



Original research article

Comparison of cardiocerebrovascular disease incidence between angiotensin converting enzyme inhibitor and angiotensin receptor blocker users in a real-world cohort

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Abstract

Background: Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are known to be effective in managing cardiovascular diseases, but more evidence supports the use of an ACEI. This study investigated the difference in cardiovascular disease incidence between relatively low-compliance ACEIs and high-compliance ARBs in the clinical setting.

Methods: Patients who were first prescribed ACEIs or ARBs at two tertiary university hospitals in Korea were observed in this retrospective cohort study for the incidence of heart failure, angina, acute myocardial infarction, cerebrovascular disease, ischemic heart disease, and major adverse cardiovascular events for 5 years after the first prescription. Additionally, 5-year Kaplan–Meier survival curves were used based on the presence or absence of statins.

Results: Overall, 2,945 and 9,189 patients were prescribed ACEIs and ARBs, respectively. When compared to ACEIs, the incidence of heart failure decreased by 52% in those taking ARBs (HR [95% CI] = 0.48 [0.39–0.60], $P < 0.001$), and the incidence of cerebrovascular disease increased by 62% (HR [95% CI] = 1.62 [1.26–2.07], $P < 0.001$). The incidence of ischemic heart disease ($P = 0.223$) and major adverse cardiovascular events ($P = 0.374$) did not differ significantly between the two groups.

Conclusions: ARBs were not inferior to ACEIs in relation to reducing the incidence of cardiocerebrovascular disease in the clinical setting; however, there were slight differences for each disease. The greatest strength of real-world evidence is that it allows the follow-up of specific drug use, including drug compliance. Large-scale studies on the effects of relatively low-compliance ACEIs and high-compliance ARBs on cardiocerebrovascular disease are warranted in the future.

Keywords: ACEI; Acute myocardial infarction; ARB; Cerebrovascular disease; Heart failure

Highlights:

- This study investigated the difference in cardiovascular disease incidence between relatively low-compliance angiotensin-converting enzyme inhibitors (ACEIs) and high-compliance angiotensin II receptor blockers (ARBs).
- ARBs were not inferior to ACEIs in relation to reducing the incidence of cardiocerebrovascular disease in the clinical setting, but there were slight differences for each disease.
- It is important to note that ARBs were equally effective as ACEIs, at least in the real clinical setting.
- It will be necessary to compare a well-established randomized control study (RCTs) on the real clinical use of ACEI and ARB.

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Introduction

Renin angiotensin aldosterone system (RAAS) plays a pivotal role in blood pressure regulation and vascular-disease pathophysiology (Ames et al., 2019; Patel et al., 2017). Furthermore, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) attenuate RAAS. Both are known to have a blood pressure-dependent preventive effect on cardiovascular diseases (Atlas, 2007; Helmer et al., 2018). However, drug compliance, which may decrease due to side effects, is an important consideration when prescribing ACEIs or ARBs (Vegter et al., 2011). Many studies have shown that the degree of continuous drug use varies from drug to drug (Abraham et al., 2015; Vegter et al., 2011). Physicians tend to switch from ACEIs to ARBs due to side effects like dry cough. Moreover, ARBs have been shown to have the highest drug compliance (Abraham et al., 2015). Thus, interest in ARBs as an alternative to ACEIs' 'unmet needs' is increasing.

Though both ACEIs and ARBs are effective in managing cardiovascular diseases, more evidence supports the use of ACEIs (Blood Pressure..., 2007; Cheng et al., 2014; Ferrari and Boersma, 2013; Savarese et al., 2013; Strauss and Hall, 2016; van Vark et al., 2012). However, ARBs have an advantage over ACEIs in drug compliance (Bangalore et al., 2016; Conlin et al., 2001). Therefore, whether the replacement of ACEIs with ARBs is more desirable remains undetermined. A realistic cardiocerebrovascular comparative study of relatively low-compliance ACEIs and high-compliance ARBs is time-consuming. The comparison of the incidence of cardiovascular disease in actual clinical settings, allowing the investigation of drug compliance, is the greatest strength of real-world evidence (RWE) studies (Kim and Kim, 2019; Kim et al., 2018a).

Therefore, we retrospectively compared cardiocerebrovascular disease incidence between relatively low-compliance ACEIs and high-compliance ARBs in an RWE study. When evaluating the incidence of cardiovascular events of a specific drug in clinical studies, individual risk factors such as statins are important variables to consider (Jones and Lefer, 2001). Thus, a secondary subgroup analysis was performed to compare cardiocerebrovascular diseases according to the presence or absence of statins. Ultimately, we wanted to compare whether the benefits of ACEIs identified in a randomized control study (RCT) were also seen in ARBs via RWE.

