Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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RAAS BLOCKERS

RECOMMENDATIONS

We recommend continuing maintenance RAAS blockers for hypertension among patients with COVID-19 infection. *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues

There were no issues raised during the consensus panel meeting.

EVIDENCE SUMMARY

Should RAAS blockers be continued in patients with hypertension and COVID-19?

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Key Findings

Based on two RCTs (N=811) with moderate certainty of evidence, there is probably little or no significant reduction in the risk of deaths and severe disease for patients with hypertension and COVID-19 who continued RAAS blockers compared to those who discontinued RAAS blockers.

Introduction

Renin-angiotensin-aldosterone system (RAAS) blockers have been hypothesized to be a double-edged sword in patients with COVID-19. By upregulating the angiotensin-converting enzyme 2 (ACE2) receptors, RAAS blockers may worsen COVID-19 since it is through the ACE2 enzyme that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters human cells. On the other hand, these drugs may be beneficial since they counteract the increase in angiotensin II formation that leads to increased pulmonary vascular permeability, thus preventing the consequent pulmonary edema and the end effect of further reduction of pulmonary function. Two recent systematic reviews (34 observational studies) showed definite benefit for reduction of mortality in patients with COVID-19 on RAAS blockers, compared to those not on RAAS blockers, but this was based on very low quality of evidence.

Review Methods

We searched the following websites (COVID-19 Open Living Evidence Synthesis, Living Evidence on COVID-19, National COVID-19 Clinical Evidence Taskforce, WHO Therapeutics and COVID-19: living guideline) for living evidence on the topic. We searched trial registries (Clinicaltrials.gov, Chinese CTR and WHO ITCRP) for ongoing or completed trials. We also searched PubMED and the Cochrane Database of Systematic Reviews up to December 26, 2020 based on the following inclusion criteria:

P	Patients with HTN and COVID-19
I	Continuation of RAAS blockers
C	Discontinuation of RAAS blockers
O	Mortality, severe COVID, ICU admission, mechanical ventilation, adverse events
S	RCTs, controlled clinical trials

Results

Efficacy

We found two RCTs (N=811) that compared continuation versus discontinuation of RAAS blockers. (Cohen 2021; Lopes 2021). [1,2] The first RCT (REPLACE-COVID trial) (N=152) was a randomized open-label trial conducted in 20 large referral hospitals in seven countries worldwide. Admitted patients with COVID-19, hypertension, and who were on RAAS blockers were recruited [1]. Around half of the patients had mild COVID-19 disease on admission, while one-third had moderate disease, and severe disease was seen in only 12% to 13% of patients. The most common comorbidities were diabetes (56% vs 48%) and dyslipidemia (45 vs 52%) in the continuation and discontinuation groups, respectively. The second RCT (BRACE-CORONA trial) (N=659) was conducted in 29 centers in Brazil which recruited patients with hypertension and mild to moderate COVID-19 who were taking RAAS blockers prior to admission. Median use of RAAS blockers was five years in both groups. The most common comorbidity was diabetes in around a third of patients in both groups (33 vs 31%). Off label and adjuvant COVID- 19 therapies administered during follow-up were similar between groups.

Pooled analysis showed no significant difference in mortality (pooled RR, 1.08 (95% CI 0.60, 1.97; N=811; I^2=0%), and ICU admission or mechanical ventilation (pooled RR, 0.93, 95% CI 0.62, 1.38; N=811; I^2=0%), with moderate certainty of evidence. Downgrading was done due to imprecision. In the Cohen study, there was a trend towards reduced risk of COVID-19 progression in those who continued RAAS blockers (RR 0.84, 95%CI 0.68, 1.04).

Cohen also reported a lower global rank score for continuation group (73, 95%CI 40 to 110) compared to discontinuation group (81, 95%CI 38 to 117), but this was not significant (beta coefficient [8, - 13 to 29] p=0.61). A lower rank score means greater COVID severity. Subgroup analysis showed no effect modification by age, sex, race, baseline ACEI versus ARB therapy, chronic kidney disease, diabetes, or body-mass index for the primary endpoint or length of hospitalization.

