The role of ACEI/ARBS in reducing morbidity in non- diabetic patients with an ischemic heart disease with left ventricular ejection fraction >= 50. At North state, Sudan. From October 2026 to January 2027.

by:

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Abbreviations:

ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AHA	American heart association
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
CABG	Coronary artery bypass graft
CKD	Chronic kidney disease
CVD	Cardiovascular disease
ESC	European Society of Cardiology
FAR	Fibrinogen to albumin ratio
hsCRP	High-sensitive C-reactive protein
LDL	Low density lipoprotein
LVEF	Left ventricular ejection fraction
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NLR	Neutrophil-lymphocyte ratio
NSTEMI	Non-ST segment elevation
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention

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PLR	Platelet-lymphocyte ratio
STEMI	ST segment elevation

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Introduction:

Among the most recent years for which information is available, cardiovascular disease continued to be the leading cause of death among the member nations of the European Society of Cardiology (ESC), accounting for slightly over 1.9 million deaths in men and slightly under 2.2 million deaths in women. These account for 45 percent of all deaths in the case of women and 39 percent in the case of males. The most frequent cause of CVD mortality, ischemic heart disease, accounts for 44% of fatalities from the condition in men and 38% in women [1]. The most prevalent illness in Africa is ACS, with a pooled estimate of 22% for all-cause mortality [2].

The mortality rate for individuals with ACS has decreased due to the widespread use of revascularization through percutaneous coronary intervention (PCI) and pharmaceutical therapy [3]. In patients with ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), the American College of Cardiology/American Heart Association (ACC/AHA) recommends aspirin, statins, P2Y12 inhibitors, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), often referred to as optimal medical therapy (OMT), in patients with STEMI or NSTEMI. The early versions of the ESC guidelines contain a Class I, Level A recommendation for aspirin, P2Y12 inhibitors, and statins in all ACS patients unless contraindicated [4, 5].

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are effective and recommended therapies following myocardial infarction with reduced left ventricular ejection fraction (LVEF), symptoms of heart failure, chronic kidney disease, hypertension, and/or diabetes [6–8]. Indeed, the use of these drugs is a quality indicator for individuals with reduced LVEF [9]. There is, however, little knowledge on the effectiveness of ACEi/ARBs in those with myocardial infarction with preserved LVEF (≥50%) [10].

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Guidelines from both the European Society of Cardiology and the American Heart Association suggest a Class IIa or lower recommendation for ACEi/ARBs in all individuals with myocardial infarction regardless of LVEF [10-12]. However, the few trials that assessed ACEi/ARBs in all individuals with myocardial infarction, irrespective of left ventricular fraction, estimated little or no effect, and are from an era before the widespread use of high-sensitive troponins, percutaneous coronary intervention, anti-thrombotic agents, and high-intensity statins [13-17]. Observational studies provide conflicting evidence [18-22].

Hamish C Prosser et.al. on 2022 found in a large observational study that ACEi/ARB therapy was associated with significant long-term survival benefit in patient's post-PCI for STEMI/NSTEMI. This survival benefit is apparent in patients with both preserved and reduced LV function. These findings provide contemporary evidence to support the use of these agents in patients treated with PCI for STEMI/NSTEMI, irrespective of their baseline left ventricular function [23].

In our region and Sudan no available data on long-term survival benefit from using ACEI/ARB therapy in ischemic heart disease patients.

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Statement of the problem:

- cardiovascular disease continued to be the leading cause of death, and the most prevalent illness in Africa is ACS, with a pooled estimate of 22% for all-cause mortality [2].
- Indeed, the use of renin-angiotensin system inhibitors is a quality indicator for individuals with reduced LVEF following myocardial infarction [9], there is, however, little knowledge on the effectiveness of them in those with preserved LVEF (≥50%) [10].

