β2-Adrenergic Receptor Gene Polymorphisms Are Associated with Cardiovascular Events But not All-Cause Mortality in Coronary Artery Disease Patients: A Meta-Analysis of Prospective Studies

Yanrong Li,1 Huiping Yuan,2 Liang Sun,2 Qi Zhou,2 Fan Yang,2 Ze Yang,2 and Deping Liu1

Aims: β-Adrenergic receptors (ADRBs) play a pivotal role in cardiovascular disease. Recently, genetic polymorphisms of ADRB1 and ADRB2 have been suggested to be associated with cardiovascular events and all-cause mortality in coronary artery disease (CAD) patients, but the results of relevant studies are inconsistent and controversial. Therefore, we performed a meta-analysis to investigate the association between ADRB1 and ADRB2 polymorphisms with cardiovascular events and all-cause mortality in CAD patients.

Materials and Methods: The PubMed, Ovid, EMBASE, Cochrane, and CINAHL databases were searched for eligible studies published before April 2018. A total of 5495 patients from eight studies were included in our meta-analysis.

Results: We found that CAD patients harboring the ADRB2 rs1042714 Glu27 allele exhibited a positive association with cardiovascular events (risk ratio [RR] = 1.31, 95% confidence interval [CI]: 1.08–1.58, p = 0.006), but not with all-cause mortality (RR = 0.97, 95% CI: 0.70–1.35, p = 0.859), compared with patients who were Gln27 homozygotes. No other significant associations were observed between ADRB1 (rs1801252, rs1801253), ADRB2 (rs1042713, rs1800888) polymorphisms and cardiovascular events or all-cause mortality in CAD patients.

Conclusion: This study suggests that the identified ADRB2 polymorphism could influence the outcomes of CAD patients, showing important clinical value.

Keywords: β-adrenergic receptor, polymorphism, coronary artery disease, meta-analysis

Introduction

Coronary artery disease (CAD) is one of the leading causes of disease in developed and developing countries. The β1-adrenergic receptor (ADRB1) and β2-adrenergic receptor (ADRB2) play a pivotal role in the regulation of the cardiovascular system (Dhein et al., 2017; Xia et al., 2017). There are two major single nucleotide polymorphisms (SNPs) in the ADRB1 gene: the Ser49Gly (rs1801252) and Arg389Gly (rs1801253) polymorphisms; the ADRB2 gene exhibits three major SNPs: the Arg16Gly (rs1042713), Gln27Glu (rs1042714), and Thr164Ile (rs1800888) polymorphisms.

Several studies have examined the influence of the ADRB1 and ADRB2 polymorphisms on cardiovascular events and all-cause mortality in CAD patients. For example, Zaugg et al. (2007) observed that carriers of at least one Gly allele of the ADRB1 rs1801253 polymorphism showed a greater number of cardiovascular adverse events than Arg homozygotes among CAD patients. However, Li et al. (2013) found no relationship between the ADRB1 rs1801253, ADRB2 rs1042713, and ADRB2 rs1042714 polymorphisms and cardiovascular events or all-cause mortality in Han Chinese patients with CAD.

To better understand the interactions between the ADRB1 (rs1801252 and rs1801253) and ADRB2 (rs1042713, rs1042714, and rs1800888) polymorphisms and cardiovascular events as well as all-cause mortality in CAD patients, we undertook a meta-analysis with the aim of obtaining information for individual CAD prognostication and potential clinical application.
Materials and Methods

Search strategy

We carried out a comprehensive search of electronic databases, including PubMed, Ovid, EMBASE, Cochrane, and CINAHL, to identify relevant publications reporting an association between ADRB1 and ADRB2 polymorphisms and cardiovascular events as well as all-cause mortality in CAD patients, with the most recent publication date being April 2018. We used the search terms “coronary artery disease (CAD)” or “coronary heart disease (CHD)” or “ischemic heart disease (IHD)” or “myocardial infarction (MI)” or “acute coronary syndrome (ACS)” or “angina pectoris” or “atherosclerosis” or “ASCVD” and “beta adrenergic receptor” or “beta adrenergic receptor” or “ADRB” in combination with “polymorphism” or “variation” or “variant” or “allele” or “mutation” or “SNP.” Additional relevant publications were identified through manual searches of the bibliographies of the retrieved studies and recent reviews.

