Jurnal
Kardiologi Indonesia
J Kardiol Indones. 2012;33:91-8
ISSN 0126/3773

Case Report

ARB Compared with non-ARB in Preventing Cardiac Events in High Risk Hypertensive Patients: An Evidence Based Case Report

Alvin Nursalim,* Yoga Yuniadi#

Background: High risk hypertensive patients have an increased risk of developing cardiovascular complication. It is better to use a proven cardioprotective drugs to reduce blood pressure in high risk hypertensive patients. Angiotensin II Receptor Blocker (ARB) is one type of antihypertensive drugs with cardioprotective effect for hypertensive patients without other risk factor. Whether cardioprotective effect of ARB also apply for a more specific population such as high risk hypertensive patients need to be investigated.
Aim: To determine the efficacy of ARB compared to non-ARBs in preventing cardiac event in a more specific population, such as high risk hypertensive patients.
Methods: A search was conducted on PubMed and Cochrane. The selection of title and abstract was done using inclusion and exclusion criterias. Three original articles were found and used as the evidence for the clinical question. The selected studies were critically appraised for validity, importance and applicability.
Result: According to Sawada et al, the blood pressure lowering effect was similar between valsartan and non-ARB groups. The cardiovascular events in valsartan group is lower compared to non-ARB groups (relative risk: 0.54, 95% confidence interval 0.4-0.7, p< 0.001). The administration of valsartan as compared to non-ARB, also reduce the occurence of angina pectoris (Relative risk : 0.52, 95% Confidence Interval 0.31–0.86, P =0.01058). Cohn JN et al showed that there was no significant differences in the candesartan group in terms of total death and primary endpoints. The only significant finding in this article was the lower rate of diabetes mellitus in the candesartan group.
Conclusion: Valsartan, as compared to non-ARB, reduce cardic event in high risk hypertensive patients.

(J Kardiol Indones. 2012;33:91-8)

Keywords: Angiotensin II receptor blocker, valsartan, high risk hypertension, cardiovascular complication.

*Student of Faculty of Medicine University of Indonesia,
#Departement of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, and National Cardiovascular Center Harapan Kita, Jakarta

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ISSN 0126/3773

Laporan Kasus

ARB dibandingkan non-ARB dalam Menurunkan Komplikasi Kardiovaskular pada Pasien Hipertensi dengan Risiko Tinggi: Laporan Berbasis Bukti

Alvin Nursalim,* Yoga Yuniadi#

Latar belakang: Pasien hipertensi dengan risiko tinggi mempunyai kemungkinan lebih tinggi mendapatkan komplikasi kardiovaskular. Pada pasien hipertensi risiko tinggi lebih baik digunakan obat hipertensi yang memiliki efek kardioprotektif. Angiotensin II Receptor Blocker (ARB) adalah salah satu golongan obat hipertensi yang memiliki efek kardioprotektif pada pasien hipertensi tanpa risiko. Apakah ARB juga efektif untuk menurunkan kejadian kardiovaskular baru atau perburukan kardiovaskular pada populasi hipertensi dengan risiko tinggi?
Tujuan: Mengetahui efektivitas ARB dibandingkan non-ARB dalam menurunkan komplikasi kardiovaskular pada pasien hipertensi dengan risiko tinggi.
Metode: Pencarian terstruktur dilakukan menggunakan Pubmed dan Cochrane. Setelah dilakukan penapisan judul dan abstrak, Tiga studi ditemukan yang kemudian digunakan penulis.Studi ini ditelaah dengan menggunakan kriteria yang mencakup *validity, importance,* dan*applicability* untuk menentukan derajat kegunaan studi.
Hasil: Berdasarkan studi oleh Sawada et al, valsartan memiliki efek penurunan tekanan darah sebanding dengan pengobatan non-ARB. Komplikasi kardiovaskular lebih rendah pada kelompok valsartan dibandingkan kelompok non-ARB (relative risk: 0.54, 95% confidence interval 0.4-0.7, p< 0.001). Valsartan menurunkan kejadian angina pectoris dibandingkan grup non-ARB (relative risk : 0.52, 95% Confidence Interval 0.31–0.86, P =0.01058). Cohn JN et al menyimpulkan tidak ada perbedaan signifikan dalam pencegahan mortalitas dan parameter akhir lainnya. Namun penggunaan candesartan secara signifikan mengurangi kejadian diabetes.
Kesimpulan: Valsartan, dibandingkan pengobatan non-ARB, menurunkan kejadiaan kardiovaskular pada pasien hipertensi dengan risiko tinggi.