Justification:

Clinical guidelines for ACEi/ARB use in IHD are strongest for patients with concomitant conditions such as diabetes, hypertension, or reduced EF. For patients with preserved EF and no diabetes, the level of evidence supporting routine use is notably lower. Much of the existing evidence in preserved EF populations is derived from trials where a significant proportion of patients had diabetes—a condition that itself is a strong indication for ACEi/ARB therapy. By focusing specifically on the non-diabetic subgroup, the study isolates the effect of these drugs in a population where the indication is less clear (6-8, 10)

no randomized trials are planned to evaluate the effect of ACEi/ARBs vs. no treatment on the risk of angina worsening,reinfarction, and heart failure following myocardial infarction with preserved LVEF and no indications for these drugs. The next best solution is, therefore, to use observational data.

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Literature review:

One of the main causes of mortality globally, cardiovascular illnesses continue to have a significant impact on morbidity, mortality, and healthcare costs [24,25]. The term "acute coronary syndrome" (ACS) explains a variety of illnesses that are indicative of an abrupt decrease in coronary blood flow and are therefore consistent with acute myocardial infarction [26,27]. The formation of coronary atherosclerotic plaque, which causes intracoronary thrombosis and ischemia, is the most frequent cause of ACS. Prolonged cessation of coronary blood flow can result in myocyte necrosis or infarction [28, 2]. Despite advancements in therapy, ACS, which encompasses unstable angina and myocardial infarction (MI) with and without ST-segment elevation, remains a life-threatening condition with significant rates of morbidity and mortality [26]. It is estimated that there are 7 million cases of ACS worldwide, making it one of the most prevalent diseases globally [27, 28].

Among the most recent years for which information is available, cardiovascular disease continued to be the leading cause of death among the member nations of the European Society of Cardiology (ESC), accounting for slightly over 1.9 million deaths in men and slightly under 2.2 million deaths in women. These account for 45 percent of all deaths in the case of women and 39 percent in the case of males. The most frequent cause of CVD mortality, ischemic heart disease, accounts for 44% of fatalities from the condition in men and 38% in women [1]. The most prevalent illness in Africa is ACS, with a pooled estimate of 22% for all-cause mortality [2].

Early prediction of outcomes is crucial for patients with acute coronary syndrome, as it can greatly improve their prognosis and help control the progression of the disease. While several cardiovascular risk markers have been identified, further research is needed to confirm their usefulness and diagnostic effectiveness [29, 30]. Available data suggests that inflammation plays a prominent role in all stages of coronary atherosclerosis [31]. Prior research has demonstrated that fibrinogen is involved in both the initiation and progression of inflammation by turning on the


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synthesis of pro-inflammatory proteins through the nuclear factor transcription pathway. In addition to the advancement of atherosclerosis by binding to glycoprotein receptors on platelet surfaces, promoting platelet aggregation [32, 33]. On the other hand, the negative inflammatory protein albumin has a negative correlation with erythrocyte aggregation. In patients with ACS, a decrease in serum albumin levels has been linked to higher mortality rates [34]. Furthermore, a study has revealed that individuals with ACS are more likely to develop poor outcomes if they have a high fibrinogen to albumin ratio (FAR), syntax score II, neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio, high-sensitive C-reactive protein (hsCRP), and low HALP (hemoglobin, albumin, lymphocyte, and platelet) levels below 3.72 [29, 35-39]. Additionally, lifestyle education was also found to be a reliable and independent predictor of worse outcomes [37]. These biomarkers can be easily detected using non-invasive and innovative techniques. However, these biomarkers are not applicable in our setup.

The first few hours after symptom onset are the most critical in AMI and over 50% of cardiac deaths occur within the first 30 minutes, when the patient has not yet reached the hospital [40]. Several studies focused on the effect the overall system delay on adverse outcomes, including all components of delay modifiable by the health care system, both pre-hospital and door-to-balloon time [41–44]. Thus, reducing the interval between symptom onset and the hospital arrival (emergency phase) as well as receiving a timely and appropriate in-hospital medical treatment, are crucial factors in the survival of these patients [45, 46]. In particular, for patients with ST-elevation myocardial infarctions (STEMI), the European Society of Cardiology and the American College of Cardiology/American Heart Association recommend primary percutaneous coronary intervention (PCI) within 90 minutes of first medical contact and a total ischemic time, from symptom onset to reperfusion, within 120 minutes [47,48].

