ORIGINAL ARTICLE

Anti-hypertensive prescription practices in private hospitals in Malaysia: a prospective, non-interventional, observational study

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ABSTRACT

Introduction: In managing hypertension, monotherapy and sometimes a combination of more than one agent are used to achieve blood pressure (BP) control. The objective of this prospective, observational, multi-centre study was to assess the level of BP control in patients receiving one or more anti-hypertensive drugs in private medical centres in Malaysia according to the treatment regimens (monotherapy, free drug combinations and single pill combinations).

Materials and Methods: Data were collected through medical records and interview sessions with patients on current pharmacotherapy for hypertension management at baseline and 2–3 months later. Results are expressed as mean ± SD for continuous data and as frequencies and percentages for categorical data.

Results: Among 182 recruited patients, 89 (49%) achieved BP control by the end of the study. Majority (62/89) patients were on single-pill (monotherapy or SPC) anti-hypertensives. Majority (63/89) required more than two anti-hypertensives to achieve BP control.

Conclusion: Both SPC and free drug combination anti-hypertensives reduced BPs, but physicians preferred SPC to improve BP control and increase treatment compliance.

KEYWORDS:
Systolic pressure, diastolic pressure, pharmacotherapy, tablet, therapeutic adherence and compliance, epidemiological monitoring, multicentre studies

INTRODUCTION

The prevalence of hypertension in Malaysia has been on the rise. According to the 2019 National Health and Morbidity Survey, about 3 in 10 people or 6.4 million in Malaysia had hypertension.[1] However, only half of them were aware of their condition. And among those who were on medication, only 45% had their blood pressure (BP) under control. These problems need to be urgently addressed as hypertension is one of the leading preventable causes of premature death worldwide. It is believed to result in 7.5 million deaths (12.8% of deaths due to all causes) and 57 million disability-adjusted life years (DALYS) which is 3.7% of total DALYS.[2]

Hypertension is primarily managed through pharmacotherapy. The anti-hypertensive drugs belong to various classes according to their unique mechanism of action. Monotherapy and sometimes a combination of more than one agent are used to achieve BP control. Studies have assessed the effects of combination therapy in achieving and maintaining BP goals as per clinical practice guidelines.[3,4]

In Malaysia, clinical practice guidelines are regularly updated for guiding physicians on current anti-hypertensive goals and therapies. Physicians play a major role in putting these recommendations into clinical practice. In a study in a tertiary hospital in Malaysia, about 67% of the patients received guidelines-compliant pharmacotherapy.[5] In another study, doctors' knowledge of hypertension guidelines and their prescription practices were analysed, and about 73% were noted to have adequate knowledge of current guidelines.[6] Despite these encouraging results, there are still gaps between guideline recommendations and actual practice.[6]

The objective of this study was to assess the level of BP control in patients receiving one or more anti-hypertensive drugs in private medical centres in Malaysia, depending on the number and type of regimen of anti-hypertensive treatments used.

MATERIALS AND METHODS

Study Design

This prospective, non-interventional, observational study involved outpatients who were seen and treated by physicians (cardiologists or other specialists) in 18 private medical centres throughout Malaysia between January and November 2019.

The participating physicians were asked to establish and continue care and treatment according to their current medical practice. They were free to initiate any form of treatment according to their own medical decision and could initiate a single-pill strategy as mentioned by the guidelines.

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No specific analysis or specific treatment introduction was required. As the objective of the study was focussed on the number of anti-hypertensive agents, the class and doses of these agents were not reported.

The study was performed in compliance with the requirements of the International Conference of Harmonization and Good Clinical Practice. The study gained full regulatory approval from Malaysia's Medical Research Ethics Committee on 8 November 2018.

Study Participants
Participants were adult outpatients (age >18 years) of either gender who were on at least one anti-hypertensive medication and were seen and treated by physicians from private medical centres in Malaysia. Patients hospitalised for cardiovascular diseases in the last 3 months (including revascularisation) were excluded.

