OBJECTIVE: To measure the comorbid effect on blood pressure and therapy expenditure in 4 secondary care hospitals in Jogjakarta.

METHODS: We conducted an 8-month prospective pharmacoeconomic study with hospital perspective. All hypertensive outpatients, with Askes-insurance whose beneficiaries were governmental employees, with at least 2 moly visits at the index date were included. The subjects with malignancy, hemodialysis, and less than 4 visits were excluded. The expenditure comprised the cost for cardiovascular medicine, doctor, physical/laboratory test, emergency visit, and physiotherapy. We analyzed the expenditure change and sensitivity analysis with Anova-test, whereas the proportion of subjects with good controlled blood pressure with the chi-square test.

RESULTS: The eligible subjects (N=656) consisted of no comorbid (n=105), stroke (n=82), cardiovascular (n=209), diabetes mellitus/chronic kidney disease or DM/CKD (n=149), and combined comorbid (n=111) groups. The baseline blood pressure was similar to no comorbid (p=0.05), except for the diastolic blood pressure in a cardiovascular group. The stroke and cardiovascular groups had more subjects at mean systolic blood pressure lower than 140 mmHg with odds ratio (OR) 2.01 (CI95%:1.12-3.62) and 2.10 (CI95%:1.31-3.39) respectively than no comorbid group, but the mean blood pressure was not clinically different. The total therapy expenditure increased at 6.5% (p=0.61); 22.7% (p<0.03); 78.6% (p<0.01); 78.5% (p<0.01) per subject-visit for stroke, cardiovascular, DM, and combined-comorbid groups than no comorbid group respectively. Except for stroke group, the incremental expenditure was price-sensitive (p<0.05).

CONCLUSION: The total therapy expenditure but not blood pressure was likely to be influenced by hypertension comorbidity. We suggest that preventing hypertension comorbidity has the benefit to reduce total therapy expenditure.

KEYWORDS: Hypertension, Comorbidity, Diabetes mellitus, Blood pressure, Stroke, Therapy expenditure

INTRODUCTION

Worldwide hypertension prevalence will reach 1.5 billion people in 2050 [1]. Hypertension was responsible for 12.8% of annual mortality. Inadequate blood pressure control, diabetes mellitus (DM), and dyslipidemia raise major cardiovascular diseases [2]. The cardiovascular disease caused the highest mortality in 2012 including 7.4 million for coronary heart disease and 6.7 million for stroke [3]. Hypertension became health burden in worldwide including the low and middle-income countries [4-7]. Diabetes, previously known as heart disease equivalent, [8] and hypertension also caused the incidence of chronic kidney disease (CKD) at 44% and 28% [9].

The pharmacoeconomic value has the benefit to establish health policy, [10] but the utility of the value is still low in Indonesia [11]. The annual incremental direct medication expenditure for hypertension was US$ 55.0 billion in US or US$1,131 per individual. Medicines contributed>90% of the incremental expenditure [12]. The hypertension medicine expenditure comprised 47.9% of direct health expenditure [13]. The hypertension subjects with comorbidity spent higher total therapy expenditure in a survey with 385 subjects than those without comorbidity [14]. The more comorbid items had, the higher expenditure [13]. The hypertension subjects with comorbidity had the hypertension blood pressure control in both groups [14].

Although national basic health survey reported the declined hypertension prevalence in Indonesia from 31.7% in 2007 to 25.8% in 2013, the rate remained high [17]. Barriers in hypertension control found in a study done among the community in Jogjakarta included lack of hypertension awareness and routine therapy at 27.5% and 8.8% versus 38.8% and 16.1% among those without and without health coverage. The study showed the result of very low blood pressure control in both groups [14].

The blood pressure goal was 140/90 mmHg. Furthermore the higher level of blood pressure alone or with the comorbid diseases augmented the related cardiovascular diseases [18]. The aims of the study were to evaluate the incremental therapy expenditure in Rupiahs and percentage; and the difference of mean blood pressure due to the hypertension comorbidity. We had the hypothesis that the therapy expenditure among the comorbid groups were significantly higher than the no comorbid group (p<0.05).

MATERIALS AND METHODS

Study design and setting

This study was an 8-month analytical perspective pharmacoeconomic survey and done with hospital perspective in 4 secondary care hospitals in Jogjakarta Province. We purposively selected the hospitals with at least 2000 visits of Askes patients monthly and owned the clinic of internists, neurologists, and cardiologists. The study analyzed the direct medical expenditure with hospital perspective. Prior to the study, the protocol was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine Gadjah Mada University Jogjakarta Indonesia with the approval letter No. KE/FK/229/EC; dated April 18, 2012.

