

Clinical Study

# A retrospective cohort analysis of the effects of renin-angiotensin system inhibitors on spinal fusion in ACDF patients

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## Abstract

**BACKGROUND CONTEXT:** Recently, preclinical and clinical studies suggest an association between renin-angiotensin system (RAS) blockers and bone healing, particularly in the context of osteoporotic bone fractures.

**PURPOSE:** To determine the correlation between the use of RAS inhibitors and fusion outcomes and neurologic status in anterior cervical discectomy and fusion (ACDF) surgery.

**STUDY DESIGN:** Retrospective observational study.

**PATIENT SAMPLE:** Patients who underwent ACDF for degenerative disorders.

**OUTCOME MEASURES:** Spinal fusion status and neurologic function (modified Japanese Orthopedic Association [mJOA] and Nurick grading scales).

**METHODS:** A retrospective chart review was performed, including 200 patients who underwent ACDF for degenerative disorders with 1-year minimum follow-up. Demographic data, comorbidities, antihypertensive medication, neurologic examination, and fusion status were collected. Spinal fusion was assessed via plain cervical x-ray, resorting to dynamic radiographs and/or computer tomography (CT) in cases of uncertainty. Preoperative mJOA and Nurick scores and recovery rates were calculated to determine neurologic status.

**RESULTS:** Of the 200 patients (42.5% females, 57.5% males, median age of 53.7 years), 82 hypertensive patients were identified. Seventy-seven (93.9%) were taking antihypertensive medication as follows: 36.4% angiotensin-II receptor blockers (ARBs), 35.1% angiotensin-converting enzyme inhibitors (ACEIs), and the remaining patients were taking other medication. In the analysis of fusion rates, patients treated with ARBs exhibited a higher fusion rate, while those treated with ACEIs displayed a lower fusion rate compared to untreated nonhypertensive patients ( $p = .04$  and  $.02$ , respectively). The difference in fusion rates between ARBs and ACEIs was also significant, with the former displaying higher rates ( $p < .001$ ). Smoking exhibited a negative correlation with spinal fusion ( $p < .001$ ). In the multivariate analysis, ARBs remained an independent factor for successful fusion ( $p = .02$ ), while smoking remained a risk factor for failed fusion ( $p = .002$ ). In the neurologic examination, ACEIs, hypertension status, and older age correlated with lower modified Japanese Orthopedic Association (mJOA) recovery rates ( $p = .001$ ,  $<.001$ , and  $<.001$ , respectively) in the univariate analysis.

FDA device/drug status: Not applicable.

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**CONCLUSIONS:** In ACDF patients, we observed that ARBs were associated with higher fusion rates. Conversely, ACEIs and smoking were related to failed fusion. Prospective case-control studies are needed to confirm these RAS inhibitors effects on spinal fusion. © 2019 Elsevier Inc. All rights reserved.

**Keywords:** Angiotensin-II receptor blockers; Angiotensin-converting enzyme inhibitors; Anterior cervical discectomy and fusion; Cervical spondylosis; Osteoblast; Osteoclast; Pseudarthrosis; Renin-angiotensin system; Spinal fusion

## Introduction

The renin-angiotensin system (RAS) is well known for its significant role in circulatory homeostasis; and therefore, RAS blocker drugs are commonly used in the treatment of cardiovascular diseases [1], such as arterial hypertension, which affects 50% to 80% of spinal fusion patients [2]. Recent evidence suggests an association between RAS blockers and bone metabolism, particularly in the context of bone healing. In animal models, angiotensin-II (AngII) has been shown to decrease bone mass, while blockage of RAS signaling (mainly via angiotensin-II receptor blockers [ARBs]) seems to counteract these effects. For example, in ovariectomized mice, Zhou et al. [3] demonstrated that AngII accelerated osteoporotic bone resorption, while treatment with AT1R and AT2R blockers relieved AngII-induced osteoporosis. In ovariectomized rats that underwent transverse osteotomy of the proximal metaphysis of the femur, Rajkumar et al. reported that angiotensin-converting enzyme inhibitors (ACEIs) and ARBs increased the consolidation of experimental osteoporotic fractures and the average value of the microcirculation in the fracture zones [4]. In addition, clinical studies have suggested a potential correlation between the use of RAS blockers and reduced osteoporotic fracture risk. Chen et al. [5] reported a significantly higher incidence of osteoporotic fractures in hypertensive patients not treated with RAS inhibitors compared to those who were treated. This association between RAS inhibitors and bone metabolism may play a critical role in spinal fusion patients who also suffer from arterial hypertension. The purpose of this study was to determine whether there is a correlation between the use of antihypertensive medication, particularly AngII inhibitors, and outcomes in anterior cervical discectomy and fusion (ACDF) surgery.

