

Impact of renin–angiotensin system blocker after aortic valve replacement—a systematic review and meta-analysis

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Background: Data reporting the impact of renin-angiotensin system inhibitor (RASi) after aortic valve replacement (AVR) is controversy.

Methods: The PubMed database was systematically searched for studies reporting the mortality and hazard ratios (HRs) of RASi following surgical and transcatheter AVR (SAVR, TAVR). Random-effects model was used when the I² statistic was more than 50% and its P value was less than 0.05, otherwise, the fixed-effects model was conducted.

Results: Nine articles incorporating 33,063 patients were eligible. Patients having the description of RASi were associated with lower all-cause mortality at 30 days (OR, 0.80, 95% CI, 0.69 to 0.94), 1 year (OR, 0.75, 95% CI, 0.69 to 0.81) and beyond 1 year (OR, 0.52, 95% CI, 0.38 to 0.73) after AVR. Consistently, patients with RASi had lower risk for all-cause mortality (HR, 0.87, 95% CI, 0.84 to 0.91) beyond 1 year following AVR albeit adjusting confounders. Interestingly, beneficial effect of RASi was still observed in patients with preserved ejection fraction following TAVR (HR, 0.90, 95% CI, 0.87 to 0.94). In addition, patients taking RASi had lower cardiovascular mortality than those patients without RASi after TAVR (30 days, OR, 0.63, 95% CI, 0.44 to 0.90; 1 year, OR, 0.60, 95% CI, 0.50 to 0.73; beyond 1 year, OR, 0.63, 95% CI, 0.54 to 0.74). **Conclusion:** Patients with RASi exhibited better short- and long-term survival following AVR compared to those patients without RASi, which warranted further studies to support such findings.

Keywords: Aortic valve replacement (AVR); transcatheter aortic valve replacement (TAVR); renin-angiotensin system inhibitor (RASi)

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Introduction

Aortic stenosis (AS) is a common valvular heart disease in the aging population, which is always associated with cardiac hypertrophy in response to the increased afterload (1). The activation of renin-angiotensin system (RAS) was considered to accelerate the left ventricular (LV) remodeling in patients with AS (2). Inhibition of RAS was demonstrated to decrease blood pressure, modulate myocardial hypertrophy and improve clinical outcomes in patients having heart failure with reduced left ventricular ejection fraction (LVEF), which made RAS inhibitors (RASi) to be widely used in patients with cardiovascular disease (3,4). While, use of RASi including angiotensin-converting enzyme inhibitors (ACEIs)

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Figure 1 The process of study selection. AVR, aortic valve replacement.

and angiotensin II receptor blockers (ARBs) has traditionally been avoided in patients with AS, inasmuch as the concern of deteriorated hemodynamic results and subsequent hypotension (5). In fact, more increasing data demonstrate the safety and even potential beneficial effect of ACEIs/ARBs in patients with AS (6-9).

Aortic valve replacement (AVR) including surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR), was an effective strategy to treating patients with AS. However, if patients with AS were not treated timely, excessive LV hypertrophy and fibrosis would compromise the clinical outcome after AVR (10,11). Numerous data demonstrated that patients with persistence of LV hypertrophy and fibrosis were at high risk for increased long-term mortality after AVR (12,13). However, there is no specific recommendation for the use of ACEIs/ARBs after AVR to attenuate LV hypertrophy and fibrosis, and debate surrounded the impact of ACEIs/ARBs on clinical outcome after AVR. Therefore, we performed the meta-analysis and systematic review to explore the effect of RASi on clinical outcome after AVR including SAVR and TAVR in patients with AS. We reported the present article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1155).

Methods

Data sources and study selection

A literature search of the PubMed online database was

conducted to identify studies reporting the impact of RASi on clinical outcome after AVR on February 9, 2020 (*Figure 1*). The electronic search terms were as follows: (renin-angiotensin system inhibitor OR ACEI OR ARB OR renin-angiotensin system OR ACE inhibitor OR renin-angiotensin system blockade) AND (surgical aortic valve OR SAVR OR transcatheter aortic valve OR aortic valve replacement OR AVR OR TAVR OR TAVI). Additionally, reference lists of pertinent articles were also screened manually in case of omitting potential relevant citations. All citations were initially identified at the level of title and abstract. And then the full-length articles were assessed further. Two authors checked the citations separately, a discussion was made to achieve consensus once controversies existed.