Based on the second study (Lopes), there was no significant reduction in in-hospital mortality (RR 0.80, 95% CI 0.30, 2.12) and cardiovascular events (RR 0.80, 0.30, 2.12). There was significant reduction in mean length of hospitalization (MD -1.10, -2.15, -0.05; P=0.04). Subgroup analysis in the second study (Lopes) did not show significant differences based on age, obesity, type of RAAS blockers, day of symptoms to randomization, opacities on chest CT scan. However there was significant interaction among the treatment effect, oxygen saturation, and COVID-19 clinical severity at admission, with results slightly favoring the continuation group among patients with lower oxygen saturation and greater disease severity at presentation.

Adverse events

The risk of any SAE was reported in the RCT by Cohen [1] in 39% (29/75) of the Continuation group and 36% (28/77) of the Discontinuation group (RR 1.06, 95%CI 0.71, 1.60). For both RCTs,

some outcomes reported as SAEs were also efficacy outcomes (e.g. all-cause death, ICU transfer for Cohen, and respiratory failure requiring mechanical ventilation for Lopes). The other reported SAEs were mainly cardiovascular, renal, and neurological (i.e. shock requiring vasopressors, acute arrhythmia, acute myocardial infarction, myocarditis, new or worsening congestive heart failure, acute kidney injury requiring dialysis, delirium and encephalopathy, pulmonary embolism or deep vein thrombosis). There were no significant differences in all reported serious events (Cohen). There was also no indication if these events were related to the RAAS blockers or not. Reasons for switching of the assigned intervention that were reported by Cohen for the Continuation group were: hypotension (n=11), hyperkalemia (n=2), poor oral intake with concern for volume depletion, and other reasons for clinical decision (n=4). For the Discontinuation group, ACEIs or ARBs were re-initiated due to hypertension (n=6) and acutely worsening heart failure (n=1). Both groups of patients switched after a median of 5 days (IQR 3-7). Sensitivity analysis using switching "as-treated" data showed no change in conclusion for mortality (pooled RR 0.84, 95%CI 0.42, 1.69), ICU admission or mechanical ventilation (pooled RR 0.90, 95%CI 0.61, 1.34). As-treated analysis by Lopes for all SAEs and only one SAE by Cohen – namely, hypotension requiring hemodynamic support - did not show any significant difference from main ITT analysis.

Recommendations from other groups

Position statements from numerous organizations and groups support the continuation of ACEIs/ARBs in patients with COVID-19 (including ESC, ISH, AHA) (March 2020).[5–7] The WHO issued a scientific brief stating that patients on long-term therapy with ACE inhibitors or ARBs are not at higher risk of poor outcomes from COVID-19, but this came from low-certainty evidence (7 May 2020).[8] NICE Guidance (May 2020) did not find any evidence that showed either increased or decreased risk of COVID-19 and its complications. Findings were based on two low-quality observational studies [9,10] from its search until April 1, 2020, NICE noted the well-understood risks of stopping treatment with an ACEI or an ARB, such as worsening heart failure or hypertension.[11] The Australian Guidelines for the clinical care of people with COVID-19 stated there is currently no evidence to deviate from usual care, and strongly recommended that the use of ACEIs/ARBs should be continued unless contraindicated (4 March 2021).[12] This was based on substantial net benefits of the recommended alternative despite lack of RCTs at the time the recommendations were drafted. The recommendation was based only on very low quality evidence from three large systematic reviews of observational studies, noting that there was high certainty of evidence of harm from abruptly stopping the medications which could result in acute heart failure or unstable blood pressure.[13–15]

Ongoing Studies

There are nine registered clinical trials: one completed trial (IRCT20151113025025N3) has not been published, one suspended trial (NCT04330300), and seven ongoing trials (Appendix 4).

