


REVIEW

An evidence-based systematic review of the off-label uses of lisinopril

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AIMS

Lisinopril is an angiotensin-converting-enzyme inhibitor that is largely administered for off-label uses. This study aims to provide a comprehensive review of off-label uses of lisinopril to aid physicians to make evidence-based decisions.

METHODS

The following bibliographic databases were searched from inception up to 30 March 2017: PubMed, EMBASE, the Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, Ovid and Proquest. This systematic review sought all randomized trials conducted on adult individuals comparing lisinopril on its off-label uses with alternative drugs or placebos and reported direct or alternative clinical outcomes. Risk of bias assessment by using the Cochrane Collaboration risk-of-bias tool and quality evaluation took place.

RESULTS

Included studies demonstrated significant positive effects of lisinopril on proteinuric kidney disease; however, lisinopril caused a slight reduction of glomerular filtration rate (GFR) especially for patients with GFR < 90 ml min⁻¹. Lisinopril offered better outcomes in comparison to other standard treatments of diabetic nephropathy. Other studies showed positive effects of lisinopril for migraine, prevention of diabetes, myocardial fibrosis, mitral valve regurgitation, cardiomyopathy in patients with Duchenne muscular dystrophy, oligospermia and infertility, and diabetic retinopathy. Conversely, the studies reported that lisinopril was ineffective for five other off-label uses.

CONCLUSIONS

The identified studies showed that lisinopril was highly effective for proteinuric kidney disease with a minor but inconsiderable decrease in GFR. Positive effects of lisinopril were demonstrated in seven other off-label uses; however, lisinopril cannot be recommended as the first choice for these until further clinical trials confirm these positive effects.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Off-label administration of some drugs, including lisinopril has a remarkable prevalence among physicians. However, there is still a need for a comprehensive review to aid physicians to base their decision on the strong evidence and make safe and positive decisions

WHAT THIS STUDY ADDS

- We searched the literature and found related studies for each of lisinopril's off-label uses, assessed the quality of them, illustrated the eligibility of prescription, and summarized the supporting evidence

Introduction

Hundreds of new drugs emerge each year. Before they can be widely used, they need to be approved by regulatory organizations such as the US Food and Drug Administration (FDA), European Medicines Agency and the Therapeutic Goods Administration. The FDA was initially established to regulate the production of food, drugs and cosmetics in the USA but nowadays it also supervises international drug products [1]. In addition to approved FDA uses of drugs, there are a variety of unapproved uses that are called *off-label*. The off-label administration is not the same as the unlicensed use of a drug or substance. While the safety of these drugs has been previously confirmed by the FDA, their efficiency has been established only for their approved uses. The efficiency for their off-label uses is yet to be confirmed by taking the complicated procedure of approval. Therefore, clinicians may consider the off-label uses for these drugs if they find them useful for their patients. Off-label administration of drugs has a remarkable prevalence among physicians [2]. Recent North American surveys show that 11% [3] to 21% [4] of the administrations of commonly used drugs were off-label; among these, up to 80.0% lacked strong scientific evidence of efficacy [3]. It has been shown that the prevalence of off-label prescriptions was higher in some special groups; almost 80% of the children discharged from a paediatric hospitals in the USA received at least one off-label drug [5]. Although these off-label uses are not approved, it does not necessarily mean that their prescription is unsafe, as some off-label uses of drugs are recommended by prominent guidelines (e.g. use of tricyclic antidepressants for neuropathic pain or spironolactone for hirsutism [6–8]). That said, clinicians and guideline developers require research syntheses and critical evaluations of available information to assess the extent and quality of the evidence before supporting a drug's off-label uses.

Lisinopril is an angiotensin-converting-enzyme (ACE) inhibitor that is largely being used off-label [9]. Lisinopril was initially approved by the FDA as an oral tablet for the treatment of hypertension in adults and children aged >6 years, adjunct therapy for heart failure and treatment of acute myocardial infarction (Prinivil and Zestril) [10, 11] and in combination with hydrochlorothiazide for the treatment of hypertension (Zestoretic) [12]. Lately, an oral solution form (Qbrelis), has been approved for the same indications [13]. Lisinopril has been identified as one of the top 10 drugs that require further evidence for its off-label uses: data from the USA, July 2005–June 2007 showed that 2 374 000 of 2 601 000 records of administrations in its off-label uses had

inadequate supporting evidence [9]. Through this paper, we aim to comprehensively review the off-label uses of lisinopril.

Methods

This study was conducted as a systematic review of randomized clinical trials (RCTs) conducted on patients aged ≥18 years who received lisinopril (on its off-label uses) as compared to other alternative drugs or placebos and reported direct or alternative clinical outcomes.

Data sources and searches

An expert librarian defined individualized search strategies for the following bibliographic databases, from inception up to 30 March 2017: PubMed, EMBASE, the Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, Ovid and Proquest. A primary search (Table 1) was conducted by a librarian for any possible off-label administrations of lisinopril using any available research design. Two reviewers (S.R.S.E., N.P.) independently screened the titles and abstracts to identify all off-label uses for lisinopril. A comprehensive search was then performed based on the keywords identified in our primary search. The search terms and strategies are available in our electronic supplementary material. A librarian expert on grey literature (sources produced by organizations which are not controlled by commercial publishers) searched regulatory sites, clinical trial registries, conference proceedings and grant-funded and federally-funded research sites. We also contacted experts and then reviewed bibliographies and files supplied by the manufacturers' website.