Materials and methods

This multicenter electronic medical record (EMR)-based retrospective cohort study examined the difference in the incidence of cardiocerebrovascular disease between ACEIs and ARBs according to the presence or absence of statins (Kim et al., 2018b). Patients who were first prescribed ACEIs or ARBs between 2009 and 2012 at Seoul St. Mary's Hospital or Seoul National University Hospital were followed up for 5 years. The date when an ACEI or ARB was first prescribed at each hospital was defined as the index date. Patients were excluded from this study if: ACEIs and ARBs were taken at the same time, an ACEI was changed to an ARB, or the dose was not maintained for the full follow-up period.

To determine the incidence of each cardiocerebrovascular disease, the date of first diagnosis was extracted based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10 classification) for each disease. Diseases extracted from EMRs included heart

failure (HF) (I50, I11.0, I13.0, I13.2), acute myocardial infarction (AMI) (I21–23), ischemic heart disease (IHD) (I20–25), angina pectoris (I20), and cerebrovascular disease (CeVD) (I60–66). Previously diagnosed cancer was identified using the code C-. Each cardiovascular disease included a combination of three disease outcomes (death + IHD + CeVD) and major adverse cardiovascular events (MACE) to consider the association between diseases rather than considering them alone. In addition, the occurrence of cancer (C-) after the index data was confirmed. The patient was checked for diabetes mellitus (DM) (ICD-10 E10–E14, H28.0, H36.0, N08.3, O24). If the initial diagnosis of a condition was recorded before the index date, it was assumed to be an underlying disease, and if the diagnosis was recorded after the index date, it was identified as a new disease occurrence. The ACEIs included in this study were captopril, enalapril, imidapril, lisinopril, moexipril, perindopril, ramipril, and zofenopril. The ARBs included were candesartan, eprosartan, fimasartan, irbesartan, olmesartan, telmisartan, and valsartan. From the EMRs, patient age and sex were extracted. Body mass index (BMI) was calculated using height and weight. We collected information on creatinine and estimated glomerular filtration rate (eGFR) and the presence or absence of antihypertensive drugs such as beta-blockers, calcium channel blockers (CCBs), diuretics, and K-sparing diuretics. The use of statins with a strong preventive effect on the occurrence of cardiovascular disease was investigated separately, and the occurrence of cardiovascular disease was stratified and analyzed. Survival was estimated using a Kaplan–Meier survival curve, and the univariate/multivariate Cox proportional hazard ratio was calculated for each cardiovascular disease occurrence.

Ethics approval

The data used in this study were anonymized and extracted, and secondary data reprocessing was performed using data quality management. Data were stored in an encrypted computer in the form of an encrypted file, and were only accessible to the principal investigator in charge of each hospital. The patients' personal information and all personally identifiable data were deleted for statistical analysis. Due to the anonymized data and the retrospective nature of this cohort study, the study did not pose a mental or physical threat to the patient and so did not require consent from the subjects. Our study was approved by the Institutional Review Board of the Catholic University of Korea and Seoul National University Hospital.

Statistical analysis

Descriptive statistics are presented as means (\pm standard deviations) or percentages of participants. To compare the differences in antihypertensive drugs (ACEIs vs. ARBs) and the cumulative incidence of various disease entities, Kaplan–Meier survival curves were used. The relationship between ACEI/ARB and cardiocerebrovascular disease stratified by statin prescription was used by the Cox proportional hazard model to calculate hazard ratios, 95% confidence intervals (CIs), and corresponding *P* values. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA), and two-sided *P* < 0.05, was considered statistically significant.

Results

Overall, 12,134 patients who maintained an ACEI or ARB prescription for 5 years were included in this study (Table 1).

ACEIs and ARBs were prescribed for 24.3% (2,945/12,134) and 75.7% (9,189/12,134) of the patients, respectively. Altogether, 22.2% (2,695/12,134) of the patients did not take statins, of which 19.6% (529/2,695) took ACEIs and 80.4% (2,166/2,695) took ARBs. Moreover, 77.8% (9,439/12,134) of the patients took statins. Among these, 25.6% (2,416/9,439) took ACEIs and 74.4% (7,023/9,439) took ARBs. In the group not taking statins, there were significant differences in age, sex, and eGFR

< 60 ml/min/1.73 m² between those taking ACEIs and those taking ARBs (all $P < 0.001$). However, there were no significant differences in BMI and eGFR between the antihypertensives. In the group taking statins, there were significant differences in age, sex, BMI, and eGFR < 60 ml/min/1.73 m² between the two antihypertensives (all $P < 0.001$). However, there was no difference in eGFR.

