

ADHERENCE TO GUIDELINE RECOMMENDATIONS ON ANTI-HYPERTENSIVE MEDICATION PRESCRIBING BY PRIMARY CARE PHYSICIANS IN MALAYSIA

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Abstract. Anti-hypertensive medication guidelines are intended to improve health outcomes. We aimed to determine adherence to the Malaysian guidelines by primary care physicians regarding the prescribing of anti-hypertensive medications for hypertensive patients with diabetes mellitus, proteinuria and those aged ≥ 65 years. We retrospectively reviewed medical records of patients who attended a primary care clinic from January to May 2012. One out of every four records of hypertensive patients aged >18 years who had been followed-up for at least a year, were randomly sampled. Records of 1,060 patients were reviewed: 507 subjects (47.8%) had diabetes mellitus and 374 (73.8%) were prescribed renin-angiotensin-system blockers (RAS-blockers). Eighty-six out of 367 subjects tested (23.4%) had proteinuria, of which 46 (53.5%) were prescribed RAS-blockers. All subjects (100%) with diabetes mellitus and proteinuria ($n=65$) were prescribed angiotensin converting enzyme inhibitors as per guidelines. Of the 431 patients aged ≥ 65 years, the anti-hypertensive medications prescribed were calcium channel blockers (67.7%), RAS-blockers (52.4%), diuretics (35.5%), beta blockers (31.8%) and alpha blockers (6%). Adherence of primary care physicians to anti-hypertensive medication guidelines was good, but there is still room for improvement in the use of RAS-blockers to treat hypertensive subjects with proteinuria.

Keywords: hypertension, guidelines, primary care, diabetes, proteinuria, older persons, anti-hypertensive agents

INTRODUCTION

Clinical practice guidelines (CPGs)

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for managing hypertension have been developed to standardize and enhance the quality of hypertension care (American Diabetes Association, 2013; Hackam *et al*, 2013). Blood pressure (BP) control is important to reduce the morbidity and mortality of patients with hypertension, in particular those with diabetes mellitus (DM), proteinuria and in those aged ≥ 65

years (Turner *et al*, 1993; McLean *et al*, 2006; Musini *et al*, 2009; Chen *et al*, 2011). International and local CPGs recommend lower BP target levels for patients with DM and proteinuria (Ministry of Health Malaysia, 2008; *idem*, 2009; American Diabetes Association 2012). Among adults aged ≥ 65 years with hypertension and those with isolated systolic hypertension, the BP target is similar to the general population (US Department of Health and Human Services 2003; Ministry of Health Malaysia, 2008). The Malaysian guideline for anti-hypertensive medication recommends prescribing renin-angiotensin-system-blockers (RAS-blockers) for hypertensive patients with DM or proteinuria and other classes of anti-hypertensive drugs [RAS-blockers, calcium channel blockers (CCB) and diuretics] for those aged ≥ 65 years except beta-blockers, which is not recommended to be used as initial therapy without compelling indications and consideration of patient cardiovascular risks and co-morbidities (Ministry of Health Malaysia, 2008).

In Malaysia, CPGs regarding the management of hypertension have been in existence since 1998 (Ministry of Health Malaysia, 1998) and have been updated regularly (Ministry of Health Malaysia, 2008; *idem*, 2009; *idem*, 2013). These guidelines were developed for use by all healthcare professionals involved in hypertensive care based on current best evidence, local publications, clinical expertise and patient values, to ensure local relevance.

One review of the literature found most primary care physicians were not aware if they were adhering to CPGs (Steinman *et al*, 2004). CPGs were also found to have limited effect on changing a physician's behavior (Hayward, 1997;

Cabana *et al*, 1999). Physicians' adherence to CPGs on anti-hypertensive medications prescribing ranged between 18.3% and 72.9% (Chan, 2005; Ahmad *et al*, 2012; Theodorou *et al*, 2012; Huang *et al*, 2013). In Malaysia, only one study had been conducted on anti-hypertensive medication prescribing adherence; 73.5% of anti-hypertensive medications prescribed for patients with cardiovascular diseases were adherent to the CPG (Ahmad *et al*, 2012).