Table 1

Search terms and strategy for our primary search

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((((((Lisinopril [Title/Abstract]) OR Lisinopril [Title/Abstract]) OR
Lysinopril [Title/Abstract]) OR "Lisinopril"[Mesh])) NOT (((("heart
failure"[Title/Abstract]) OR "Heart Failure"[Mesh]) OR "Cardiac
Failure"[Title/Abstract]) OR "myocardial failure"[Title/Abstract])) NOT
((((("High Blood Pressures"[Title/Abstract]) OR "High Blood
Pressure"[Title/Abstract]) OR "Hypertension"[Mesh]) OR hypertension
[Title/Abstract])) NOT (((((((("Myocardial Infarcts"[Title/Abstract]) OR
"Myocardial Infarct"[Title/Abstract]) OR "Heart Attacks"[Title/
Abstract]) OR "Heart Attack"[Title/Abstract]) OR "Cardiovascular
Strokes"[Title/Abstract]) OR "Cardiovascular Stroke"[Title/Abstract])
OR "Myocardial Infarction"[Mesh]) OR "myocardial infarction"[Title/
Abstract]) OR "myocardial infarctions"[Title/Abstract])

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Inclusion criteria and study selection

We included RCTs on adult patients aged ≥ 18 years who received an off-label use of lisinopril as compared to control [i.e. other alternative drugs, usual care (e.g. β -blockers, calcium channel blockers, other ACE inhibitors, diuretics) or placebos]. These RCTs should have reported direct or alternative clinical outcomes. Full texts of English-language studies and references of studies in non-English languages published from inception until November 2017 were reviewed. We excluded the following studies: nonrandomized clinical trials or observational studies, studies published only as abstracts, studies on transplanted patients (due to possible confounding effects of drugs used in these patients [14]), studies based on lisinopril for approved uses, studies of lisinopril combined with or adjunct to other drugs (or combination/adjunct arm of the multiarm studies), studies based on the negative effects of lisinopril or effects of dose adjustments, studies whose outcome measures were not relevant to efficacy, effectiveness or safety (e.g. drug half-life).

Risk of bias assessment

Two authors (S.R.S.E., N.P.) independently assessed the quality of RCTs using the Cochrane Collaboration Risk-of-Bias tool [15]. Six domains (i.e. sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues) were evaluated based on what was reported in each study. A judgement (such as *high risk*, *low risk* or *unclear risk* of bias) relating to the risk of bias for that particular domain was assigned to these domains. Other coauthors were consulted in case of absent agreement between the two reviewers. We also took a very conservative approach when evaluating the risk of *other bias*.

Data extraction

Two reviewers (S.R.S.E., N.P.) independently abstracted study characteristics (study design, population, lisinopril dosing and administration, outcomes assessed, etc.) by using specific forms. We contacted field experts to determine the most important variables. We extracted only the baseline and the final values of variables (or changes if the actual number were not reported). If the outcomes were reported only by means of figures and plots, we used Get Data Graph Digitizer (version 2.24) to extract the numbers. Other coauthors were consulted in case the two reviewers failed to agree.

Results

Our primary search identified 24 off-label uses for lisinopril (Table 2). Through our complementary search, 9164 articles were found after removing duplicates, all of which were screened by title and abstract. Finally, full papers of 259 studies were assessed for eligibility, 231 studies were excluded [studies on the combination of lisinopril with other drugs ($n = 166$), adverse effects of lisinopril ($n = 16$) and approved uses ($n = 49$)] and the full texts of 28 articles were critically reviewed (Figure 1). Our final pool of 28 papers presented support for 12 off-label uses. The characteristics of these studies are described in Table 3. Assessments of the risk of bias of

Table 2

Off-label uses of lisinopril

Supported by RCTs	Not supported by RCTs
<ul style="list-style-type: none"> • Proteinuric kidney disease [16–28] • Atrial fibrillation [30, 31] • Cardiomyopathy in patients with Duchenne muscular dystrophy [32] • Diabetic retinopathy [36, 37] • Myocardial fibrosis [34] • Inflammatory cystoid macular oedema [40] • Left ventricular hypertrophy [33, 34] • Migraine [41] • Mitral valve regurgitation [35] • Oligospermia and infertility [42] • Prevention of diabetes [38, 39] • Prevention of pneumonia [43] 	<ul style="list-style-type: none"> • Fontan circulation [56] • Peripheral artery diseases [57] • Neoplasm, cancer and tumours [58] • Angioplasty [59] • Aortic aneurysm [60] • Prolonged vascular access patency [61] • Connective tissue disease [62] • Headache caused by nitrates [63] • Polycystic kidney disease [64] • Polycystic ovary syndrome [65] • Diabetic neuropathy [66] • Dementia and Alzheimer [67]

RCT: randomized clinical trial

the studies are described in Figure 2. An 89% agreement was seen between the authors (S.R.S.E., N.P.) in the evaluation of risk of bias; discrepancies were resolved by discussion and consulting other authors. Most of the studies provided appropriate details about blinding of participants and personnel; however, few trials presented clear details of the blinding of outcome assessment. The most frequent biases were *other bias* and *selective reporting*, as well as ambiguity about *random sequence generation* – the most prevalent problems of included studies. The most common biases presented as *other bias* were: a potential source of bias related to the specific study design used and lack of a complete elucidation of supporting organization and funding *source*.

Proteinuric kidney disease

Impact of lisinopril on proteinuria and glomerular filtration rate.

We found thirteen studies (Table 4) evaluating lisinopril among patients with proteinuria [16–28]. These studies were conducted on diabetic nephropathy patients [20–28], on patients with proteinuria due to essential hypertension [17–19], and on patients with other underlying conditions (e.g. membranous glomerulopathy, chronic pyelonephritis, membranoproliferative, glomerular nephropathy, IgA nephropathy, hypertensive glomerulosclerosis, adult polycystic kidney disease, focal glomerulosclerosis, and hereditary nephritis) [16]. Overall, these studies except one [20], reported significant effects of lisinopril on proteinuria. Most studies showed that lisinopril resulted in statistically, yet not clinically, significant reduction in glomerular filtration rate (GFR), but not if patients had estimated