## Methods

### *Study design, setting, and participants*

We performed a retrospective study according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [6] guidelines to investigate whether there is a correlation between spinal fusion outcomes in a cohort of ACDF patients and

treatment with AngII inhibitors. A chart review of patients who underwent ACDF at a single institution was performed, with prior Institutional Review Board approval (IRB00178932). A cohort of adult patients of both sexes, with symptomatic cervical degenerative disorders as the indication for surgery, operated on from January 2016 to June 2017, using allograft as bone graft, and with a 1-year minimum follow-up was considered eligible. Patients with a past medical history of spine surgery at any other level besides cervical, incomplete data, or lost to follow-up were excluded.

### *Variables and data sources*

Information on demographic data, comorbidities (especially hypertension status), antihypertensive medication, neurologic examination, and fusion status were collected. Two blinded researchers extracted the clinical and imaging data separately. Hypertension diagnosis was established according to the American College of Cardiology and the American Heart Association (ACC/AHA) 2017 Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults [7]. Antihypertensive medication was classified by type into five groups: angiotensin-II type-1 receptor blockers (ARB), angiotensin-2 converting enzyme inhibitors (ACEI), beta-blockers (BB), calcium channel blockers (CCB), and diuretics. Neurologic examination was evaluated at two separate time points (before surgery and during the last clinical visit) via the modified Japanese Orthopedic Association (mJOA) [8] and Nurick [9] grading scales. Recovery rate was calculated using the pre- and postoperative mJOA scores according to the following formula:  $mJOARR = (\text{follow-up mJOA} - \text{preoperative mJOA}) \times 100 / (18 - \text{preoperative mJOA})$  [10]. Spinal fusion was evaluated via plain cervical x-ray, resorting to dynamic radiographs and/or computer tomography (CT) in cases of doubt, using the Vue Picture Archiving Communication System (PACS) (Carestream Health Inc, Rochester, NY). Fusion criteria in static radiographs were increased opacification and bridging trabecular bone at the margins of the graft [11]. In dynamic radiographs, fusion criteria were interspinous motion of <1 mm and superjacent interspinous motion of <4 mm [12]. For CT scans, fusion criteria were solid bridging of bone across the disc space of the intended fusion.

*Bias, study size, quantitative variables, statistical methods*

Statistical analysis was performed by a third blinded researcher. Minimal sample size was calculated as described by Schoenfeld [13]. Complete-case analysis was performed with no missing data identified. Univariate analyses were performed using unpaired *t* test and Mann-Whitney *U* test. Contingency tables and Fisher's exact test were implemented, and relative risks (RR) were calculated within a 95% confidence interval (CI). Two-tailed *p* values were considered statistically significant when lower than .05. Pearson and Spearman's tests were applied for assessing correlations. Median follow-up time was calculated using the Schemper and Smith method. Multivariate analyses were also performed, including the resulting significant variables from the univariate analyses. All analyses were performed using GraphPad Prism 7 (GraphPad Software, Inc., La Jolla, CA) and JMP Pro 13 (SAS Institute Inc, Cary, NC).