Table 1. Baseline characteristics according to statin prescription ($n = 12,134$)

	Without statin ($n = 2,695$)			With statin ($n = 9,439$)		
	ACEI	ARB	<i>P</i> value	ACEI	ARB	<i>P</i> value
Number, <i>n</i> (%)	529	2,166		2,416	7,023	
Age, years	61.4 ± 13.1	58.9 ± 12.5	<0.001	57.9 ± 16.4	60.7 ± 12.1	<0.001
Female, <i>n</i> (%)	200 (37.8)	1,027 (47.4)	<0.001	852 (35.3)	3,268 (46.5)	<0.001
BMI, kg/m ²	24.1 ± 3.3	24.3 ± 3.5	0.340	23.3 ± 3.5	24.6 ± 3.6	<0.001
Creatine, mg/dl	1.1 (0.9–1.3)	1.0 (0.8–1.2)	0.005	1.0 (0.9–1.3)	1.0 (0.8–1.3)	<0.001
eGFR, ml/min/1.73 m ²	77.9 ± 17.9	76.1 ± 26.4	0.563	76.9 ± 28.8	74.4 ± 25.4	0.193
eGFR <60 ml/min/1.73 m ² , <i>n</i> (%)	501 (94.7)	1749 (80.8)	<0.001	2223 (92.0)	5841 (83.2)	<0.001
Comorbidity						
heart failure	25 (4.7)	38 (1.8)	<0.001	136 (5.6)	99 (1.4)	<0.001
ischemic heart disease	127 (24.0)	186 (8.6)	<0.001	688 (28.5)	1,225 (17.4)	<0.001
cerebrovascular disease	43 (8.1)	147 (6.8)	0.280	180 (7.5)	715 (10.2)	<0.001
diabetes mellitus	8 (1.5)	109 (5.0)	<0.001	21 (0.9)	293 (4.2)	<0.001
	9 (1.7)	125 (5.8)	<0.001	40 (1.7)	148 (2.1)	0.170
Medication						
β-blocker	194 (36.7)	594 (27.4)	<0.001	1162 (48.1)	2434 (34.7)	<0.001
CCB	180 (34.0)	818 (37.8)	0.110	752 (31.1)	2670 (38.0)	<0.001
diuretics	166 (31.4)	581 (26.8)	0.036	737 (30.5)	1779 (25.3)	<0.001
K-sparing	51 (9.6)	44 (2.0)	<0.001	407 (16.9)	298 (4.2)	<0.001

Data are expressed as the number of patients (percentage of total), mean ± standard deviation, and median (quartiles).

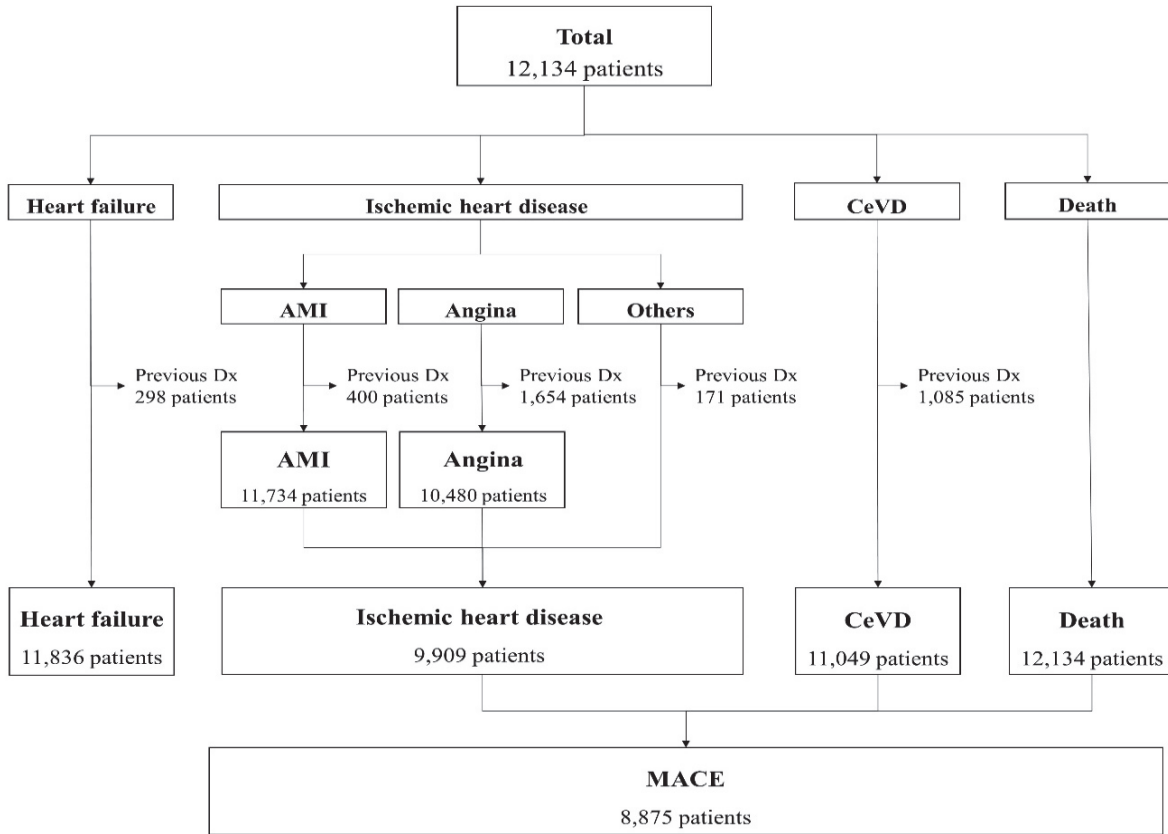
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; GFR, glomerular filtration rate; CCB, calcium channel blocker.