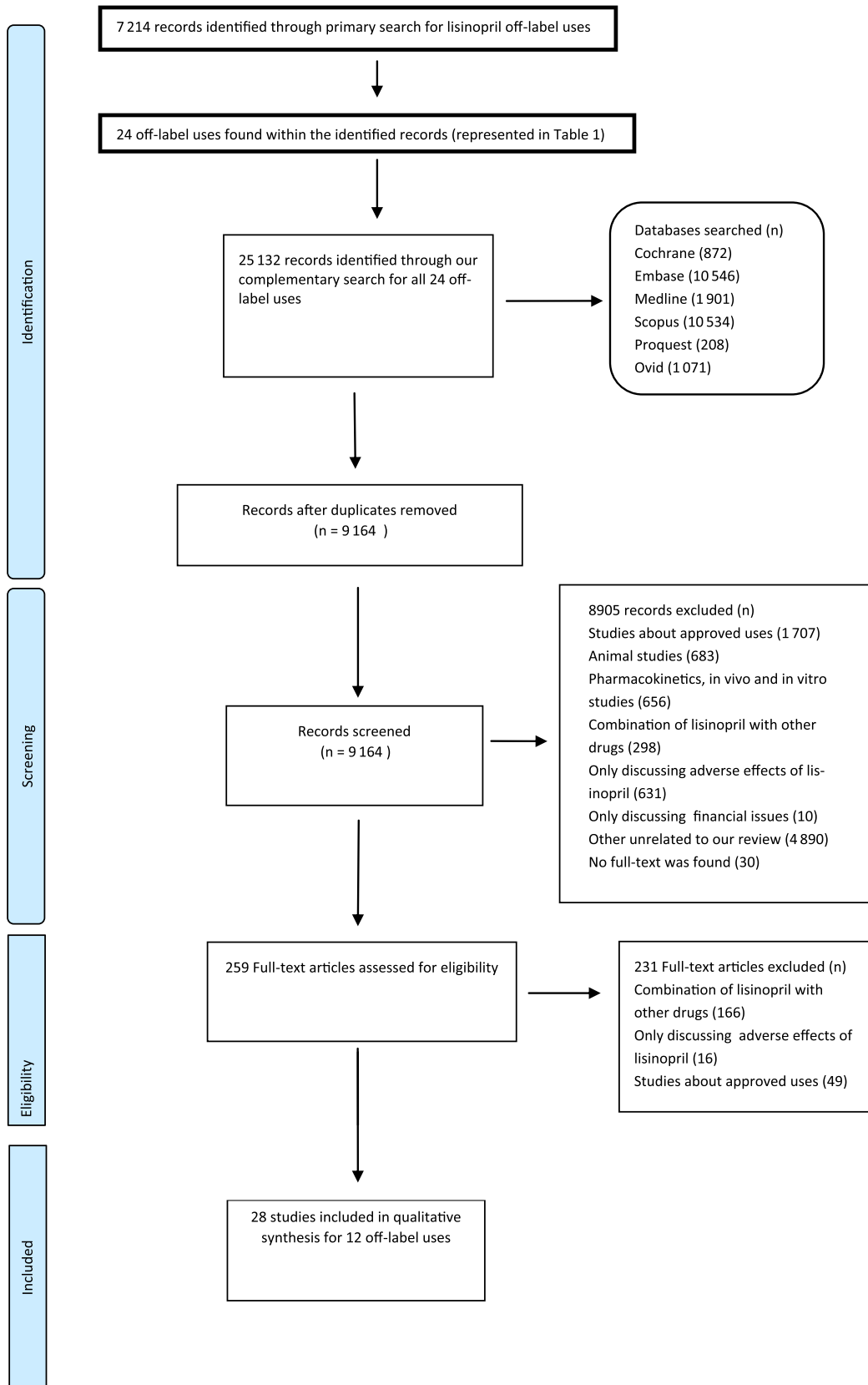


Figure 1

PRISMA flow diagram summarizing retrieved, included, and excluded randomized controlled trials

Table 3

Characteristics of studies on lisinopril for off-label uses

Off-label	Author (reference)	Comparison	Duration of study (months)	Dosing (mg day ⁻¹)	Mean age (years; if NA lisinopril group)	Final comparison group number	Final lisinopril group number	Total number
Proteinuric kidney disease	Juarez <i>et al.</i> [20]	ARB (irbesartan)	32	40 or 10	68.7 ± 6.8	28	35	133
	Menne <i>et al.</i> [18]	ARB (valsartan)	7.5	40 or 10	59.7 ± 9.5	42	47	133
	Laverman <i>et al.</i> [17]	ARB (losartan)	3	40 or 10	51	9	9	10
	Poulsen <i>et al.</i> [25]	Placebo	24	20	29.3 ± 8.6	10	11	22
	Mogensen <i>et al.</i> [23]	ARB (candesartan)	6	20	60	66	64	199
	Tarnow <i>et al.</i> [27]	CCB (nisoldipine)	48	20 or 10	35 ± 6	24	24	52
	Crepaldi <i>et al.</i> [21]	CCB (nifedipine) and placebo	36	2.5 or 10 or 20	38 ± 11	60	32	137
	Janssen <i>et al.</i> [16]	CCB (amlodipine)	4	5 or 10	47 ± 3.2	9	11	21
	Mitchell <i>et al.</i> [22]	ACE inhibitor (fosinopril)	5.5	20 or 40	67	14	13	94
	Chaturvedi <i>et al.</i> [28]	Placebo	24	20 or 10		265	265	530
	Rossing <i>et al.</i> [26]	CCB (nisoldipine)	12	20 or 10	35 ± 7	35	34	71
	Nielsen <i>et al.</i> [24]	β-blocker (atenolol)	42	20 or 10	61 ± 8	16	16	43
	Ranieri <i>et al.</i> [19]	CCB (amlodipine)	12	20	51 ± 3	18	18	36
Proteinuric kidney disease	Juarez <i>et al.</i> [20]	Overt proteinuria	<180/95	2	•	153 ± 18/80 ± 11		Diabetic nephropathic patient and stage 2 or 3 chronic kidney disease
	Menne <i>et al.</i> [18]	Microalbuminuria	85 < DP < 115	2	∅	153 ± 14.3/90.6 ± 8.3		Essential hypertensive patient
	Laverman <i>et al.</i> [17]	Overt proteinuria	80 < DP < 110	-	o	137/80		Nondiabetic renal patients with median proteinuria
	Poulsen <i>et al.</i> [25]	Microalbuminuria	<160/90	1	•	128 ± 10.5		Diabetic nephropathic patient
	Mogensen <i>et al.</i> [23]	Microalbuminuria	90 < DP < 110	2	•	162.6/85.7		Hypertensive patients with diabetic nephropathy
	Tarnow <i>et al.</i> [27]	-	-	1	•	-		Hypertensive patients with diabetic nephropathy
	Crepaldi <i>et al.</i> [21]	Microalbuminuria	115 < SP < 140, 75 < DP < 90	1	•	126 ± 8/82 ± 5		Diabetic nephropathic patient
Janssen <i>et al.</i> [16]	Overt proteinuria	DP < 100 with antihypertensive treatment or < 115 without medication	-	o	163 ± 7/101 ± 3		Membranous glomerulopathy, chronic pyelonephritis, membranoproliferative, glomerular nephropathy, IgA nephropathy, hypertensive glomerulosclerosis, adult polycystic kidney disease, focal glomerulosclerosis, hereditary nephritis (Alport syndrome)	

