Title

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Journal

Coronary Artery Disease, 26(8)

ISSN

0954-6928

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Publication Date

2015-12-01

DOI

10.1097/mca.0000000000000303

Peer reviewed

CAC Score as Possible Criteria for Administration of Angiotensin Converting Inhibitors and/or Angiotensin Receptor Blockers: The Multi Ethnic Study of Atherosclerosis

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Keywords: Angiotensin Converting Enzyme Inhibitor, Coronary artery calcium score

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Introduction:

The Renin-Angiotensin-Aldosterone System (RAAS) plays an important role in blood pressure (BP), cardiovascular disease and renal function. Angiotensin converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) are part of medications that were developed to attenuate the effect of The Renin-Angiotensin-Aldosterone System (RAAS). Currently, these medications are widely utilized for treatment of congestive heart failure (CHF), myocardial infarction, hypertension, and prevention of diabetes's macro and micro-vascular complications. Also, they have been shown to slow progression of chronic kidney disease (CKD) to end stage renal disease. In 2009, ACE inhibitors were the fourth most utilized drug class in the United States, and they were prescribed 162.8 million times by US physicians.[1]

Both ACEIs and ARBs are medications that have proven effects to lower mortality and morbidity rates[2]. Among patients with congestive heart failure, the SOLVD trial showed that enalapril significantly improved survival and reduced further hospitalization rates.[2] Moreover, in the Survival And Ventricular Enlargement (SAVE) trial, captopril was able to decrease risk of recurrent myocardial infarction.[3] In the Heart Outcomes Prevention Evaluation (HOPE) study, among high risk patients, ramipril lowered the risk of atherosclerotic events including all stroke, myocardial infarction and cardiovascular death. Benefits were independent of ramipril's effect on blood pressure and cardiac systolic function.[4] However, in the Captopril Prevention Project (CAPPP) study of 10,985 patients, there was no difference in cardiovascular morbidity and mortality rates. In this study, Captopril failed to show any advantages over conventional therapy in preventing cardiovascular morbidity and mortality.[5] The discrepancies regarding the effect of these medications on the rate of cardiovascular events across different trials suggest that we need to find better criteria to predict who may benefit from these medications. The

evaluation of Framingham Risk Score (FRS) has been a poor predictor of whom will benefit from ACE inhibition. In this study, we sought to examine if the Coronary Artery Calcium (CAC) score can determine which individuals would benefit from ACEI or ARB effects (in the form of fewer cardiovascular events). There are no guidelines for instituting ACEI or ARB therapies based on CAC score or Framingham risk. The goal of this study is to identify a subgroup of primary prevention patients who may benefit from ACE inhibition for reducing CV risk, not reducing complications of DM (albuminuria) or hypertension (left ventricular hypertrophy).

Methodology:

Population characteristics:

The Multi Ethnic Study of Atherosclerosis (MESA) is a prospective study intended to evaluate development and progression of subclinical cardiovascular disease in clinically asymptomatic individuals among different ethnic groups. In this study, participants were enrolled from four different ethnicities (white, African American, Hispanic, and Asian, predominantly of Chinese descent) at 6 Field Centers (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago and the village of Maywood, IL; and Los Angeles County, CA.). All participants underwent extensive evaluation at baseline, including clinical history, physical examination, and many laboratory tests. The MESA protocol, including information about the details of populations and recruitment method, details of inclusion and exclusion criteria, investigators' contact information, and other detailed information, is available on the World Wide Web at www.mesa-nhlbi.org. Out of 6,814 the MESA population, we enrolled all 2,906 participants who never used ACEIs or ARBs (n=2,457, 84.5 %) or were taking any of these medications (n=449, 15.5%) during the baseline and all follow up years. Participants that were taking these medications intermittently were excluded.

They were followed for an average of 8.0±1.7 years (range 0.02 to 10.9 years). Our selected population, with 49.0% male and the average age of 60.1± 9.7 years (ranged 45-84) had no apparent clinical cardiovascular disease (CVD) at the baseline.(See table-1) All participants underwent a non-contrast enhanced cardiac computerized tomography (Cardiac CT) and evaluated for CAC score. According to the participants CAC score and self-reported utilization of ACEIs and ARBs, they were categorized into six different groups; Zero CAC with ACEI/ARBs (n=163), Zero CAC without ACEI/ ARBs (n=1,440), intermediate CAC scores (1 to 399) with ACEI/ARBs (n=203), intermediate CAC scores (1 to 399) without ACEI/ARBs (n=865), higher CAC scores (>=400) with ACEI/ARBs (n=83), and high CAC scores without ACEI/ARBs (n=152). Moreover, to examine superiority of the CAC score over the Framingham risk score (FRS), we also divided participants into the six groups of three FRS Groups (low, intermediate and high) and with or without ACE/ARB use. Low FRS with ACEI/ARBs constituted 92 participants, Low FRS without ACEI/ARBs (n=1,531), intermediate FRS with ACEI/ARBs (n=126), Intermediate FRS without ACEI/ARBs (n=575), high FRS with ACEI/ARBs (n=231), and high FRS without ACEI/ARBs (n=351). Out of all participants, 55.2% (n=1,603) had zero CAC score, and 8.1% (n=235) had CAC score of more than 400 (See Table-2 and 3)