Inclusion and exclusion criteria

Only articles in English were included. The inclusion criteria were: (I) studies that reported the impact of RASi on mortality after SAVR; (II) studies that reported the impact of RASi on mortality after TAVR; (III) studies that illustrated the particular number of death or survival curve regarding the RASi after AVR. Studies were excluded if one of the following existed: (I) studies were case reports, reviews, abstracts, guidelines, editorials, comments and conference presentations; (II) studies that were not related to human.

Data extraction and quality assessment

Two independent authors (L Zeng and J Li) extracted the

data and reached a consensus on all items from eligible studies including author, publication year, research category, type of RASi, sort of AVR, follow-up time and mortality. If mortality or number of death was not presented directly, digitizing software (Engauge Digtizer 4.1) were utilized to acquire relevant data from survival curve (14).

Study quality was evaluated using the Cross-Sectional/ Prevalence Study Quality Assessment Form or Newcastle-Ottawa Quality Assessment Scale (NOS) accordingly (15,16).

Data synthesis and statistical analysis

We combined data that reporting the impact of RASi on all-cause mortality and cardiac-cause mortality after AVR. Pooled odds ratios (OR) were gained using the Review Manage 5.3 software. Hazard ratios (HRs) were combined by using generic inverse variance method. Heterogeneity was evaluated by calculating the I^2 statistic and its P value. Random-effects model was used when the I^2 statistic was more than 50% and its P value was less than 0.05, otherwise, the fixed-effects model was carried out. Two-sided P values of 0.05 were considered statistically significant.

Publication bias analysis

Publication bias was assessed by visual inspection of the symmetry of the funnel plot. However, if the number of pooled studies was small, publication bias was not performed.

Subgroup analysis

Several subgroup analyses were performed including the impact of RASi on all-cause mortality within 30 days, 1 year and beyond 1 year, the impact of RASi on cardiac mortality beyond 1 year. The effect of RASi after SAVR and TAVR were carried out respectively. And, the influence of RASi on all-cause mortality after AVR based on the baseline LVEF was also performed. Besides, the impact of ACEI versus ARB after AVR was also conducted.

Results

Studies selection

The process of study selection was presented in Figure 1.

A total of 126 potential relevant citations were identified after initial search from PubMed database. After careful review of the title and abstract, 114 studies were excluded. There were 9 (17-25) articles incorporating 33,063 patients were eligible after reading full text. A summary of included studies is illustrated in *Table 1*.

Quality assessment

The quality of included single-arm studies were assessed using Cross-Sectional/Prevalence Study Quality, while the quality of eligible cohort studies was evaluated by using the NOS scale. Overall quality of these included studies was good.

Impact of RASi on all-cause mortality after AVR

A total of 6 (17,19,21,22,24,25), 6 (18,19,21,22,24,25), 6 (17-19,21,24,25) studies recruiting 27,435, 22,864 and 9,753 patients reported the effect of RASi after AVR, which revealed that patients taking RASi had a significant lower risk for mortality at 30 days (OR, 0.80, 95% CI, 0.69 to 0.94, I^2 =0%, *Figure 2*), 1 year (OR, 0.75, 95% CI, 0.69 to 0.81, I^2 =77%, *Figure 3*) and beyond 1 year (OR, 0.52, 95% CI, 0.38 to 0.73, I^2 =86%, *Figure 4*) after AVR respectively, compared to those patients without RASi.

Impact of RASi on all-cause mortality after TAVR

Consistently, there were 4 (17,21,22,25), 4 (18,21,22,25), and 4 (17,18,21,25) studies reporting that patients who took RASi had lower mortality at 30 days (OR, 0.76, 95% CI, 0.63 to 0.92, I^2 =0%, *Figure 2*), 1 year (OR, 0.76, 95% CI, 0.70 to 0.95, I^2 =86%, *Figure 3*) and beyond 1 year (OR, 0.65, 95% CI, 0.45 to 0.94, I^2 =80%, *Figure 4*) on the basis of incorporating 22,829, 20,604 and 7,493 patients separately.

Impact of RASi on all-cause mortality after SAVR

While, pooled studies displayed that patients having the description of RASi was associated with lower mortality at 1-year (OR, 0.53, 95% CI, 0.29 to 0.95, I^2 =41%, *Figure 3*) and beyond 1-year (OR, 0.39, 95% CI, 0.25 to 0.61, I^2 =73%, *Figure 4*) mortality, but not at 30-day (OR, 0.90, 95% CI, 0.68 to 1.19, I^2 =48%, *Figure 2*), based on 2 (19,24), 2 (19,24) and 2 (19,24) studies including 2,260, 2,260 and 4,606 patients.