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The relationship between timely PCI with respect to both short-term and long-term mortality has been widely studied [49–54]. However, a recent study showed that the protective effect of a timely reperfusion of STEMI is reduced with increasing travel time from home to hospital [44], suggesting a strong effect of the quality of care on survival.

The mortality rate for individuals with ACS has decreased due to the widespread use of revascularization through percutaneous coronary intervention (PCI) and pharmaceutical therapy [3]. In patients with ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), the American College of Cardiology/American Heart Association (ACC/AHA) recommends aspirin, statins, P2Y12 inhibitors, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), often referred to as optimal medical therapy (OMT), in patients with STEMI or NSTEMI. The early versions of the ESC guidelines contain a Class I, Level A recommendation for aspirin, P2Y12 inhibitors, and statins in all ACS patients unless contraindicated [4, 5].

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are effective and recommended therapies following myocardial infarction with reduced left ventricular ejection fraction (LVEF), symptoms of heart failure, chronic kidney disease, hypertension, and/or diabetes [6-8]. Indeed, the use of these drugs is a quality indicator for individuals with reduced LVEF [9]. There is, however, little knowledge on the effectiveness of ACEi/ARBs in those with myocardial infarction with preserved LVEF (≥50%) [10].

Guidelines from both the European Society of Cardiology and the American Heart Association suggest a Class IIa or lower recommendation for ACEi/ARBs in all individuals with myocardial infarction regardless of LVEF[10-12] However, the few trials that assessed ACEi/ARBs in all individuals with myocardial infarction, irrespective of left ventricular fraction, estimated little or no effect, and are from an

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era before the widespread use of high-sensitive troponins, percutaneous coronary intervention, anti-thrombotic agents, and high-intensity statins.[13-17] Observational studies provide conflicting evidence.[18-22].

Anna B C Humphreys et.al, found that The estimated risk of a composite of death, myocardial infarction or heart failure was similar in recipients and non-recipients of ACEi/ARB. Their estimates suggest ACEi/ARB treatment in myocardial infarction with preserved LVEF does not confer a benefit [55].

Hamish C Prosser et.al. found in a large observational study that ACEi/ARB therapy was associated with significant long-term survival benefit in patient's post-PCI for STEMI/NSTEMI. This survival benefit is apparent in patients with both preserved and reduced LV function. These findings provide contemporary evidence to support the use of these agents in patients treated with PCI for STEMI/NSTEMI, irrespective of their baseline left ventricular function [23].

The Heart Outcomes Prevention Evaluation (HOPE) [56]; showed the effectiveness of an ACE inhibitor, ramipril, in reducing mortality and morbidity from cardiovascular events among patients with known vascular disease, as well as those with diabetes mellitus and another cardiovascular risk factor who did not have a history of heart failure or left ventricular systolic dysfunction. The findings of that study, recently confirmed by the results of the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) [57]; changed clinical practice and led to increased use of ACE inhibitors in patients with vascular disease but without heart failure or left ventricular systolic dysfunction. The scientific basis for the use of ACE inhibitors in preventing the progression of vascular disease and ischemic events in patients with vascular disease is strong. ACE inhibitors, by inhibiting angiotensin II or by increasing the concentration of bradykinin, are associated with a decrease in vascular NADPH activity and reactive oxygen species. They also lead to reduced activation of important signaling pathways (including pathways involving nuclear factor-κB and activator protein 1);

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reductions in vascular inflammation, endothelial dysfunction, progression of atherosclerosis, and activation of metalloproteinases 2 and 9; an improvement in plaque stability; a decrease in the tendency toward thrombosis; and an improvement in fibrinolysis.