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Appendix 1. Characteristics of Included Studies

Study ID/Country/Setting	Sample Size	Participants	Intervention	Comparison	Cointerventions	Outcomes
Cohen 7 countries worldwide/20 large referral hospitals	N=152	Inclusion: aged 18 years and older who were admitted to hospital with COVID-19 and HTN and were receiving a renin–angiotensin system inhibitor before admission All were RT-PCR for SARS-CoV-2 positive except for 1 in RAAS continuation group due to limited testing ability and who died in the interim Exclusion: contraindications to continuation or discontinuation of renin–angiotensin system inhibitor therapy	Continuation of RAAS group n=75	Discontinuation RAAS group n=77	Co-interventions: Remdesivir: 23 vs 18% HCQ: 4 vs 8 Systemic anticoag: 15 vs 10 High dose steroids: 15 vs 10 Convalescent plasma: 3 vs 1 Lopinavir/ritonavir: 1 vs 3	<u>Primary outcome:</u> Global rank score* <u>Secondary outcomes:</u> Time to all cause death Length of hosp. stay Length of ICU stay or invasive mechanical ventilation AUC of the SOFA <u>Exploratory endpoints</u> ICU admission or invasive mechanical ventilation Hypotension requiring haemodynamic

Study ID/Country/Setting	Sample Size	Participants	Intervention	Comparison	Cointerventions	Outcomes
		Mean age of participants was 62 years (SD 12), 68 (45%) were female, mean BMI, 33 kg/m² (SD 8), and 79 (52%) had diabetes Baseline char: similar, except for ACEI slightly more common in discontinue RAAS group (49%) than continue RAAS (33%) Severity of disease: Mild in 51% (Continue RAAS) and 55% (discontinue RAAS); Severe in 12 vs 13				support Any severe adverse event †
Lopes Brazil/26 hospitals	N= 659	Hospitalized patients with HTN and mild to moderate	Continuation (n = 325) of ACEIs or	Discontinuation (n = 334) for duration of	Concomitant therapies: Azithromycin 91.1	Primary: Mean days alive and out of hospital

Study ID/Country/Setting	Sample Size	Participants	Intervention	Comparison	Cointerventions	Outcomes
		COVID-19 who were taking ACEIs or ARBs prior to hospitalization Median age 55.1 years (IQR, 46.1-65.0 years), 14.7%were aged 70 years or older, 40.4% were women	ARBs. for duration of 30 days	30 days	vs 90.1 % Anticoag 67.1 vs 66.5 Antiviral 41.5 vs 42.5 CQ or HCQ 17.8 vs 21.6 Tocilizumab 2.2 vs 5.1 Corticosteroid 48.3 vs 50.6 <u>Cointervention:</u> Did not recommend any specific treatment modification beyond discontinuing or continuing use of ACEIs or ARBs. The study team provided oversight on drug replacement, and those decisions	Secondary outcomes: Length of hospitalization Death In-hospital death Cardiovascular death COVID-19 progression Respiratory failure requiring invasive mechanical ventilation Shock requiring vasopressors Cardiovascular outcomes: Acute MI New or Worsening heart failure Acute Kidney

Study ID/Country/Setting	Sample Size	Participants	Intervention	Comparison	Cointerventions	Outcomes
					were made based on current treatment guidelines Patients were treated for COVID-19 according to current local standards of supportive care without systematic use of experimental therapies.	failure requiring hemodialysis Thromboembolic events Stroke or TIA

* incorporates: time to death, duration of mechanical ventilation, time on renal replacement or vasopressor therapy, and multiorgan dysfunction during the hospitalisation (lower rank score signifies more severe COVID)

† Worsening dyspnea or resp. failure; AKI requiring RRT; AKI >2x creatinine increase; Acute arrythmia; Pulmonary embolism or DVT; AMI; Myocarditis; New or worsening HF; Delirium or encephalopathy