(continues)

Table 3
(Continued)

Off-label	Author (reference)	Amount of proteinuria	BP range	Type of diabetes	Diabetes	BP at baseline: mean of lisinopril group SP/DP	Underlying disease of patients with proteinuria	Total number enrolled
	Mitchell <i>et al.</i> [22]	Microalbuminuria	95 < DP < 110	2	Ø	156 ± 3/85 ± 2	Arteriolar nephrosclerosis or diabetic nephropathy	30
	Chaturvedi <i>et al.</i> [28]	Microalbuminuria	75 < DP < 90, SP < 155	1	•	122/79	Diabetic nephropathic patient	39 056
	Rossing <i>et al.</i> [26]	Overt proteinuria	90 < DP < 105	1	•	155/86	Diabetic nephropathic patient	
	Nielsen <i>et al.</i> [24]	Overt proteinuria	-	2	•	162/85 ± 2	Diabetic nephropathic patient	
	Ranieri <i>et al.</i> [19]	Microalbuminuria	95 < DP < 115	-	Ø	169.6 ± 15.3/104.2 ± 3.3	Essential hypertensive patient	
Off-label	Author (reference)	Comparison (dose mg day ⁻¹)	Duration of study	Dose of lisinopril (mg day ⁻¹)	Mean age of total sample (years; if NA lisinopril group)	Final comparison group number	Final lisinopril group number	Total number enrolled
Atrial fibrillation	Van Den Berg <i>et al.</i> [30]	Placebo	12 m	5–10	68 ± 6	14	11	30
	Haywood <i>et al.</i> [31]	Chlorthalidone (12.5, 25), Amlodipine (2.5, 5, 10), doxazosin (2, 4, 8)	6 y	10–20–40	>55	Chlorthalidone (11 695) Amlodipine (6935) doxazosin (6392)	6702	39 056
CM in patients with DMD	Allen <i>et al.</i> [32]	Losartan (25)	1 y	5	median of 12.5 y (range, 10 to 21 y)	8	7	23
Diabetic retinopathy	Mehlsen <i>et al.</i> [36]	Amlodipine (5)	49 d	10	27.9 ± 0.8	25	25	25
	Chaturvedi <i>et al.</i> [37]	Placebo	2 y	10–20	34 ± 9	168	156	530
Myocardial fibrosis	Brilla <i>et al.</i> [34]	Hydrochlorothiazide (25)	6 m	5–20	57 ± 2	14	11	35
	Kooji <i>et al.</i> [40]	Placebo	8 m	10	54.6 ± 12.3	36	36	40
Inflammatory cystoid macular oedema	Christian <i>et al.</i> [34]	Hydrochlorothiazide (25)	6 m	5–20	57 ± 2	14	11	35
Left ventricular hypertrophy	Ernst <i>et al.</i> [33]	Chlorthalidone (12.5, 25), Amlodipine (2.5, 5, 10)	4 y	10–20–40	>55	Chlorthalidone (12 102) Amlodipine (7151)	7121	26 376
Migraine	Schrader <i>et al.</i> [41]	Placebo	8 m	10	41 ± 9	47	47	60
Mitral valve regurgitation	Wong <i>et al.</i> [35]	Placebo	1 y	5–10–20	53.2 ± 2.4	11	12	23
Oligospermia and infertility	Mbah <i>et al.</i> [42]	Placebo	5 y	2.5	30.86 ± 8.8	14	14	33
Prevention of diabetes	ALLHAT Group [39]	Chlorthalidone (12.5, 25), Amlodipine (2.5, 5, 10)	5 y	10–20–40	>55	Chlorthalidone (15 255) Amlodipine (9048)	9054	42 418
	Fogari and Roberto [38]	Losartan (50)	16 w	20	55 ± 2	25	25	25
Prevention of pneumonia	Lee <i>et al.</i> [43]	Placebo	26 w	2.5	83.4 ± 6.8	38	33	93

Table 3

(Continued)

Off-label	Author (reference)	Most important inclusion criteria
Atrial fibrillation	Van Den Berg <i>et al.</i> [30] Haywood <i>et al.</i> [31]	Mild to moderate stable CHF and chronic AF CVD risk factor
CM in patients with DMD	Allen <i>et al.</i> [32]	Duchenne muscular dystrophy, EF <55%
Diabetic retinopathy	Mehlsen <i>et al.</i> [36] Chaturvedi <i>et al.</i> [37]	Diabetes (type 1) Diabetes (type 1)
Myocardial fibrosis	Brilla <i>et al.</i> [34] Kooji <i>et al.</i> [40]	Symptomatic patients (dyspnoea or angina pectoris), LVH, LV diastolic dysfunction Inactive or chronic low-grade activity of uveitis, inflammatory cystoid macular oedema
Inflammatory cystoid macular oedema	Christian <i>et al.</i> [34]	Symptomatic patients (dyspnoea or angina pectoris), LVH, LV diastolic dysfunction
Left ventricular hypertrophy	Ernst <i>et al.</i> [33].	CVD risk factor
Migraine	Schrader <i>et al.</i> [41]	Migraine for more than a year
Mitral valve regurgitation	Wong <i>et al.</i> [35]	at least moderate, isolated, organic MR and an EF > 60%
Oligospermia and infertility	Mbah <i>et al.</i> [42]	being on treatment for oligospermia for at least 2 years
Prevention of diabetes	ALLHAT Group [39] Fogari and Roberto [38]	CVD risk factor Nondiabetic, nonobese
Prevention of pneumonia	Lee <i>et al.</i> [43]	Tube-fed patients