Data Collection:

All participants signed informed consent and were evaluated at baseline examination between July 2000 and July 2002. Also they were evaluated at four follow up examinations as follows: a second examination between July 2002 and January 2004, a third examination between January 2004 and July 2005, a forth examination between July 2005 and July 2007 and a fifth examination between April 2010 and April 2012. The components of each examination are described in table-3. Participant's demographic data, medical condition, family history of CVD, and current use of prescription and non-prescription medication were collected by questionnaires. During the examination, height, weight, and

waist and hip circumferences are measured. Resting blood pressure was measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida).

Coronary artery calcification score:

Cardiac CT was performed by utilizing either a cardiac-gated electron-beam CT scanner (the Chicago, Los Angeles, and New York field centers) (Imatron C-150; Imatron, San Francisco, California) or a prospectively electrocardiogram-triggered scan acquisition at 50% of the R-R interval with a multi-detector CT, acquiring a block of four 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (the Baltimore, Forsyth County, and St. Paul field centers) (Lightspeed, General Electric Medical Systems, Waukesha, Wisconsin; or Volume Zoom, Siemens, Erlanger, Germany). All participants were scanned over phantoms with known physical density. CAC scores were evaluated centrally at the Los Angeles Biomedical Research Center at Harbor-UCLA in Torrance, California.

Cardiovascular events:

Events were defined as all CVD events including myocardial infarction, resuscitated cardiac arrest, definite and probable angina (only if followed by revascularization), stroke, stroke death, coronary heart disease death, other atherosclerotic death as well as all other cardiovascular deaths. Silent myocardial infarctions identified using criteria applied to the follow-up electrocardiogram. Resuscitated cardiac arrest and other CVD endpoints were identified from medical records. In order to classify CVD events occurring during follow-up time, information have been collected from death certificates, hospital medical records, autopsy reports, interviews with participants, and for those who died out of the hospital, interviews with or questionnaires were administered to physicians, relatives, or friends.

Statistical analysis methods:

To address the objective of the study, a number of statistical analyses were conducted. Subjects were classified into groups of using and not using ACEIs and/or ARBs. To assess risk factors, the chi-square test (for categorical variables) and 1-way analysis of variance (for continuous variables) were performed. Continuous variables were presented as mean ± SD, categorical variables were presented as frequency/percentage. Mann-Whitney U test (Wilcoxon signed-rank test) was performed to compare the Framingham risk score distribution between using and not using ACEIs and/or ARBs groups. Framingham risk score values were presented by median (interquartile range (IQR)). The chi-square test of proportion was also performed to examine the relationships between the distribution of CAC score (low 0, intermediate 0-400, high >400), FRS (low 0-10, intermediate 10-20, high >20), and all cardiovascular events. Subjects were then cross-classified into six groups according to their CAC score levels (low, intermediate, high)/FRS levels (low, intermediate, high) and ACEIs/ARBs use. We assessed the cardiovascular events rate per 1,000 person-year of both ACEIs/ARBs user and non-user groups, stratified by CAC score or FRS levels. In addition to the univariate Cox regression analysis, unadjusted and adjusted multivariate Cox proportional hazard model were used to calculate hazard ratios (HR) in the relationship among ACEI/ARBs usage stratified by CAC score/FRS levels, and all cardiovascular events. We considered the user group as the references for these analyses. Further adjustments were performed in two steps. Covariates were entered into the model based on their potential roles as confounders. The first step was performed with demographics, smoking, diabetes, hypertension, hyperlipidemia, and family history of premature CVD; in the second step, aspirin and statin usage were added to the model. Kaplan-Meier plots were presented for all cardiovascular events over ACEIs and/or ARBs and CAC score/FRS groups. All statistical analysis were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC), and statistical significance levels of all the analysis were set at p=0.05 (2-sided).

Results:

In total, 2,906 participants (52.6% female) with the mean age of 60.1 (ranged 45-84) were followed up for an average of 8.0 ± 1.7 years (ranged 0.02-10.9 years). Of these participants, 449 (49.0% female, mean age of 64.4 years) had taken ACEIs and/or ARBs through the all follow-up years and non-users had never utilized these medications (mean age of 59.3, and 53.2% female). In average, 96.7% of participants in the ACEI/ARB group had hypertension, whereas, only 20.4% of non-ACE/ARB participants had hypertension. Similarly, diabetes was significantly more common among ACE/ARB group (32.1%) while only 3.4% of non-user participants reported having diabetes. (See Table-1)

In total, 248 (8.5%) CVD events were recorded. Event rates were greater among the groups with greater levels of CAC and/or FRS (see Figure-1, table-4 and table -5). Moreover, the ACEIs and/or ARBs user population had significantly greater rate of CVD events than the non-user group (17.1% and 7.0%, in order) (See Table 2).