The aim of our study was to determine the adherence of primary care physicians to the Malaysian CPG regarding the management of hypertension when prescribing anti-hypertensive medications for hypertensive patients with DM, proteinuria, and adults aged ≥ 65 years.

MATERIALS AND METHODS

This study was conducted at a primary care clinic in Kuala Lumpur, Malaysia. The clinic has 25-30 medical officers, family medicine trainees and family physicians who see 400-600 patients daily; a quarter of whom have hypertension. Physicians at the clinic have access to all classes of anti-hypertensive medications and laboratory testing appropriate for monitoring hypertensive patients.

We retrospectively reviewed medical records of patients who attended the clinic during January-May 2012. One out of every four records of hypertensive patients, aged >18 years who had been followed-up for at least a year, were randomly sampled. Data obtained were: patient socio-demographics, clinical profile (cardiovascular risk factors, target organ damage, secondary causes of hypertension and investigation results), BP, presence of proteinuria and medications prescribed (Wong *et al*, 2015).

We defined patients with DM as having a diagnosis of DM, or a fasting blood glucose of ≥ 7.0 mmol/l, or who were taking diabetic medication(s). Microalbuminuria was defined as having 30-300 mg/dl of albumin in the urine, whilst proteinuria was defined as having >300 mg/dl of proteins in the urine. For this study, the term proteinuria includes the presence of microalbuminuria.

The CPG used in this study was the Malaysian CPGs on the Management of Hypertension (Third Edition; 2008) (Ministry of Health Malaysia, 2008), which was the version in effect when this study was carried out. Angiotensin-converting-enzyme inhibitors (ACEI) are recommended as first-line therapy for all hypertensive patients with DM. In the presence of microalbuminuria or overt proteinuria, patients should be treated with ACEI or angiotensin-receptor blockers (ARB). Alpha- and beta-blockers are not recommended as first line monotherapy. For older patients with no co-morbidity, other classes of drugs (RAS-blockers, calcium channel blockers (CCB), and diuretics can be used as first-line therapy but a stronger recommendation is given for CCB and diuretics. Beta-blockers are not recommended to be used as initial therapy without compelling indications. The recommended BP for hypertensive patients with DM and those with proteinuria is $<130/80$ mmHg and the recommended BP for patients aged ≥ 65 years is $<140/85$ mmHg (Ministry of Health Malaysia, 2008).

This study was approved by the University Malaya Medical Centre Ethics Committee (approval no: 890.14). Written informed consent was obtained from all participants for their clinical records to be used in this study.

Data analyses

All data were analysed using the Statistical Package for Social Sciences (SPSS) version 22 (IBM Corporation, Armonk, NY). Continuous data were summarized using means \pm standard deviations (SD) while categorical variables were summarized as absolute numbers and relative frequencies (percentages). Demographic data for patients were compared using the independent *t*-test for continuous variables and the chi-square (χ^2) test for comparisons of proportions among groups. We compared adherence to CPGs for anti-hypertensive medications in hypertensive patients with concomitant DM, proteinuria or who were aged ≥ 65 years. A *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 1,060 medical records were included in the study. Overall, the mean [\pm standard deviation (SD)] number of types of anti-hypertensive medications prescribed per study subject was 1.89 ± 0.86 . The most commonly prescribed anti-hypertensive monotherapy was CCBs (169, 45.7%), followed by ACEIs (111, 30.0%) and ARBs (44, 11.9%). A total of 370 study subjects (34.9%) were on monotherapy for hypertension.

Study subjects with diabetes mellitus

A total of 507 study subjects with hypertension (47.8%) had DM. The mean (\pm SD) duration of DM was 8.0 (\pm 6.5) years. A total of 374 subjects (73.8%) had been prescribed RAS-blockers, 271 (53.5%) had been prescribed ACEI, 106 (20.9%) had been prescribed ARBs and 297 (58.6%) had been prescribed CCBs. A total of 151 subjects with DM (29.8%) were on anti-hypertensive monotherapy, of which 93

(61.6%) were on RAS-blockers. Only 216 subjects with DM (42.6%) had been tested for proteinuria, of which 65 (30.1%) had proteinuria, and all (100%) had been prescribed ACEIs, following the recommendations of the CPG. Significantly more ($p<0.001$) study subjects with DM (374, 73.8%), had been prescribed RAS-blockers than those without DM (260, 47.0%). Diabetic subjects were prescribed significantly more ($p<0.001$) anti-

hypertensive medications (2.0 ± 0.9) than those without DM (1.8 ± 0.8). Significantly more ($p<0.001$) study subjects without DM had adequately controlled hypertension ($<140/90$ mmHg, 62.4%) than those with DM ($<130/80$ mmHg, 19.7%) (Table 1).