The results of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial [58]; reported in this issue of the Journal, are therefore surprising. In this well-designed and well-executed study, patients with known vascular disease but without a history of heart failure or left ventricular systolic dysfunction (after the exclusion of high-risk patients with diabetes mellitus) were randomly assigned either to a placebo or to the ACE inhibitor trandolapril at a dose previously shown to reduce mortality and morbidity from cardiovascular events among patients with left ventricular systolic dysfunction after myocardial infarction. The patients assigned to receive trandolapril did not have any benefit in terms of mortality or morbidity from cardiovascular causes.

One possible explanation for the negative results of ACE inhibition in the PEACE Trial comes from the Trial on Reversing Endothelial Dysfunction (TREND) [59]; in which the ACE inhibitor quinapril was shown to be effective in improving endothelial function in patients with coronary artery disease but without left ventricular systolic dysfunction. A retrospective analysis of the data showed that quinapril was significantly effective in improving coronary endothelial function only among patients whose low-density lipoprotein (LDL) cholesterol concentration was above the median in that study (approximately 125 mg per deciliter [3 mmol per liter]). This observation was strengthened by a similar analysis in the Quinapril Ischemic Event Trial (QUIET), which involved patients with coronary disease who did not have left ventricular systolic dysfunction. In that trial, quinapril failed to reduce the rate of cardiovascular events overall but did appear to be effective in reducing the rate of progression of coronary artery disease and cardiovascular events among patients with an increased concentration of LDL cholesterol [60].

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Thus, the failure of ACE inhibition to reduce the rate of cardiovascular events in the PEACE Trial might be explained by the fact that patients in that trial, many of whom were being treated with a statin, had a relatively low concentration of LDL cholesterol. ACE inhibitors and statins have a common mechanism of action: they both reduce activation of the lectin-like oxidized LDL receptor and thus reduce oxidation of LDL cholesterol [61]. If the concentration of LDL cholesterol is sufficiently low, ACE inhibitors may no longer be effective in reducing the rate of cardiovascular events.

The possibility that not all ACE inhibitors are equally effective for all indications should also be considered [62]. For example, in a recent prospective, randomized study involving patients who had had a myocardial infarction [63]. the ACE inhibitor quinapril was shown to be significantly more effective than enalapril (at doses previously shown to be effective in reducing the rate of cardiovascular events among patients with left ventricular systolic dysfunction) in reducing the concentration of C-reactive protein, an important marker of vascular inflammation and cardiovascular risk [64]. Thus, the finding that trandolapril at a given dose reduced mortality and morbidity from cardiovascular events among patients with left ventricular systolic dysfunction after a myocardial infarction does not necessarily mean that the same dose will be effective in reducing the rate of cardiovascular events among patients with vascular disease who do not have left ventricular systolic dysfunction. Left ventricular systolic dysfunction is an important stimulus for the activation of various neurohormones, cytokines, growth factors, and signaling pathways. A higher dose of a given ACE inhibitor may be required in patients who do not have left ventricular systolic dysfunction than in those who do have such dysfunction. Alternatively, efficacy in the former group may depend on lipophilicity or other as-yet unidentified factors.

Regardless of the mechanisms accounting for the failure of trandolapril to reduce the rate of cardiovascular events, the most important finding in the PEACE Trial is

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that, after the exclusion of high-risk patients with diabetes mellitus, patients with known vascular disease who do not have a history of heart failure or left ventricular systolic dysfunction have a low risk of subsequent cardiovascular events when treated with a statin and other contemporary therapies. In view of the low cardiovascular risk in this group of patients, it is doubtful that the use of an ACE inhibitor or an angiotensin-receptor blocking agent — even if effective in reducing the rate of cardiovascular events — would be cost-effective. The finding that contemporary therapy has reduced cardiovascular risk in these patients to a normal level holds promise for a reduction in cardiovascular risk among high-risk patients with vascular disease, including those with diabetes mellitus. Wider application of strategies known to be effective (such as statin therapy, weight reduction, and glucose and blood-pressure control) as well as strategies currently under investigation could minimize the risk of cardiovascular events and possibly reduce the financial burden associated with vascular disease — a burden that is projected to increase as our population ages.