Studies that met the following criteria were included: (1) prospective study design with patients who underwent follow-up for more than 1 year; (2) investigation of the association between ADRB1 and ADRB2 polymorphisms and cardiovascular events or all-cause mortality in CAD patients among unrelated subjects; (3) diagnosis of CAD based on previous myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting, angiographic evidence, or angina patients with a positive stress test; and (4) the primary outcomes were cardiovascular events or all-cause mortality, wherein cardiovascular events included death, cardiac death, MI, heart failure, unstable angina, coronary revascularization, cardiac hospitalization, stroke, and cerebrovascular insult. Two investigators (Y.L. and H.Y.) screened all eligible studies independently. Any disagreements between the two investigators were resolved through discussion.

Data extraction

Data were extracted from all eligible studies by primary investigators using a standardized extraction form. The following information was collected: first author’s name, publication year, country, ethnicity of the population studied, age, gender, sample size, polymorphisms, outcomes, duration of follow-up, genotyping methods, Hardy–Weinberg equilibrium (HWE) in controls, quality scores, cases and controls with wild and variant genotypes, risk ratios (RRs), and 95% confidence intervals (95% CIs) of cardiovascular events or all-cause mortality. If any of this information was not

---

FIG. 1. Flow diagram of study identification. ADRB1, β1-adrenergic receptor gene; ADRB2, β2-adrenergic receptor gene.
### Table 1. Characteristics of Studies Included in the Meta-Analysis

| First author (year) | Country | Ethnicity                  | Age (years) | Sex (male%) | Sample size | Polymorphisms                                  | Outcomes                                           | Follow-up (years) | Method                                      | HWE | Quality score |
|---------------------|---------|----------------------------|-------------|-------------|-------------|------------------------------------------------|--------------------------------------------------|------------------|-------------------------------------------|-----|---------------|
| Zaugg (2007)        | Switzerland | Caucasian               | NA          | NA          | 189         | rs1801252, rs1042713, rs1042714                  | Cardiovascular events                              | 1                | TaqMan assay                              | Yes | 8             |
| Li (2013)           | China   | Han Chinese               | NA          | NA          | 545         | rs1801253, rs1042714, rs1042714, rs1801253       | Cardiovascular events                              | 1                | Sequenom                                  | Yes | 7             |
| Pacanowski (2008)   | USA     | NA                        | 62 ± 12     | 0           | 227         | rs1801253                                       | Cardiovascular events, All-cause mortality         | 5.8              | PCR and single-primer extension, PCR and luciferase-based assays | Yes | 8             |
| Tseng (2008)        | USA     | Caucasian, African American, Hispanic | NA          | 0           | 2223        | rs1801252, rs1801253, rs1042713, rs1042714       | All-cause mortality                                | 6.8              | Sequenom                                  | Yes | 7             |
| Lanfear (2005)      | USA     | Caucasian, African American | 60 (12)     | 64          | 735         | rs1801252, rs1801253, rs1042714                  | All-cause mortality                                | 3                | Applied Biosystems genotyping assays       | Yes | 7             |
| Feldman 1 (2015)    | USA     | Caucasian                 | 61.2 (54.8, 69.1) | 86.5        | 532         | rs1801252, rs1801253, rs1042713, rs1042714, rs1800888 | Cardiovascular events, All-cause mortality         | NA               | PCR-RFLP                                  | NA  | 8             |
| Feldman 2 (2015)    | USA     | Caucasian                 | 62.1 (55.2, 69.3) | 86.4        | 714         | rs1801252, rs1801253, rs1042713, rs1042714, rs1800888 | Cardiovascular events, All-cause mortality         | NA               | PCR-RFLP                                  | NA  | 8             |
| Piscione (2008)     | Italy   | NA                        | NA          | NA          | 330         | rs1801252, rs1042713, rs1042714, rs1800888       | Cardiovascular events                              | 3 ± 0.33         | PCR-RFLP                                  | NA  | 5             |