All participants provided written informed consent. Patients were free to withdraw from the study at any time without giving a reason. They were also told that there would be no negative consequences for withdrawing from the study. The treating physician could also withdraw patients from the study if they deemed it appropriate for safety or ethical reasons or if it was detrimental to the well-being of the patient.

Due to the study design and objectives, a formal sample size calculation was not performed. About 320 total patients were estimated from the initially planned 32 physicians (based on clinical practice history of ten patients per physician). However, due to the busy schedule of the investigators, only 18 investigators participated.

Data Collection
Data were collected through medical records and interview sessions with the patient on current pharmacotherapy for hypertension management at baseline and at 3-month follow-up (according to the International Society of Hypertension 2020 Hypertension Guideline's recommendation for monitoring BP control).7 The names of the patients were blinded to prevent bias.

Clinical information such as patient demographics, systolic blood pressure (SBP)/diastolic blood pressure (DBP) values, anti-hypertensive treatment details, concomitant diseases, and BP control status were collected at baseline and subsequent visit (within 2–3 months).

No investigational products were assessed for safety or efficacy.

Statistical Analysis
Results were expressed as mean ± SD for continuous data and as frequencies and percentages for categorical data. All descriptive statistics were carried out using STATA, version 13.

RESULTS

Baseline Demographic and Other Patient Characteristics
From a planned sample size of 320 patients, 207 (from 18 centres) met the eligibility criteria and were recruited into the study. Six of these centres recruited between two and nine patients each, while the remaining centres recruited more than ten patients each (11 patients [n=1], 13 patients [n=1], 15 patients [n=8], 16 patients [n=1], and 17 patients [n=1]).

By the end of the study, 25 patients were lost to follow-up. The final analysis included 182 patients.

The patients ranged from 23 to 81 years old (mean age of 52.9 years [SD 12.5]) (Table 1). Majority of the patients were between the ages of 30 and 60 years old, with the most common age group being the 50–60 years group (34%). Among the patients, 44% were Chinese, followed by 42% Malay, and 8% and 5% Indian and other races, respectively (Table I). The study population comprised an almost equal proportion of males and females (53% and 47%, respectively). More than half (62%) had primary/secondary education.

At baseline, patients generally had a healthy mean body mass index (BMI) of 28.27 (SD 6.54) (Table I). The most common concomitant diseases were dyslipidaemia (38%) and diabetes (26%) (Table I).

Anti-hypertensive Treatment
At baseline, patients in the study were on at least one type of anti-hypertensives with 43% on monotherapy (one agent), 23% on free drug combinations (more than one agent in multiple loose pills) and 29% on SPC of dual or triple therapy (2 or 3 agents in a single pill) (Table II).

According to the physicians, 65% and 32% of the patients were suitable for SPC dual and triple therapies, respectively, to improve BP control, treatment compliance, and cardiovascular risk management. At the 3-month assessment, most patients had either the same (64%) or higher (32%) number of anti-hypertensives prescribed from baseline. Most patients were on two or more anti-hypertensive treatments (74%) (Table II). By the end of the study (month 3), there was increased use of SPC (42%) compared to baseline (29%), and a slight increase in the use of free drug combinations (32% versus 28% at baseline). However, the use of monotherapy reduced by month 3 (43% versus 26% at baseline) (Table II).

Blood Pressure Control
Over the course of the study, there was a reduction in BPs of the study participants (SBP by 10 mmHg and DBP by 5 mmHg) (Table II).