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Kata kunci: Angiotensin II receptor blocker, valsartan, hipertensi risiko tinggi, komplikasi kardiovaskular

Clinical scenario

A 58 years old man with dyslipidemiaand type 2 diabetes mellitus diagnosed one year ago, came to the outpatient clinic for a regular check up in a private hospital. His physical examination was within

Alamat Korespondensi:
Dr. dr. Yoga Yuniadi, SpJP. Departemen Kardiologi dan Kedoteran Vaskular FKUI, dan Pusat Jantung Nasional Harapan Kita, Jln. S Parman Kav 87 Slipi Jakarta 11420. E-mail: *yogayun@yahoo.com*

normal limit except for his high blood pressure (150/90). He was taking an ACE-inhibitors drug for his hypertension, but he complained of coughing not long after taking the drug. Due to the high incidence of cardiovascular complication among diabetic hypertensive patients, the doctor was thinking of changing his hypertensive drugs regimen to maximize the cardioprotective effect of the drug. The doctor wonders whether the administration of ARB, instead of non-ARBs, is more effective in preventing new onset or worsening of cardiac complication in high risk hypertensive patients.

Introduction

It is well established that hypertensionis a cardiovascular disease risk factor. Hypertension also increases the risk of atherosclerosis progression.[1]Currently, the main cardiovascular disorderresponsible for the rise in mortality has changed. As the substitute ofrheumatic heart disease, atherosclerotic is now the leading cause for cardiovascular mortality. It is oftenassumed that atherosclerosis is a disease of high-income, industrializedcountries. However, 80% of cardiovascular mortality occur inlow-to-middle income countries.[2]Therefore, Indonesia as a developing country pose a high risk of having a high cardiovascular mortality.

High risk hypertensive patients will have an accelerated rate of atherosclerotic progression.In this report we try to determine the cardioprotective property of ARBs in high risk hypertensive patients (defined by patients withtype 2 diabetes mellitus, lipid metabolism abnormality, obesity, and heart failure). Dyslipidemia is a strong risk predictor for coronary artery disease (CAD)[3]. Diabetic patients have twice to four times the risk of developing CAD as compared to those who do not have diabetes. Concomitanthypertension triples the already high risk of CAD, doubles total mortalityand stroke risk.[4]

Angiotensin II Receptor Blockers (ARB) have protective clinical effects similar to those of Angiotensin Converting Enzym Inhibitors (ACE-Is)but better tolerated due to less side effect.[5]Many studies have investigated the comparison of ARB and non-ARBs for stroke prevention, cardiac protection and renal protection.[6,7] However, the efficacy of ARB as compared to non-ARBs to prevent new onset or worsening of cardiac complication on a more specific population, such as high risk patients need to be further elaborated.

The wide arrays of antihypertensive drugs available and therisk factors differences of each hypertensive patients made it tricky to choose the best anti-hypertensive regimen to reduce cardiac complication for these patients. This report is made to assist physician and investigate the efficacy of ARB compared to non-ARBs medication to prevent new onset or worsening of cardiac complication in high risk hypertensive patients.

Clinical question

Is ARB more effective compared to non-ARBs in preventing cardiac event in high risk hypertensive patients?

Methods

Search Strategy

The search was conducted on PubMed,® and Cochrane,®on Febuary 8th 2011, using the keywords "angiotensin receptor blocker", "hypertension" and

Table 1. Search strategy used in PubMed and Google (Conducted on November 11th 2011)

Database	Searchterms	Results
Pubmed (8thFebuary 2011)	ARB[All Fields] AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND complication[All Fields] AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms])	7
Cochrane (8thFebuary 2011)	"Hypertension"and"ARB"and "cardiovascular complication"	26

"cardiovascular complication"along with its synonyms and related terms (**Table 1**).). Searchstrategy, results, the inclusion and exclusion criteria are shown in a flowchart (**Figure 1**).

