55.2 percent) of the 116 patients with sub-optimal BP regulation, ABPM results were available. Nine patients

with white coat hypertension had ABPM (n=64), the remaining 55 had sub-optimal BP power, with average daytime readings >134/84 mmHg.<sup>19-22</sup>

#### **DISCUSSION**

### Summary of main findings

In approximately one-third (35.4 percent) of patients, blood pressure regulation was sub-optimal in compliance with ESH/ESC 2013 and National institute for health and care excellence (NICE) (NG136) recommendations, where BP <140/90 mmHg is considered satisfactory. Compared to the WHO-DDD criterion, anti-hypertensive drug doses tend to be sub-optimal in almost half of these patients.<sup>23</sup>

### Comparison with existing literature

Of those reported with a prior stroke or TIA, 63.1 percent had a managed blood pressure of <140/90 mmHg. This compares well with the findings of a study in Norwegian general practice that found that 47 percent of patients had BP regulated to <140/90 mmHg for one year post stroke. However, in the primary care setting, there is a lack of research investigating blood pressure management and secondary prevention of stroke.<sup>24</sup>

The number of people with strokes is set to increase by 58 percent between 2007 and 2021 due to an aging population. This expected increase in the number of strokes would have a huge effect on spending on health care. The cost of stroke in Ireland has been calculated at EUR 557 million per year, EUR 4,11 billion (£3,6 billion) per year in the UK and EUR 45 billion per year in the EU. Therefore, with increasing health care costs, it is important that preventive measures be implemented to minimize the occurrence of strokes or other strokes.

It is difficult for clinicians to determine which is the most suitable target in this community of patients for blood pressure management. Each recommendation of different goals with two or three different guidelines may trigger uncertainty about the most effective clinical management. The United Kingdom, NICE-Clinical Guideline NG136

has recently reviewed the evidence and decided that the current goal of <140/90 mmHg should be maintained for all adults under 80 years of age (NICE, 2019) and will not comply with the American heart association (AHA) guidelines to reduce the goal of blood pressure to <130/80 mmHg, as evidenced by the SPRINT (SPRINT e) study. NICE reported that at this point in clinical care environments, the approach used to calculate BP in SPRINT is simply not feasible. From a target BP of <140/90 mmHg (as used in our study), the latest ESC/ESH guideline has updated its recommendation to <130/80 mmHg. However, if tolerated, it advises caution with lower targets, especially in patients over 65 years, where the target is 130-140/80 mmHg. In all patients, caution must be exercised, as lowering systolic blood pressure to <120 mmHg can be helpful for some individuals, but problems for others.<sup>25-27</sup>

It can be hard to reach blood pressure goals in this complex co-morbid group of patients with a mean age of 73 years and a quarter of CKD. There are times in practice where it is not necessary to comply with blood pressure guidelines and elevated blood pressure measurements are reasonable, such as those with concurrent severe coronary artery disease, those with established acute kidney injury dependent on anti-hypertensive or cerebral hypoperfusion. Those with severe variability in blood pressure measurements (mixed high and low) or those with discrete systolic hypertension and great pulse pressure are another category worth noting. Based blood pressure control programs cannot always be accepted by these populations and treating doctors should not seek further care after trial, as this can have a significant effect on their quality of life. For certain patients, we agree this could be a fact.<sup>28</sup>

Interestingly, of those with uncontrolled BP ??140/90 mmHg (n=116), 22 patients were not prescribed any antihypertensive drugs and a further 31 patients were prescribed only a single agent. Current ESC/ESH guidelines advise that in most cases, two anti-hypertensive agents are needed to ensure BP regulation, and these should be initially started as a combination therapy with a fixed dose.

Of the 93 patients who received one or more antihypertensive drugs, 47.3% (n=44) did not meet the prescribed dose when calculated against the WHO-DDD recommendations in all of their antihypertensive drugs. We agree that the WHO-DDD is a strict indicator of the adequacy of dosing. However, from a technique used by Egan et al. 2013, we also examined drug dosing to counter balance. Here, where the dosing adequacy level is much lower, nearly a quarter of patients are still inadequately dosed while BP is still >140/90 mmHg.<sup>29</sup>

It is known that the medication may often not be administered to a patient with a valid indication for drug treatment due to reasons such as liver or kidney failure, weight, patient end-of - life care, and/or prior adverse reaction to the drug in question. It should be acknowledged

that failure to obtain a prescription treatment does not necessarily reflect inadequate medical treatment or clinical nihilism in certain cases. However, as indicates, up to 70 percent of the time, physician inertia to improve medication dosing in hypertension may be a serious problem.

When examining elevated office blood pressure measurements, the ESC/ESH recommendations endorse the use of ABPM. When investigating white coat hypertension, it is an important instrument. It also offers substantial data on BP regulation at night, which is an independent indicator of death and negative cardiovascular outcomes. Nevertheless, it can be expensive to have ABPM in general practice and is not acceptable for all patients, such as those with pulse disturbances such as atrial fibrillation, those who are easily confused or those who find it too difficult to wear. Results from this study show that as just over half of the cohort has ever had ABPM, ABPM could be used to a greater extent. For all PCRS registered patients, reimbursement for the use of ABPM by primary care practitioners in Ireland has been available since 2018. This is expected to lead to an expanded use of ABPM as a tool in the future for diagnosis and monitoring.30

## Implications for practice and analysis

Significant information on blood pressure regulation in patients who have had a previous stroke or TIA has been provided by the results of this research. The focus of recent stroke audits has been largely on acute hospital care. In primary care, there is a shortage of study. Despite recommendations from recent stroke audits to health authorities to resolve this shortfall, community care and long-term follow-up in primary care have been underfunded and under-resourced. Deficiencies in secondary prevention may be addressed through EU-wide policies, implementation of national and regional guidelines and strategies, and direct intervention-based reimbursement.<sup>31</sup>

To explore how GPs could be assisted to improve the management of BP, further research is required. This could include an analysis of prescriber inertia to increase doses of anti-hypertensive medications, promoting the use of out-of-office readings to validate sub-optimal regulation and boost BP management, and patient strategies to facilitate drug therapy adherence and healthy lifestyle adoption. By incorporating innovative approaches to BP management in primary care, such as home care and self-care approaches, these challenges can be faced.

### **CONCLUSION**

In at least one-third of patients with a prior stroke or TIA, blood pressure regulation remains sub-optimal. Half of these patients were able to respond to an elevation of the anti-hypertensive dose. Further analysis is needed to see how best to control blood pressure in primary care patients with a previous stroke or TIA, since the majority of hypertension consultations take place in this setting.

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