The BP reduction varied with the number of anti-hypertensives prescribed. Patients who had an increase in the number of anti-hypertensives showed an average reduction in SBP of 19 mmHg and DBP of 10 mmHg, while patients who had a decrease in prescribed anti-hypertensives had a reduction in SBP of 2 mmHg and increase in DBP of 4 mmHg. Patients who had no change in anti-hypertensive medication registered a decrease of 5 and 3 mmHg, respectively, for SBP

Table I: Demographics and baseline characteristics of adult outpatients with hypertension

Patient characteristics	N = 182
Age, years	
Mean (SD)	52.9 (12.5)
Median (IQR)	53.5 (44, 59)
Min, Max	23, 81
Age group (years), n (%)	
<30	2 (1)
30–<40	27 (15)
40–<50	47 (26)
50–<60	61 (34)
60–<70	22 (12)
≥70	23 (13)
Gender, n (%)	
Male	97 (53)
Female	85 (47)
Race, n (%)	
Malay	77 (42)
Chinese	80 (44)
Indian	15 (8)
Others	10 (5)
Education level, n (%)	
Primary/Secondary	113 (62)
Diploma	32 (18)
Degree	28 (15)
Others	9 (5)
Height, cm	
Mean (SD)	163.2 (8.7)
Median (IQR)	164 (156, 169)
Min, Max	142.5, 184
Weight, kg	
Mean (SD)	75.4 (19.0)
Median (IQR)	73.8 (63.9, 83.0)
Min, Max	40.5, 193.4
BMI, kg/m^2	
Mean (SD)	28.3 (6.5)
Median (IQR)	27.2 (24.6, 30.2)
Min, Max	16.0, 71.9
Concomitant diseases, n (%)	
Diabetes	74 (26)
Renal disease	22 (8)
Dyslipidaemia	108 (38)
Ischaemic heart disease	18 (6)
Cerebrovascular disease	20 (7)
None of the above	43 (15)

BMI, body mass index; IQR, Interquartile range; SD, standard deviation

and DBP. Patients on SPC and free drug combination medications registered a decrease in systolic and diastolic BPs except for free drug combination of two anti-hypertensives where diastolic BPs increased (Figure 1). However, only patients on SPC-dual therapy registered a lowering of SBPs to below 140 mmHg.

Only 89 patients (49%) of the patients reached BP target levels of below 140/90 mmHg by the end of the study (Table 2). Among the 89 patients who reached BP control, more than two-thirds (62 out of 89) were on single pill (including monotherapy, SPC 2 and 3 drugs) while the rest were on multiple pills (Figure 2). Close to three-fourths of the patients (71%) needed a minimum of two or more anti-hypertensive agents to reach BP control.

For dual therapy, more patients on SPC (55%) achieved BP control than those on free drug combination (47%). However, for triple therapy, more patients on free drug combination (38%) achieved BP control than those on SPC (22 %).

Treatment Compliance

According to patient responses, compliance to treatment was moderate at baseline and improved to good at the final visit. By the end of the study, fewer patients reported having ran out of medications (5% versus 95% at baseline), forgetting to take their medications (5% versus 7% at baseline), or taking their medication later than the usual time (29% versus 43% at baseline).

DISCUSSION

This observational study aimed to explore the prescription practices of doctors in private medical hospitals and achievement of adequate BP control in patients in Malaysia. The results found that based on physicians' perception, BP

Table II: Anti-hypertensive treatments and BP control of adult outpatients with hypertension

Patient characteristics	Baseline (n=182)	At 3 months (n=182)
Anti-hypertensive treatment		
Number of anti-hypertensive treatments, n (%)		
1	79 (43)	47 (26)
2	62 (34)	73 (40)
3	31 (17)	47 (26)
≥4	10 (6)	15 (8)
Type of medication prescribed, n (%)		
Monotherapy	79 (43)	47 (26)
Free drug combination pills	50 (28)	59 (32)
Only SPC	53 (29)	76 (42)
BP control		
SBP, mmHg		
Mean (SD)	149.3 (20.9)	139.6 (16.8)
Median (IQR)	147.5 (133, 160)	137 (130, 150)
Min, Max	102, 210	101, 190
DBP, mmHg		
Mean (SD)	87.2 (12.7)	81.6 (9.9)
Median (IQR)	88.0 (80, 96)	80.0 (77, 89)
Min, Max	53, 120	58, 115
BP < 140/90 mmHg, n (%)	55 (30)	89 (49)*
BP ≥ 140/90 mmHg, n (%)	127 (70)	93 (51)