Study subjects with proteinuria with and without diabetes

A total of 367 study subjects (34.6%) had been tested for proteinuria; of these 86 (23.4%) had proteinuria, 46 (53.5%) had been prescribed RAS-blockers as recommended by CPG (Fig 1). Only 18 study subjects with proteinuria (18.6%) had achieved BP control ($<130/80$ mmHg).

Study subjects aged ≥ 65 years

A total of 431 study subjects (40.7%) were aged ≥ 65 years. The most common anti-hypertensive medications prescribed in this age group were CCBs (67.7%), RAS-blockers (52.4%), diuretics (35.5%), beta-blockers (31.8%) and alpha-blockers (6%). A total of 129 subjects aged ≥ 65 years (29.9%) were on treatment with only

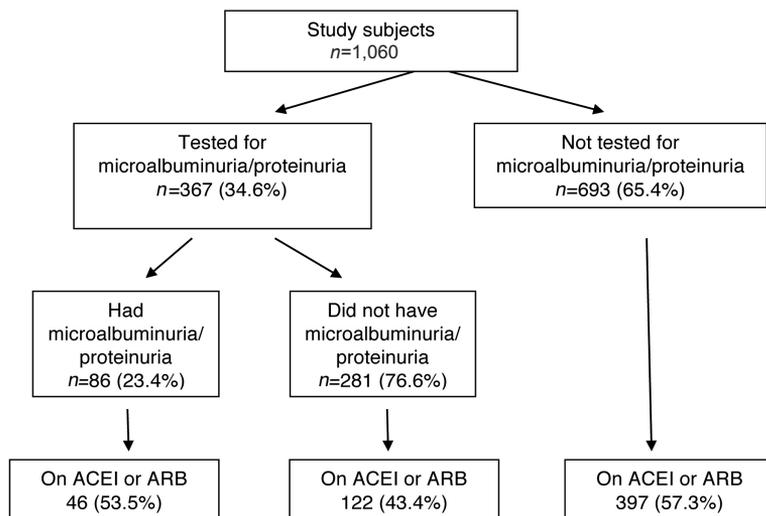


Fig 1—Study subjects tested for microalbuminuria/proteinuria and anti-hypertensive medications prescribed.

one anti-hypertensive, 8 (6.2%) had been prescribed a beta-blocker; seven had no history of cardiovascular disease. Table 2 shows the anti-hypertensive medications prescribed for subjects by age group. Compared to younger subjects, older subjects were more likely to have been prescribed alpha-blockers (6.0% versus 1.3%, $p<0.001$), diuretics (35.5% versus 29.7%, $p=0.048$), and beta blockers (31.8% versus 22.6%, $p=0.001$), and fewer RAS-blockers (52.4% versus 64.9%, $p<0.001$). There was no significant difference in the use of CCBs between younger and older age groups (62.0% vs 67.7%, $p=0.06$). A total of 66.8% of older subjects achieved their target BP ($<140/85$ mmHg), similar to younger subjects ($<140/85$ mmHg, 65.7%, $p=0.695$). A significantly greater percentage of older male subjects had been prescribed alpha-blockers for hypertension than older female subjects (88.5% vs 11.5%, $p<0.001$).