There was also a significant difference in the presence of HF, IHD, and DM between the ACEI and ARB groups (all $P < 0.001$). However, the survival curve was created using patients without existing comorbidities (Fig. 1), so the results of this study were not affected. In total, 298 people who were previously diagnosed with HF, 400 people who were previously diagnosed with AMI, 1,654 people who were previously diagnosed with angina, and 1,085 people who were previously diagnosed with CeVD were excluded. As a result, 11,836 people were checked for the occurrence of HF, 11,734 for AMI, 10,480 for angina, and 11,049 for CeVD. In the case of IHD, including AMI and angina, 9,909 subjects were enrolled. MACE was defined to represent IHD, CeVD, and death, and was checked for in 8,875 people in this study.

The cumulative incidence rate for each disease over 5 years was confirmed (Fig. 2). In the case of HF, the cumulative incidence rate of ARBs was significantly lower than that of ACEIs (HR [95% CI] = 0.48 [0.39–0.60], $P < 0.001$) (Fig. 2a). The ARB group had a significantly higher incidence of AMI ($P < 0.01$) (Fig. 2b) but did not have a significantly lower incidence of angina ($P = 0.117$) (Fig. 2c). Similarly, in IHD patients with AMI and angina, ARBs showed a dominant trend compared to ACEIs, but the difference was not statistically significant ($P = 0.223$) (Fig. 2d). On the contrary, patients taking ACEIs had a significantly lower incidence of CeVD than those taking ARBs (HR [95% CI] = 1.62 [1.26–2.07], $P < 0.001$) (Fig. 2e).