Appendix 2. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAAS blockers be continued	discontinued	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2 (N=811) (Cohen; Lopes)	randomised trials	not serious	not serious	not serious	serious [a]	none	20/400 (5.0%)	19/411 (4.6%)	**RR 1.08** (0.60 to 1.97)	**4 more per 1,000** (from 18 fewer to 45 more)	⨁⨁⨁◯ MODERATE	
ICU or Mech ventilation												
2 (N=811) (Cohen; Lopes)	randomised trials	not serious	not serious	not serious	serious [a]	none	41/400	46/411	**RR 0.93** (0.62 to 1.38)	**8 fewer per 1,000 (from 43 fewer to 43 more)**	⨁⨁⨁◯ MODERATE	
COVID progression												
1 (N=659) (Lopes)	not serious	not serious	not serious	serious [a]	none	105/325 (32.3%)	128/334 (38.3%)	**RR 0.84** (0.68 to 1.04)	**61 fewer per 1,000** (from 123 fewer to 15 more)	⨁⨁⨁◯ MODERATE		
Any SAE												
1 (N=152) (Cohen)	not serious	not serious	not serious	serious [a]	none	29/75 (38.7%)	28/77 (36.4%)	**RR 1.06** (0.71 to 1.60)	**22 more per 1,000** (from 105 fewer to 218 more)	⨁⨁⨁◯ MODERATE		

