Original Article

Prescribing Trends of Renin-Angiotensin System Inhibitors and Mortality among Acute Coronary Syndrome Patients: Insights from the Malaysian National Cardiovascular Disease Registry

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Abstract

Background: Despite guideline recommendations, suboptimal prescription rates of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been observed in patients with acute coronary syndrome.

Objective: This study aimed to examine the temporal trends, variations, and mortality outcomes among acute coronary syndrome patients prescribed ACEIs/ARBs in the multi-ethnic population of Malaysia.

Methodology: This retrospective study utilized data from the Malaysian National Cardiovascular Disease–Acute Coronary Syndrome registry, encompassing consecutive patient records from 2008 to 2017 (N = 60,854). Ten-year temporal trends of on-discharge ACEIs/ARBs prescription were examined. Demographics, clinical characteristics and 1-year all-cause mortality outcomes were compared between patients prescribed and not prescribed ACEIs/ARBs.

Results: The 10-year prescription rate of on-discharge ACEIs/ARBs was 52.8% (n = 32,140), with a significant decline over the years [linear trend test, P = 0.008; SD = 0.03; SE = 0.001; 95% CI = 0.55-0.64]. Patients aged ≥65 years (aOR = 0.79; 95% CI = 0.73–0.86) were less likely to be prescribed ACEIs/ARBs than those aged <65 years. In addition, patients with comorbid diabetes mellitus (DM) (aOR = 0.85; 95% CI = 0.79–0.92) and chronic kidney disease (CKD) (aOR = 0.34; 95% CI = 0.30–0.40) were significantly less likely to receive ACEIs/ARBs. IPW-adjusted survival analysis revealed a 38% lower 1-year all-cause mortality rate in patients prescribed on-discharge ACEIs/ARBs (HR = 0.62; 95% CI = 0.56–0.69; P < 0.001).

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Submitted: 19-Sep-2023 **Revised:** 10-Jan-2024 **Accepted:** 07-Feb-2024 **Published:** 05-Apr-2024

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/sjmm
	DOI: 10.4103/sjmms.sjmms_422_23

How to cite this article: Suki SZ, Zuhdi AS, Yahya A, Adnan WA, Zaharan NL. Prescribing trends of renin-angiotensin system inhibitors and mortality among acute coronary syndrome patients: Insights from the malaysian national cardiovascular disease registry. Saudi J Med Med Sci 2024;12:145-52.

Conclusion: Acute coronary syndrome patients with concomitant DM and CKD were less likely to receive on-discharge ACEIs/ARBs in Malaysia. Suboptimal prescription rates of ACEIs/ARBs persisted over the 10-year period, despite improved 1-year survival in ACS patients prescribed ACEIs/ARBs.

Keywords: ACE inhibitors, acute coronary syndrome, angiotensin receptor blockers, Malaysia, mortality, prescriptions, propensity score, survival analysis, trends

INTRODUCTION

The management of acute coronary syndrome (ACS) involves a complex interplay of evidence-based pharmacological treatments, including antiplatelets, lipid-lowering agents, and medications targeting the renin–angiotensin system. Landmark clinical trials such as HOPE,[1] MICRO-HOPE,[2] and EUROPA[3] have unequivocally demonstrated the ability of angiotensin-converting enzyme inhibitors (ACEIs) to reduce mortality and morbidity following an ACS episode, even among those with comorbidities such as diabetes mellitus (DM). Consequently, international cardiology guidelines[4,5] have recommended the use of ACEIs/angiotensin receptor blockers (ARBs) in post-ACS patients, particularly in cases with left ventricular dysfunction or heart failure.

Adherence to ACEIs/ARBs has shown a clear association with the reduction of cardiovascular disease (CVD) events and improved patient survival.[6,7] Nonetheless, reports of suboptimal prescribing trends for ACEIs/ARBs among ACS patients persist in some countries,[8,9] especially among older populations[10,11] and those with conditions such as DM.[12,13] This paradoxical phenomenon, described as a treatment–risk paradox, underscores the importance of investigating factors influencing prescription patterns in ACS management.

While substantial progress has been made in improving access to cardiology interventions and the utilization of evidence-based pharmacotherapies for ACS patients,[14] ACS remains the leading cause of mortality in Malaysia, exerting a substantial burden on the country's healthcare system.[15] The high cost of treatment of ACS within a heavily subsidized healthcare system indirectly impacts Malaysia's social and economic development.[15] Despite this, the utilization of ACEIs/ARBs in Malaysia has remained suboptimal.[16-18] This disparity highlights the need to explore the trends and variations in ACEIs/ARBs prescription practices and their implications for mortality outcomes.