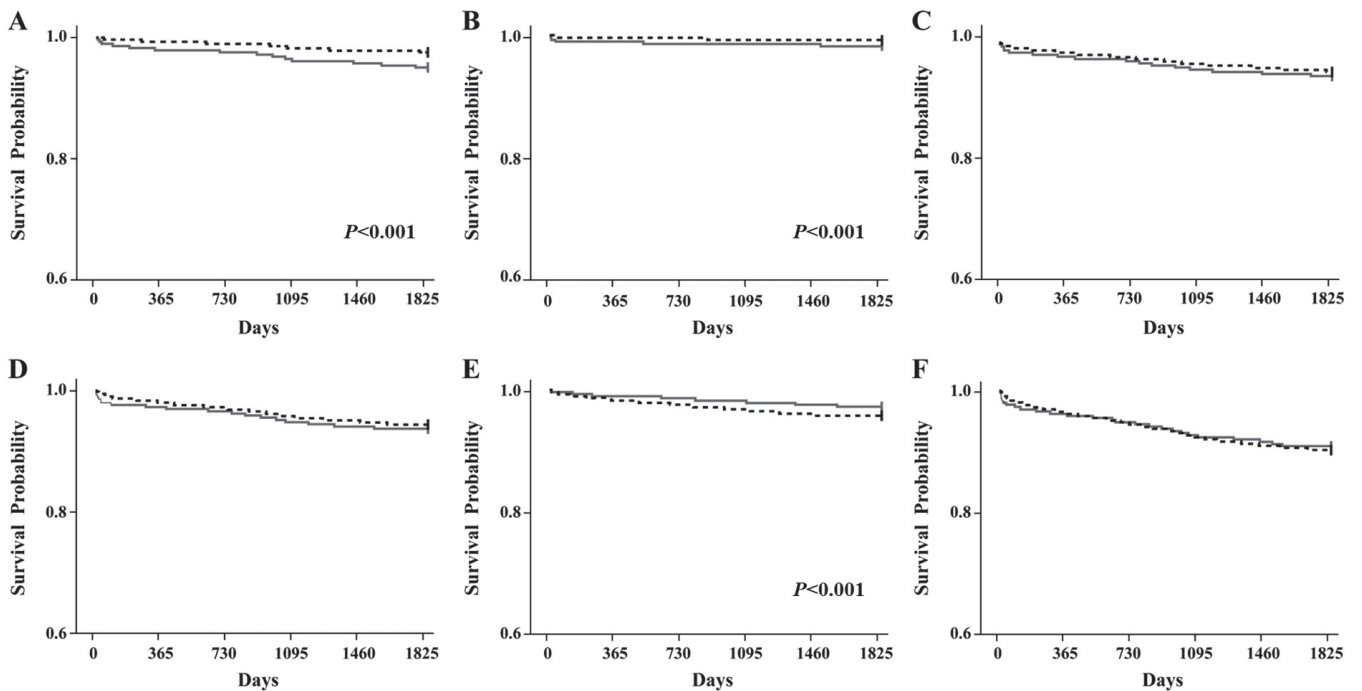
In the case of IHD, CeVD, and death, there was no significant difference between ACEI and ARB (HR [95% CI] = 1.08 [0.91–1.27], $P = 0.374$) (Fig. 2f).

Since the number of outcome events for each disease was small, only statistically meaningful results were included in the subgroup analysis of the incidence rate according to the presence or absence of statins (Fig. 3). In both the group not taking statins, (HR [95% CI] = 0.41 [0.24–0.70], $P < 0.001$) (Fig. 3A-1) and the group taking statins (HR [95% CI] = 0.50 [0.40–0.64], $P = 0.001$) (Fig. 3A-2), ARBs were significantly superior to ACEIs for reducing HF risk. In the case of IHD, there was no significant difference between antihypertensives in the group not taking statins (HR [95% CI] = 0.92 [0.58–1.48], $P = 0.737$) (Fig. 3B-1). In the group taking statins (HR [95% CI] = 0.90 [0.73–1.11], $P = 0.315$) (Fig. 3B-2), ARBs showed a dominant trend compared to ACEIs, though this was not statistically significant. There was no significant difference in CeVD incidence between ARBs and ACEIs in the group not taking statins (HR [95% CI] = 1.03 [0.62–1.73], $P = 0.897$) (Fig. 3C-1). However, in the group taking statins, ACEIs were significantly superior to ARBs (HR [95% CI] = 1.82 [1.37–2.42], $P < 0.001$) (Fig. 3C-2). When considering MAC-ES, there was no significant difference in effect between ARBs and ACEIs with (HR [95% CI] = 0.89 [0.61–1.29], $P = 0.532$) (Fig. 3d-1) and without (HR [95% CI] = 1.15 [0.95–1.38], $P = 0.145$) (Fig. 3d-2) statins.