BP, blood pressure; SP, systolic blood pressure; DP, diastolic blood pressure; NA, Not available; •, diabetic patients; ○, nondiabetic patients; Ø, both diabetic and nondiabetic or no data provided; M, month; y, year; d, day; CM, cardiomyopathy; DMD, Duchenne muscular dystrophy; CVD, cardiovascular disease; CHF, congestive heart failure; AF, atrial fibrillation; EF = ejection fraction; LVH, left ventricular hypertrophy; MR, mitral regurgitation

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Janssen <i>et al.</i> (1998) [16]	?	?	+	+	?	-	?
Laverman <i>et al.</i> (2002) [17]	?	?	?	?	?	+	?
Ranieri <i>et al.</i> (1994) [19]	?	+	+	?	?	+	-
Menne <i>et al.</i> (2008) [18]	+	+	+	+	+	+	?
Rossing <i>et al.</i> (1997) [26]	?	+	+	?	?	+	-
Juarez <i>et al.</i> (2013) [20]	+	-	-	+	+	+	?
Crepaldi <i>et al.</i> (1998) [21]	+	+	+	?	+	-	?
Poulsen <i>et al.</i> (2001) [25]	?	?	+	?	-	+	-
Nielsen <i>et al.</i> (1997) [24]	?	?	+	?	?	+	-
Tarnow <i>et al.</i> (2000) [27]	?	?	+	?	+	+	?
Mitchell <i>et al.</i> (1997) [22]	?	+	+	?	+	+	-
Mogensen <i>et al.</i> (2000) [23]	?	+	+	?	+	+	-
Chaturvedi <i>et al.</i> (1997) [28]	?	+	+	+	+	?	-
Chaturvedi <i>et al.</i> (1998) [37]	+	?	+	?	+	?	-
Mehlsen <i>et al.</i> (2011) [36]	?	+	+	?	?	?	-
Ernst <i>et al.</i> (2016) [33]	+	+	+	?	+	+	?
Brilla <i>et al.</i> (2000) [34]	+	+	+	+	+	+	?
Chaturvedi <i>et al.</i> (1998) [37]	+	?	+	?	+	?	-
Haywood <i>et al.</i> (2009) [31]	+	?	+	?	-	-	?
Van Den Berg <i>et al.</i> (1995) [30]	?	-	+	?	?	+	-
Allen <i>et al.</i> (2013) [32]	+	?	+	?	-	+	?
Kooij <i>et al.</i> (2006) [40]	+	?	+	?	+	-	?
Schrader <i>et al.</i> (2001) [41]	+	+	+	?	+	-	?
Wong <i>et al.</i> (2006) [35]	+	?	+	?	?	+	-
Mbah <i>et al.</i> (2012) [42]	+	+	+	?	+	+	?
Fogari <i>et al.</i> (1998) [38]	+	?	+	?	?	-	?
The ALLHAT Group [39]	+	?	+	+	+	+	?
Lee J <i>et al.</i> (2015) [43]	+	+	+	?	+	+	?

Yes
 No
 Unclear

Figure 2

Risk of bias assessment for studies of Lisinopril's off-label uses

Table 4
Outcomes of comparison group within included studies

Off-label	Author (reference)	Main outcome	Baseline vs. final outcome in comparison group
Proteinuric kidney disease	Juarez <i>et al.</i> [20]	Geometric mean (95%CI) of UPCR (g g^{-1}) Mean and SD of GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	1.33 (0.83–2.18) to 1.01 (0.69–1.80; $P = \text{NS}$) Baseline = 46 ± 16 and decreased with a median rate of 3.3 (95%CI, 1.8–4.7) 9.1 to 4.5
	Menne <i>et al.</i> [18] Laverman <i>et al.</i> [17]	Mean UACR (mg mmol^{-1})-adjusted ratio Mean (95%CI) of total proteinuria (g 24-h^{-1})	4.5 (3.5, 6.4) to 2.2 (1.2, 4.8; $P < 0.05$) 80 (66, 96) to 73 (59, 89)
	Poulsen <i>et al.</i> [25]	Mean (95%CI) of creatinine clearance (ml/min) Geometric mean \pm tolerance factor E-UAE ($\mu\text{g min}^{-1}$)	150.1 \pm 3.7 to 213.6 \pm 6.9 24 (0 to 43) [Baseline = 5.9 (1.1)] ($P = 0.05$)
	Mogensen <i>et al.</i> [23]	Adjusted mean reduction in UACR [Geometric mean (tolerance factor)]	
	Tamow <i>et al.</i> [27]	Mean (95%CI) albuminuria mg 24-h^{-1} Mean and SE of GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	Baseline = 1033 (760–1406) and increased by 12% (–10 to 40; $P = \text{NS}$) Baseline = 85 ± 6 and declined $0.5 \pm 0.1 \text{ ml. min}^{-1} \cdot \text{month}^{-1}$ ($P < 0.001$)
	Crepaldi <i>et al.</i> [21]	Mean and SD of AER ($\mu\text{g/min}$) Mean and SD of creatinine clearance ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	70 (28–174) to 58 (2–198; $P < 0.03$) 105 \pm 14 to 101 \pm 15 [≡] 88 (21–187) to 119 (4–176)* 110 \pm 15 to 105 \pm 15*
		Mean and SD of urinary albumin concentration (g dl^{-1})	4.4 \pm 0.3 to 4.2 \pm 0.4 [≡]
		Mean (95%CI) reduction of risk of progression to macroalbuminuria	41.4% (22.1–64.3%; $P = 0.05$) [≡]
		regression rate from macroalbuminuria to normoalbuminuria	0% [≡]
		Mean \pm SEM of GFR (ml min^{-1}) Mean \pm SEM of FF (%) Mean \pm SEM of UPCR (g mmol^{-1}) Mean \pm SEM (range) of GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) Mean \pm SEM (range) of RPF rate ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) Mean \pm SEM (range) of FF (%)	45 \pm 8 to 45 \pm 8 ($P = \text{NS}$) 23 \pm 2 to 25 \pm 2 ($P = \text{NS}$) 0.56 to 0.69 ($P = \text{NS}$) 56 \pm 5 (23–65) to 53 \pm 7 (13–108; $P = \text{NS}$) 282 \pm 27 (130–456) to 319 \pm 38 (160–594; $P = \text{NS}$) 21 \pm 2 (11–33) to 19 \pm 3 (9–46)
	Geometric mean (IQR) of AER ($\mu\text{g min}^{-1}$) Means \pm antilog SE of urinary IgG (mg 24-h^{-1}) Means \pm antilog SE of fractional clearance of albumin ($\times 10^{-3}$) Means \pm antilog SE of GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$) albuminuria (mg 24-h^{-1}) Means \pm antilog SE of GFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	8 (4.7–14) to 9.4 71 \pm 1.19 to 81 \pm 1.19 ($P = \text{NS}$) 215 \pm 1.23 to 297 \pm 1.29 ($P < 0.05$) 85 \pm 6 to 81 1087 \pm 1.2 to 1271	
	Geometric mean \pm antilog SE of Albuminuria (mg 24-h^{-1}) means \pm SE of Fractional albumin clearance ($\times 10^{-3}$)	74 \pm 8 and –0.60 \pm 0.11 decreased during the study Baseline = 1578 \pm –1.2 and reduced 15% (–13 to 34%; $P = \text{NS}$) 553 \pm 1.0 and increased 6% (–31 to 31%)	