Selection

The first selection was based on title and abstract using inclusion criteriasand exclusion

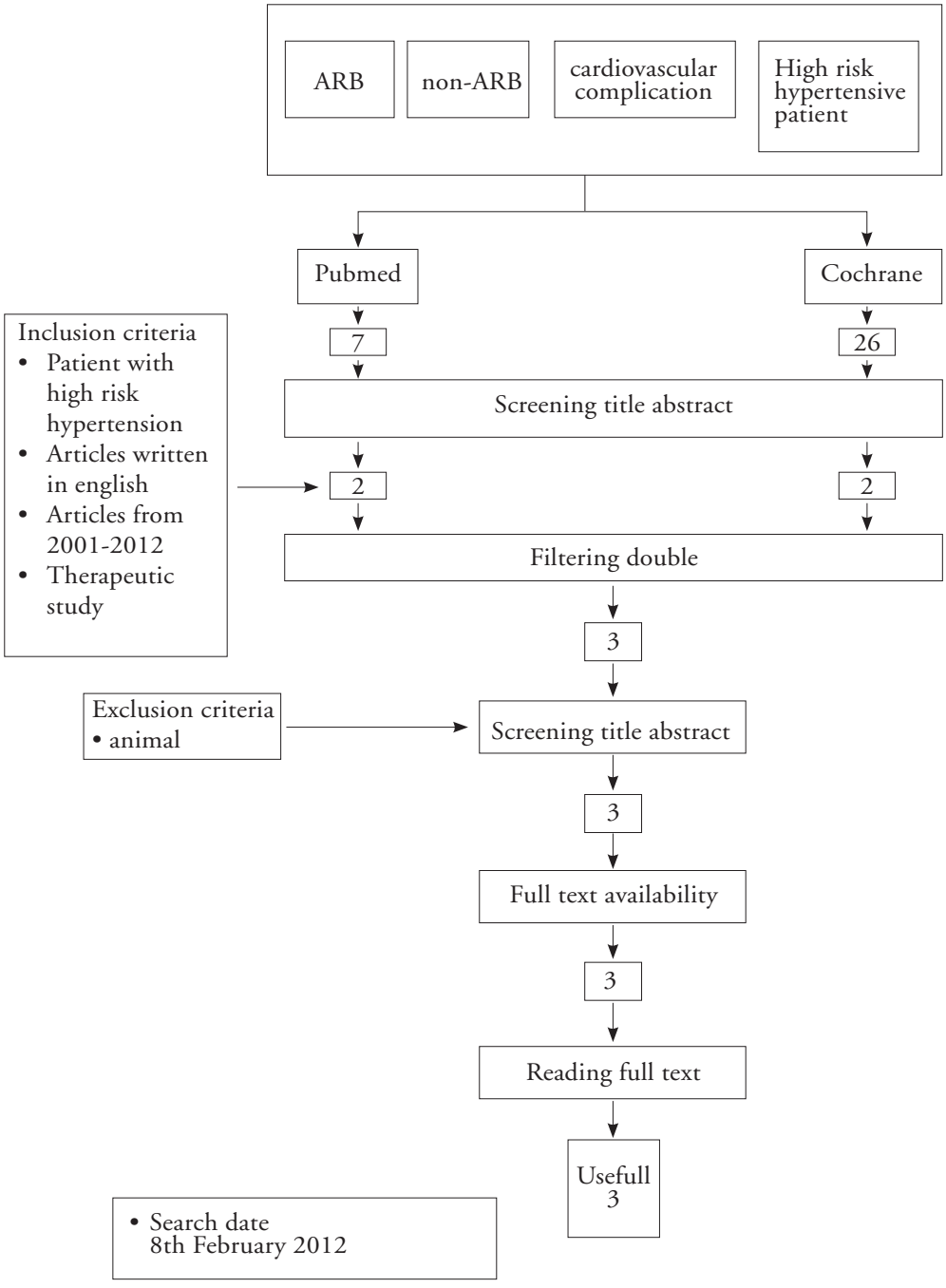

Figure 1. Flow Chart of Search Strategy

criteria. After selection three full-text articles were available.