Since two cohorts of patients were enrolled in the study by Feldman et al. (2015), the two cohorts were considered as independent studies (Feldman 1 and Feldman 2). HWE, Hardy–Weinberg equilibrium; NA, not available; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.
### Table 2. Association of ADRB1 and ADRB2 Gene Polymorphisms with Clinical Outcomes According to Eligible Studies

| Polymorphism  | Outcome                  | First author (year) | Wild type, n (cases/controls) | Variants, n (cases/controls) | RR  | 95% CI      | p    |
|---------------|--------------------------|---------------------|-------------------------------|-------------------------------|-----|------------|------|
| rs1801252     | Cardiovascular events    | Feldman 1 (2015)    | 305/112                       | 74/41                         | 0.90| 0.70–1.16  | 0.404|
|               |                          | Feldman 2 (2015)    | 338/221                       | 95/59                         | 1.02| 0.81–1.28  | 0.874|
|               |                          | Zaugg (2007)        | NA                            | NA                            | 1.57| 0.82–2.98  | 0.170|
|               | All-cause mortality      | Feldman 1 (2015)    | 172/245                       | 43/72                         | 0.97| 0.69–1.36  | 0.861|
|               |                          | Feldman 2 (2015)    | 162/397                       | 46/108                        | 1.02| 0.74–1.42  | 0.893|
|               |                          | Tseng (2008)        | NA                            | NA                            | 0.85| 0.63–1.15  | 0.300|
|               |                          | Lanfear (2005)      | 49/360                        | 18/129                        | 1.02| 0.58–1.82  | 0.933|
| rs1801253     | Cardiovascular events    | Li (2013)           | 23/276                        | 21/196                        | 1.05| 0.54–2.02  | 0.887|
|               |                          | Feldman 1 (2015)    | 198/98                        | 180/55                        | 1.23| 1.00–1.50  | 0.046|
|               |                          | Feldman 2 (2015)    | 227/141                       | 206/140                       | 0.94| 0.78–1.13  | 0.511|
|               | All-cause mortality      | Feldman 1 (2015)    | 172/245                       | 43/72                         | 1.16| 0.67–2.01  | 0.598|
|               |                          | Feldman 2 (2015)    | 162/397                       | 46/108                        | 1.16| 0.89–1.52  | 0.282|
|               |                          | Tseng (2008)        | NA                            | NA                            | 0.96| 0.75–1.23  | 0.750|
|               |                          | Pacanowski (2008)   | 14/92                         | 24/97                         | 1.63| 0.79–3.33  | 0.182|
| rs1042713     | Cardiovascular events    | Li (2013)           | 14/185                        | 27/272                        | 0.81| 0.37–1.77  | 0.599|
|               |                          | Feldman 1 (2015)    | 60/22                         | 319/131                       | 0.94| 0.71–1.24  | 0.661|
|               |                          | Feldman 2 (2015)    | 56/51                         | 377/230                       | 1.25| 0.95–1.66  | 0.316|
|               | All-cause mortality      | Feldman 1 (2015)    | 37/45                         | 178/272                       | 0.82| 0.58–1.17  | 0.281|
|               |                          | Feldman 2 (2015)    | 28/79                         | 180/427                       | 1.08| 0.73–1.61  | 0.702|
|               |                          | Tseng (2008)        | NA                            | NA                            | 1.33| 0.91–1.92  | 0.880|
|               |                          | Lanfear (2005)      | 82/327                        | 15/132                        | 2.21| 1.23–3.97  | 0.010|
| rs1042714     | Cardiovascular events    | Li (2013)           | 32/378                        | 12/112                        | 1.66| 0.81–3.42  | 0.166|
|               |                          | Feldman 1 (2015)    | 135/51                        | 244/102                       | 0.88| 0.72–1.09  | 0.248|
|               |                          | Feldman 2 (2015)    | 125/105                       | 308/176                       | 1.27| 1.03–1.56  | 0.116|
|               | All-cause mortality      | Feldman 1 (2015)    | 82/104                        | 133/213                       | 0.81| 0.62–1.07  | 0.139|
|               |                          | Feldman 2 (2015)    | 56/174                        | 152/332                       | 1.29| 0.95–1.75  | 0.106|
|               |                          | Tseng (2008)        | NA                            | NA                            | 1.27| 0.97–1.67  | 0.086|
|               |                          | Lanfear (2005)      | 36/188                        | 34/308                        | 0.58| 0.35–0.95  | 0.030|
| rs1800888     | Cardiovascular events    | Feldman 1 (2015)    | 368/150                       | 10/3                          | 1.14| 0.61–2.14  | 0.679|
|               |                          | Feldman 2 (2015)    | 420/273                       | 13/7                          | 1.02| 0.59–1.78  | 0.937|
|               | All-cause mortality      | Piscione (2008)     | NA                            | NA                            | 4.10| 1.95–8.64  | 0.0001|
|               |                          | Feldman 1 (2015)    | 209/309                       | 5/8                           | 1.19| 0.49–2.89  | 0.699|
|               |                          | Feldman 2 (2015)    | 200/493                       | 8/12                          | 1.47| 0.73–2.99  | 0.282|