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Table 4
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Off-label	Author (reference)	Main outcome	Baseline vs. final outcome in comparison group
	Ranieri <i>et al.</i> [19]	Mean \pm SD of GFR (ml min^{-1})	133.06 ± 15.75 to 120.17 ± 11.84 ($P = \text{NS}$) ^{†‡} 115.5 ± 1 to 116.94 ± 11.11 ($P = \text{NS}$) [♠]
		Mean \pm SD of FF (%)	18.39 ± 2.17 to 19.78 ± 2.44 ($P = \text{NS}$) ^{†‡} 20.06 ± 3.81 to 19.72 ± 2.07 ($P = \text{NS}$) [♠]
		Mean \pm SD of UAE ($\text{mg } 24\text{-h}^{-1}$)	44.7 ± 9.5 to 69.3 ± 6.4 ($P < 0.01$) ^{†‡} 76.6 ± 5.6 to 71.7 ± 7.5 ($P = \text{NS}$) [♠]

*placebo, [†]baseline to first phase with lisinopril, [‡]baseline to first phase of amlodipine, [♠]end of first phase with amlodipine to second phase of lisinopril

Off-label	Author (reference)	Main outcome	Baseline vs. final outcome in lisinopril group	P-value lisinopril vs. comparison
Proteinuric kidney disease	Juarez <i>et al.</i> [20]	Geometric mean (95%CI) of UPCR (g g^{-1})	0.92 ($0.52\text{--}1.66$) to 0.68 ($0.38\text{--}1.20$; $P = \text{NS}$)	
		Mean and SD of GFR ($\text{ml min}^{-1} 1.73\text{-m}^{-2}$)	48 ± 14 and decreased with a median rate of 3.8 (95%CI, $1.8\text{--}6.3$)	
	Menne <i>et al.</i> [18]	Mean UACR (mg mmol^{-1})-adjusted ratio	9.6 to 5.7 adjusted ratio: 76% , CI: $48\text{--}118\%$	0.213
	Laverman <i>et al.</i> [17]	Mean (95%CI) of total proteinuria ($\text{g } 24\text{-h}^{-1}$)	4.5 ($3.5\text{--}6.4$) to 1.4 ($0.5\text{--}2.9$; $P < 0.05$)	< 0.05
	Poulsen <i>et al.</i> [25]	Mean (95%CI) of creatinine clearance (ml/min)	80 ($66\text{--}96$) to 72 ($52\text{--}92$)	0.04
	Mogensen <i>et al.</i> [23]	Geometric mean \pm tolerance factor E-UAE ($\mu\text{g min}^{-1}$)	96.8 ± 1.8 to 48.3 ± 3.1	
	Tarnow <i>et al.</i> [27]	Adjusted mean reduction in UACR [Geometric mean (tolerance factor)]	39 (20 to 54) [Baseline = 6.6 (1.1)] (< 0.001)	
		Mean (95%CI) albuminuria $\text{mg } 24\text{-h}^{-1}$	Baseline = 1554 ($980\text{--}2465$) and reduced by 52% (95%CI $14\text{--}73$)	< 0.001
		Mean and SE of GFR ($\text{ml min}^{-1} 1.73\text{-m}^{-2}$)	Baseline = 85 ± 5 and declined $0.5 \pm 0.1 \text{ ml min}^{-1} \text{ month}^{-1}$ ($P < 0.001$)	NS
	Crepaldi <i>et al.</i> [21]	Mean and SD of AER ($\mu\text{g/min}$)	54 ($20\text{--}128$) to 29 ($5\text{--}173$; $P < 0.003$)	
		Mean and SD of creatinine clearance ($\text{ml min}^{-1} 1.73\text{-m}^{-2}$)	113 ± 16 to 109 ± 19	
		Mean and SD of Urinary albumin concentration (g/dl)	4.4 ± 0.4 to 4.3 ± 0.3	
		Mean (95%CI) reduction of risk of progression to macroalbuminuria	49.1% ($26.8\text{--}63.4\%$; $P < 0.03$)	
		Regression rate from macroalbuminuria to normoalbuminuria	15%	< 0.001