**Results***Demographic and clinical data*

A total of 200 patients with cervical degenerative disorders who underwent ACDF were identified, including 85 females (42.5%) and 115 males (57.5%), with a median age of 53.7 (range 24–90) years. Median follow-up was 21.7 months (range 12.2–44.3). Out of the included patients, 32 smokers (16%), 39 diabetic patients (19.5%), and 82 hypertensive patients (41%) were identified. Out of the 82 hypertensive patients, 77 (93.9%) were taking antihypertensive drugs (28 [36.4%] received ARBs, 27 [35.1%] received ACEIs, and the remaining patients were taking other medication). Reporting results, the term “untreated” was employed for patients not taking antihypertensive medication (ie, mostly nonhypertensive patients). Regarding the number of levels operated upon, 89 (44.5%), 87 (43.5%), and 24 (12%) patients underwent a single-level, two-level, and three-level discectomy, respectively, with C5–C6 (35; 17.5%), C5–C7 (47; 23.5%), and C4–C7 (14; 7%) as the most frequently treated levels. More detailed demographic data are shown in Table 1.

*Fusion assessment*

The overall pooled fusion rate was 69.5%. Hypertensive patients treated with ARBs exhibited a higher fusion rate compared to those who were untreated nonhypertensive (88.9% vs. 69.7%, respectively,  $p = .04$ ). By contrast, hypertensive patients treated with ACEIs displayed a lower fusion rate than untreated nonhypertensive patients (45.8% vs. 69.7%, respectively,  $p = .02$ ). The difference in fusion rates between ARB and ACEI treatment was significant in favor of the former ( $p < .001$ ). Even

Table 1  
Demographic and clinical data

	n = 200	
Age (y)	53.7±11.6	
Gender		
Female	85	42.5%
Male	115	57.5%
Follow-up period (mo)	22.2±7.3	
Smoking	32	16%
Previous cervical surgery	24	12%
Diabetes	39	19.5%
Hypertension	82	41%
Antihypertensive medication	77	38.5%
ARB	28	36.4%
ACEI	27	35.1%
Others	24	31.1%
Fusion	139	69.5%
Functional status		
Preoperative mJOA score	14.4±2.3	
Preoperative Nurick grade	1.2±1.3	
mJOA recovery rate (%)	72.5±30.2	
Number of operated levels		
One-level	89	44.5%
Two-level	87	43.5%
Three-level	24	12%
Most frequent operated levels		
C5–C6	35	17.5%
C5–C7	47	27.5%
C4–C7	14	7%

ARB, angiotensin-II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; mJOA, modified Japanese Orthopaedic Association.

though treatment with ARBs and ACEIs displayed a significant disparity, there was no difference between the group of patients taking antihypertensives as a whole and the group of untreated nonhypertensive patients (69.2% and 69.7%, respectively,  $p > .05$ ). Smoking presented a negative correlation with fusion compared to nonsmokers (37.5% vs 74.5%, respectively,  $p < .001$ ). Age, hypertension, and diabetes status did not display any significant effect on fusion rates (Table 2). Comparisons between successful fusion and failed fusion groups identified smoking (RR = 0.5, 95% CI 0.2, 0.8) and treatment with ACEIs (RR = 0.6, 95% CI 0.4, 1.0) as risk factors for the development of pseudarthrosis. Treatment with ARBs displayed a trend toward being a favorable factor for fusion (RR = 1.2, 95% CI 1.0, 1.5); however, this trend did not reach statistical significance.

*Functional evaluation*

The correlation between fusion status and neurologic assessment was examined. Higher preoperative mJOA and lower preoperative Nurick scores were correlated with successful fusion ( $r = 0.21$ ,  $p = .004$ ; and  $r = -0.16$ ,  $p = .03$ , respectively), indicating that patients with better preoperative clinical status were more likely to fuse. As well, the mJOA recovery rate was positively associated with fusion ( $r = 0.20$ ,

$p = .007$ ), suggesting that patients who fused tended to recover to a more significant extent.