This study aims to examine 10-year (2008–2017) temporal trends in on-discharge ACEIs/ARBs prescribing and their effect on 1-year all-cause mortality among ACS patients within the Malaysian population. To achieve this, the National Cardiovascular Disease–ACS (NCVD-ACS) registry, a dedicated registry housing information on patients admitted to Malaysian hospitals with ACS, was leveraged. This registry is one of the few comprehensive CVD registries in the Asia-Pacific region.

METHODOLOGY

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure reporting transparency.

Study design and population

This retrospective cohort study utilized Malaysia's largest prospective single disease registry, the NCVD-ACS registry, which is governed by the Ministry of Health (MOH) of Malaysia and maintained by the National Heart Association of Malaysia (NHAM).[17] All consecutive adult Malaysian citizens (aged ≥20 years) admitted with ACS from 2008 to 2017 were identified (N = 60,854). ACS diagnoses included ST-elevated myocardial infarction (STEMI), non-ST-elevated myocardial infarction (NSTEMI), or unstable angina (UA), following established guidelines.[4,5,19] Data extracted included demographic information, clinical characteristics, and 1-year all-cause mortality status obtained from the National Registration Department. The major ethnicities in Malaysia are Malays, Chinese and Indians, while all other minority ethnicities were categorized as "other Malaysians."

The study protocol received approval from the Medical Review and Ethics Committee of MOH under the approval code of NMRR-19-4066-52,389 (IIR).

Statistical analyses

Categorical data are presented as frequencies and percentages, while continuous data, such as age, are presented as standard mean differences. Comparisons of clinical characteristics between patients prescribed on-discharge ACEIs/ARBs and those not prescribed were performed using Student's *t*-test and Chi-square test, as appropriate. Linear trend test was used to analyse the

prescribing trends of ACEIs/ARBs over the 10-year period. The variations in prescribing ACEIs/ARBs were analysed using multivariate binary logistic regression, adjusted for demographics, risk factors and comorbidities, and previous history of percutaneous coronary intervention, with the reference group being those without the respective risk factors and comorbidities. The variation results were presented as an adjusted odds ratio (aOR) with a 95% confidence interval (CI).

The association between on-discharge ACEIs/ARBs prescription and 1-year all-cause mortality was examined through Cox regression survival analysis. Risk adjustments were performed with all variables associated with ACS [Tables 1 and 2], based on published literature, clinical plausibility, and a *P* value of <0.05 in the univariate Cox regression analysis. This study complemented the analysis with a propensity score (PS) model, using the inverse proportional weighting (IPW) adjustment method.

PS analysis was performed using data with complete information, without missing or unknown values (n = 18,910). Each patient's unique demographics and clinical characteristics were represented by a single predictive value ("score") or propensity score generated through a multivariate logistic regression model. Extreme PS values in both treatment groups were removed (trimming), involving 1% of patients to improve compatibility between treatment exposures. IPW reweighted the entire datasets, producing a pseudo-population with near-perfect covariates between treatment groups. Those in the treatment group were applied weights (inverse probability) of 1/PS, while those in the control group were applied weights of [1/(1-PS)]. The proportional hazard assumption of ACEIs/ARBs prescription on survival was represented in Cox survival curves adjusted by IPW. PS and IPW methods were described elsewhere in detail.[20,21]

Statistical analysis was performed using the IBM Statistical Package for Social Science (SPSS) software (version 26.0) with a significance level set at 5%.

Table 1: Demographic characteristics of the patients prescribed on-discharge ACEIs/ARBs (*N*=60,854)

Demographic characteristics	Prescribed ACEIs/ARBs, *n* (%)	Not prescribed ACEIs/ARBs, *n* (%)	*P*
Male	25,367 (61.2)	16,058 (38.8)	<0.001
Female	6773 (59.3)	4652 (40.7)	
Aged <65 years	22,411 (62.6)	13,375 (37.4)	<0.001
Aged ≥65 years	9729 (57.0)	7335 (43.0)	
Malays	16,269 (60.4)	10,656 (39.6)	<0.001
Chinese	6821 (59.3)	4680 (40.7)	
Indians	6599 (62.7)	3933 (37.3)	
Other Malaysians	2451 (63.0)	1441 (37.0)	

ACEIs/ARBs – Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Table 2: Clinical characteristics of the patients prescribed on-discharge ACEIs/ARBs (*N*=60,854)