Table I Characte	1150105 01	included studies					
Author	Year	Study design	Type of AVR	Number	Medication	Follow-up	Outcome
Rodriguez- Gabella (17)	2019	Retrospective cohort	TAVR	2,785	ACEI, ARB, ARNI, spironolactone, eplerenone	3 years	All-cause mortality, cardiovascular mortality
Ochiai (18)	2018	Prospective cohort	TAVR	560	ACEI, ARB	2 years	All-cause mortality
Magne (19)	2018	Retrospective cohort	SAVR	508	ACEI, ARB	8 years	All-cause mortality
Lassnigg (20)	2013	Prospective observational	SAVR	1,848	ACEI	5.8 years	All-cause mortality
Klinkhammer (21)	2019	Retrospective cohort	TAVR	169	ACEI, ARB	2 years	All-cause mortality
Inohara (22)	2018	Retrospective cohort	TAVR	21,312	ACEI, ARB	1 year	All-cause mortality, readmission for heart failure
Herron (23)	2019	Retrospective observational	TAVR	150	ACEI	3 years	All-cause mortality
Goel (24)	2014	Retrospective cohort	SAVR	1,752	ACEI, ARB	5.8 years	All-cause mortality
Chen (25)	2019	Prospective cohort	TAVR	3,979	ACEI, ARB	2 years	All-cause mortality, cardiovascular mortality

Table 1 Characteristics of included studies

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor.



Figure 2 The impact of RASi on 30-day all-cause mortality after AVR. RASi, renin-angiotensin system inhibitor; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

	RAS	51	No-R	ASI		Odds Ratio		Odds Ra	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed,	95% CI	
1.2.1 Patients under	went SAV	R								
Goel 2014	7	741	11	1011	0.7%	0.87 [0.33, 2.25]			-	
Magne 2018 Subtotal (95% CI)	10	268 1009	22	240 1251	1.6% 2.3%	0.38 [0.18, 0.83] 0.53 [0.29, 0.95]		•		
Total events	17		33							
Heterogeneity: Chi ² =	1.70, df	= 1 (P =	0.19); 1	= 41%						
Test for overall effect:	Z = 2.13	(P=0,	03)							
1.2.2 Patients under	went TAV	R								
Chen 2019	187	1736	388	2243	21.8%	0.58 [0.48, 0.70]		+		
Inohara 2018	994	7948	1184	7948	74.7%	0.82 [0.75, 0.89]				
Klinkhammer 2019	0	71	0	98		Not estimable				
Ochiai 2018 Subtotal (95% CI)	9	371 10126	13	189 10478	1.2% 97.7%	0.34 [0.14, 0.80] 0.76 [0.70, 0.82]				
Total events	1190		1585							
Heterogeneity: Chi ² =	14.10, di	F = 2 (P)	= 0.000	9); $l^2 = 8$	6%					
Test for overall effect:	Z = 6.73	(P < 0.	00001)							
Total (95% CI)		11135		11729	100.0%	0.75 [0.69, 0.81]				
Total events	1207		1618							
Heterogeneity: Chi ² =	17.16, di	f = 4 (P)	= 0.002)	$ 1^2 = 77$	%		0.01	a11	10	100
Test for overall effect:	Z = 6.96	(P < 0.	00001)				0.01	Eavours RASi Fa	TU NO-RAS	100
Test for subgroup diff	ferences: ($Chi^2 = 1$.43, df =	1 (P = 0)).23), l ² =	= 30.2%		ravours (ASI Ta		

Figure 3 The impact of RASi on mortality within 1 year after AVR. RASi, renin-angiotensin system inhibitor; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

