PHARMACOGENETIC of ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

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ABSTRACT

Angiotensin-converting enzyme inhibitors (ACEIs) was indicated to treat hypertension, left ventricular dysfunction, heart failure. Several genes are involved in ACEIs responses. These genes are ACEIs, BK1, BK2, BDKRB2 and ABO genes. This review was performed by data searching in Pubmed and Science Direct data bases with keywords Pharmacogenetics and ACEIs. There are 5 article from Pubmed and 122 from science direct. Only 7 articles were reviewed due to suitable theme. We add 19 articles to complete the discussion. Polymorphism of ACEIs, BK1, BK2, BDKRB2 and ABO genes influence the treatment responses of ACEIs.

Key words: ACEIs, ACEIs gene, BK-1, BK-2, BDKRB2 and ABO genes

No: of References: 26
INTRODUCTION

According JNC VII committee, hypertension is classified as increasing blood pressure more than 140 mmHg (systolic blood pressure) and or >90mmHg (diastolic blood pressure).\(^1\) Hypertension is a great factor leads to cardiovascular morbidity, chronic kidney disease, and death.\(^2,3\) People more than 40 years old, increasing of 20 mmHg in systolic BP (SBP) or 10 mmHg diastolic BP (DBP) will increase the risk of CVD 2x at blood pressure between 115/75 to 185/115 mmHg.\(^4\)

Several classes of drugs that indicated as antihypertension are angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), beta-blockers (BB), calcium channel blockers (CCBs), and thiazide type diuretics.\(^5-7\)

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

ACEIs are a class of drugs that block of the enzyme angiotensin-converting enzyme (ACE) that plays a role in the body's renin-angiotensin system that regulates extracellular volume and cause vasoconstriction. Angiotensin-converting enzyme inhibitors (ACEIs) is indicated the treat of hypertension, asymptomatic left ventricular dysfunction, heart failure. This drugs can decrease microvascular complications of diabetes and cardiac events following infarct myocardial.\(^8\)

ACEIs is an anti-hypertensive class that inhibits peptidyl dipeptidase converting enzyme that hydrolyzes angiotensin I to angiotensin II.\(^9\) There are several drugs including ACE is, among others are captopril, Lisinopril, Benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.\(^9\) This drugs were also recommended in patients with chronic disease Kidney\(^10\) and in patients with type 2 diabetes.\(^11\)

In pregnant women, ACE inhibitors can cause congenital malformations, neonatal mortality and stillbirth. The impact of ACEIs treatment are fetal abnormalities include hypotension, oligohydramnios, renal dysplasia, retardation of intrauterine growth, hypoplasia of pulmonal, and PDA (Patent Ductus Arteriosus).\(^12,13\)

Adverse affects
The common adverse of ACEIs include: cough, fatique, hyperkalemia, headache, nausea, and renal impairment.\(^13,14\) The less common of side effects are: hepatotoxicity, angioedema, dysgeusia and skin rashes.\(^14\) The angioedme usually was caused by increased bradykinin levels.\(^15\)

PHARMACOGENETICS

JNC VIII committee recommends ACE inhibitor as an option for early management of hypertension in non-black patients.\(^10\) Some genes are involved in the response to ACEIs, among others: ACEIs gene \(^16,17\), BK-1 \(^16\), BK-2 \(^18\), BDKRB2 gene and ABO gene \(^19,20\).

Research by McNamara et al involving in 479 patients, found that patients with ACE-D (deletion) who received ACEIs had an increased risk of death.\(^21\) A study involving 37939 found no
significant association between ACE gene I / D polymorphism and increasing CV risk or pharmacologic treatment response.\textsuperscript{22} BK2 gene polymorphism and ACE-deletion have been associated with ACEi induced cough in East Asian populations.\textsuperscript{23,24}

A study involving 125 subjects showed that the T allele of M235T polymorphisms responded better to the drop in blood pressure on the administration of ACEIs inhibitors compared with the homozygous M allele carriers.\textsuperscript{25}

Research by Oliveira et al., found that ACEIs slow the cognitive decline for patients with Alzheimer’s disease specially for APOE4 (Apolipoprotein (Apo) E) carrier.\textsuperscript{20}

A study was done by Kristensen et al., on 667 patients with CHF, concluded that there no association ACEIs gene (rs275651 and rs5182) and the bradykinin receptor B1 gene (rs12050217) with fatal outcomes in patients with CHF treated by ACEIs. There is no association between combined SNPs of the angiotensin-converting enzyme gene (rs4343) and ABO blood group genes (rs495828 and rs8176746) with outcomes in ACEI-treated patients with CHF.\textsuperscript{26} The polymorphisms of BDKRB2 (rs8016905) gene and ABO (rs495828) gene were associated with ACEIs-induced cough.\textsuperscript{19}

**Conclusion**
The polymorphism of ACEIs, BK-1, BK-2, BDKRB2, ABO, APOE4 gene influences the ACEIs responses.

**References**


Sorensen AM, Christensen S, Jonassen TE. et al., Teratogenic effects of ACE-inhibitors and angiotensin II receptor antagonists. Ugeskrift for Laeger (in Danish). 1998;160 (10): 1460–4


Alderman CP, Adverse Effects of the Angiotensin-Converting Enzyme Inhibitors, Annals of Pharmacotherapy. 1996:1:


Kristensen KEN, Madsen MB, Pedersen CT. et al. Pharmacogenetic Risk Stratification in Angiotensin-Converting Enzyme Inhibitor-Treated Patients with Congestive Heart Failure: A Retrospective Cohort Study. Plos one, 2015; 10(12): e0144195