Critical Appraisal

After the selection, critical appraisal was done using several aspects based on Center of Evidence-based Medicine, University of Oxford for therapy study (**Table 2**).

preventing morbidity and mortality in high risk hypertensive patients.The study was a multicentre, prospective, randomized, open-label, blinded-endpoint trial. A total of 3.031 high risk hypertensive patients were randomized to either valsartan add-on or non-ARB treatment (ACE-Inhibitor was excluded) .Patients with one or more of these risk factors is included: type 2 diabetes mellitus, current smoking, lipid metabolism abnormality, obesity (defined as BMI >25 kg/m2), and left ventricular hypertrophy defined

Table 2. Critical Appraisal of theusefull articles based on criterias by Centre of Evidence Medicine University of Oxford[11]

	Validity							Relevance				
Articles	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding	Comparable treatment	Intention to treat	Domain	Determinant	Meassurement of outcome	Result	Levels of evidence *
Sawada et al8	+	3,301	+	+	+	+	+	+	+	+	A	1B
Kasanuki et al9	+	2049	+	+	+	+	?	+	+	+	B	1B
Cohn J N et al10	+	5010	+	+	+	+	?	-	+	+	C	1B

Legend: + stated clearly in the article
- not being done
? not stated clearly
*Levels of evidence based on The Oxford Centre of Evidence-based Medicine
Domain: High risk hypertensive patients
Determinant: Valsartan add-on therapy, Comparison: non-ARB therapy
Outcome: New onset and/or worsening of cardiovascular event.
A:The cardiovascular events in valsartan group was lower compared to non-ARB groups (relative risk: 0.54, 95% confidence interval 0.4-0.7, p< 0.001).
B:There was no significant differences in the number of total death and primary endpoints. The only significant finding in this study is the occurence of diabetes mellitus (Hazard ratio: 0.37; 95% CI,0.16–0.89; P= 0.03).
C:The rate of mortality was similar in the two treatment groups. The combined endpoint of mortality and morbidity was significantly reduced among patients in the valsartan group as compared to those in the placebo group (relative risk: 0.87, 95% confidence interval 0.77-0.97, p= 0.009).

Result

Sawada T et al[8] performed a study to determined the efficacy of valsartan as compared to non ARBin

by electrocardiogram.The endpoints to be analyzed include new onset or worsening cardiovascular events, cerebrovascular events, mortality, worsening of cardiac function, new occurence or exacerbation

of arrhythmias and new occurence or exacerbation of diabetes mellitus.

The blood pressure lowering effect was similar between valsartan andnon-ARB groups. The cardiovascular events was 83 out of 1517and 155 out of 1514 in valsartan and non-ARB groups respectively (Hazard ratio:0.55, 95% confidence interval 0.4-0.7, P=0.00001).The Control Event Rate (CER) was 10.2%,Experimental Event Rate (EER) was 5.5%, Relative Risk Reduction (RRR) was 46%, Absolute Risk Reduction (ARR) was 4.7% and Number Needed to Treat (NNT) was 21.

Another significant outcome in this study was the occurence of angina pectoris.The administration of valsartan was superior to non ARB in reducing angina pectoris.22 patients given valsartan had angina pectoris compared with 44 in non ARB group. The CER was 2.9%,EER was 1.5%, RRR was 48%, ARR was 1.4% andNNT was 71 (Hazard ratio : 0.51, 95% Confidence Interval 0.3–0.9, P =0.01058).

Cerebrovascular event represented by the occurence of stroke also showed a significant reduction in the valsartan group compared to non-ARB group(Hazard ratio: 0.55, 95% Confidence Interval 0.3–0.9, P =0.01488).

Kasanuki H et al[9] conducted a study to evaluate the afficacy of candesartan administration in reducing the incidence of cardiovascular events compared with non-ARB therapy in coronary artery disease patients with hypertension. A total of 2,049 patients were randomized to either candesartan therapy or non-ARB therapy (ACE-inhibitor was included).

The result of this study showed that there was no significant differences in the number of total death and primary endpoints, which include: cardiovascular deaths, non fatal myocard infarction and heart failure. The only significant finding in this study is the occurence of diabetes mellitus (hazard ratio: 0.37; 95% CI,0.16–0.89; P= 0.03).

Cohn J L et al[10] evaluated the long term effects of the addition of valsartan to standard therapy for heart failure. This study was a randomized, placebo-controlled, double blind clinical trial. This is a large study involving5,010 patients from 302 centers in 16 countries.Patients with heart failure were randomly assigned to received 160 mg of valsartan or placebo twice daily. The primary endpoint was mortality dan morbidity.

The result of this study showed that the rate of mortality was similar in the two treatment groups. The combined endpoint of mortality and morbidity (hospitalization, cardiac arrest with resuscitation and intravenous therapy) was significantgly reduced among patients in the valsartan group as compared to those in the placebo group. There were 723 patients of cases in the valsartan group and 801 cases in the placebo group (relative risk: 0.87, 95% confidence interval 0.77-0.97, p= 0.009). The value of CER was 32%, EER was 29%, RRR was 9,4%, ARR was 3% and NNT was 33.