	RAS	51	No-R	ASi		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
1.3.1 Patients underwent	SAVR								
Goel 2014	170	741	392	1011	21.5%	0.47 [0.38, 0.58]		+	
Magne 2018 Subtotal (95% CI)	41	268 1009	91	240 1251	17.0% 38.5%	0.30 [0.19, 0.45] 0.39 [0.25, 0.61]			
Total events	211		483						
Heterogeneity: $Tau^2 = 0.0$	8; Chi ² =	3.69, d	f = 1 (P)	= 0.05); $l^2 = 73$	%			
Test for overall effect: Z =	4.15 (P <	0.000	1)						
1.3.2 Patients underwent	TAVR								
Chen 2019	316	1736	606	2243	22.5%	0.60 [0.52, 0.70]		-	
Klinkhammer 2019	2	71	13	98	3.9%	0.19 [0.04, 0.87]			
Ochiai 2018	27	371	24	189	13.6%	0.54 [0.30, 0.96]			
Rodriguez-Gabella 2019 Subtotal (95% CI)	235	1622 3800	178	1163 3693	21.5% 61.5%	0.94 [0.76, 1.16] 0.65 [0.45, 0.94]		•	
Total events	580		821						
Heterogeneity: $Tau^2 = 0.0$	9; Chi ² =	14.66,	df = 3(1)	P = 0.0	$(02); I^2 =$	80%			
Test for overall effect: Z =	2.27 (P =	= 0.02)							
Total (95% CI)		4809		4944	100.0%	0.52 [0.38, 0.73]		•	
Total events	791		1304					United and a second second	
Heterogeneity: $Tau^2 = 0.1$	2; Chi ² =	35.31,	df = 5(1)	P < 0.0	0001); l ²	= 86%	0.01		100
Test for overall effect: Z =	3.86 (P =	0.000	1)				0.01	Eavours PASi Eavours No. PAS	100
Test for subgroup differen	ces: Chi ²	= 3.04.	df = 1(P = 0.0	(8), $l^2 = 6$	7.1%		ravours RASI Favours NO-RAS	6

Figure 4 The impact of RASi on all-cause mortality beyond 1 year after AVR. RASi, renin-angiotensin system inhibitor; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

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Impact of RASi on all-cause mortality after AVR by using univariate and multivariate analysis

In order to exclude the influence of confounders on outcome, we also pooled studies that reported the HR of RASi after AVR. We found that patients taking RASi was associated with reduced mortality beyond 1 year compared to those did not take RASi after AVR (HR, 0.84, 95% CI, 0.77 to 0.91, I^2 =82%, Figure S1) by using univariate analysis based on the combination of 7 (17-19,22-25) studies. In line with pooled univariate analysis, combined multivariate analysis also revealed a significant improvement of long-term survival in patients with RASi after AVR (HR, 0.87, 95% CI, 0.84 to 0.91, I^2 =0%, Figure S2) on the basis of pooling 5 (18-20,24,25) studies.

Impact of RASi on all-cause mortality after TAVR by using univariate and multivariate analysis

A total of 5 (17,18,22,23,25) studies found that patients taking RASi had lower risk for mortality beyond 1 year than those patients without RASi after TAVR (HR, 0.89, 95% CI, 0.82 to 0.96, I^2 =71%, Figure S1) by using univariate analysis. Consistently, combined multivariate analysis also figured out that patients with RASi after TAVR were associated with significant reduced mortality beyond 1 year (HR, 0.87, 95% CI, 0.84 to 0.91, I^2 =0%, Figure S2) by pooling 2 (18,25) studies.

Impact of RASi on all-cause mortality after SAVR by using univariate and multivariate analysis

Except for the impact of RASi after TAVR, we also pooled studies that reported the impact of RASi after SAVR by using univariate and multivariate analysis. There were 2 (19,24) and 3 (19,20,24) studies displaying that patients taking RASi were associated lower mortality beyond 1 year compared to those patients without RASi after SAVR by using univariate analysis (HR, 0.73, 95% CI, 0.56 to 0.96, I^2 =88%, Figure S1) and multivariate analysis (HR, 0.89, 95% CI, 0.84 to 0.93, I^2 =0%, Figure S2) respectively.

Impact of RASi on all-cause mortality regarding the baseline LVEF

Combined results (22,25) found that patients with reduced LVEF, taking RASi were associated with numerically lower mortality (HR, 0.91, 95% CI, 0.77 to 1.07, I^2 =76%,

Figure S3). While, interestingly, patients with preserved LVEF (22,25), having a prescription of RASi had significant lower mortality (HR, 0.90, 95% CI, 0.87 to 0.94, $I^2=0\%$, Figure S3) than those patients without RASi. Besides, Goel *et al.* (24) also found that the favorable effect of RASi after SAVR was consistent across patients with reduced (P<0.05) and preserved LVEF (P<0.05).