95% CI, 95% confidence interval; ADRB1, β1-adrenergic receptor gene; ADRB2, β1-adrenergic receptor gene; NA, not available; RR, risk ratio.

### Table 3. Association of ADRB1 and ADRB2 Polymorphisms with Cardiovascular Events and All-Cause Mortality

| Outcome                  | Polymorphism | RR  | 95% CI      | p    |
|--------------------------|--------------|-----|------------|------|
| Cardiovascular events    | rs1801252    | 1.00| 0.82–1.22  | 0.965|
|                          | rs1801253    | 1.07| 0.91–1.26  | 0.389|
|                          | rs1042713    | 1.06| 0.85–1.33  | 0.619|
|                          | rs1042714    | 1.31| 1.08–1.58  | 0.006*|
|                          | rs1800888    | 1.63| 0.73–3.65  | 0.234|
| All-cause mortality      | rs1801252    | 0.95| 0.79–1.13  | 0.534|
|                          | rs1801253    | 1.02| 0.88–1.17  | 0.816|
|                          | rs1042713    | 1.21| 0.85–1.73  | 0.295|
|                          | rs1042714    | 0.97| 0.70–1.35  | 0.859|
|                          | rs1800888    | 1.36| 0.78–2.35  | 0.281|

*p < 0.05.
FIG. 2. Forest plots of the association of ADRB1 and ADRB2 polymorphisms with cardiovascular events under the dominant model. (A) ADRB1 rs1801252 polymorphism. (B) ADRB1 rs1801253 polymorphism. (C) ADRB2 rs1042713 polymorphism. (D) ADRB2 rs1042714 polymorphism. (E) ADRB2 rs1800888 polymorphism. CAD, coronary artery disease; CI, confidence interval; RR, risk ratio.
provided in the publication, the authors were contacted via e-mail for more detailed data.

**Quality assessment**

The quality of the identified studies was assessed according to a “methodological quality assessment scale,” which was modified from the study by Yuan et al. (2016). Five items, including the representativeness of the cases, the source of controls, sample size, quality control of the genotyping methods, and HWE, were evaluated on this scale. The quality scores ranged from 0 to 10, with a high score indicating a good-quality study.

**Statistical methods**

The dominant models were evaluated for the association of ADRB1 and ADRB2 polymorphisms with cardiovascular events.