BP, blood pressure; DBP, diastolic blood pressure; IQR, Interquartile range; SD, standard deviation; SBP, systolic blood pressure; SPC, single-pill combination
*p<0.0001

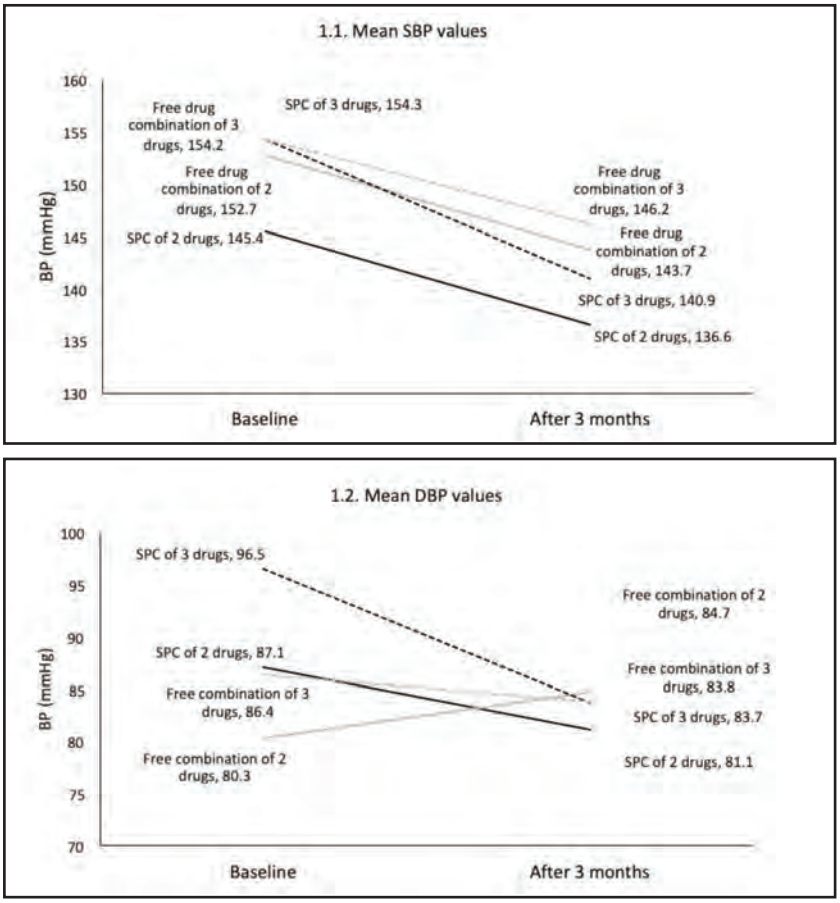

Fig. 1: Blood pressure values for adult outpatients with hypertension on SPC versus free drug combination anti-hypertensive treatments

Number of patients	Baseline	After 3 months
SPC of 2 drugs	48	58
Free drug combination of 2 drugs	14	15
SPC of 3 drugs	4	18
Free drug combination of 3 drugs	27	29