Impact of RASi on all-cause mortality regarding the type of RASi

Magne *et al.* (19) described the relationship between the type of RASi and mortality, reporting that ARB had the best long-term survival, ACEI had the intermediate survival as compared with those patients without RASi (8-year survival, ARB *vs.* ACEI *vs.* no-RASi, 87% *vs.* 79% *vs.* 52%, P<0.0001). Besides, after multivariable adjustment, they also demonstrated that patients with ARB was associated with lower risk for long-term all-cause mortality after SAVR (HR, 0.66, 95%, 0.48 to 0.93), compared to those patients with ACEI.

We also pooled studies that reported the impact of ACEI and ARB on all-cause mortality beyond 1 year in patients undergoing TAVR. The combined results showed that both ARB (22,25) (HR, 0.89, 95% CI, 0.85 to 0.94, I^2 =0%, Figure S4) and ACEI (22,25) (HR, 0.89, 95% CI, 0.81 to 0.99, I^2 =79%, Figure S4) had lower all-cause mortality than those patients without RASi. Furthermore, there was no significant difference between patients taking ARB and ACEI after TAVR beyond 1 year (22,25) (ARB *vs.* ACEI, HR, 0.98, 95% CI, 0.89 to 1.09, I^2 =62%, Figure S4).

Impact of RASi on cardiovascular mortality after TAVR

In addition to all-cause mortality, we also performed analysis to investigate the effect of RASi on cardiovascular mortality after TAVR. Pooled studies demonstrated that patients with RASi had lower cardiovascular mortality than those patients without RASi after TAVR [30 days (17,25), OR, 0.63, 95% CI, 0.44 to 0.90, I^2 =22%; 1 year (17,25), OR, 0.60, 95% CI, 0.50 to 0.73, I^2 =0%; beyond 1 year (17,25), OR, 0.63, 95% CI, 0.54 to 0.74, I^2 =0%, Figure S5].

Consistently, pooled univariate (17,25) (HR, 0.83, 95% CI, 0.78 to 0.89, I²=0%, Figure S6) and multivariate (17,25) (HR, 0.84, 95% CI, 0.78 to 0.91, I²=0%, Figure S6) analyses showed that patients taking RASi after TAVR were correlated with reduced cardiovascular mortality beyond 1-year follow-up, compared to those patients who did not

take RASi.

Discussion

The main results of the present study were as follows: (I) patients with RASi had lower all-cause mortality at 30 days (OR, 0.80, 95% CI, 0.69 to 0.94), 1 year (OR, 0.75, 95% CI, 0.69 to 0.81) and beyond 1 year (OR, 0.52, 95% CI, 0.38 to 0.73) after AVR; (II) the combined results showed that both ARB (HR, 0.89, 95% CI, 0.85 to 0.94) and ACEI (HR, 0.89, 95% CI, 0.81 to 0.99) had lower all-cause mortality after TAVR, compared to those without RASi; (III) patients with preserved LVEF having a prescription of RASi were associated with reduced mortality (HR, 0.90, 95% CI, 0.87 to 0.94) TAVR; (IV) pooled multivariable analysis also revealed that patients taking RASi after TAVR was associated with lower risk for cardiovascular mortality (HR, 0.84, 95% CI, 0.78 to 0.91).

Myocardial hypertrophy was common in patients with AS, secondary to LV outflow obstruction and increased afterload (26). Progressive myocardial hypertrophy would yield fibrosis and subsequent LV dysfunction (26). More evidence found that RAS contributed to the occurrence of myocardial hypertrophy and fibrosis, RASi could reverse myocardial fibrosis to some extent (2). However, in the past, taking RASi in patients with AS was considered to be unsafe because the vasodilation effect in the presence of LV outflow obstruction would cause hypotension (5). In fact, patients with AS taking RASi was not only safe but also engendered favorable effect on survival, LV regression and even AS progression (6,7).

Existing data reported that patients with LV hypertrophy and fibrosis undergoing AVR was associated with increased mortality, and irreversible LV hypertrophy as well as fibrosis after AVR was not rare which also affected long-term mortality (10,11,13). However, no specific recommendations were provoked to take optimal medication following AVR to enhance the outcome of AVR including SAVR and TAVR. Therefore, there was still a gap regarding the optimal medication after AVR that could improve longterm prognosis.