Population and subjects

The population was the hypertension out-patients with medium to high adherence in therapy in four secondary care hospitals. We included the patients with the criteria of: adults; covered with Askes-insurance; with at least 2 visits at index date; with hypertension diagnosis or blood pressure reading at 140/90 mmHg and higher; and/or received at least 1 hypertensive medicines. The subjects with hemodialysis, pregnancy, malignancy, and fewer than 4 visits during
the follow-up period were excluded. The study was done among the Askes subjects. The Askes was the Indonesian government-owned insurance and eligible only for Indonesian government employees and retirees. The study was limited to Askes beneficiaries in order to obtain the subjects with the homogeneous social-economic background.

Variables

The independent variable of the study was the hypertension comorbidity, whereas the dependent variables were the systolic/diastolic blood pressure (SBP/DBP) level and the therapy expenditure. The subjects were grouped into no comorbid as a control group and 4 comorbid groups of stroke; cardiovascular (CVD) including dyslipidemia, heart failure, arrhythmia, and coronary heart disease; diabetes mellitus and/or chronic kidney disease (DM/CKD); and combined-comorbid of the previously mentioned groups. We selected these comorbidity diseases because from the preliminary survey these comorbid diseases had the highest prevalence in the hospitals.

The hypertension medicine in this study consisted of the classes of thiazide diuretics; angiotensin converting enzyme inhibitors (ACEI); angiotensin receptor blockers (ARB); calcium channel blockers (CCB); beta-blockers; and centrally acting hypertension medicine. The cardiovascular medicines with the hypertensive effect: e.g. isosorbide-dinitrate in the ischemic coronary artery; furosemide in heart failure and CKD; spironolactone in cardiovascular disease; and prazosin in benign prostate hypertrophy comorbid patients were not included as hypertension medicine but as the cardiovascular medicines.

The other observed variables included frequency of visit, adherence, and a number of items of hypertension and cardiovascular medicine. The subject adherence was calculated as medication possession ratio (MPR). The formula of MPR in percentage was determined as benign prostate hypertrophy comorbid patients were not included as follow-up in the latest visits.

The total therapy expenditure comprised the expenditure for cardiovascular medicine, doctor service, physical-laboratory test, other expenditure including the emergency-room visit and physiotherapy. Further on, we divided the CVD medicine expenditure into hypertensive and non-hypertensive medicine expenditure; and also based on the financing resource of the medicine paid by the Askes insurance and of the out-of-pocket medicine. The expenditure was presented as mean expense per subject hospital visit in Indonesian currency of Rupiahs (Rps). At the moment of study Rps 10,000 was approximately equivalent to 1 USD.

Data collection

We collected the data of expenditure covered by Askes from the hospital claim to the insurance institution and the out-of-pocket from pharmacy department; whereas the subject and medication profiles including age, gender, comorbidity, doctor, date of visit, diagnosis, and blood pressure level per visit from the medical record. The out-of-pocket expenditure included the non-formulary therapy or the medicine in the formulary with more units than allowed for a prescription.

Outcomes measurement

The outcomes included the mean systolic/diastolic blood pressure (SBP/DBP); the proportion of subjects with mean SBP reached the target of<140 mmHg; and the therapy expenditure.

Analyses

All prices from the equivalent item of medicine or composition or service in the study sites were recorded and determined for the median, lowest, and highest calculation for analyses. The median price was used in the mean expenditure calculation and future analysis, because the prices of medicine and service were not normally distributed. Mean expenditure per subject-hospital visit of each component was calculated as the sum of expenditure in all visits and divided by numbers of visit. Expenditure was calculated as the percentage of total cost, i.e.; the cost component divided by total cost and multiplied with 100. The expenditure of hypertension and out of pocket medicine was also calculated as the proportion of cardiovascular medicine.

The variables of age, number of visits, adherence as MPR, number of hypertension and cardiovascular medicine, SBP/DBP level and all expenditure components were presented in the mean and standard deviation. Prior to the analyses, the normality test was evaluated based on the Q-Q plot graph. The comparison of mean value among groups was done with One-way Anova and LSD post-hoc analysis between four comorbid and no comorbid groups (p<0.05). The proportion of subjects with mean SBP reached the goal was analyzed with chi-square test and odds ratio with 95% confidence intervals. The comorbid groups were expected to have higher therapy expenditure and lower OR for the controlled-SBP than no comorbid group (p<0.05).