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPC, single-pill combination

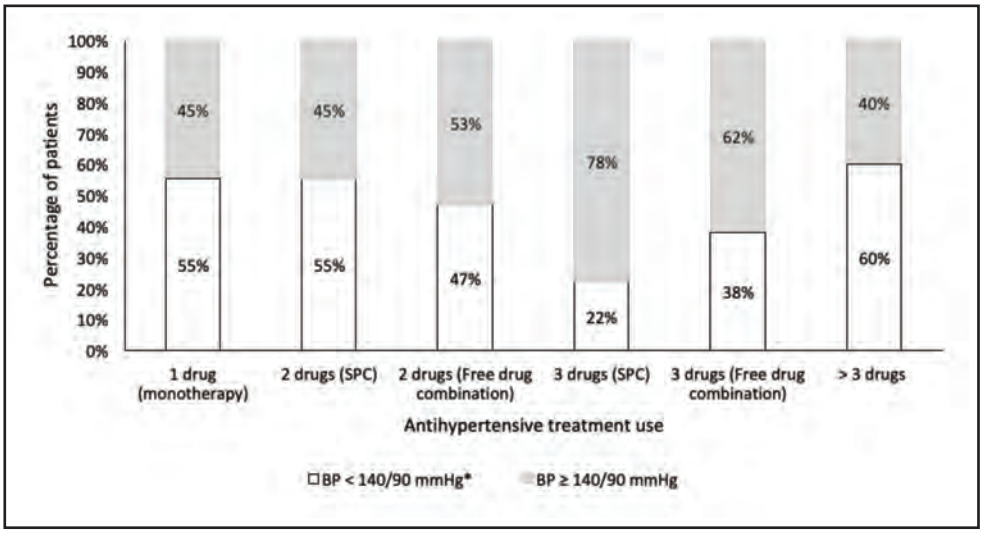

Fig. 2: Blood pressure control of adult outpatients with hypertension after 3 months of treatment based on anti-hypertensive medication regimens

Number of patients	1 drug (monotherapy)	2 drugs (SPC)	2 drugs (Free drug combination)	3 drugs (SPC)	3 drugs (Free drug combination)	>3 drugs
BP ≥ 140/90 mmHg	21	26	8	14	18	6
BP < 140/90 mmHg*	26	32	7	4	11	9

BP, blood pressure; SPC, single-pill combination
*p=0.11

results, and patients' response, SPC regimens improved BP control and increased treatment compliance.

Earlier studies revealed gaps in local healthcare practices for hypertension management. According to the 2014 National Medical Care Survey, private primary care healthcare settings in Malaysia do not perform as well as the public sector in treating chronic conditions and prescribing practices.[8] Another study revealed suboptimal prescription practices in both public and private primary care clinics in the country.[9] In our study, only half of the patients achieved target BP control and majority of the patients required more than two anti-hypertensives to achieve BP control. Our results showed good BP control with more than one anti-hypertensive agent in contrast to another study on hypertension management in public primary care clinics in Malaysia, which showed a negative association between two or more anti-hypertensives and good BP control.[10] However, there is an observed difference in the age groups, sex distribution, and ethnicity between both studies. Our study had a younger population (76% ≤ 60 years versus 61.6% < 65 years); more males (53% versus 39.6%); and fewer patients of Malay ethnicity (42% versus 66%). The use of more than one anti-hypertensive agent for patients who did not achieve target BP levels was in line with guidelines.[11]

Our study also specifically looked at the efficiency of anti-hypertensive control in patients taking more than one anti-hypertensive medication as free drug combination versus SPC therapy. The physicians in our study felt that majority of the patients would benefit from a SPC regimen primarily for BP control. The results showed that although free combination anti-hypertensive treatments did reduce BPs, SPC of two drugs reduced SBP to target levels of below 140 mmHg. This was consistent with international guidelines, which recommend SPC for patients with BP of ≥140/90 mmHg or for patients with more than 20/10 mmHg above the BP goal.11 However, our study showed that those on free drug combination triple therapy had better BP control than SPC triple therapy. Nevertheless, another study showed that SPC with three drugs reduced BP better than free drug combination of three drugs.[12]