Although several studies reported the impact of RASi on mortality after AVR, their results were controversy (18,23-25). The present study found that patients receiving RASi who underwent AVR were associated with reduced all-cause mortality at 30 days, 1 year and beyond 1 year, as compared with those patients without RASi, which is in consistence with previous propensity score-matched population studies (17,22,25). The combined results were still positive after adjusting confounders independent of the type of RASi including ACEI and ARB. The beneficial effect of RASi on all-cause mortality may be attributed to the decreased cardiovascular mortality in patients with RASi as the present study also revealed that patients undergoing TAVR with RASi had lower cardiovascular mortality than those patients without RASi. This might be account for the potential role of RASi in further attenuation of LV hypertrophy and fibrosis after AVR, since incompletely reversed LV hypertrophy and fibrosis after AVR were correlated with increased mortality (17,18,24,27).

Increasing evidence demonstrated the significant benefit of RASi in patients with reduced ejection fraction, while the impact of RASi on clinical outcome in patients with preserved ejection fraction was negative (28). However, we found that the beneficial effect of RASi after TAVR was independent of LVEF which is in line with prior study incorporating patients after SAVR described by Goel et al. (24). This might be related to the different pathophysiological mechanism for preserved ejection fraction in patients with AS and other cardiovascular diseases (29). A randomized clinical trial (RCT) containing 114 patients with preserved ejection fraction undergoing SAVR demonstrated that description of candesartan was associated with increased reverse LV remodeling as compared to those patients without RASi, which also might be suggestive of positive effect in patients with TAVR (27). Since the effect of RASi in patients following AVR primarily based on retrospective analysis, RCTs are warranted to evaluate the impact of RASi on mortality after AVR including SAVR and TAVR. Fortunately, RASTAVI, an ongoing RCT, could provide more information to determine the use of RASi (30).

Limitation

Firstly, all the included studies are not RCTs, which might have selection bias. Patients receiving RASi might be more stable and healthier that could tolerate the treatment of RASi. However, the present study found that patients having description of RASi was associated with reduced long-term mortality even after adjustment of confounders; Secondly, several combined results were based on fewer studies with considerable heterogeneity, which needed more studies to confirm these hypothesis-generating findings.

Conclusions

Patients with RASi had reduced short-term and long-term all-cause mortality after AVR than those without RASi. Description of RASi was associated with lower risk for cardiovascular mortality in patients undergoing TAVR. Further studies were needed to confirm these findings.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/apm-20-1155). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Study or Subaroup	loo[Hazard Ratio]	SE	Weight	Hazard Ratio IV. Random, 95% CI	Hazard Ratio IV. Random, 95% Cl
1.4.1 Patients underwent	SAVR				
Goel 2014	-0.18	0.052	17.3%	0.84 [0.75, 0.92]	
Magne 2018	-0.46	0.082	12.8%	0.63 [0.54, 0.74]	<u> </u>
Subtotal (95% CI)			30.1%	0.73 [0.56, 0.96]	
Heterogeneity: $Tau^2 = 0.0$	3; Chi ² = 8.32, df =	1 (P = 0)	.004); I ²	= 88%	
Test for overall effect: $Z =$	2.24 (P = 0.03)				
1.4.2 Patients underwent	TAVR				
Chen 2019	-0.19	0.029	20.7%	0.83 [0.78, 0.88]	
Herron 2019	-0.057	0.21	3.7%	0.94 [0.63, 1.43]	
Inohara 2018	-0.086	0.018	21.9%	0.92 [0.89, 0.95]	
Ochiai 2018	-0.33	0.15	6.3%	0.72 [0.54, 0.96]	+
Rodriguez-Gabella 2019	-0.032	0.053	17.2%	0.97 [0.87, 1.07]	
Subtotal (95% CI)			69.9%	0.89 [0.82, 0.96]	•
Heterogeneity: $Tau^2 = 0.0$	0; Chi ² = 13.77, df =	= 4 (P =	0.008); 1	$^{2} = 71\%$	
Test for overall effect: Z =	3.01 (P = 0.003)				
Total (95% CI)			100.0%	0.84 [0.77, 0.91]	•
Heterogeneity: $Tau^2 = 0.0$	1: Chi ² = 32.58. df =	= 6 (P <	0.0001);	$l^2 = 82\%$	- da da da da da da
Test for overall effect: Z =	3.98 (P < 0.0001)	10.0	111111	en contration	0.7 0.85 1 1.2 1.5 Favours PASi Favours No PASi
Test for subgroup differen	ices: Chi ² = 1.75, df	= 1 (P =	0.19), I ²	= 42.8%	ravours KASI Favours NO-KASI