The pharmacoeconomic evaluation was subject to the sensitive analysis [20]. The sensitivity analysis is evaluated the uncertainty of the expenditure changes in the study. In this study, we did one-way sensitivity of analysis by replacing the median calculation with the lowest and highest calculation of the expenditure, and comparing the groups with Anova one-way test (p<0.05). The overall analyses were done with IBM SPSS Statistics version 18 program.

RESULTS AND DISCUSSION

Subject’s profile

The total subjects (N=656) were distributed into cardiovascular group (n=209), DM/CKD group (n=149), combined-comorbid group (n=111), stroke group (n=82), and no comorbid or control group (n=105). Each group had relatively different subjects because the study was done in real world setting and all eligible subjects were included. Young male subjects were generally at higher risk than female subjects,[18] meanwhile in another study it was known that the gender factor on hypertension and cardiovascular disease was generally inconsistent.[21] We found the similar gender profile with the last mentioned study, the male subjects were fewer in no comorbid, cardiovascular, and DM/CKD groups, whereas more in stroke and combined-comorbid groups at 50.0% and 52.3%.

Table 1: Profiles of the hypertensive outpatients in the secondary care hospitals based on the subject comorbidity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Comorbid</th>
<th>Stroke</th>
<th>CVD</th>
<th>DM/CKD</th>
<th>Combined-Comorbid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>105</td>
<td>82</td>
<td>209</td>
<td>149</td>
<td>111</td>
</tr>
<tr>
<td>Male (%)</td>
<td>34.3</td>
<td>50.0</td>
<td>41.6</td>
<td>39.9</td>
<td>52.3</td>
</tr>
<tr>
<td>Age years</td>
<td>61±10.1</td>
<td>64.9±9.9*</td>
<td>65.5±9.9*</td>
<td>64.2±8.7*</td>
<td>63.9±8.9*</td>
</tr>
<tr>
<td>Visit frequencies</td>
<td>6.5±1.3</td>
<td>6.8±1.3</td>
<td>6.7±1.4</td>
<td>6.8±1.3</td>
<td>6.6±1.4</td>
</tr>
<tr>
<td>Adherence **</td>
<td>84.5±16.3</td>
<td>86.4±15.7</td>
<td>83.1±21.5</td>
<td>83.2±18.9</td>
<td>85.2±21.1</td>
</tr>
<tr>
<td>Items of cardiovascular medicine</td>
<td>2.5±0.9</td>
<td>2.2±0.7</td>
<td>3.7±1.3*</td>
<td>3.9±1.2*</td>
<td>4.5±1.9*</td>
</tr>
<tr>
<td>Items of hypertension medicine</td>
<td>2.0±0.8</td>
<td>1.4±0.5*</td>
<td>1.7±0.9*</td>
<td>1.5±0.7*</td>
<td>1.7±0.8*</td>
</tr>
<tr>
<td>Baseline SBP mmHg</td>
<td>143.9±16.1</td>
<td>140.0±14.1</td>
<td>140.7±12.3</td>
<td>145.3±17.0</td>
<td>141.3±16.4</td>
</tr>
<tr>
<td>Baseline DBP mmHg</td>
<td>87.1±9.6</td>
<td>88.1±9.1</td>
<td>85.2±8.7</td>
<td>84.8±8.5*</td>
<td>85.2±9.8</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease, DM/CKD: diabetes mellitus/chronic kidney diseases, SBP: DBP: systolic blood pressure; diastolic blood pressure, Data, except for gender, were given in mean±SD and analyzed by one-way ANOVA posthoc LSD 95%, *p<0.05 when compared to no comorbid group, ** Adherence values were in percentage of medication possession ratio (MPR). Cardiovascular medicine included hypertension medicine.
The elderly was a risk factor for hypertension, its comorbidity, and higher therapy cost [7]. The subjects in all groups had relatively old age exceeding 60y due to the study setting is done in the secondary care hospitals that generally served more subjects with comorbidity. The age at ≥45 for male and ≥55 for female subjects was considered as higher cardiovascular risk [18]. Mean age in all groups was older than the threshold for cardiovascular risk, and the subjects in comorbid groups were older than the subjects in no comorbid group (p<0.05). The visit frequency and adherence were not significantly different between groups. The adherence in all groups at ≥80% MPR was classified as high [22] and adherence subjects was likely to have appropriate blood pressure control [19, 22].