Table 3 shows the adherence of primary care physicians to CPG regarding

Table 1
Demographic characteristics of study subjects with and without diabetes mellitus and the anti-hypertensive medications prescribed.

| | Subjects with DM <i>n</i> =507 | Subjects without DM <i>n</i> =553 | <i>p</i> -value |
|---|-----------------------------------|--------------------------------------|-----------------|
| Mean age in years \pm SD (range) | 61.8 \pm 9.8 (27-94) | 62.2 \pm 10.9 (26-88) | 0.571 |
| Gender, <i>n</i> (%) | | | |
| Male | 208 (41.0) | 219 (39.6) | 0.637 |
| Female | 299 (59.0) | 334 (60.4) | |
| Ethnicity, <i>n</i> (%) | | | |
| Malay | 164 (32.3) | 159 (28.8) | <0.001* |
| Chinese | 199 (39.3) | 310 (56.1) | |
| Indian | 141 (27.8) | 77 (13.9) | |
| Others | 3 (0.6) | 7 (1.3) | |
| Mean BMI at baseline \pm SD in kg/m ² | 28.0 \pm 5.3 | 27.2 \pm 4.9 | 0.117 |
| Mean duration of hypertension in years \pm SD | 9.1 \pm 7.0 | 8.0 \pm 5.7 | 0.004* |
| Subjects with proteinuria/microalbuminuria, <i>n</i> (%) (<i>n</i> =367) | 65 (30.1) | 21 (13.9) | <0.001* |
| Mean number of all medications currently consumed \pm SD | 5.6 \pm 1.9 | 3.7 \pm 1.6 | <0.001* |
| Mean total number of anti-hypertensive medications prescribed \pm SD | 2.0 \pm 0.9 | 1.8 \pm 0.8 | <0.001* |
| Achieved BP target of <130/80, <i>n</i> (%) | 100 (19.7) | 345 (62.4) | <0.001* |
| Anti-hypertensive medications prescribed, <i>n</i> (%): | | | |
| ACEIs or ARBs | 374 (73.8) | 260 (47.0) | <0.001* |
| CCB | 297 (58.6) | 385 (69.6) | <0.001* |
| ACEIs | 271 (53.5) | 180 (32.5) | <0.001* |
| ARBs | 106 (20.9) | 83 (15.0) | 0.012* |
| (ACEIs or ARBs) and CCB | 196 (38.7) | 138 (25.0) | <0.001* |
| ARBs and diuretics | 14 (2.8) | 11 (2.0) | 0.408 |
| Diuretics | 169 (33.3) | 171 (30.9) | 0.401 |
| Beta blockers | 137 (27.0) | 142 (25.7) | 0.620 |
| Diuretics or beta blockers | 251 (49.5) | 263 (47.6) | 0.526 |
| Alpha blockers | 14 (2.8) | 20 (3.6) | 0.430 |
| Spironolactone | 1 (0.2) | 0 | 0.296 |
| Monoxidine | 1 (0.2) | 0 | 0.296 |

SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; BP, blood pressure; CCB, calcium channel blockers; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; *statistically significant.

Table 2
Demographic characteristics and anti-hypertensive medications by age group.