**FIG. 3.** Sensitivity analyses of the association of ADRB1 and ADRB2 polymorphisms with cardiovascular events under the dominant model. (A) ADRB1 rs1801252 polymorphism. (B) ADRB1 rs1801253 polymorphism. (C) ADRB2 rs1042713 polymorphism. (D) ADRB2 rs1042714 polymorphism. (E) ADRB2 rs1800888 polymorphism.
events and all-cause mortality in CAD patients because there were insufficient data for specific cases and controls according to genotype in a few studies. The distribution of the genotypes in the control group was tested for HWE, where \( p < 0.05 \) was considered to indicate that the distribution of genotypes in the control group deviated from HWE. RRs and 95% CIs were calculated for the cardiovascular events and all-cause mortality in CAD patients. Statistical heterogeneity between eligible studies was evaluated by using the Cochrane's Q statistic and \( I^2 \) test. \( p < 0.1 \) indicated substantial heterogeneity across studies, and a random-effects model was chosen to perform analyses; otherwise, a fixed-effects model was selected. Sensitivity analyses were conducted to evaluate the stability of the results. The leave-one-out method was used to evaluate each study, and a pooled estimate was calculated for the remaining studies. Begg's funnel plots were generated to qualitatively evaluate publication bias; Egger's test was performed to quantitatively assess the publication bias. All \( p \) values were two sided. All statistical analyses were performed using STATA software version 11.0 (STATA Corporation, College Station, TX).

**Results**

**Study characteristics**

The process of literature retrieval and exclusion is shown in Figure 1. Eight studies were included in our meta-analysis (Lanfear et al., 2005; Zaugg et al., 2007; Pacanowski et al., 2008; Piscione et al., 2008; Tseng et al., 2008; Li et al., 2013; Feldman et al., 2015). Women with obstructive CAD (Pacanowski et al., 2008), the Heart and Estrogen Replacement Study cohort (Tseng et al., 2008), and CAD patients who were treated with \( \beta \)-blockers (Lanfear et al., 2005) were enrolled in this meta-analysis. Since two cohorts of patients were enrolled in the study by Feldman et al. (2015), the two cohorts were considered as independent studies. A total of 5495 patients from eight studies were included in our meta-analysis. The detailed characteristics of eligible studies

---

**FIG. 4.** Forest plots of the association of ADRB1 and ADRB2 polymorphisms with all-cause mortality under the dominant model. (A) ADRB1 rs1801252 polymorphism. (B) ADRB1 rs1801253 polymorphism. (C) ADRB2 rs1042713 polymorphism. (D) ADRB2 rs1042714 polymorphism. (E) ADRB2 rs1800888 polymorphism.
included in our meta-analysis are shown in Table 1. In the study by Zaugg et al. (2007), deviation from HWE was found for the ADRB1 rs1801253 polymorphism; therefore, we excluded this study from the analysis of the association with cardiovascular events in CAD patients. The specific wild-type/variant patients and the associations of ADRB1 and ADRB2 polymorphisms with clinical outcomes according to the eligible studies are shown in Table 2.

**Association of ADRB1 and ADRB2 polymorphisms with cardiovascular events**

A positive association was found between the ADRB2 rs1042714 polymorphism and cardiovascular events in CAD patients (RR = 1.31, 95% CI: 1.08–1.58, \( p = 0.006 \); Table 3 and Fig. 2D). Compared with patients who were Gln27 homozygotes, being a Glu27 carrier was associated with a 31%
increase in the risk of cardiovascular events. No significant association was found between ADRB1 (rs1801252, rs1801253), ADRB2 (rs1042713, rs1800888) and cardiovascular events in CAD patients (Table 3 and Fig. 2A–C, E).

Significant heterogeneity was observed for the associations of ADRB2 rs1042714 ($I^2 = 62.8\%$) and rs1800888 ($I^2 = 79.1\%$) with cardiovascular events. We performed a random-effects analysis, followed by sensitivity analyses. The results of the sensitivity analyses demonstrated that data from the Feldman study deviated from data from other studies with respect to the association of the ADRB2 rs1042714 polymorphism and the cardiovascular events (Fig. 3D). After removing this study, $I^2$ was reduced from 62.8% to 0% ($p=0.893$). Therefore, we excluded this study from the analysis of the association of the ADRB2 rs1042714 polymorphism with cardiovascular events. None of the other studies showed deviations with respect to the association of the ADRB2 rs1800888 polymorphism with cardiovascular events in CAD patients (Fig. 3E).