Clinical characteristics	Prescribed ACEIs/ARBs, *n* (%)	Not prescribed ACEIs/ARBs, *n* (%)	*P*
STEMI	14,040 (58.4)	10,001 (41.6)	<0.001
NSTEMI	8498 (59.8)	5722 (40.2)	
UA	9602 (65.8)	4987 (34.2)	
Hypertension	21,019 (64.0)	11,825 (36.0)	<0.001
Diabetes mellitus	13,793 (60.4)	9060 (39.6)	NS
Dyslipidaemia	12,216 (63.6)	6991 (36.4)	<0.001
Smoking	18,197 (61.7)	11,297 (38.3)	<0.001
BMI ≥23.0	11,699 (62.2)	7107 (37.8)	<0.001
Intervened with PCI	7453 (61.0)	4767 (39.0)	0.038

NS (*P*>0.05). ACEIs/ARBs – Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; NS – Not significant; BMI – Body mass index, NSTEMI – Non-ST-elevated myocardial infarction; STEMI – ST-elevated myocardial infarction; UA – Unstable angina; PCI – Percutaneous coronary intervention

RESULTS

Frequencies of ACEIs/ARBs prescriptions

At the time of hospital discharge, ACEIs/ARBs were prescribed to 52.8% (N = 32,140) of the 60,854 ACS patients. Over the 10-year period, despite suboptimal prescription rates, a significant decline in ACEIs/ARBs prescribing was observed [linear trend test, P = 0.008; SD = 0.03; SE = 0.001; 95% CI = 0.55-0.64] [Figure 1]. Notable differences in gender, age groups, and ethnicities were identified between those prescribed ACEIs/ARBs (mean age: 58 ± 11.7 years) and those not prescribed (mean age: 59 ± 12.6 years) [Table 1]. For instance, 63% of patients aged <65 years received ACEIs/ARBs compared with 57% of those aged ≥65 years. Additional clinical characteristics of the patients are summarized in Table 2 and Appendix 1.

Variations in ACEIs/ARBs prescription on the day of hospital discharge

Patients aged ≥65 years (aOR = 0.79; 95% CI = 0.73–0.86) were less likely to be prescribed ACEIs/ARBs than

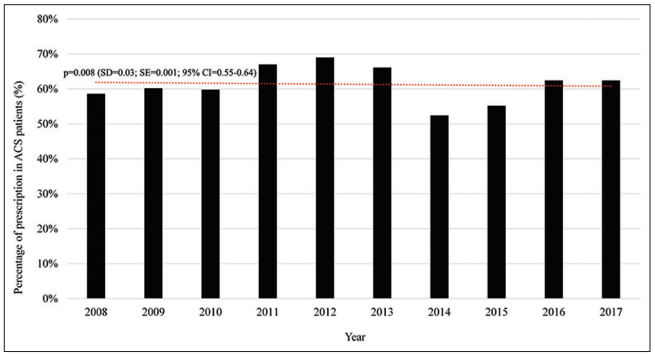

Figure 1: The distribution of acute coronary syndrome patient prescribed on-discharge renin-angiotensin system blockers according to calendar year and its linear trend line (P < 0.05)

their counterparts aged <65 years. Similarly, patients of Chinese (aOR = 0.81; 95% CI = 0.74–0.89) and other Malaysian ethnicities (aOR = 0.77; 95% CI = 0.67-0.89) were less likely to receive ACEIs/ARBs than Malays. Furthermore, individuals with concurrent DM (aOR = 0.85; 95% CI = 0.79–0.92) and CKD (aOR = 0.34; 95% CI = 0.30–0.40), and those presenting with cardiogenic shock (Killip Class IV) (aOR = 0.44; 95% CI = 0.37–0.52) were less likely to be prescribed on-discharge ACEIs/ARBs compared with those without these conditions [Table 3].

Outcome of 1-year all-cause mortality in patients prescribed with ACEIs/ARBs

The 1-year all-cause mortality data were available for 52,850 patients. Mortality was reported in 7279 (13.8%) cases, with two-thirds (n = 4541; 62.4%) not having prescribed on-discharge ACEIs/ARBs. Unadjusted univariate Cox regression analysis indicated a significantly higher survival rate among those prescribed ACEIs/ARBs than those not prescribed (N = 60,854; HR = 0.57; 95% CI = 0.54–0.60; P < 0.001). After applying the IPW adjustment method, patients prescribed ACEIs/ARBs continued to exhibit a 38% better survival assumption compared with those who were not (n = 18,910; HR = 0.62; 95% CI = 0.56–0.69; SE = 0.06, P < 0.001) [Figure 2] [Table 4].