| | Subjects aged <65 years, <i>n</i> =629 | Subjects aged ≥65 years, <i>n</i> =431 | <i>p</i> -value |
|--|---|---|-----------------|
| Mean age in years ± SD (range) | 55.4±7.4 (26-64) | 71.6±5.5 (65-94) | |
| Gender, <i>n</i> (%) | | | |
| Male | 262 (41.7) | 165 (38.3) | 0.272 |
| Female | 367 (58.3) | 266 (61.7) | |
| Ethnicity, <i>n</i> (%) | | | |
| Malay | 245 (39.0) | 78 (18.1) | <0.001* |
| Chinese | 226 (35.9) | 283 (65.7) | |
| Indian | 150 (23.8) | 68 (15.8) | |
| Others | 8 (1.3) | 2 (0.5) | |
| Mean BMI at baseline ± SD in kg/m ² | 29.0 ± 5.3 | 25.6 ± 3.9 | <0.001* |
| Mean duration of hypertension in years ± SD | 7.9 ± 5.7 | 9.5 ± 7.2 | <0.001* |
| Mean duration of DM in years ± SD | 7.4 ± 5.9 | 8.9 ± 7.3 | 0.016* |
| Subjects with proteinuria or microalbuminuria, <i>n</i> (%) | 49 (22.7) | 37 (24.5) | 0.686 |
| Mean total number of all medications currently consumed ± SD | 4.6 ± 2.0 | 4.7 ± 1.9 | 0.120 |
| Mean total number of anti-hypertensive medications ± SD | 1.8 ± 0.9 | 2.0 ± 0.9 | 0.008* |
| Achieved BP target <140/85, <i>n</i> (%) | 413 (65.7) | 288 (66.8) | 0.695 |
| Anti-hypertensive medications prescribed, <i>n</i> (%) | | | |
| CCBs | 390 (62.0) | 292 (67.7) | 0.055 |
| ACEIs or ARBs | 408 (64.9) | 226 (52.4) | <0.001* |
| ACEIs | 297 (47.2) | 154 (35.7) | <0.001* |
| Diuretics | 187 (29.7) | 153 (35.5) | 0.048* |
| Beta blockers | 142 (22.6) | 137 (31.8) | 0.001* |
| ARBs | 115 (18.3) | 74 (17.2) | 0.642 |
| Alpha blockers | 8 (1.3) | 26 (6.0) | <0.001* |
| Spironolactone | 0 | 1 (0.2) | 0.227 |
| Monoxidine | 0 | 1 (0.2) | 0.227 |
| Diuretics and/or beta blocker (ACEIs or ARBs) and CCBs | 277 (44.0) | 237 (55.0) | <0.001* |
| Fixed dose combination of ARBs and diuretic | 211 (33.5) | 123 (28.5) | 0.085 |
| Fixed dose combination of ARBs and diuretic | 14 (2.2) | 11 (2.6) | 0.731 |

SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; BP, blood pressure; CCB, calcium channel blockers; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; *statistically significant.

Table 3
Adherence of primary care physicians to clinical practice guidelines regarding prescribing of anti-hypertensive medications in hypertensive patients with diabetes, proteinuria and those aged ≥ 65 years.

| Hypertensive subjects | Recommended class of drugs | Prescribed according to guidelines, <i>n</i> (%) | Target BP achieved*, <i>n</i> (%) |
|---|----------------------------|--|-----------------------------------|
| With diabetes (<i>n</i> =507) | ACEI | 271 (53.5) | 100 (19.7) |
| | ARBs | 106 (20.9) | |
| | RAS-blockers | 374 (73.8) | |
| With diabetes and proteinuria (<i>n</i> =65) | RAS-blockers | 65 (100.0) | |
| With proteinuria (<i>n</i> =86) | RAS-blockers | 46 (53.5) | 18 (20.9) |
| Aged ≥ 65 years (<i>n</i> =431) | CCBs | 292 (67.7) | 288 (66.8) |
| | Diuretics | 153 (35.5) | |

*The target blood pressure for hypertensive patients with diabetes mellitus for those with proteinuria is $<130/80$ mmHg; the target blood pressure for patients aged ≥ 65 years is $<140/85$ mmHg (Ministry of Health Malaysia, 2008). ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin-receptor blockers; RAS-blockers, renin-angiotensin system blockers; CCBs, calcium channel blockers.

the prescribing of anti-hypertensive medications for hypertensive patients with DM, proteinuria and those aged ≥ 65 years.

DISCUSSION

Adherence of the studied physicians to the CPG regarding prescribing RAS-blockers for hypertensive subjects with DM was satisfactory. However, for hypertensive subjects with non-diabetic proteinuria, prescribing of RAS-blockers was not satisfactory. Older subjects were prescribed CCBs and diuretics, as recommended by CPGs, but there were a small number of subjects who were prescribed beta-blockers as monotherapy, without compelling indications.

A total of 73.8% of hypertensive subjects with DM had been prescribed RAS-blockers in our study, similar to a study from the United States (69.7%) (Sessoms *et al*, 2015), and better than a

previous study from Malaysia (18.3%) (Chan, 2005). There are several possible reasons for this: 1) increasing awareness of the CPG over time (Lee *et al*, 2015) as the study conducted by Chan (2005) was 10 years previously; 2) differences in study setting, since our study was conducted at an academic institution and the study by Chan (2005) was conducted at a district health clinic; 3) greater availability of RAS-blockers over time.