Among the patients with normal CAC scores, unadjusted Cox regression model analysis showed that compared to the user group, the non-users had significantly lower risk of events (HR=0.37, 95% CI: 0.18-0.78, P<0.05). However, when they were adjusted by major cardiovascular disease risk factors (adjusted model 1) or major cardiovascular disease risk factors plus statin and aspirin use (adjusted model 2), no significant difference persisted.

In contrast, among the patients with intermediate CAC score, both of adjusted models showed a significantly greater event rate among those who did not used ACEi/ARBs. In this group, the non-ACEI/ARBs users showed a significantly higher hazard ratio for all CVD events (HR = 1.6, 95%CI: 1.0-2.6, P<0.05 in model one and HR=3. 3, 95% CI:1.1- 10.4, P<0.05 in model two). (See figures ~~1~~2, ~~2~~ 3 and ~~3~~4)

Among the patients with a high CAC score, in spite of significant differences in unadjusted models, adjusted models failed to show any significant difference over the use of ACEI/ARBs. (See table-6)

In contrast to the CAC score, no significant difference was observed between groups when they were classified over FRS levels. (Table-7)

Discussion:

RAAS inhibitors reduce pro-thrombotic activity, modify anti-inflammatory mediators, and reduce plaque rupture. In addition, ACEIs have been shown to improve coronary artery endothelial function. There are many studies demonstrating a significant improvement in both survival and quality of life with ACEIs and/or ARBs among patients with heart failure.[6] However, appropriate selection of patients for treatment with ACEIs and/or ARBs is challenging. Currently many patients without heart failure are using these medications. Despite data that indicate ACEIs may decrease event rates in patients with hypertension, it is not clear which patients will benefit. Furthermore, some trials were not able to show any overall benefits.[7] The PEACE trial, which enrolled 8290 participants with normal or near normal left ventricular ejection fraction, reported that cardiovascular event rates did not differ when they were adjusted for major cardiovascular risk factors.

In our study, patients who over the all follow up years received ACEIs and/or ARBs had greater average of both FRS and CAC scores. Therefore, generally, patients who took ACEIs and/or ARBs had greater risk and event rates, most likely due to the underlying indications for ACE and ARB use (See figures 1, 2 and 3). Similarly, when we divided patients based on their FRS, the non ACE/ARB group had lower events than ACEI or ARBs users, but this effect was attenuated by the presence of diabetes and other non FRS risk factors.

When we classified our population based on their CAC scores, even after adjustment with risk factors or risk factors plus statin and aspirin use, patients with intermediate CAC scores had fewer events if they were on ACEIs or ARBs. In contrast, in the groups with zero CAC score or CAC scores higher than 400, our results showed there was no significant difference between the participants taking ACE/ARB and those not. It has been demonstrated that patients with zero CAC have very low CV event rates. Therefore, it is difficult to show benefit from further risk reduction. Regarding CAC >400, it is possible that these participants, while at high cardiovascular risk, have more established atherosclerosis that may be less amenable to different therapies.[8,9,10] Some clinical and biomechanical studies revealed that plaque composition has an important role in acute clinical events. It is possible that more calcified lesions are less vulnerable to rupture and spotty calcification and mixed plaques are more likely to be associated with future CV events.[11],[12],[13] Interestingly, in contrast to the CAC score, our study shows that Framingham risk score did not help in stratification of whom would benefit from ACE inhibitors or ARBs.. No FRS levels were associated with lower cardiovascular event rates between ACEI/ARB users and the non-users. (See table-7)

Limitations:

We excluded participants with temporary use of ACEIs and/or ARBs, as the follow up reflected both time on and time off these medications. We considered all participants who were consistently taking ACEI/ARBs from the baseline visit and continued all through the years of follow up. Of course, a randomized trial in patients with intermediate CAC score would be most definitive, but this is unlikely to be performed.

Conclusion:

Participants with intermediate CAC scores (defined as scores 1-399), who were on ACEIs and/or ARBs, experienced less future cardiovascular events than those not taking these therapies. Also, Framingham risk score could not define patients who may or may not benefit from ACE/ARBs in this observational study. These CAC results can be obtained on a dedicated heart scan or thoracic imaging for lung cancer screening.[14] While a randomized prospective trial would be confirmatory, this study adds critical information that the cardioprotective effects of agents may be dependent on baseline CV risk, and the prognostic information received with CAC scores may help determine optimal medical regimens.

Acknowledgement:

This research was supported by R01-HL071739 contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-RR-024156 and UL1-RR-025005 from NCRR. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

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