In our population, mJOA and Nurick scores improved after surgery ( $p < .001$ ), with an overall mJOA recovery rate of 70.9% (95% CI 66.3, 75.6). In the neurologic examination analysis, treatment with ACEIs was correlated with lower preoperative mJOA ( $p = .001$ ) and higher preoperative Nurick ( $p < .001$ ) scores compared to untreated nonhypertensive patients. Also, patients treated with ACEIs displayed a lower mJOA recovery rate ( $p = .001$ ) than patients with no treatment. Although patients treated with ARBs did not exhibit any significant difference when were compared to untreated nonhypertensive patients, they displayed lower preoperative Nurick ( $p = .04$ ) scores and a higher mJOA recovery rate ( $p = .05$ ) than those treated with ACEIs. Hypertensive patients showed lower preoperative mJOA ( $p = .002$ ) and higher preoperative Nurick ( $p < .001$ ) scores, in addition to lower mJOA recovery rates ( $p < .001$ ), compared to nonhypertensive patients. Smoking was associated with a lower preoperative mJOA score ( $p = .007$ ); however, no significant difference was seen either in the preoperative Nurick score or in the mJOA recovery rate ( $p > .05$ ). Older age was correlated with worse preoperative functional scores ( $p < .001$ ) and lower mJOA recovery rates ( $p < .001$ ). Diabetes status did not significantly influence neurologic examination scores (Table 3).

### Multivariate analysis

In the multivariate nominal logistic analysis, the model was adjusted for clinical covariables that were considered relevant or were significant in the univariate analysis for fusion and recovery rate. After adjusting for age, smoking, and treatment with ARBs and ACEIs, smoking ( $p = .002$ )

and ARB ( $p = .02$ ) treatment remained an independent risk and beneficial factor, respectively, for fusion. Additionally, in the multivariate least squares fitting, age and hypertension status remained independent risk factors for lower recovery rate after adjusting ( $p = .003$  and  $.02$ , respectively; Tables 2 and 3).

### Discussion

In this study, the statistical analysis revealed RAS blockade to be a significant factor for fusion in ACDF patients. With a median follow-up of 22 months, patients treated with ARBs presented a significantly higher fusion rate ( $p = .04$ ), while patients treated with ACEIs displayed a higher rate of fusion failure ( $p = .02$ ). As in previous studies [14,15], smoking was also correlated with a higher rate of pseudarthrosis ( $p < .001$ ). Age, hypertension status, and treatment with ACEIs were associated with worse functional status and recovery rates in the univariate analysis. Similar to previous reports on the influence of RAS blockers on bone, our findings suggest an effect of these drugs on spinal arthrodesis.

Recently, bone researchers have become increasingly interested in RAS signaling. In vitro and in vivo studies suggest that RAS may play a role in bone metabolism, osteoporosis, and bone healing [4,16–18], while clinical studies have shown a reduction in osteoporotic fracture risk in hypertensive patients treated with RAS blockers [19,20]. However, the effects of RAS on fusion outcomes have yet to be explored. As in the circulatory system, the effects of RAS in bone tissue seem to be mainly mediated by angiotensin-II via angiotensin-II type-1 (AT1R) and type-2 (AT2R) receptor signaling [3]. Interestingly, in this study, we identified that treatment with ARBs and ACEIs

Table 2  
Univariate and multivariate analysis on predictors of fusion

	Fusion rates		Univariate p	Multivariate			
	Yes	No		OR [95% CI]	p		
Age	−0.0012 [95% CI −0.16, 0.13]*		.86	0.7 [−0.02, 0.04]	.70		
Gender (F:M)	77	75.3 ± 4.9	100	65.0 ± 4.7	.14	0.2 [−0.5, 0.1]	.29
Smoking	24	37.5 ± 10.0	153	74.5 ± 3.5	<b>&lt;.001</b>	0.003 [−1.2, −0.2]	<b>.002</b>
Previous cervical surgery	24	75.0 ± 4.9	153	68.6 ± 3.7	.53		
Diabetes	37	59.4 ± 8.1	140	72.1 ± 3.8	.13	0.3 [−0.6, 0.2]	.33
Hypertension	101	70.3 ± 4.5	76	68.4 ± 5.3	.78		
Antihypertensive therapy	78	69.2 ± 5.2	99	69.7 ± 4.6	.94		
ARB	27	88.8 ± 6.1			<b>.04</b>	0.4 [0.1, 1.4]	<b>.02</b>
ACEI	24	45.8 ± 10.3			<b>.02</b>	0.2 [−0.8, 0.2]	.24
BB	38	65.7 ± 7.7			.66		
CA	22	63.6 ± 10.5			.58		
Diuretics	31	64.5 ± 8.7			.59		
Number of operated levels	1.288†				.27		

F, female; M, male; ARB, angiotensin-II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blockers; CA, calcium antagonists. Statistically significant values are written in bold.