DISCUSSION

This study found that in Malaysia, less than two-thirds of ACS patients received on-discharge ACEIs/ARBs, and this trend persisted over the 10-year period. Notably, ACEIs/ARBS were preferred in younger patients and males, with variations among different ethnic groups. Paradoxically, patients with DM, CKD, or those presenting with cardiogenic shock were less likely to be prescribed ACEIs/ARBs. Despite these variations, patients prescribed ACEIs/ARBs continued to show a survival benefit in terms of 1-year all-cause mortality.

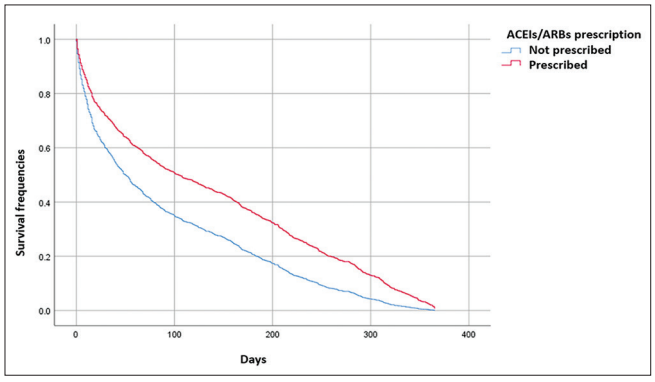

Figure 2: Cox survival curves comparing patients prescribed on-discharge ACEIs/ARBs and those not prescribed, using propensity score covariates adjustment, inverse proportional weighting

The observed suboptimal prescription trends of ACEIs/ARBs post-ACS are consistent with trends seen in other parts of the world, including Qatar (ACEIs = 63.5%; ARBs = 11.3%),[8] Mid-Atlantic states (ACEIs/ARBs = 63.9%),[9] and Montenegro (ACEIs/ARBs = 72%).[22] Low prescription rates of on-discharge ACEIs/ARBs were also reported in high-risk patients according to the Global Registry of Acute Coronary Events,[13] older patients,[9,23] and individuals with comorbidities such as DM[12] and CKD.[24] In the elderly, comorbidities such as hypertension

Table 3: Variations in on-discharge ACEIs/ARBs for Malaysian patients with acute coronary syndrome

Characteristics	aOR	95% CI	*P*
Male	Reference		
Female	0.99	0.89–1.10	NS
Aged <65 years	Reference		
Aged ≥65 years	0.79	0.73–0.86	<0.001
Malay	Reference		
Chinese	0.81	0.74–0.89	<0.001
Indian	0.95	0.87–1.05	NS
Other Malaysian	0.77	0.67–0.89	<0.001
STEMI	Reference		
NSTEMI	1.00	0.91–1.09	NS
UA	1.11	1.00–1.23	NS
Hypertension	1.70	1.56–1.84	<0.001
DM	0.85	0.79–0.92	<0.001
Dyslipidaemia	1.05	0.97–1.13	NS
Smoking	1.05	0.97–1.15	NS
High BMI (≥23.0)	1.15	1.06–1.25	0.001
CHF	0.98	0.83–1.15	NS
CLD	0.99	0.81–1.21	NS
CKD	0.34	0.30–0.40	<0.001
Cerebrovascular disease	1.05	0.86–1.28	NS
Peripheral vascular disease	0.70	0.39–1.27	NS
Cardiogenic shock	0.44	0.37–0.52	<0.001
MI	1.14	1.02–1.27	0.022
CAP	0.97	0.88–1.07	NS
2-weeks angina	1.13	1.05–1.22	0.002
Intervened with PCI	1.08	1.00–1.17	NS

NS (P>0.05). aOR – Adjusted odds ratio; CI – Confidence interval; BMI – Body mass index, NSTEMI – Non-ST-elevated myocardial infarction; STEMI – ST-elevated myocardial infarction; UA – Unstable angina; CHF – Congestive heart failure, CLD – Chronic lung disease; CKD – Chronic kidney disease; NS – Not significant; PCI – Percutaneous coronary intervention; DM – Diabetes mellitus

Table 4: One-year all-cause mortality and proportional hazard assumption in patients prescribed on-discharge ACEIs/ARBs (*N*=52,850)

1-year all-cause mortality status	Prescribed ACEIs/ARBs, *N* (%)	Not prescribed ACEIs/ARBs, *N* (%)	*P*
Alive (*n*=45,571)	29,402 (64.5)	16,169 (35.5)	<0.001
Dead (*n*=7279)	2738 (37.6)	4541 (62.4)	
Cox regression	**HR**	**95% CI**	
Univariate	0.57	0.54–0.60	<0.001
Multivariate	0.70	0.62–0.77	<0.001
Adjusted by IPW	0.62	0.56–0.69	<0.001