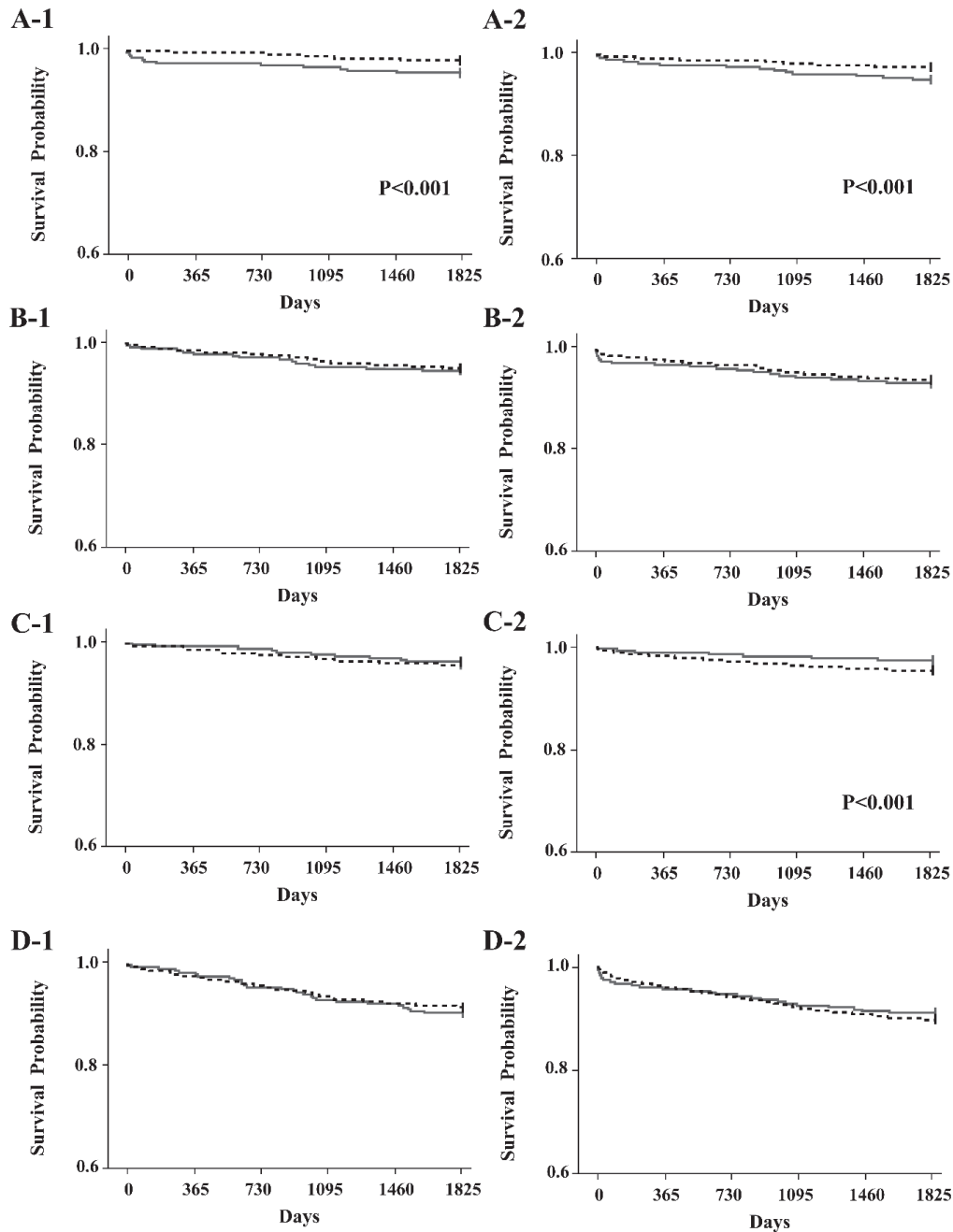
Legend: AMI, acute myocardial infarction; CeVD, cerebrovascular disease; MACE, major adverse cardiovascular events.

Fig. 1. Trial profile



Legend: Dashed line, ACEIs; Dotted line, ARBs.

Fig. 2. Kaplan–Meier curve for incidence of: (A) heart failure, (B) acute myocardial infarction, (C) angina, (D) ischemic heart disease, (E) cerebrovascular disease, and (F) major adverse cardiovascular events.



Legend: Dashed line, ACEIs; Dotted line, ARBs.

Fig. 2. Kaplan–Meier curve for the incidence of various types of disease according to statin prescription: (A-1) heart failure without statin; (A-2) heart failure with statin; (B-1) ischemic heart disease without statin; (B-2) ischemic heart disease with statin; (C-1) cerebrovascular disease without statin; (C-2) cerebrovascular disease with statin; (D-1) death, ischemic heart disease, and cerebrovascular disease without statin; (D-2) death, ischemic heart disease, and cerebrovascular disease with statin.

Discussion

The greatest strengths of ACEIs and ARBs are their ability to control blood pressure and their cardioprotective effects (Atlas, 2007; Helmer et al., 2018). According to the treatment guidelines of various studies, ACEIs are recommended as the first-line therapy for IHD. Several placebo-controlled studies, such as HOPE (Sleight, 2000) and PEACE (Pedersen et al.,

2008), have also shown that ACEIs improve vascular disease significantly more than ARBs. These studies suggest a clear rationale for the preventive effect of ACEIs on cardiovascular disease (Dagenais et al., 2006; PROGRESS..., 2001; The EUROpean trial, 2003; The Heart Outcomes..., 2000). However, due to the side effects of ACEIs, there is hesitancy around their use and the tendency to use ARBs instead has increased (Cicardi et al., 2004; Conlin et al., 2001). Even if ARBs have a similar or slightly weaker cardioprotective effect when compared with

ACEIs, this effect may differ further due to drug compliance. Therefore, in real-world circumstances, compliance should be considered when understanding the status of cardiovascular disease occurrence according to ACEI or ARB prescription.