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Table 4
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Off-label	Author (reference)	Main outcome	Baseline vs. final outcome in lisinopril group	P-value lisinopril vs. comparison
	Janssen <i>et al.</i> [16]	Mean ± SEM of GFR (ml/min)	55 ± 11 to 50 ± 10 ($P < 0.01$)	
		Mean ± SEM of FF (%)	24 ± 2 to 21 ± 2 ($P < 0.001$)	
		Mean ± SEM of UPCR (g/mmol)	0.39 ± 0.17 to 0.26 ± 0.11 ($P < 0.05$)	<0.05
	Mitchell <i>et al.</i> [22]	Mean ± SEM (range) of GFR (ml min ⁻¹ 1.73-m ⁻²)	46 ± 6 (18–78) to 42 ± 6 (18–83; $P = NS$)	NS
		Mean ± SEM (range) of RPF rate (ml min ⁻¹ 1.73-m ⁻²)	262 ± 37 (122–570) to 247 ± 42 (62–523; $P = NS$)	NS
		Mean ± SEM (range) of FF (%)	19 ± 2 (9–37) to 21 ± 4 (8–65; $P = NS$)	NS
	Chaturvedi <i>et al.</i> [28]	Geometric mean (IQR) of AER (µg min ⁻¹)	8 (4.4–14.8) to 7.3	0.03
	Rossing <i>et al.</i> [26]	Means ± antilog SE of Urinary IgG (mg 24-h ⁻¹)	101 ± 1.29 to 64 ± 1.38 ($P < 0.05$)	<0.05
		Means ± antilog SE of Fractional clearance of albumin (× 10 ⁻⁶)	380 ± 1.29 to 213 ± 1.35 ($P < 0.05$)	<0.05
		Means ± antilog SE of GFR (ml min ⁻¹ 1.73-m ⁻²)	85 ± 5 to 73.5	<0.05
		albuminuria (mg 24-h ⁻¹)	1513 ± 1.3 to 790	0.001
	Nielsen <i>et al.</i> [24]	Means ± antilog SE of GFR (ml min ⁻¹ 1.73-m ⁻²)	75 ± 6 and -0.67 ± 0.10 decreased during the study	0.63
		Geometric mean ± antilog SE of Albuminuria (mg 24-h ⁻¹)	Baseline = 963 ± 1.2 and reduced 55% (29–72%; $P < 0.05$)	0.01
		Means ± SE of Fractional albumin clearance (×10 ⁶)	(323 ± 1.2 and reduced 52% (8–75%))	0.03
	Ranieri <i>et al.</i> [19]	Mean ± SD of GFR (ml min ⁻¹)	116.94 ± 11.11 to 127.27 ± 18.89 ($P < 0.01$) 133.06 ± 15.7 ($P < 0.01$) [‡]	
		Mean ± SD of FF (%)	19.72 ± 2.07 to 18.22 ± 2.3 ($P < 0.01$) 20.06 ± 2.01 to 18.39 ± 2.17 ($P < 0.01$) [‡]	
		Mean ± SD of UAE (mg 24-h ⁻¹)	71.7 ± 7.5 to 54.3 ± 3 ($P < 0.01$) 77.1 ± 8.1 to 44.7 ± 9.5 ($P < 0.01$) [‡]	<0.01

*placebo, ^{||}Nifedipine, [‡]baseline to first phase with amlodipine, [†]end of first phase with lisinopril, [‡]baseline to first phase of lisinopril, ^{||}end of first phase with amlodipine, ^{||}end of first phase with amlodipine to second phase of lisinopril

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Table 4

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Off-label use	Author (Ref)	Main outcome	Final outcome vs. baseline in comparison group
Atrial fibrillation	Van Den Berg <i>et al.</i> [30]	Mean ± SD of heart rate (beats min ⁻¹)	83 ± 14 to 81 + 13 (P = NS)
		Median number of isolated premature ventricular beats h ⁻¹ (range)	23 (5–340) to 109 (22–372)
CM in patients with DMD	Haywood <i>et al.</i> [31]	New AF per 1000	16.3 [†]
		Odds ratio for univariable logistic model	1.346 [‡]
		Odds ratio for multivariable logistic model	1.326 [‡]
	Allen <i>et al.</i> [32]	Mean EF (%)	48.4 to 55.2 (P = 0.03)
Diabetic retinopathy	Mehlsen <i>et al.</i> [36]	Mean (95%CI) of diameter change of retinal artery after exercise + flicker (%)	1.8 (0.1–3.5) to 2.0 (0.3–3.6)
		Mean (95%CI) of diameter change of retinal vein after exercise + flicker (%)	4.4 (2.6–6.1) to 5.3 (3.5–7.0)
Myocardial fibrosis	Chaturvedi <i>et al.</i> [37]	Incidence of retinopathy: odds ratio	15/62
		Regression of retinopathy	28/117
Inflammatory cystoid macular oedema	Brilla <i>et al.</i> [34]	Myocardial hydroxyproline concentration (µg mg ⁻¹)	9.5 ± 0.5 to 10.4 ± 0.6 (P = NS)
	Kooij <i>et al.</i> [40]	Collagen volume fraction (%)	6.4 ± 0.8 to 6.5 ± 0.8 (P = NS)
Left ventricular hypertrophy	Christian <i>et al.</i> [34]	Number (%) of patients with improvement of cystoid macular oedema	9 of 40 (23%)
	Ernst <i>et al.</i> [33]	LV mass index (g m ^{-2.7})	176 ± 17 to 145 ± 11 (P = 0.08)
Migraine		Mean ± SD of Cornell voltage overall (µV)	1451 ± 620 to 1427 ± 630 (P = 0.0045) [‡]
		Prevalence (%) of LVH by Cornell voltage	482/7151 (6.74) to 311/4753 (6.54) [‡]
		Individuals experienced regression of their LVH (%)	50.21
Mitral valve regurgitation	Schrader <i>et al.</i> [41]	Mean ± SD of h with headache	162 ± 142
	Wong <i>et al.</i> [35]	Mean ± SD of days with migraine	18.5 ± 10
Oligospermia and infertility		Mean ± SD of change in mitral regurgitant fraction (%)	+3.7% ± 3.2
		Mean ± SD of change of MR jet to LA area ratio	-10.9% ± 2.4
		Mean ± SD of LA dimension (mm) measured by M-mode techniques	45.4 ± 8 to 46.7 ± 8 (P = NS)
	Mbah <i>et al.</i> [42]	Mean ± SD (95%CI) sperm cell count (10 ⁶ ml ⁻¹)	17.1 (12.0–2.2) to 12.8 (8.2–19.0; P ≤ 0.02) [†]
		Mean ± SD (95%CI) sperm cells with good motility (%)	41.1 (32.1–50.6) to 15.3 (12.2–17.7; P ≤ 0.008) [†]
		Mean ± SD (95%CI) sperm cells with abnormal morphology (%)	15.3 (11.6–19.8) to 28.2 (22.5–33.9; P ≤ 0.03) [†]