No comorbid group had more items of hypertension medicine than comorbid groups significantly. Regardless the blood pressure level in all groups remained marginally higher than the goal; the hypertension medicine was considered to be sufficient for blood pressure control because the blood pressure reading done in the clinic was generally higher than the ambulatory or actual blood pressure [18]. On the contrary to hypertension medicine, the comorbid groups had more items of the cardiovascular medicine than the no comorbid group, except for stroke group. The mean cardiovascular medicine was found at 2-5 items, and the finding was similar to the result from the study done in India, [23] but slightly higher than the report in WHO core prescription indicators in Indonesia at 3.3 items [24].

The baseline SBP/DBP was not significantly different between groups (p>0.05) except for DBP in DM/CKD group. The DM/CKD group had the lowest mean DBP, though the DBP was not clinically different because of less than 3 mmHg difference from no comorbid group and the BP in all groups was at the range of 80-90 mmHg DBP. The outcome of mean SBP/DBP in the study was relatively adequate to the standard, [18] the high adherence of the subjects has likely contributed the funding (table 1).

**Fig. 1: Distribution of the component of the expenditure in percentage based on the comorbidity group, Note: CVD: cardiovascular disease; DM/CKD: diabetes mellitus/chronic kidney diseases; Comb Comorb.: combined comorbid. Data were presented in percentage**

Blood pressure and expenditure changes

The expenditure profile in percentage showed that the cardiovascular medicine was at the highest component among the overall expenditure in all groups, followed by the expenditure for doctor service, physical-laboratory test, and other expenditure. The cardiovascular medicine reached at 76.5% in the total subjects, the highest in DM/CKD group and the lowest in no comorbid group. All subjects were considered as routine, adherent, and relatively adequate control. Therefore the maintenance of disease was mostly from medicine. The finding of the highest expense for medicine was consistent with other studies [12-15] (fig. 1).

The mean hypertension medicine expenditure was significantly lower in the comorbid groups than no comorbid group, except for the cardiovascular group. The result was correlated to the significantly fewer items of hypertension medicine among the comorbid groups than the no comorbid group. Some doctors testified that the hypertension medicine items were reduced among the comorbidity subjects to prevent potential drug interaction. Meanwhile, the expenditure for doctor service and physical/laboratory test in DM/CKD and combined-comorbid groups; and the other expenditure component in stroke and combined-comorbid groups was significantly higher than no comorbid group. The type of specialist was likely to influence the therapy selection and the expenditure.

The mean total expenditure in comorbid groups, except for stroke group, was higher than no comorbid group. The stroke group had the lowest cardiovascular medicine and total therapy expenditure among groups due to the fewest cardiovascular medicines prescribed to the group (table 1). But the stroke group had higher other expenditure, i.e.: for physiotherapy or rehabilitation than other groups.

Within the cardiovascular medicine, the expenditure for hypertension medicine was the highest in cardiovascular medicine, and the finding was similar to the previous studies [14-15] Non-hypertension medicines were grouped as one including antiplatelet, anti-dyslipidemia, anti-diabetes, anti-arrhythmia, anti-angina, diuretics other than thiazide, and cardiovascular supplements. The expenditure of cardiovascular medicine was mostly covered by Askes-insurance, whereas the out-of-pocket cardiovascular medicine was trivial. In this quantity, the out-of-pocket money was less likely to reduce the therapy adherence [25].

We compared the therapy outcome between comorbid and no comorbid groups in 2 parameters; (1) the mean blood pressure within 8 mo observation and (2) the proportion of the subjects with mean SBP<140 mmHg. In this hospital-based study, the subjects in all groups had relatively appropriate control of blood pressure and with remarkably good therapy adherence (table 1), and the result was similar to the previous study showed that good adherence improved blood pressure control [26]. It was different from the study done in the community in Jogjakarta province; the subjects had low routine therapy and extremely low blood pressure control rate at≤5% [14]. The high adherence level and good control of blood pressure were very likely related to the financing support received by the subjects from the Askes-Insurance. The result was similar to Medicare program among 5 y that improved hypertension, hyperlipidemia, and diabetes control [27].
The SBP among no comorbid, DM/CKD, and combined-comorbid groups were higher than 140 mmHg (p<0.05), whereas it was lower than 140 mmHg among stroke and cardiovascular comorbid groups. The stroke and cardiovascular groups also had more subjects with SBP reached the target than no comorbid group with OR 201 (95% CI: 1.12-3.62) and 2.10 (95% CI: 1.31-3.39) than no comorbid group respectively. Furthermore, the cardiovascular-comorbid group had the lowest SBP/DBP and became the only group with significantly lower SBP/DBP than no comorbid group. Multi-factors contributed to blood pressure, e.g. CVD comorbid in end-stage heart failure had low blood pressure due to weaker pumping force of heart [28]. The mean SBP/CVD lower than 140/90 mmHg was considered as appropriate controlled blood pressure.[18] The DBP in all groups was similar and lower than 90 mmHg. Blood pressure with higher SBP but relatively normal DBP was attributed as isolated systolic hypertension and influenced by the age factor [7, 18].

