

**Comparing Cardiovascular Outcomes and Costs of Perindopril-, Enalapril- or Losartan-
Based Antihypertensive Regimens in South Africa: Real-World Medical Claims Database**

Analysis

Supplementary Material

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Supplementary Tables

Supplementary Table S1 International Classification of Diseases (ICD) 10th revision codes for specific outcomes

Diagnostic episode grouper (DEG)	ICD Codes
Ischaemic heart disease	I200 - Unstable angina, I259 - Chronic ischaemic heart disease, unspecified, I251 - Atherosclerotic heart disease, I209 - Angina pectoris, unspecified, I249 - Acute ischaemic heart disease, unspecified, I250 - Atherosclerotic cardiovascular disease, so described, I208 - Other forms of angina pectoris, I258 - Other forms of chronic ischaemic heart disease, I255 - Ischaemic cardiomyopathy, I248 - Other forms of acute ischaemic heart disease
Hypercholesterolaemia	E785 - Hyperlipidaemia, unspecified, E780 - Pure hypercholesterolaemia, E782 - Mixed hyperlipidaemia
Acute myocardial infarction	I219 - Acute myocardial infarction, unspecified, I210 - Acute transmural myocardial infarction of anterior wall, I211 - Acute transmural myocardial infarction of inferior wall, I214 - Acute subendocardial myocardial infarction, I213 - Acute transmural myocardial infarction of unspecified site, I212 - Acute transmural myocardial infarction of other sites
Cardiac failure	I500 - Congestive heart failure, I509 - Heart failure, unspecified, I420 - Dilated cardiomyopathy, I501 - Left ventricular failure, I429 - Cardiomyopathy, unspecified
Arrhythmia	I489 - Atrial fibrillation and atrial flutter, unspecified, I499 - Cardiac arrhythmia, unspecified, I442 - Atrioventricular block, complete, I480 - Paroxysmal atrial fibrillation, I495 - Sick sinus syndrome, I481 - Persistent atrial fibrillation, I482 - Chronic atrial fibrillation, I472 - Ventricular tachycardia, I471 - Supraventricular tachycardia, I483 - Typical atrial flutter, I455 - Other specified heart block, I421 - Obstructive hypertrophic cardiomyopathy, I441 - Atrioventricular block, second degree, I447 - Left bundle-branch block, unspecified

Aneurysm	I714 - Abdominal aortic aneurysm, without mention of rupture, I712 - Thoracic aortic aneurysm, without mention of rupture, I713 - Abdominal aortic aneurysm, ruptured, I724 - Aneurysm and dissection of artery of lower extremity, I723 - Aneurysm and dissection of Iliac artery, I728 - Aneurysm and dissection of other specified arteries, I722 - Aneurysm and dissection of renal artery, I712 - Thoracic aortic aneurysm, without mention of rupture, I721 - Aneurysm and dissection of artery of upper extremity, I253 - Aneurysm of heart, I719 - Aortic aneurysm of unspecified site, without mention of rupture
Diabetes type 1 or 2	E119 - Type 2 diabetes mellitus without complications, E109 - Type 1 diabetes mellitus without complications, E113 - Type 2 diabetes mellitus with ophthalmic complications, E103 - Type 1 diabetes mellitus with ophthalmic complications, E115 - Type 2 diabetes mellitus with peripheral circulatory complications, E105 - Type 1 diabetes mellitus with peripheral circulatory complications, E101 - Type 1 diabetes mellitus with ketoacidosis, E118 - Type 2 diabetes mellitus with unspecified complications, E108 - Type 1 diabetes mellitus with unspecified complications, E109 - Type 1 diabetes mellitus without complications, E111 - Type 2 diabetes mellitus with ketoacidosis, E162 - Hypoglycaemia, unspecified
Chronic renal failure	N189 - Chronic kidney disease, unspecified, N185 - Chronic kidney disease, stage 5, N179 - Acute renal failure, unspecified, I120 - Hypertensive renal disease with renal failure, N179 - Acute renal failure, unspecified, N184 - Chronic kidney disease, stage 4
Stroke	I613 - Intracerebral haemorrhage in brain stem, I606 - Subarachnoid haemorrhage from other intracranial arteries, I671 - Cerebral aneurysm, nonruptured, I610 - Intracerebral haemorrhage in hemisphere, subcortical, G451 - Carotid artery syndrome (hemispheric), R908 - Other abnormal findings on diagnostic Imaging of central nervous system, I634 - Cerebral infarction due to embolism of cerebral arteries, I629 - Intracranial haemorrhage (nontraumatic), unspecified, G458 - Other transient cerebral ischaemic attacks and related syndromes, I636 - Cerebral infarction due to cerebral venous thrombosis, nonpyogenic, I619 - Intracerebral haemorrhage, unspecified, I679 - Cerebrovascular disease,

unspecified, I678 - Other specified cerebrovascular diseases, I638 - Other cerebral infarction, I635 - Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries, I633 - Cerebral infarction due to thrombosis of cerebral arteries, I620 - Subdural haemorrhage (acute)(nontraumatic), I652 - Occlusion and stenosis of carotid artery, I639 - Cerebral infarction, unspecified, G459 - Transient cerebral ischaemic attack, unspecified, I64 - Stroke, not specified as haemorrhage or infarction