The results of the PEACE Trial underscore the importance of periodically reviewing previously proven strategies if concomitant therapy has changed over time. For example, percutaneous coronary revascularization has been shown to be effective in reducing the rate of cardiovascular events among patients who have unstable angina pectoris and those who have myocardial infarction without ST-segment elevation [65]. Since such studies were completed, contemporary therapy has changed, and increasing numbers of patients are being treated with effective antiplatelet drugs and high-dose statins.

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Objectives

General objective:

To study the role of ACEI/ARBS in reducing morbidity in non- diabetic patients with an ischemic heart disease with left ventricular ejection fraction>= 50. At North state, Sudan. From October 2026 to January 2027.

Specific objectives:

- To correlate between smoking and alcohol intake status and outcome of using of ACEI/ARBS in non- diabetic patients with an IHD with LVEF>= 50
- To correlate between history of previous PCI and outcome of using of ACEI/ARBS in non- diabetic patients with an IHD with LVEF>= 50
- To correlate between history of previous CABG and outcome of using of ACEI/ARBS in non- diabetic patients with an IHD with LVEF>= 50
- To identify risk factors for worse outcome in non-diabetic patients using ACEI/ARBS with an IHD with LVEF >= 50

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Materials and Methods

Study design:

This study will be an observational, descriptive, cross sectional hospital based study.

Study area:

The study will be conducted at Dongola Specialized Hospital and Sheikh Abdul Aziz Bin Abdullah Al Jemaih center. They are the main govermental centers providing cardiology services, located at Dongola, North state, Sudan.

Dongola Specialized Hospital:

It is a tertiary care facility in north state. It is a multi-speciality hospital providing a range of services through departments including general surgery, orthopedics and trauma, urology, pediatrics, dermatology, and internal medicine with its different sub-specialities and their advanced interventions (cardiology, gastroenterology, pulmonology, nephrology, neurology, and endocrinology).

Sheikh Abdul Aziz Bin Abdullah Al Jemaih center:

It functions as a large tertiary hospital offering primary, secondary, and tertiary-level medical services to diabetic patients from across the entire Northern State.

It also provide cardiology clinics for diabetic and non diabetic patients.

Study duration:

The study will be conducted during the period from October 2026 to January 2027.

Study population:

All adult non- diabetic patients with IHD with LVEF>= 50 using ACEI/ARBS . At Dongola spescialised hospital and Sheikh Abdul Aziz Bin Abdullah Al Jemaih center

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during journal study period.

Inclusion criteria:

- Patients 18 years of age or older.
- Patients with IHD with LVEF>= 50.
- Patients using ACEI/ARBS.

Exclusion criteria:

- Diabetic patients
- Patients with IHD with LVEF < 50.

Sampling:

Sampling type:

Convenient non-probability sampling.

Sampling size:

Total coverage for all the patients satisfying the inclusion criteria.

Data collection methods and tools:

Data will be collected using an interviewer-administered questionnaire that was developed by the author including all the required variables to achieve the specific objectives of the study. LVEF will be obtained from patient record.

Study variables:

Independent	Dependent
Background variables	All cause hospitalisation

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Smoking status	Cardiovascular hospitalisation
Alcohol intake status	Heart failure hospitalisation
Previous PCI	Recurrent ACS
Previuos CABG	Worsening angina
HTN	
CKD	
Duration of using ACEI/ARBS	

Ethical consideration:

- Ethical clearance will be obtained from ministry of health.
- Permission from Dongola Specialized Hospital will be obtained before accessing the patients and their data.
- A written informed consent will be taken from all selected participants before administering the questionnaire.
- Participants will have the freedom to withdraw from the study anytime during the study course.
- Private data of the patients will be kept confidential by using serial number from the questionnaire data and reporting only the required information and preserving files.
- Participant had the right to benefit from the researcher knowledge and skills (by informing the head of the department by the missed important information from the files).
- All COVID 19 precautions were considered.