Figure S1 The impact of RASi on all-cause mortality beyond 1 year after AVR by pooling univariate estimate effects. RASi, reninangiotensin system inhibitor; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Ctudie on Cubaroun	leaflight Patiol		Waight	Hazard Ratio		Hazard	Ratio	
1 5 1 Patients under	IOG[Hazard Katio]	SE	weight	IV, Fixed, 95% CI		IV, Fixed,	, 95% CI	
1.5.1 Fatients under	Went SAVK							
Goel 2014	-0.15	0.035	33.5%	0.86 [0.80, 0.92]				
Lassnigg 2013	-0.082	0.039	26.9%	0.92 [0.85, 0.99]				
Magne 2018	-0.13	0.095	4.5%	0.88 [0.73, 1.06]		-		
Subtotal (95% CI)			64.9%	0.89 [0.84, 0.93]		*		
Heterogeneity: Chi ² =	1.69, $df = 2 (P = 0.1)$.43); l ² =	= 0%					
Test for overall effect	Z = 4.79 (P < 0.00)	001)						
1.5.2 Patients under	went TAVR							
Chen 2019	-0.15	0.035	33.5%	0.86 [0.80, 0.92]				
Ochiai 2018	-0.35	0.16	1.6%	0.70 [0.51, 0.96]				
Subtotal (95% CI)		10000	35.1%	0.85 [0.80, 0.91]		•		
Heterogeneity: Chi ² =	1.49, $df = 1 (P = 0)$	22); 1 ² =	= 33%					
Test for overall effect	Z = 4.65 (P < 0.00)	001)						
Total (95% CI)			100.0%	0.87 [0.84, 0.91]		1		
Heterogeneity: $Chi^2 =$	4.02, $df = 4$ (P = 0)	40): 1 ² =	= 0%		1	10		
Test for overall effect	7 - 6 62 (P < 0.00	001)			0.01	0.1 1	. 10	100
Test for subgroup dif	L = 0.02 (1 < 0.00)		10 0 0	C) 12 00/		Favours RASi	Favours NoRASi	
lest for subgroup dif	terences: $Chr = 0.83$	$a_{1} = 1$	(P = 0.3)	$(0), \Gamma = 0\%$				

Figure S2 The impact of RASi on all-cause mortality beyond 1 year after AVR by pooling multivariate estimate effects. RASi, reninangiotensin system inhibitor; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.8.1 LVEF < 50%				- 11/2 1 20 ST	
Chen 2019	-0.19	0.074	12.4%	0.83 [0.72, 0.96]	
Inohara 2018	-0.022	0.036	29.1%	0.98 [0.91, 1.05]	-
Subtotal (95% CI)			41.5%	0.91 [0.77, 1.07]	-
Heterogeneity: Tau ² =	= 0.01; Chi ² = 4.17,	df = 1 (P = 0.04); $l^2 = 76\%$	
Test for overall effect	Z = 1.13 (P = 0.26))			
1.8.2 LVEF>=50%					
Chen 2019	-0.14	0.056	18.3%	0.87 [0.78, 0.97]	
Inohara 2018	-0.1	0.021	40.2%	0.90 [0.87, 0.94]	
Subtotal (95% CI)			58.5%	0.90 [0.87, 0.94]	•
Heterogeneity: Tau ² =	$= 0.00; Chi^2 = 0.45,$	df = 1 (P = 0.50); $I^2 = 0\%$	
Test for overall effect	Z = 5.34 (P < 0.00)	001)			
Total (95% CI)			100.0%	0.91 [0.86, 0.96]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 6.41,	df = 3(P = 0.09); $I^2 = 53\%$ —	
Test for overall effect	Z = 3.18 (P = 0.00)	1)			0.5 0.7 1 1.5 2
Test for subgroup dif	ferences: $Chi^2 = 0.02$	2, df = 1	(P = 0.8)	(9), $l^2 = 0\%$	Favours RASI Favours NO-RASI

Figure S3 The impact of RASi on all-cause mortality after TAVR regarding the baseline left ventricular ejection fraction. RASi, reninangiotensin system inhibitor; TAVR, transcatheter aortic valve replacement; LVEF, left ventricular ejection fraction.