\* R square.

† F value.

Table 3  
Univariate and multivariate analysis on predictors of functional recovery

			mJOA recovery rate (%)				
	Yes	No	Univariate		Multivariate		
			p		OR [95% CI]	p	
Age	−0.256 [95% CI −0.39, −0.11]*						
Gender (F:M)	83	70.4 ± 3.4	104	74.1 ± 2.8	.40	0.003 [−0.9, −0.1]	<b>.003</b>
Smoking	29	63.9 ± 6.3	158	74 ± 2.3	.10		
Previous cervical surgery	22	61.1 ± 6.4	166	73.1 ± 2.4	.09		
Diabetes	38	69.4 ± 4.9	149	73.2 ± 2.4	.48		
Hypertension	75	63.5 ± 3.6	112	78.4 ± 2.6	<b>&lt;.001</b>	0.02 [1.5, 21.0]	<b>.02</b>
Antihypertensive therapy	77	66.4 ± 3.7	110	76.6 ± 2.6	<b>.02</b>	0.07 [−19.3, 0.9]	.07
ARB	26	73.4 ± 5.4			.60	0.5 [−11.2, 6.3]	.58
ACEI	26	56.1 ± 6.6			<b>.001</b>	0.3 [−4.2, 12.7]	.32
BB	36	65.4 ± 5.9			.05	0.5 [−4.5, 7.9]	.58
CA	23	67.0 ± 7.1			.15		
Diuretics	28	66.0 ± 5.9			.08		
Number of operated levels	4.600 <sup>†</sup>				<b>.01</b>	0.3 [−4.4, 13.6]	.50

F, female; M, male; ARB, angiotensin-II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; BB, beta-blockers; CA, calcium antagonists. Statistically significant values are written in bold.

\* R square.

† F value.

conferred opposing effects on fusion outcomes in ACDF patients. ARB treatment yielded a higher rate of successful fusion, while treatment with ACEIs exhibited a higher rate of pseudarthrosis. Significant differences in the mechanism of action between both RAS blocker groups might explain this contradiction in fusion results.

Bone remodeling and repair involve a complex equilibrium between osteoblastic bone formation and osteoclastic resorption. Recent evidence indicates that AngII might unbalance bone homeostasis via deleterious effects on osteoblasts [21]. AngII stimulates AT1R and AT2R, which activate intracellular cyclic adenosine monophosphate (cAMP) [3]. cAMP acts in two different ways to decrease bone mass: through downregulation of runt-related transcription factor 2 (RUNX2), which is tightly associated with osteoblast differentiation and function; and, through upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL), which stimulates osteoclastic bone resorption [21,22]. In addition to these mechanisms, the AngII/AT1R/cAMP axis also alters levels of low-density lipoprotein, plasma homocysteine, and nitric oxide, which are associated with decreased bone mineral density and are considered risk factors for osteoporosis [22]. Also, AngII may decrease the expression of osteocalcin and the activity of alkaline phosphatase, both of which are important proteins for bone matrix synthesis, mineralization, and maturation [22]. Thus, selective blockade of AT1R and AT2R mitigates AngII-mediated bone mass reduction, which is compatible with the observed higher fusion rate in ACDF patients treated with ARBs (AT1R blockers). While ARBs have been shown to modify expression of RANKL, AT1R blockers do not significantly affect expression of osteoprotegerin (OPG), which inhibits osteoclastic bone resorption through binding to RANKL [23]. Although AT2R blockade

may also increase bone mass, AT2R structure slightly differs from AT1R, which may explain the observed variability in preclinical studies of AT1R and AT2R blockers [24] (Figure).