Appendix 3. Forest plots from pooled RCTs

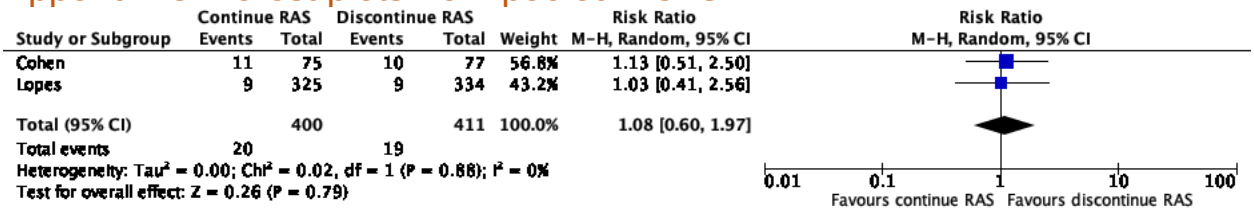

Figure 1. Mortality: Continuation vs discontinuation of RAAS

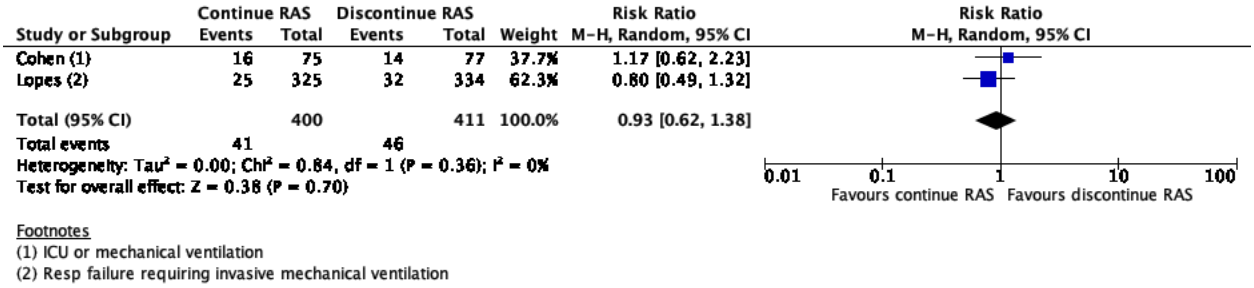

Figure 2. ICU or mechanical ventilation: Continue vs discontinue RAAS

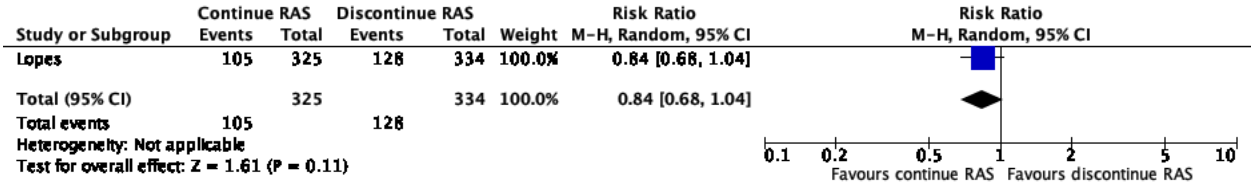

Figure 3. COVID progression: Continue vs discontinue RAAS

Appendix 4: Characteristics of Ongoing Studies

No.	Clinical Trial ID / Title	Sample Size	Population	Intervention Group(s)	Comparison Group(s)	Clinical Outcomes
1	NCT04330300 CORONAvirus Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers InvestigatiON: A Randomized Clinical Trial (CORONACION)	N=2414	Men and non-pregnant women aged 60 or over with known diagnosis of hypertension, currently using ACEi or ARB for the treatment of hypertension and COVID-19 naïve (i.e. not known to be infected)	Continue ACEi/ARB antihypertensive	Alternative anti-hypertensive medication Switch to an alternative BP medication (specifically a Calcium channel blocker [CCB] or Thiazide/Thiazide-like diuretic at an equipotent blood pressure lowering dose). The choice of either CCB or Thiazide/Thiazide-like anti-hypertensive provided as alternative therapy will be at the discretion of the physician	Primary: Death (All-cause mortality) Secondary: Intubation in ICU; Hospitalization for non-invasive ventilation (NIV)
2	NCT04351581 Effects of Discontinuing Renin-angiotensin System Inhibitors in Patients With COVID-19	N=215	Verified COVID-19; Hospital admitted; Daily administration of RAAS-inhibiting therapy; Age 18 years and above	Continuation of ACEi/ARB	Discontinuation of ACEi/ARB	Primary: Days alive and out of hospital Secondary: Worsening of COVID-19; Severe respiratory insufficiency; Referral to ICU, 30-d mortality, etc.
3	NCT04353596 Stopping ACE-inhibitors in COVID-19	N=208	Proven and symptomatic SARS-CoV2 infection ≤ 5 days; Age ≥ 18 years; Chronic (≥ 1 month) ACEI/ARB therapy for treatment of arterial hypertension, diabetes mellitus, heart failure or coronary artery disease; Stable hemodynamic conditions allowing to stop or continue treatment with ACEI/ARB (systolic blood pressure ≤180mmHg)	Continuation of ACEi/ARB	Discontinuation of ACEi/ARB	Primary: Combination of maximum Sequential Organ Failure Assessment (SOFA) Score and death Secondary: Maximum SOFA, Non-invasive ventilation, Renal replacement therapy, etc.
4	IRCT20151113025025N3 Clinical Trial of renin-angiotensin-aldosterone system inhibitors with	N=60	Patients who have suggestive signs of COVID-19 in their chest computed tomography scan, reported by a radiologist.	Continuation of RAAS inhibitors	Discontinuation of RAAS inhibitors and shift to calcium blocker or beta-blocker	Primary: Death, ICU

No.	Clinical Trial ID / Title	Sample Size	Population	Intervention Group(s)	Comparison Group(s)	Clinical Outcomes
	halting their administration and the effect on clinical outcomes of patients with corona virus disease-2019 (COVID-19) referring to Sina Hospital in 2020		Patients consuming angiotensin-converting enzyme inhibitors or angiotensin receptor blockers			
5	NCT04364893 Suspension of Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Hospitalized Patients With Coronavirus Infection (COVID-19). A Randomized Trial	N=700	Diagnosis of coronavirus (SARS-CoV)-2 infection confirmed by polymeRAASe chain reaction (PCR) test < 4 days before Visit 1 with signs of an acute respiratory infection Age > 18 and < 70 years CRP > 50 and < 150 mg/l Admitted to a hospital or controlled facility (home quarantine is not sufficient)	Maintenance of ARBs and ACEIs	Suspension of ARBs and ACEIs	Primary: Median days alive and out of the hospital Secondary: Number of participants with adverse cardiovascular outcomes and new worsening heart failure; Cardiovascular biomarkers related to COVID-19
6	NCT04508985 Management of Renin-Angiotensin-Aldosterone System Blockade in Patients Admitted in Hospital With Confirmed Coronavirus Disease (COVID-19) Infection: The McGill RAAS-COVID-19 Randomized Controlled Trial	N=40	Age ≥ 18 years old. Hospitalization with a Covid-19 infection Chronically treated with RAAS blockers (ACE inhibitors or ARBs on the last prescription prior to admission with a treatment duration ≥ 1 month	Temporarily holding the RAAS inhibitor [intervention]	RAAS inhibitor [continued standard of care]	Primary: Global rank score
7	EU CTR 2020-001206-35 Stopping ACE-inhibitors in COVID-19 - a randomized, controlled clinical trial	N=798	Age: >18 yrs Patients with proven SARS-CoV2 infection	discontinuation of prescribed ACEI/ARB-medication	Continuation of prescribed ACEI/ARB-medication	Primary: combination of the maximum SOFA scores measured during the course of the disease (≤30 days) and death; combination of intensive care admission, intubation and death.
8	NCT04493359 Switch or Maintenance of Renin-Angiotensin System Inhibitors in	N=240	Age: 18 to 80 yrs Hypertension in use of renin-angiotensin system inhibitors Confirmed COVID-19 infection	Switch therapy: Renin-angiotensin system inhibitors will be changed for other	Maintenance therapy: Renin-angiotensin system inhibitors will be kept during in-hospital stay	Primary: Need for ICU or mortality Secondary: High sensitivity troponin levels and covid-19 severity; ACE-2 activity and