RAS-blockers are recommended for hypertensive patients with proteinuria to delay or reverse progression of renal damage in patients (Bakris *et al*, 2000; de Zeeuw, 2004). In this study, only 53.5% of hypertensive patients had been prescribed RAS-blockers, which was similar to a previous study (60.5%) which examined the prescribing of RAS-blockers in hypertensive patients with proteinuria (Thilly *et al*, 2009).

All hypertensive diabetic subjects with proteinuria in our study had been

prescribed RAS-blockers. This was in contrast to previous studies, which reported prescribing rates of 27% (Boero *et al*, 2003) and 40% (Hueston *et al*, 2001) in hypertensive diabetic patients with proteinuria.

In our study, 65.4% of all of hypertensive subjects had not been tested for proteinuria. In a study from the United States, 84.8% of study subjects with hypertension had not been tested for proteinuria (Sessoms *et al*, 2015). It is important to test for proteinuria in all hypertensive patients so RAS-blockers may be prescribed.

Older persons with hypertension are more likely to have sodium sensitivity, isolated systolic hypertension, arterial stiffness and endothelial dysfunction (Wallace *et al*, 2007). The main aim of anti-hypertensive drug therapy is to prevent stroke; the choice of which medication to use is influenced by concomitant disease and past medication history. CCBs were the most commonly prescribed anti-hypertensive medication among those aged ≥ 65 years in our study (as recommended by the Malaysian CPG), similar to another study from Malaysia (Lim *et al*, 2015). However, literature suggests that in patients aged ≥ 65 years, thiazide diuretics should be prescribed as first-line therapy, followed by ACEI and/or CCBs (Stokes, 2009). Few older subjects (6%) were prescribed beta-blockers as monotherapy in our study. Beta-blockers are not generally recommended among those aged ≥ 65 years, as they do not combat the effects of increased arterial stiffness, and are less effective in lowering BP and in preventing strokes than other anti-hypertensive agents (Ministry of Health Malaysia, 2008; Stokes, 2009; Zhang *et al*, 2011; Hackam *et al*, 2013; Lim *et al*, 2015). Most of the older subjects who were on beta-blockers as monotherapy did not have concomitant

cardiovascular disease. However, it may be they had been started on beta-blockers at a younger age or they may have had other diseases for which beta-blockers are indicated (such as thyroid disease or headaches). A higher proportion of older male subjects were prescribed alpha-blockers than older female subjects. This was expected as alpha-blockers are often used to treat benign prostate hypertrophy in males.

Only 19.7% and 20.9% of study subjects with DM and proteinuria, respectively, achieved a target BP of $<130/80$ mmHg. These findings are similar to another study from India (25%) (Dhanaraj *et al*, 2012). The difficulty in controlling BP among hypertensive diabetic subjects may be due to the lower BP goal and the complex renin-angiotensin-system, which is not completely understood (Jandeleit-Dahm and Cooper, 2006). Clinician therapeutic inertia and cost can also be reasons for suboptimal control (Fine and Cutler 2006; Okonofua *et al*, 2006). The mean number of medications prescribed for hypertensive subjects with DM was two, which was not surprising as most patients require two or more drugs to achieve BP control (Bakris *et al*, 2000).

A total of 66.8% of those aged ≥ 65 years in our study achieved the target BP $<140/85$ mmHg. Other studies from low and middle income developing countries reported much lower rates of BP control (4.1%-14.1%) (Lloyd-Sherlock *et al*, 2014). BP control rates in our study were closer to developed countries (Pereira *et al*, 2009). This may be due to physician awareness in our study and the fact that it was conducted at an academic institution.

Findings from this study have prompted us to conduct a qualitative study of barriers and facilitators toward

adhering to CPGs by primary care physicians. These data can be used to develop a program to improve doctors' adherence to hypertension CPGs and BP control rates.

A strength of our study was that systematic sampling was used, making it representative of our study population. However, this was a retrospective study and the indications and dosages of the medications were not available for analysis.

The adherence of primary care physicians to the prescribing of anti-hypertensive medications was generally good. This suggests adequate knowledge of the CPG. However, there is still room for improvement, especially in prescribing anti-hypertensive medications to non-diabetic hypertensive patients with proteinuria.

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CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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