Vascular dementia

F019 - Vascular dementia, unspecified, F011 - Multi-infarct dementia, F010 - Vascular dementia of acute onset, F012 - Subcortical vascular dementia, F013 - Mixed cortical and subcortical vascular dementia, F018 - Other vascular dementia

Supplementary Table S2 Anatomical Therapeutic Chemical (ATC) codes used to identify medication claims

ATC_CODE^a	ATC_DESCRIPTION
C09AA04	PERINDOPRIL
C09BB04	PERINDOPRIL AND AMLODIPINE
C09BA04	PERINDOPRIL AND DIURETICS
C09CA01	LOSARTAN
C09DB06	LOSARTAN AND AMLODIPINE
C09DA01	LOSARTAN AND DIURETICS
C09AA02	ENALAPRIL
C09BA02	ENALAPRIL AND DIURETICS

^aThese codes represent all products containing perindopril, losartan and enalapril in the medical claims database. Other ATC codes used to denote these molecules were not assigned to actively dispensed drugs during the study period 2015–2019

Supplementary Table S3 Number of patients using each RAAS inhibitor agent

The most common RAAS inhibitors used during the study period 2015–2019 were identified using the ATC class, and both plain and combination versions of the RAAS inhibitors were included in the analyses. The top three RAAS inhibitors were perindopril, losartan and enalapril, which together accounted for 61% of all patients receiving any RAAS inhibitor in the medical insurance database over the period from 2015 to 2019

RAAS inhibitor agent	Number of patients claiming use
Perindopril	235,138
Losartan	108,943
Enalapril	99,345
Valsartan	98,776
Lisinopril	62,064
Telmisartan	60,280
Captopril	14,937
Others	42,683

ATC Anatomical Therapeutic Chemical, RAAS renin-angiotensin-aldosterone system

Supplementary Table S4 Sensitivity analyses, including all patients (*N* = 108,820)

Parameter	Perindopril	Losartan	Mean difference (95% CI) for perindopril– losartan	<i>P</i> -value	Perindopril	Enalapril	Mean difference (95% CI) for perindopril– enalapril	<i>P</i> -value
Total cost (ZAR ^a PLPM)	1458	1578	–120 (–206, –36)	0.0050	1458	1621	–163 (–369, –57)	0.0026
Primary composite outcome (events per 1000 patients over 5 years)	216	245	–	< 0.001	216	241	–	< 0.001
Patients with primary composite outcome (%)	14.9	16.7	–	< 0.001	14.9	17.1	–	< 0.001

PLPM per life per month, ZAR South African Rands

^aThe average rate of exchange for the ZAR between 2015 and 2019 (the study period) was ZAR 137 019.20 per \$US 1 [1]

Supplementary Table S5 Non-risk-adjusted outcomes

	Perindopril	Losartan	Enalapril
Clinical outcomes			
Hospitalisation event rate (per 1000 patients)	212	223	210
Heart Failure	42	42	44
Stroke	55	61	60
MI	22	23	26
IHD	93	97	80
Patients with new occurrence of a composite outcome event, %	15.6	16.9	16.2
Mortality rate (deaths per 1000 patients)	103	95	131
Cost outcomes, mean (95% CI), ZAR			
Total PLPM	1381 (87–8973)	1480 (104–9365)	1448 (77–10446)
Hospital (inpatient)	770 (0–7452)	807 (0–7586)	856 (0–8810)
Pharmacotherapy	355 (55–1273)	379 (73–1451)	330 (45–1363)
GP (outpatient)	44 (0–146)	49 (0–161)	47 (0–168)
Specialist (inpatient)	56 (0–412)	56 (0–410)	41 (0–347)
Other ^a	156 (0–547)	189 (0–621)	173 (0–554)

CI confidence interval, *GP* general practitioner, *PLPM* per life per month, *ZAR* South African Rands

^aIncludes radiology, pathology and allied healthcare services

Supplementary Table S6 Antihypertensive drug use

Therapy	Patients receiving therapy (%)			
	Perindopril	Losartan	Enalapril	Total
Monotherapy	11	10	13	11
Adjunctive therapy				
Diuretics	26	26	25	26
Diuretics + beta-blockers	14	14	12	14
CCBs	6	5	5	5
CCBs + beta-blockers	3	3	3	3
Diuretics + CCBs	19	20	20	19
Diuretics + CCBs + beta-blockers	17	19	17	17
Beta-blockers	5	4	4	4
Total	100	100	100	100

CCB calcium channel blocker

References

1. Nedbank. Average annual exchange rates. 2021.
https://www.nedbank.co.za/content/dam/nedbank/site-assets/AboutUs/Economics_Unit/Forecast_and_data/Daily_Rates/Annual_Average_Exchange_Rates.pdf. Accessed 18 July 2022.