**FIG. 6.** Begg’s funnel plots of publication bias in the meta-analysis of the association of ADRB1 and ADRB2 polymorphisms with cardiovascular events under the dominant model. (A) ADRB1 rs1801252 polymorphism. (B) ADRB1 rs1801253 polymorphism. (C) ADRB2 rs1042713 polymorphism. (D) ADRB2 rs1042714 polymorphism. (E) ADRB2 rs1800888 polymorphism. logrr, the logarithm of relative risk; s.e. of logrr, standard error of logrr.
Association of ADRB1 and ADRB2 polymorphisms with all-cause mortality

No significant associations were found between ADRB1 (rs1801252 and rs1801253) or ADRB2 (rs1042713, rs1042714, and rs1800888) polymorphisms and all-cause mortality in CAD patients (Table 3 and Fig. 4A–E).

Significant heterogeneity was found for the association of the ADRB2 rs1042713 ($I^2 = 66.7\%$) and rs1042714 ($I^2 = 76.0\%$) polymorphism with all-cause mortality. Hence, a random-effects analysis was performed. We did not find any study that deviated from the other studies, as indicated by the sensitivity analyses (Fig. 5C, D).

Publication bias

Begg’s funnel plots (Figs. 6A–E and 7A–E) were generated, and Egger’s tests (Figs. 8A–E and 9A–E) were

FIG. 7. Begg’s funnel plots of publication bias in the meta-analysis of the association of ADRB1 and ADRB2 polymorphisms with all-cause mortality under the dominant model. (A) ADRB1 rs1801252 polymorphism. (B) ADRB1 rs1801253 polymorphism. (C) ADRB2 rs1042713 polymorphism. (D) ADRB2 rs1042714 polymorphism. (E) ADRB2 rs1800888 polymorphism. logrr, the logarithm of relative risk; s.e. of logrr, standard error of logrr.
performed to evaluate the potential publication bias. The shapes of the funnel plots showed no evidence of obvious asymmetry. The results of Egger’s test did not support the existence of publication bias.

Discussion

In the present meta-analysis, we examined whether specific genetic polymorphisms in the *ADRB1* and *ADRB2* genes were associated with cardiovascular events and all-cause mortality in CAD patients. To our knowledge, this was the first meta-analysis to explore the association of *ADRB1* and *ADRB2* polymorphisms with cardiovascular events and all-cause mortality in CAD patients, and the results suggested that *ADRB2* rs1042714 presented a positive association with cardiovascular events but not with all-cause mortality in CAD patients.

*ADRB2* is expressed on coronary endothelial and vascular smooth muscle cells, which play an important role in the
vasodilatation of the coronary arteries and microcirculation in normal coronary arteries (Barbato et al., 2005; Hesse and Eisenach, 2008). Genetic polymorphisms of ADRB2 have been reported to modulate the functional responses of the receptor to adrenergic stimulation (Dhein et al., 2017), which may be associated with cardiovascular events and all-cause mortality in CAD patients. However, conflicting data regarding the association of the ADRB2 rs1042714 polymorphism with cardiovascular events and all-cause mortality in CAD patients have been reported. Lanfear et al. (2005) demonstrated that Glu27 homozygosity at the ADRB2 rs1042714 polymorphism was a protective factor for overall mortality in CAD patients treated with β-blockers. However, Tseng et al. (2008) demonstrated a trend toward increased mortality in Glu27 homozygotes compared to Gln27 carriers among postmenopausal women with CAD, and this finding...
was further confirmed by the surgical treatment for ischemic heart failure trials. Feldman et al. (2015) demonstrated that CAD patients harboring the Glu27 allele of the ADRB2 rs1042714 polymorphism were at increased risk of mortality and cardiovascular events.