Angiotensin-converting enzyme inhibitors inhibit the metalloenzyme angiotensin-converting enzyme (ACE), which converts angiotensin-I to AngII, thereby reducing AngII signaling through both AT1R and AT2R. Thus, the observation that treatment with ACEIs was correlated with increased pseudarthrosis might seem incongruous. However, in tumor studies, ACEIs have previously been shown to also inactivate the matrix metalloproteinases (MMPs) MMP-2 and MMP-9, the former of which has been shown to play roles in bone [25]. ACE shares characteristics with MMPs, including zinc-dependence [26], and ACEIs have been demonstrated to chelate zinc at the active site of ACE and MMPs, thereby inactivating their functions [27]. Loss of MMP-2 has been associated with a heterogeneous group of skeletal disorders characterized by mineralization defects, known collectively as multicentric osteolysis with arthropathy [28]. Mosig et al. reported that loss of MMP-2 expression leads to decreased osteoblastic cell proliferation due to defects in osteoblast differentiation and transcriptional deregulation of osteopontin and bone sialoprotein [29]. Besides modifying MMP-2 expression, ACEIs are associated with an upregulation of the kinin–kallikrein system by blocking the breakdown of bradykinin [30]. Previous studies reported that increased bradykinin impairs osteoblast differentiation and favors osteoclast maturation, resulting in enhanced bone resorption and reduced bone mineral density [31]. Additionally, in a mouse study, Yang et al. demonstrated that treatment with the ACEI captopril decreased the OPG/RANKL ratio and lowered the expression of RUNX2 in bone tissue through the bradykinin