Discussion

Sawada et al[8]studied the effect of ARB add on therapy on mortality and morbidity as compared to non ARB treatment. Beside cardiovascular complication, the endpoint also include cerebrovascular event, mortality and new onset diabetes.This study showed that the administration of valsartan therapy reduce the occurence of cardiovascular event as compared to non ARB therapy. The incidence of cardiovascular events was 5.5% and 10.2% invalsartan add-on and non-ARB groups, respectively. The relative risk reduction was 46% in the valsartan group as comparedto the non-ARB group. There was also lower rate of angina pectoris in valsartan group as compared to non-ARB group (RRR=48%).The administration valsartan was considered safe due to minimal adverse effects found througout the study. The NNT for cardiovascular prevention was 21, made valsartan a reasonable drug to be applied widely.

The study by Kasanuki H showed different result.[9] According to this study there was no significant difference in cardiovascular events between candesartan group and placebo group. This conflicting result might resulted from some limitations of the study which include the high usage (71%) of ACE-Inhibitors in the non-ARB therapy group and the low dose of candesartan used in the ARB group. However, the occurence of diabetes was lower in the candesartan group. This protective effect of candesartan on diabetes support the result of VALUE study[12]. According to this study ARBs were more effective in preventing diabetes compared to CCB.

The cardioprotective effect of valsartan is further ascertained in another study on valsartan performed by Cohn JN[10].The third article by Cohn JN et al might have different patients characteristics as compared to our clinical question and the first two studies. This article studied the efficacy ofvalsartan as compared

to placebo for mortality and morbidity prevention among heart failure patients. Nevertheless, this study provide important information as addition to the first two studies, so we decided to include this study to the review.The result of this large scale study showed that valsartan was superior in reducing combined endpoint of mortality and morbidity (hospitalization, cardiac arrest with resuscitation and intravenous therapy) in patients with heart failure.Despite the high dose of valsartan (160 mg) used in this study, the drug was well tolerated and side effects were only slightly more prevalent in valsartan group. We do think the efficacy of valsartan still can be applied to hipertensive patients with heart failure. That is, under the assumption that the beneficial effects of valsartan among heart failure patients also apply to hypertensive patients with heart failure.

ARBs are well tolerated due to minimal side effects but the next intriguing question would be whether ARBs are as effective as ACE-Inhibitor in preventing cardiac events among high risk individual. According to two large scale studies (VALIANT study and ONTARGET study), ARBs are as effective as ACE-inhibitors for cardiovascular endpoints among high risk patients. This primary endpoint include cardiac related mortality, myocard infarct and stroke.[13,14]

The administration of ARBs, in this case valsartan and candesartan, is considered safe due to the minimal side effect occured during the study. Beside efficacy and safety, one aspect to consider when prescribing drug in Indonesia is the price of the drug.Currently, with "out of pocket" payment system (instead of health care insurance) and the low economic background of some patients, made it prudent for clinician to always consider drug cost in every clinical decision. ARBs are usually more expensive than other hypertensive drugs, fortunatellysome ofthese drugs are now available as generic drugs. It would be wise for clinician to individually tailored every drug prescription according to patients clinical condition and socio-economic background.

One particular limitation of this report might related to the search strategy. In terms of the search strategy, we admit that we might have missed relevant articles due to the exclusion of all articles that were not available with full text on the internet. We only found two articles which perfectly related to our clinical question. Nonetheless both articles are large scale studies with adequate follow-up period and they reported similar benefit of ARBs (valsartan and candesartan). Clinical experience with these ARBs are quite extensive, for this reason ARBs can be considered as a cardioproective hypertensive agent for high risk hypertensive patients.

Conclusion and recommendation

ARB therapy, represented by valsartan and candesartan in these studies, is effective in reducing cardiovascular event in high risk hypertensive patients (defined by patients withtype 2 diabetes mellitus, lipid metabolism abnormality, obesity, and heart failure). Valsartan therapy is well tolerated, as shown by the minimum adverse effects found throughout these studies. ARBs tend to be more expensive, therefore, the best implementation of this evidence requires risk factorsand socio-economic assestment of each patient.

This new insight can be translated into clinical practise. Based on this evidence, we recommend the administration of valsartan, an ARB drug, forhigh risk hypertensive patient in the clinical scenario mentioned above.

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