Figure S4 The impact of RASi on all-cause mortality after TAVR regarding the type of RASi. RASi, renin-angiotensin system inhibitor; TAVR, transcatheter aortic valve replacement; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

	RAS	ii 🛛	No-F	ASi		Odds Ratio		Odds Ra	tio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed,	95% CI	
1.6.1 at 30 days										
Chen 2019	32	1736	56	2243	6.2%	0.73 [0.47, 1.14]				
Rodriguez-Gabella 2019	19	1622	28	1163	4.2%	0.48 [0.27, 0.86]				
Subtotal (95% CI)		3358		3406	10.4%	0.63 [0.44, 0.90]		•		
Total events	51		84							
Heterogeneity: $Chi^2 = 1.28$	df = 1 (l)	P = 0.20	6); $l^2 = 2$	2%						
Test for overall effect: Z =	2.56 (P =	0.01)								
1.6.2 at 1 year										
Chen 2019	130	1736	267	2243	27.8%	0.60 [0.48, 0.75]		-		
Rodriguez-Gabella 2019	55	1622	62	1163	9.0%	0.62 [0.43, 0.90]				
Subtotal (95% CI)		3358		3406	36.8%	0.60 [0.50, 0.73]		•		
Total events	185		329					1.1		
Heterogeneity: Chi ² = 0.03	df = 1 (1)	P = 0.80	$(5); 1^2 = 0$	%						
Test for overall effect: Z =	5.21 (P <	0.0000)1)							
1.6.3 beyond 1 year										
Chen 2019	203	1736	378	2243	37.6%	0.65 [0.54, 0.78]				
Rodriguez-Gabella 2019	90	1622	107	1163	15.2%	0.58 [0.43, 0.78]				
Subtotal (95% CI)		3358		3406	52.8%	0.63 [0.54, 0.74]		•		
Total events	293		485							
Heterogeneity: Chi ² = 0.46	df = 1 (l)	P = 0.50	0); $l^2 = 0$	%						
Test for overall effect: Z =	5.79 (P <	0.0000)1)							
Total (95% CI)		10074		10218	100.0%	0.62 [0.56, 0.70]				
Total events	529		898							
Heterogeneity: $Chi^2 = 1.90$), $df = 5$ (1	P = 0.8	6); $I^2 = 0$	%			10.01	-	ta	100
Test for overall effect: Z =	8.19 (P <	0.0000)1)				0.01		10	100
Test for subgroup differen	ces: Chi ² =	0.13.	df = 2 (P	= 0.94)	$1^2 = 0\%$			ravours RASI Fa	VOUIS NO-KA	51

Figure S5 The impact of RASi on cardiovascular mortality after TAVR. RASi, renin-angiotensin system inhibitor; TAVR, transcatheter aortic valve replacement.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% Cl
1.7.1 univariate analysis					
Chen 2019	-0.18	0.037	48.0%	0.84 [0.78, 0.90]	
Rodriguez-Gabella 2019 Subtotal (95% CI)	-0.21	0.081	10.0% 58.0%	0.81 [0.69, 0.95] 0.83 [0.78, 0.89]	•
Heterogeneity: $Chi^2 = 0.1$	1, $df = 1 (P = 0.74)$;	$^{2} = 0\%$			
Test for overall effect: Z =	5.50 (P < 0.00001)				
1.7.2 multivariate analys	sis				
Chen 2019	-0.16	0.045	32.4%	0.85 [0.78, 0.93]	
Rodriguez-Gabella 2019 Subtotal (95% CI)	-0.23	0.083	9.5% 42.0%	0.79 [0.68, 0.93] 0.84 [0.78, 0.91]	•
Heterogeneity: $Chi^2 = 0.5$	5, $df = 1 (P = 0.46); I$	$^{2} = 0\%$			
Test for overall effect: Z =	4.45 (P < 0.00001)				
Total (95% CI)			100.0%	0.83 [0.79, 0.88]	•
Heterogeneity: $Chi^2 = 0.70$	0, df = 3 (P = 0.87); I	$^{2} = 0\%$			to also also also also
Test for overall effect: Z =	7.07 (P < 0.00001)				0.7 0.85 1 1.2 1.5 Favours BASi Favours No BASi
Test for subgroup differen	nces: Chi ² = 0.03, df =	= 1 (P =	0.86), l ²	= 0%	Favours RASI Favours NO-RASI

Figure S6 The impact of RASi on cardiovascular mortality beyond 1 year after TAVR by pooling univariate and multivariate estimate effects. RASi, renin-angiotensin system inhibitor; TAVR, transcatheter aortic valve replacement.