Our data demonstrated that Glu27 carriers at the ADRB2 rs1042714 polymorphism exhibited an increased risk for cardiovascular events but not all-cause mortality. Potential reasons for this finding include the following: the ADRB2 rs1042714 polymorphism results in the substitution of Glu for Gln at codon 27, and the “gain-of-function” of the receptor conferred by the Glu27 allele could cause target tissues to be overexposed to catecholamine, thus accelerating the development of CAD and exacerbating heart dysfunction (Barbato et al., 2007). In addition, several studies have demonstrated an independent association of the Glu27 allele of the ADRB2 rs1042714 polymorphism with a number of diseases, such as obesity, dyslipidemia, diabetes, and stroke (Kumar et al., 2015). These disorders usually coexist with each other and could lead to development and progression of CAD (Jakovljevic and Ostojic, 2013). Lanfear et al. (2005) demonstrated that Glu27 homozygosity of the ADRB2 rs1042714 polymorphism was a protective factor against all-cause mortality only in CAD patients who were treated with β-blockers, whereas they failed to demonstrate any protective effects in patients who were not treated with β-blockers. The reason could be that β-blockers that specifically target ADRB2 might attenuate adverse effects observed in Glu27 carriers at the ADRB2 rs1042714 polymorphism (McLean et al., 2011). Although we concluded that being a Glu27 carrier at the ADRB2 rs1042714 polymorphism presented a positive association with cardiovascular events, we failed to observe this association for all-cause mortality in CAD patients. A possible explanation for this finding is that the influence of the ADRB2 rs1042714 polymorphism on cardiovascular outcomes is subtle and therefore might not increase the risk of all-cause mortality, but can still influence cardiovascular events.

No significant associations of the ADRB1 (rs1801252, rs1801253) and ADRB2 (rs1042713, rs1800888) polymorphisms with cardiovascular events and all-cause mortality in CAD patients were found. This result was in line with the conclusion of a large prospective cohort study that failed to find any association of the ADRB1 rs1801253 and ADRB2 rs1042713 polymorphisms with mortality under an additive model in CAD patients (Cresci et al., 2012). Another study that examined the ADRB2 rs1042713 and rs1800888 haplotype also found no association with revascularization and MI in patients with stable angina undergoing elective PCI (Rywik et al., 2011).

**Limitations**

Although our study was the first meta-analysis to address the association of ADRB1 and ADRB2 polymorphisms with cardiovascular events and all-cause mortality in CAD patients, it has some limitations. First, the number of studies involved in our meta-analysis was limited, which rendered the revealed associations less robust. Second, we could not obtain the specific cases and controls according to each genotype of the ADRB1 and ADRB2 polymorphisms; hence, we only calculated pooled RRs and 95% CIs under the dominant model. Third, we could not adjudicate causes of death although cardiovascular death is more likely to predominate. Because all-cause mortality instead of cardiovascular death was used for the primary outcome in most studies of this meta-analysis. Fourth, there were differences in the age, gender, and populations of the study cohorts as well as the inclusion and exclusion criteria, cardiovascular events, and duration of follow-up among these studies, which might account for the observed heterogeneity. In the study by Feldman et al., patients with left ventricular dysfunction who present a different risk profile than the cohorts of other studies were enrolled.

In conclusion, this study suggests that ADRB2 rs1042714 polymorphism might play a role in the prognosis of cardiovascular events and ultimately represent as an important genetic marker. CAD patients harboring the ADRB2 rs1042714 polymorphism may need aggressive management to optimize their prognosis.

**Acknowledgments**

We thank Cheng Zhao and Menghua Jiang for their linguistic assistance with this article. Funding: National Natural Science Foundation of China (51672030).

**Author Disclosure Statement**

No competing financial interests exist.

**References**

Barbato E, Berger A, Delrue L, et al. (2007) GLU-27 variant of beta2-adrenergic receptor polymorphisms is an independent risk factor for coronary atherosclerotic disease. Atherosclerosis 194:e80–e86.

Barbato E, Piscione F, Bartunek J, et al. (2005) Role of beta2 adrenergic receptors in human atherosclerotic coronary arteries. Circulation 111:288–294.