Regardless some comorbid groups had significantly different blood pressure; the mean blood pressure level was not clinically different among groups because of ≤5 mmHg difference among groups. The presence of comorbidity did not change the SBP/DBP in identical level. Multi-factors involve in blood pressure control, and the comorbid factor alone was less likely to give significant influence on the blood pressure level. (table 2)

![Image 325x141 to 561x317]
Providing the above discussion, we found that the hypertension comorbidity increased the total therapy expenditure in most groups based on the hospital perspective. Effort on the blood pressure control was likely to avoid the disease comorbidities and the incremental total therapy expenditure. In accordance with the implementation of the universal health coverage (UHC) system in 2014 in Indonesia, the Askes insurance had been merged into the UHC and the beneficiaries were automatically transferred to the UHC system. We recommend further study to confirm the effect of comorbidity on blood pressure control and incremental therapy expenditure in the new health coverage system.

Limitation of the study
We evaluated the blood pressure measured in the doctor clinic that was potentially higher than the ambulatory blood pressure. We only analyzed the therapy and expenditure recorded in medical record and pharmacy department, whereas the other out-of-pocket therapy expenditure was likely not included this study.

CONCLUSION
The stroke and cardiovascular groups had more subjects at mean systolic blood pressure lower than 140 mmHg with an odds ratio (OR) 2.01 (CI95%:1.12-3.62) and 2.10 (CI95%:1.31-3.39) respectively than no comorbid group; but the mean blood pressure was not clinically different among groups. The total therapy expenditure increased at 6.5% (p<0.01); 22.7% (p<0.03); 78.6% (p<0.01); 78.5% (p<0.01) per subject-visit for stroke, cardiovascular, DM/CKD, and combined-comorbid groups than no comorbid group respectively. Except for stroke group, the incremental expenditure was price-sensitive (p<0.05). To prevent hypertension comorbidity was suggested to reduce the total therapy expenditure.

ACKNOWLEDGEMENT
The researchers convey the sincere gratitude to:
1. Director of the hospitals, Heads of Pharmacy Department, and staff in the 4 hospitals for the technical support during the research and the provision of the research permit.
2. Director General of Higher Education, Indonesian Ministry Education for funding this research in Doctoral Research Scheme.

CONFLICTS OF INTERESTS
Declared none

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<table>
<thead>
<tr>
<th>Expenditure component</th>
<th>Mean incremental expenditure per hospital visit compared to no comorbid group (in 1000 Rupiah)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Hypertension medicine</td>
<td>-35.8±13.6*</td>
</tr>
<tr>
<td>Median calculation</td>
<td>-33.0±13.6*</td>
</tr>
<tr>
<td>Lowest calculation</td>
<td>-44.3±14.2*</td>
</tr>
<tr>
<td>Cardiovascular medicine</td>
<td>16.9±31.5</td>
</tr>
<tr>
<td>Median calculation</td>
<td>16.0±30.4</td>
</tr>
<tr>
<td>Lowest calculation</td>
<td>16.0±34.4</td>
</tr>
<tr>
<td>Total therapy</td>
<td>16.8±33.2</td>
</tr>
<tr>
<td>Median calculation</td>
<td>16.7±31.7</td>
</tr>
<tr>
<td>Highest calculation</td>
<td>15.9±36.2</td>
</tr>
</tbody>
</table>

The sensitivity analysis cost was presented in mean expenditure in 1000 Rp±SD, *mean p-value<0.05 with Anova-test among comorbid groups compared to no comorbid group, (−) negative incremental cost: cost reduction. The median, lowest, and highest calculation were determined within the identical types of composition and strength of medicine; and service among 4 study sites.


How to cite this article