In this study, as estimated by the Kaplan–Meier curves for 5 years, ARBs tended to be superior to ACEIs in preventing IHD, including AMI and angina, but without statistically significant differences. Even when IHD, CeVD, and death were considered, no significant difference between ACEIs and ARBs was observed. Moreover, most clinical studies have contradicting results on the effect of ACEIs and ARBs in treating cardiocerebrovascular disease, with most ACEIs tending to be superior to ARBs. In one study that confirmed the incidence of coronary heart disease (CHD) regardless of blood pressure, ACEIs reduced CHD risk by 9%, but risk was increased with ARB use (Blood Pressure..., 2007). In a meta-analysis, ACEIs were associated with reduced mortality, but ARB use had no statistically significant effect (van Vark et al., 2012). A study on the occurrence of AMI in high-risk patients also discussed the strength of ACEIs (Ferrari and Boersma, 2013; Strauss and Hall, 2016). In a meta-analysis of 26 clinical trials, ARBs did not reduce the incidence of AMI, while ACEIs reduced AMI incidence by 17.7% (Savarese et al., 2013). The same effect was seen in other meta-analyses (Cheng et al., 2014). The results of these studies indicate that both ACEIs and ARBs effectively lower blood pressure, but their effects on cardiovascular events and mortality remain unclear.

In our study, the incidence of AMI was significantly higher in ARBs than in ACEIs. However, many recent studies have reported that ARBs are as effective as ACEIs. Based on clinical evaluation, as in the above studies, there is a lack of evidence that the ARB itself increases the risk of cardiovascular disease. In 37 randomized studies, the risk of MI when taking ARBs was only 0.3% higher than that of a placebo (Bangalore et al., 2011). Additionally, in this study, ARBs were as safe and effective as ACEIs in patients without HF. In a meta-analysis of the effects of ACEIs and ARBs in hypertensive patients without HF, ACEIs were superior to ARBs, but both drugs significantly lowered the risk of cardiovascular events and stroke (Savarese et al., 2013). Another meta-analysis of 106 randomized studies also found that ARBs were safe and could prevent cardiovascular diseases such as MI and HF when compared to a placebo (Bangalore et al., 2016).

However, besides these real-world effects, when ACEIs and ARBs were directly compared, ARBs had a much lower discontinuation rate than ACEIs due to adverse reactions (Bangalore et al., 2016). In addition, as clinical evidence for ARBs has accumulated, studies have shown that this antihypertensive group is not inferior to ACEIs. Whether cardiovascular disease prevention differs between ACEIs and ARBs according to drug compliance in the clinical environment should be considered. RWE is the result of a study that includes information on drug compliance with existing RCT studies (Kim and Kim 2019; Kim et al., 2018a). While RCTs look at the natural effect of the drug itself, RWE examines drug compliance through the drug's own effect. This study intended to determine the actual clinical results of ACEIs with relatively poor compliance.

Unlike previous RCT results, our RWE study showed the superiority of ARBs in reducing the risk of various cardiovascular diseases such as HF, AMI, angina, and IHD. In our study, those taking ARBs had a significantly lower incidence of HF and AMI than those taking ACEIs. In the case of IHD, including angina and MI, there was no significant difference between ACEIs and ARBs, but ARBs showed a more effective trend compared to ACEIs. These results are inconsistent with

the various RCTs mentioned above. Because of the nature of RWE, the causal relationship is difficult to clarify, and only the correlation can be estimated (Kim et al., 2019). Therefore, we must interpret these findings cautiously. The results may be explained by medication compliance, which is higher in those taking ARBs. Of course, several confounding factors that are not included in the EMRs must also be considered, but based on the results of this study, the difference between ACEIs and ARBs in the clinical environment is not large. ARBs do not seem to be inferior to ACEIs in the clinical setting.

In contrast to the risk of cardiovascular disease, ACEIs are more effective in preventing against CeVD than ARBs in this study. Surprisingly, the results for IHD and CeVD were different; a more significant risk reduction was observed in the group administered statins. According to various meta-analyses, although ARB prescription reduced the risk of stroke, its reduction of the cardiovascular disease mortality rate was insignificant (Elgendy et al., 2015). This content is helpful for interpreting the results of this study. Furthermore, the ONTARGET study evaluated hospitalization for cardiovascular causes of death, MI, stroke, and HF, and found no difference between the two antihypertensives (Teo et al., 2004). Some studies have reported that ARBs are slightly more effective in reducing the risk of stroke, but the difference is mostly insignificant. Since both ACEIs and ARBs have shown similar effects in the prevention of cardiovascular disease, eventually drugs with better tolerance and compliance will probably be preferred. In our study, ACEIs showed a more effective trend for MACE prevention over ARBs, but the difference in CeVD incidence is presumed to have had a significant impact.