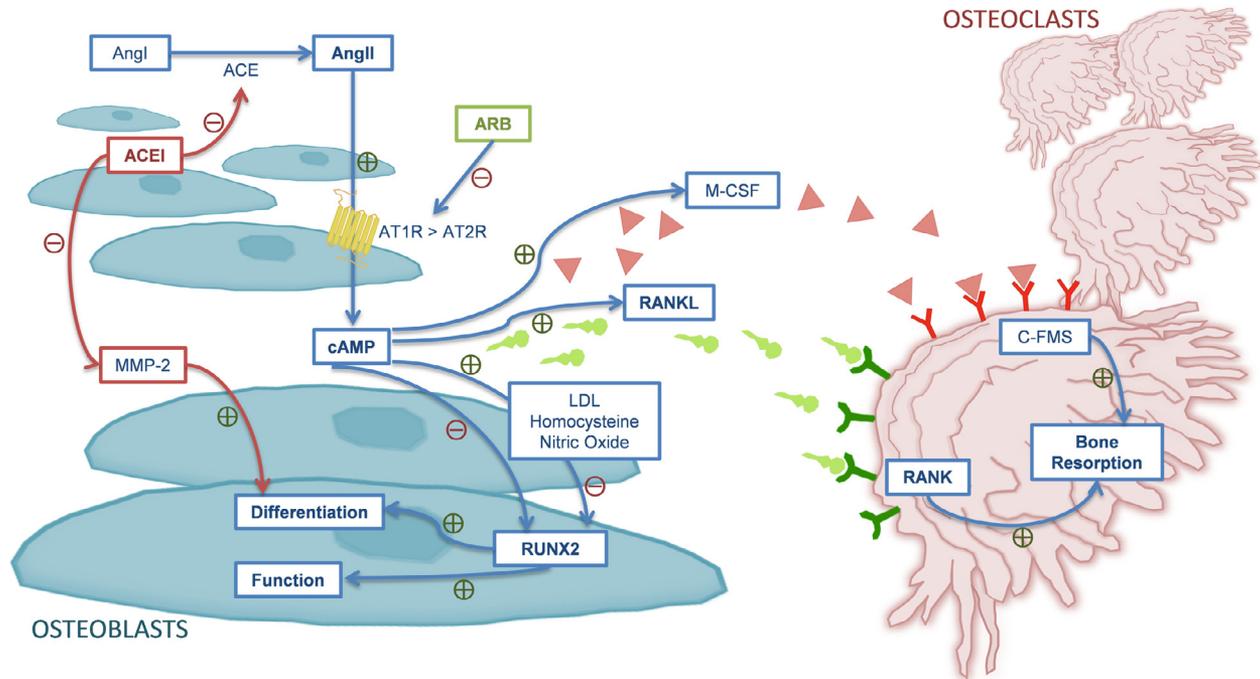


Figure. Hypothetical mechanisms of RAS blockers on osteoblast-osteoclast signaling. RANKL and RUNX2, crucial factors for bone homeostasis and critical regulators of osteoblast and osteoclast differentiation and function, are both controlled by cAMP-dependent signaling. AngII stimulates an increase of intracellular cAMP via AT1R and AT2R, inhibiting osteoblastic bone deposition and enhancing osteoclastic bone resorption. Blocking this pathway (blue arrows), ARBs are capable of counteracting AngII-induced effects on bone. On the other hand, ACEIs decrease the activity of MMP-2, and in turn, the loss of MMP-2 expression has been associated with decreased osteoblast proliferation (red arrows). ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; AngI, angiotensin-I; AngII, angiotensin-II; ARB, angiotensin receptor blocker; AT1R and AT2R, angiotensin-II type-1 and -2 receptors; cAMP, cyclic adenosine monophosphate; C-FMS, macrophage colony-stimulating factor receptor; LDL, low-density lipoprotein; M-CSF, macrophage colony-stimulating factor; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; RUNX2, runt-related transcription factor 2. ⊕, enable, ⊖, disable.

receptor B2 signaling pathway [32]. Based on this evidence, we therefore hypothesize that the observed increase in pseudarthrosis in patients treated with ACEI was due to a reduction in both MMP-2 activity and degradation of bradykinin.

Although the results presented in this study alongside the literature discussed strongly suggest that ARB treatment should be continued in antihypertensive patients undergoing fusion due to their potential positive effects on fusion outcomes, the question about any ARB advantages for non-hypertensive patients remains. Currently, ARBs have shown a steady safety window in nonhypertensive patients who are taking these drugs for other indications, such as prophylaxis of nephropathy and cardiovascular disease in diabetes mellitus [33,34]. Repurposing ARBs for use in spinal fusion surgery is thus highly feasible, independent of the hypertension status of patients.

#### Study limitations

Our retrospective study carries the inherent limitations of any observational study. A significant limitation is the heterogeneity of antihypertensive therapy in our hypertensive patients, since a few patients were taking more than one drug. Adjusted multivariate analyses were performed

to demonstrate significance in the context of other covariables and to estimate the weight of each variable in the outcomes of interest. Another possible limitation is the method used for determining fusion, which may have overestimated the nonunion rate in this cohort. Although plain films are the method routinely used at follow-up visits to assess instrumentation and fusion status over time, CT is considered the most reliable imaging test for evaluating fusion since it correlates better with surgical findings than plain x-rays [11]. According to a survey study among spine surgeons practicing in the United States [35], 96% of surgeons order plain films as part of routine follow-up after ACDF, while dynamic radiographs and CT scans are taken less often or not at all, except if failed fusion is suspected. To that end, two blinded researchers independently reviewed the imaging studies to determine the fusion status, and any discordance between the reviewers was resolved by the senior author (T.W.). Another fact that should be taken into consideration is that the study was performed in a single tertiary referral center. Thus, the results presented here must be validated in other populations in future studies. Also, it is worth mentioning that no specific medical rationale motivated us to choose ACDF procedures as the type of fusion to study, but it was logistically more suitable for our research group to identify these patients in our

electronic database. However, we are currently seeking to verify these findings in the lumbar spine as well as posterior cervical fusions.

## Conclusions

In our cohort of ACDF patients, treatment with ARBs was associated with an increased fusion rate, while treatment with ACEIs and smoking were identified as risk factors for pseudarthrosis. Further preclinical and clinical studies are warranted to confirm the beneficial effects of ARBs and deleterious influence of ACEIs on spinal fusion.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.spinee.2019.04.017>.

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