By the end of the study, there was increased use of SPC and free drug combinations. Physicians in our study felt that other than BP control, SPC would improve treatment compliance. Consequently, by the end of the study, patients reported being more compliant with their treatment. In addition, multiple other studies showed that SPC improved compliance compared to free drug combinations.[11,13] Another reason cited by the physicians for recommending SPC was to achieve better cardiovascular risk management. This is imperative as about 7.5 million cardiovascular deaths globally are due to hypertension[2] and studies showed that cardiovascular risk reduction can be achieved through control of BP.[14-16]

The strength of our study lies in its real-world design, which provides valuable information on treatment practices and patient characteristics. The study is focussed on patients attending private healthcare centres, which are not often captured in studies. Patients who attend private healthcare settings in the country are usually those who can afford the higher cost of medications which are covered by insurance or paid out-of-pocket.[17] Private healthcare patients may benefit from longer consultations, with more time for education and advice.[17-19] In addition, as this study involved multiple centres,

it may be a good reflection of private healthcare practices in the country. Furthermore, due to the prospective design, the study reflected more recent practices which would not have been captured with a retrospective study. Other studies on anti-hypertensive prescription practices have used similar prospective, observational designs.[20,21]

However, our study had several limitations. Firstly, the focus of this study is private hospitals, which only cater for about 2.1% of patients with hypertension in Malaysia.[22] Although the findings of this study represent a small segment of hypertension care in the country, there are differences in primary care service delivery between public and private sectors in Malaysia,[23] of which are important to capture. Secondly, the study did not include information on the drug classes and doses, duration of the disease, and when the treatment the patient was on was initiated. Nevertheless, our focus was treatment regimen (SPC or free dose combinations) and the inclusion of multiple variables may require a bigger sample size. Thirdly, our relatively small sample size and short follow-up may not adequately assess a chronic condition such as hypertension. Changes in therapy take a long time to affect the condition. And finally, the treating physician could withdraw patients from the study if they deemed it appropriate for safety or ethical reasons or if it was detrimental to the well-being of the patient. This was, however, inevitable due to the study being non-interventional and observational. This was also common for studies on prescription practices. In a meta-analysis on medication nonadherence in adult hypertensive patients, only two of the 28 studies included were interventional studies.[24]

CONCLUSION

This study showed that both SPC and free combination anti-hypertensive treatments reduced BPs. The SPC-dual therapy reduced systolic hypertension to lower than 140 mmHg (the target level of SBP) to achieve optimum health. In addition, the convenience of taking two different medications in a single pill would improve treatment compliance. Nevertheless, based on physicians' opinion, number of study subjects studied, and the duration of the study, the outcomes do not give a clear direction. Further studies may be required to elucidate the impact of prescription practices in the management of hypertension in Malaysia.