Many studies have been conducted in Korea, and ACEIs or ARBs are recommended in patients with coronary artery disease in this population. One comparative Korean study of ACEIs and ARBs using RWE found no difference in the risk of future mortality due to ACEIs and ARBs among 50,000 patients with angina. Concerning AMI, a lower risk of mortality when taking ACEIs was reported (Ann et al., 2020). Likewise, in another study by Park et al. (2021), the risk of mortality was reduced in the ACEI group. These two Korean studies differ from this study in that the mortality rate of the existing cardiocerebrovascular disease changes rather than its occurrence. In both studies, there was no difference in the incidence of cardiovascular events between ACEIs and ARBs in the low-risk group without symptoms of HF, but ACEIs had a better prognosis than ARBs in the corresponding high-risk patients.

This study has various limitations owing to its retrospective cohort design. First, most of the patients included in this study may have had hypertension. Indeed, ACEIs or ARBs are used for hypertension and renal protection in patients with diabetes (Vejakama et al., 2012). However, in many cases, ACEIs or ARBs are prescribed without adding the diagnosis of hypertension in the EMR, so why ACEIs or ARBs were prescribed is not clear (Kim et al., 2019). In addition, although ACEI or ARBs have a preventive effect on cardiovascular disease due to their blood pressure-lowering effect, blood pressure was not monitored in this study, so it was difficult to interpret the results accordingly. Second, patients who changed to an ARB after ACEI treatment (or changed from an ARB to an ACEI) were not included in this study. These individuals might have changed to ARBs due to side effects of their ACEI prescription. Including these cases in the study would have been beneficial, but they were ultimately excluded because of their varied time points of change. Third, due to the nature of the retrospective cohort study, various unexpected confounding factors exist (Kim et al., 2019). For example, there will likely be differenc-

es according to the type or dose of each ACEI class (captopril, enalapril, imidapril, etc.) or each ARB class (candesartan, eprosartan, fimasartan, etc.). In addition, concurrent use of beta-blockers, calcium channel blockers, diuretics, or K-sparing diuretics may have affected the study results. These situations were not sufficiently considered in this study and will need to be supplemented with detailed analysis in the future. Finally, this study did not consider the patients' medication adherence. In fact, it was not easy to confirm the patient's medication adherence during the five-year study period, which may have affected the results. These factors need to be taken into account in the future.

In summary, research shows that the blood pressure-lowering effects of ACEIs and ARBs are similar, while the results on their effect on cardiovascular disease prevention are diverse. ARBs showed benefits other than those of ACEIs, but their superiority over ACEIs cannot be conclusively stated. The switch from ACEIs to ARBs is still questioned, despite their effectiveness. However, the side effects of ACEIs, such as dry cough and angioedema, have always been pointed out. ACEI-induced dry cough appears to be more common in Asians than in Westerners (Adigun and Ajayi, 2001; Coleman and McDowell, 2005; Teklay et al., 2014). Thus far, ARBs are rarely discontinued due to adverse reactions. Therefore, due to the side effects of ACEIs, ARBs have a relatively significant safety advantage and thus promote patient compliance.

Conclusions

In this study, some ARBs appeared to be considerably superior to ACEIs, but careful attention is required to avoid exaggerating interpretations. It is important to note that ARBs were equally effective as ACEIs, at least in the real clinical setting. Given that RWE is more advantageous compared to RCTs for comparing drug properties such as purity, and considering that ARBs were superior to ACEIs in this study, it would be difficult to exclude the impact of the relatively high drug compliance of ARBs. Finally, how to explain the difference in the incidence of each disease when using RWE and not RCTs seems to be key. In the future, it will be necessary to compare well-established RCTs on the real clinical use of ACEI and ARB, including the impact of drug compliance, and their preventive effects against cardiovascular diseases. Most studies do not directly compare ACEIs and ARBs, but instead provide indirect comparisons with a placebo. Future clinical studies are warranted to compare the effects of ACEIs and ARBs in preventing cardiovascular disease.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Institutional Review Board of the Catholic University of Korea and Seoul National University Hospital.

Conflict of interests

The authors have no competing interests to declare.

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