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بحث لدراسة: دور مثبطات الإنزيم المحول للأنجيوتنسين/حاصرات مستقبلات الأنجيوتنسين في الحد من معدلات الإصابة بالأمراض والوفيات لدى المرضى غير المصابين بداء السكري والذين يعانون من مرض القلب الإقفاري مع كسر قذفي للبطين الأيسر ≤ 50 في الفترة من أكتوبر ا

2027الى يناير 20260

اسم الباحث: د. دلال نورالدين فضل المولى محمدالامين – اختصاصي الطب الباطن

رقم التلفون: 0112555989

:بيان الباحث

أنا أطلب منك المشاركة في دراسة بحثية. الغرض من فورم الاقرار هذا أن نعطيك المعلومات التي ستحتاجها لتساعدك على أن تقرر ما إذا كنت ستشارك في الدراسة أم لا. الرجاء قراءة هذا الفورم بعناية. يمكنك طرح أسئلة حول الغرض من البحث؛ حقوقك كمتطوع؛ أو أي شئ آخر غير واضح بالنسبة لك بخصوص البحث أو هذا الفورم. عندما نجيب على كل أسئلتك يمكنك أن تقرر ما .اذا كنت ستشارك في الدراسة أم لا

الغرض من الدراسة

دور مثبطات الإنزيم المحول للأنجيوتنسين/حاصرات مستقبلات الأنجيوتنسين في الحد من

معدلات الإصابة بالأمراض والوفيات لدى المرضى غير المصابين بداء السكري والذين يعانون من .مرض القلب الإقفاري مع كسر قذفي للبطين الأيسر ≤ 50

.2027الى يناير 2026في الفترة من أكتوبر

:اجراءات الدراسة

اذا قررت المشاركة في هذه الدراسة؛ سأجري معك مقابلة عن طريق ستبيان مكتوب سأملأه بنفسي و سأسألك أسئلة متعلقة بالدراسة. هذه المقابلة ستستغرق من حوالي 5-10 دقائق؛ لست . ملزم بالاجابة على كل الأسئلة؛ سأدون اجابتك و سأستخدمها في الدراسة

*هذه المعلومات التي أخذتها منك ستكون سرية. إذا تم نشر أو عرض نتائج هذه الدراسة فإننا لن نستخدم اسمك مع النتائج المنشورة أو المعروضة

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الفوائد:

.لا توجد فوائد مباشرة أو شخصية تعود إليك إذا شاركت في هذا البحث

المشاركة في هذه الدراسة طوعية.. يمكنك التوقف عن المشاركة في أي لحظة ولن يتم استخدام .بياناتك

توقيع المشارك

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التاريخ

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the role of ACEI/ARBS in reducing morbidity in non- diabetic patients with an ischemic heart disease with left ventricular ejection fraction >= 50. At North state, Sudan. From October 2026 to January 2027

Questionnaire

Serial number: .....

1. Gender: male (.). Female (.)

2. Age: .....

3. Occupation status: working (.). Not-working (.). Student (.)

4. Smoking status: Never smoking (.). Ex-smoker(>1month) (.). Smoker (.)

5. Alcohol intake: yes (.). No (.)

6. Previous PCI: Yes (.). No (.)

7. Previous CABG: Yes (.). No (.)

8. Hypertension: Yes (.). No (.)

9. CKD: Yes (.). No (.)

10. Duration of using ACEI/ARBS: .....

11. All cause hospitalisation: Yes (.). No (.)

12.Cardiovascular hospitalisation: Yes (.). No (.)

13. Heart failure hospitalisation: Yes (.). No (.)

14. Recurrent ACS: Yes (.). No (.)

15. Worsening angina: Yes (.). No (.)

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