NS (P>0.05). HR – Hazard ratio; CI – Confidence interval; IPW – Inverse propensity score weighting; ACEIs/ARBs – Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

may predetermine the use of drug combinations that include ACEIs/ARBs to protect the cardiovascular and renal systems.[25,26] The complexity of prescribing ACEIs/ARBs in these subgroups may be attributed to the lack of comprehensive, evidence-based clinical studies, particularly regarding chronic usage of these medications.[27,28] For example, the effectiveness of ACEIs/ARBs in severe CKD and their impact on renal function recovery remain the subject of investigations.[24,29,30]

Despite these prescribing challenges, the efficacies of ACEIs/ARBs in post-ACS are well supported by favorable RCTs,[31-33] observational cohort studies[34,35] and meta-analyses.[36] The European ACS guidelines recommended ACEIs/ARBs for most patients, irrespective of their left ventricular ejection fraction status or risk factors such as DM, hypertension, and heart failure, unless contraindicated.[37,38] The recommendation extends to patients with CKD, especially those with diabetic nephropathy or proteinuria.[39] This study was conducted in Malaysia's government-subsidized hospitals, where all patients should have equal access to prescribed medications. However, the treatment–risk paradox persists, reflecting individualized physicians' preferences in clinical decision-making, which require further explorations.

Strengths and limitations of the study

This study, based on extensive local patient data, aimed to make a valuable contribution to improving guideline adherence in Malaysia. Leveraging the NCVD-ACS registry offers a unique opportunity for pharmacoepidemiological research on cardiovascular diseases in Malaysia. The registry's one-time capturing method effectively reduces duplicate patient entries, although it has a limitation of no follow-up data being available. Furthermore, information related to other diseases relies on self-reporting, and the absence of accompanying laboratory reports hinders confirmation. As a result, risk factors and comorbidities such as CKD and DM are interpreted based on the information provided in the NCVD registry. Nevertheless, the well-maintained database, its integration into the National Clinical Practice Guidelines, and its representation of the local clinical setting enhance its relevance.

Without randomized clinical trials, the PS covariates adjustment model and the IPW approach were employed as robust alternatives for risk adjustments.[21,40] However, it is worth noting that hospitals in the registry are predominantly located in urban areas, potentially introducing selection bias. Furthermore, the lack of follow-up data limited the ability to assess medication adherence, which may affect outcomes.

CONCLUSION

The persisting trend of suboptimal ACEIs/ARBs on-discharge prescription in Malaysia over a decade, along with variations in prescribing patterns across demographics and clinical conditions, underscores the imperative need to enhance the utilization of ACEIs/ARBs, given their demonstrated survival benefits in this population.

Ethical considerations

The NCVD registry study was approved by the Medical Review and Ethics Committee (MREC), Ministry of Health of Malaysia in 2007 (Approval Code: NMRR-07-20250). MREC waived the requirement for informed consent for NCVD. This study is a part of research approved by MREC with Approval Code: NMRR-19-4066-52389 (IIR). The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: S.Z.S., N.L.Z., and A.S.M.Z.; Methodology: S.Z.S., N.L.Z., and A.Y.; Data analysis: S.Z.S.; Writing–original draft preparation: S.Z.S.; Writing – review and editing: S.Z.S. and N.L.Z.; Supervision: N.L.Z., A.S.M.Z., A.Y., and W.A.H.W.M.A.

All authors have read and agreed to the published version of the manuscript.

Acknowledgement

The authors would like to thank all the medical and non-medical staff involved in the data collection and organization of NCVD and NHAM, Malaysia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Other clinical characteristics of the patients prescribed with on-discharge ACEIs/ARBs

Other clinical characteristics	Prescribed with ACEIs/ ARBs, *N* (%)	Not prescribed with ACEIs/ ARBs, *N* (%)	*P*
CHF	1692 (57.4)	1256 (42.6)	<0.001
CLD	912 (55.4)	734 (44.6)	<0.001
CKD	1524 (40.3)	2261 (59.7)	<0.001
Cerebrovascular disease	1106 (58.5)	785 (41.5)	NS
Peripheral vascular disease	155 (54.6)	129 (45.4)	0.046
Cardiogenic shock	1063 (34.1)	2053 (65. 9)	<0.001
Myocardial infarction	5576 (64.0)	3131 (36.0)	<0.001
Family history	7597 (63.2)	4419 (36. 8)	<0.001
Angina past 2-weeks	20,592 (62.3)	12,441 (37.7)	<0.001

NS ($P>0.05$). ACEIs/ARBs – Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CHF – Congestive heart failure; CLD – Chronic lung disease; CKD – Chronic kidney disease; NS – Not significant