No.	Clinical Trial ID / Title	Sample Size	Population	Intervention Group(s)	Comparison Group(s)	Clinical Outcomes
	Patients With Covid-19: A Randomized Proof of Concept Trial		by rt-PCR, serology tests or typical clinical presentation and chest CT. Symptoms onset < 96h	anti-hypertensive classes		disease severity; ACE-2 activity with different Renin-angiotensin system inhibitors; Blood control and acute renal failure
9	EudraCT Number: 2020-001544-26 Effects of discontinuing renin-angiotensin system inhibitors in patients with COVID-19	N=215	1. Verified COVID-19 2. Hospital admitted 3. Daily administration of RAAS-inhibiting therapy 4. Age 18 years and above	Continued treatment with angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists	Discontinued treatment with angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists	Primary: days alive and out of hospital within 14 days after recruitment Secondary: occurrence of worsening of COVID-19, occurrence and time to occurrence of each of the components of the primary composite endpoint, kidney function (as assessed by plasma creatinin and eGFR), duration of index hospitalisation, 30 days-mortality, number of days alive during the intervention period, discharge beyond 30 days and number of readmissions after 30 days

Appendix 5. Summary of Serious Adverse Events

Type of SAE	No. of studies (No. of participants)	Continue RAS blocker No. (%)	Discontinue RAS blocker No. (%)	RR (95% CI)
Acute myocardial infarction (ITT)	2 (811)	16/400 (4)	26/411 (6.3)	0.63 [0.34, 1.16]

Type of SAE	No. of studies (No. of participants)	Continue RAS blocker No. (%)	Discontinue RAS blocker No. (%)	RR (95% CI)
Shock requiring vasopressors (ITT)	2 (811)	32/400 (8)	36/411 (8.8)	0.92 [0.58, 1.44]
Shock requiring vasopressors (AT)	2 (691)	21/367 (5.7)	31/324 (9.6)	0.60 [0.35, 1.03]
Myocarditis (ITT)	2 (811)	1/400 (0.25)	2/411 (4.9)	0.51 [0.05, 5.54]
Pericarditis (ITT)	1 (659)	0/325 (0)	1/344 (0.29)	0.34 [0.01, 8.41]
Hypertensive crises (ITT)	1 (659)	3/325 (0.92)	1/344 (0.29)	3.08 [0.32, 29.49]
Hypertensive crises (AT)	1 (539)	2/302 (0.66)	1/237 (0.42)	1.57 [0.14, 17.21]
New or worsening heart failure (ITT)	2 (811)	17/400 (4.25)	14/411 (3.4)	1.23 [0.62, 2.43]
AKI requiring dialysis (ITT)	2 (811)	18/400 (4.5)	15/411 (3.6)	1.23 [0.63, 2.41]
Thromboembolic events (ITT)	2 (811)	8/400 (2)	7/411 (1.7)	1.34 (0.24, 7.41)
Stroke or TIA (ITT)	1 (659)	3/325 (0.92)	3/344 (0.87)	1.03 [0.21, 5.05]

ITT, Intent to treat; AT, As treated; AKI, acute kidney injury; TIA Transient ischemic attack