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REFERENCES

1. National Institutes of Health (NIH). Ministry of Health Malaysia. National Health and Morbidity Survey (NHMS) 2019: Non-communicable diseases, healthcare demand, and health literacy – key findings. MOH/S/IKU/173.20(BK)-e.
2. World Health Organization. The Global Heath Observatory: Blood Pressure/Hypertension. [cited October 2021] Accessed from https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3155
3. Düsing R, Waeber B, Destro M, Santos Maia C, Brunel P. Triple-combination therapy in the treatment of hypertension: a review of the evidence. J Hum Hypertens 2017; 31(8): 501–10.
4. Chrysant SG. Single-pill triple-combination therapy: An alternative to multiple-drug treatment of hypertension. Postgrad Med 2011; 123(6): 21-31.
5. Ahmad N, Hassan Y, Tangiisuran B, Meng OL, Abd Aziz N, Ahmad FU et al. Guidelines adherence and hypertension control at a tertiary hospital in Malaysia. J Eval Clin Pract 2013; 19(5): 798-804.
6. Ahmad N, Khan AH, Khan I, Khan A, Atif M. Doctors' knowledge of hypertension guidelines recommendations reflected in their practice. Int J Hypertens 2018; 2018: 8524063.
7. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens 2020;38(6): 982-1004.
8. Chin MC, Sivasampu S, Wijemunige N, Rannan-Eliya RP, Atun R. The quality of care in outpatient primary care in public and private sectors in Malaysia. Health Policy Plan 2020; 35(1): 7-15.
9. Tong SF, Khoo EM, Nordin S, Teng CL, Lee VK, Zailinawati AH, et al. Process of care and prescribing practices for hypertension in public and private primary care clinics in Malaysia. Asia Pac J Public Health 2012; 24(5): 764-75.
10. Teh XR, Lim MT, Tong SF, Husin M, Khamis N, Sivasampu S. Quality of hypertension management in public primary care clinics in Malaysia: An update. PLoS One 2020; 15(8): e0237083.
11. Tsioufis K, Kreutz R, Sykara G, van Vugt J, Hassan T. Impact of single-pill combination therapy on adherence, blood pressure control, and clinical outcomes: a rapid evidence assessment of recent literature. J Hypertens 2020; 38(6): 1016-28.
12. Koval S, Snihurska I, Starchenko T, Penkova M, Mysnychenko O, Yushko K, et al. Efficacy of fixed dose of triple combination of perindopril-indapamide-amlodipine in obese patients with moderate-to-severe arterial hypertension: an open-label 6-month study. Biomed Res Ther 2019; 6(11): 3501-12.
13. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension 2021; 77(2): 692-705.
14. Antonakoudis G, Poulimenos I, Kifnidis K, Zouras C, Antonakoudis H. Blood pressure control and cardiovascular risk reduction. Hippokratia 2007; 11(3): 114-19.
15. Yang Q, Chang A, Ritchey MD, Loustalot F. Antihypertensive medication adherence and risk of cardiovascular disease among older adults: a population-based cohort study. J Am Heart Assoc 2017; 6(6): e006056.
16. Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. Health Technol Assess 2003; 7(31): 1-94.

17. Risso-Gill I, Balabanova D, Majid F, Ng KK, Yusoff K, Mustapha F, et al. Understanding the modifiable health systems barriers to hypertension management in Malaysia: A multi-method health systems appraisal approach. BMC Health Serv Res 2015; 15: 254.
18. Rannan-Eliya RP, Wijemanne N, Liyanage IK, Jayanthan J, Dalpatadu S, Amarasinghe S, et al. The quality of outpatient primary care in public and private sectors in Sri Lanka – How well do patient perceptions match reality and what are the implications? Health Policy Plan 2015; 30 Suppl 1: i59-74.
19. Ng JX, Chia JCH, Loo LY, Lim ZK, Kho K, Chen C, et al. Chronic disease self-management competency and care satisfaction between users of public and private primary care in Singapore. Ann Acad Med Singap 2021; 50(2): 149-58.
20. Márquez PHP, Torres OH, San-José A, Vidal X, Agustí A, Formiga F, et al; Potentially Inappropriate Prescription in Older Patients in Spain (PIPOPS) Investigators' Project. Potentially inappropriate antihypertensive prescriptions to elderly patients: results of a prospective, observational study. Drugs Aging 2017; 34(6): 453-66.
21. Jarari N, Rao N, Peela JR, Ellafi KA, Shakila S, Said AR, et al. A review on prescribing patterns of antihypertensive drugs. Clin Hypertens 2016; 22: 7.
22. Yusoff K, Razak A, Rahman ARA, Feisul M, Mckee M. Hypertension control: lessons from Malaysia, a upper-middle-income country. J Cardiol Curr Res 2021; 14(4): 69-73.
23. Ong SM, Lim MT, Fah Tong S, Kamaliah MN, Groenewegen P, Sivasampu S. Comparative performance of public and private primary care service delivery in Malaysia: an analysis of findings from QUALICOPC. PLoS One 2022; 17(10): e0276480.
24. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs: a systematic review and meta-analysis. Medicine (Baltimore) 2017; 96(4): e5641.