Cresci S, Dorn GW 2nd, Jones PG, et al. (2012) Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. J Am Coll Cardiol 60:898–907.

Dhein S, Dohmen PM, Sauer M, et al. (2017) Effects of β-adrenoceptor and catechol-O-methyl-transferase (COMT) polymorphism on postoperative outcome in cardiac surgery patients. Med Sci Monit Basic Res 23:223–233.

Feldman AM, She L, McNamara DM, et al. (2015) Genetic variants are not associated with outcome in patients with coronary artery disease and left ventricular dysfunction: results of the Genetic Substudy of the Surgical Treatment for Ischemic Heart Failure (STICH) trials. Cardiology 130: 69–81.

Hesse C, Eisenach JH (2008) Genetic variation in the beta(2)-adrenergic receptor: impact on intermediate cardiovascular phenotypes. Curr Pharmacogenomics Personal Med 6:160–170.

Jakovljevic M, Ostojic L (2013) Comorbidity and multimorbidity in medicine today: challenges and opportunities for bringing separated branches of medicine closer to each other. Psychiatr Danub 25(Suppl 1):18–28.

Kumar A, Prasad M, Kumar P, et al. (2015) Association between beta adrenergic receptor polymorphism and ischemic stroke: a meta-analysis. J Stroke 17:138–143.

Lanfear DE, Jones PG, Marsh S, et al. (2005) Beta2-adrenergic receptor genotype and survival among patients receiving beta-blocker therapy after an acute coronary syndrome. JAMA 294:1526–1533.
Li ZG, Wu H, Zhou YL, et al. (2013) Association of β-adrenergic receptor genes polymorphisms with incidence of subsequent cardiovascular events in Han Chinese patients with coronary artery disease. Chin Med J (Engl) 126:4679–4684.

McLean RC, Hirsch GA, Becker LC, et al. (2011) Polymorphisms of the beta adrenergic receptor predict left ventricular remodeling following acute myocardial infarction. Cardiovasc Drugs Ther 25:251–258.

Pacanowski MA, Zineh I, Li H, et al. (2008) Adrenergic gene polymorphisms and cardiovascular risk in the NHLBI-sponsored women’s ischemia syndrome evaluation. J Transl Med 6:11.

Piscione F, Iaccarino G, Galasso G, et al. (2008) Effects of Ile164 polymorphism of beta2-adrenergic receptor gene on coronary artery disease. J Am Coll Cardiol 52:1381–1388.

Rywik TM, Szperl M, Ploski R, et al. (2011) Is evaluation of complex polymorphism helpful in the assessment of prognosis after percutaneous coronary intervention. A prospective study. Kardiol Pol 69:881–888.

Tseng ZH, Aouizerat BE, Pawlikowska L, et al. (2008) Common beta-adrenergic receptor polymorphisms are not associated with risk of sudden cardiac death in patients with coronary artery disease. Heart Rhythm 5:814–821.

Xia K, Ding R, Zhang Z, et al. (2017) The association of eight potentially functional polymorphisms in five adrenergic receptor-encoding genes with myocardial infarction risk in Han Chinese. Gene 624:43–49.

Yuan HP, Sun L, Li XH, et al. (2016) Association of adiponectin polymorphism with metabolic syndrome risk and adiponectin level with stroke risk: a meta-analysis. Sci Rep 6:31945.

Zaugg M, Bestmann L, Wacker J, et al. (2007) Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. Anesthesiology 107:33–44.

Address correspondence to:
Ze Yang, PhD
The MOH Key Laboratory of Geriatrics
Beijing Hospital
National Center of Gerontology
NO.1 Dahua Road
Dongcheng District
Beijing 100730
People’s Republic of China
E-mail: yang_ze@sina.com

Deping Liu, MD
Department of Cardiology
Beijing Hospital
National Center of Gerontology
NO.1 Dahua Road
Dongcheng District
Beijing 100730
People’s Republic of China
E-mail: lliudeping@263.net