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Table 4

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Off-label use	Author (Ref)	Main outcome	Final outcome vs. baseline in comparison group
Prevention of diabetes	ALLHAT Group [39]	Number (%) of patients with FBS ≥ 126 mg dl ⁻¹ among baseline-nondiabetics	1.54 (9.8) [†] 302 (11.6) [‡]
Prevention of pneumonia	Fogari and Roberto [38]	Glucose infusion rate (mg min ⁻¹ kg ⁻¹) Total glucose requirement (g)	5.79 \pm 0.33 to 6.21 \pm 0.41 (P = NS) 31.9 \pm 3.4 to 33.8 \pm 3.3 (P = NS)
	Lee et al. [43]	Unadjusted OR (95%CI) of Pneumonia or death The incidences of pneumonia (%)	47.4

*Chlorthalidone, [†]Amlodipine, [‡]Doxazosin, [§]baseline to the first phase of lisinopril, ^{††}end of the first phase with lisinopril to the second phase of placebo, ^{‡‡}end of the first phase with placebo to the second phase of lisinopril

Off-label use	Author (reference)	Main outcome	Final outcome vs. baseline in lisinopril group (P value)	P-value lisinopril vs. comparison
Atrial fibrillation	Van Den Berg et al. [30]	mean \pm SD of heart rate (beats/min) Median number of isolated premature ventricular beats/h (range)	92 \pm 9 to 88 + 9 (P = NS) 34 (2–228) to 27 (4–335)	0.040
CM in patients with DMD	Haywood et al. [31]	New AF per 1000 Odds ratio for univariable logistic model Odds ratio for multivariable logistic model	20.6 0.987 0.939	0.90 [‡] 0.59 [‡]
	Allen et al. [32]	Mean EF (%)	47.5 to 54.6 (P = 0.02)	NS
	Diabetic retinopathy	Mehlsen et al. [36]	Mean (95%CI) of diameter change of retinal artery after exercise + flicker (%) Mean (95%CI) of diameter change of retinal vein after exercise + flicker (%)	1.8 (0.1–3.5) to 1.0 (1.4–3.4) 4.4 (2.6–6.1) to 2.3 (0.2–4.8)
Chaturvedi et al. [37]		Incidence of retinopathy -Odds ratio Regression of retinopathy	13/72 OR = 0.69 (95%CI 0.30–0.59) 33/103 OR = 1.48 (95%CI 0.82–2.68)	0.4 0.2
Brilla et al. [34]		Myocardial hydroxyproline concentration (μ g mg ⁻¹) Collagen volume fraction (%)	9.9 \pm 0.3 to 8.3 \pm 0.4 (P = 0.001) 6.9 \pm 0.6 to 6.3 \pm 0.6 (P < 0.01)	<0.00001 <0.05
Inflammatory cystoid macular oedema	Kooji et al. [40]	Number (%) of patients with improvement of cystoid macular oedema	10 of 40 (25)	0.79
Left ventricular hypertrophy	Christian et al. [34]	LV mass index lisinopril (g m ^{-2.7})	170 \pm 16 to 177 \pm 15 (P = NS)	0.9433 [‡] NS [‡]
	Ernst et al. [33].	Mean \pm SD of Cornell voltage overall (μ V) Prevalence (%) of LVH by Cornell voltage	1425 \pm 615 to 1435 \pm 637 (P = 0.24) 473/7123 (6.64) to 292/4494 (6.50)	

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Table 4

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Off-label use	Author (reference)	Main outcome	Final outcome vs. baseline in lisinopril group (P value)	P-value lisinopril vs. comparison
Migraine	Schrader <i>et al.</i> [41]	Individuals experienced regression of their LVH (%)	49.27	NS ^{§*}
Mitral valve regurgitation	Wong <i>et al.</i> [35]	Mean ± SD of hours with headache Mean ± SD of days with migraine Mean ± SD of change in mitral regurgitant fraction (%) Mean ± SD of change of MR jet to LA area ratio Mean ± SD of LA dimension (mm) measured by M-mode techniques	129 ± 125 14.5 ± 11 -6.4% ± 3.5 -15.7% ± 3.7 44.3 ± 7 to 44.1 ± 8 (P = NS)	<0.05 <0.05 <0.05 NS NS
Oligospermia and infertility	Mbah <i>et al.</i> [42]	Mean ± SD (95%CI) sperm cell count (10 ⁶ ml ⁻¹) Mean ± SD (95%CI) sperm cells with good motility (%) Mean ± SD (95%CI) Sperm cells with abnormal morphology (%)	7.0 (4.2–10.1) to 13.9 (8.7–17.5); P < 0.004 22.2 (18.6–25.7) to 30.3 (26.0–35.1); P ≤ 0.005 44.1 (39.1–50.2) to 11.8 (6.0–17.2); P ≤ 0.03	5.29 ± 2.6 to 17.1 (12.0–22.2); P < 0.03 [‡] 17.33 ± 3.2 to 41.1 (32.1–50.6); P < 0.05 [‡] 42.91 ± 5.1 to 15.3 (11.6–19.8); P ≤ 0.04 [‡]
Prevention of diabetes	ALLHAT Group [39]	Number (%) of patients with FBS ≥ 126 mg dl ⁻¹ among baseline-nondiabetics	119 (8.1)	<0.001 [*]
Prevention of pneumonia	Fogari and Roberto [38]	Glucose infusion rate (mg min ⁻¹ kg ⁻¹) Total glucose requirement (g)	5.74 ± 0.31 to 7.21 ± 0.39 (P = 0.05) 32.5 ± 3.2 to 39.8 ± 3.6	0.05
	Lee <i>et al.</i> [43]	Unadjusted OR (95%CI) of Pneumonia or death The incidences of pneumonia (%)	1.80 (0.69, 4.72); P = 0.232 57.6	0.390

*Chlorthalidone, [‡]Amlodipine, [§]Doxazosin, ^{||}baseline to the first phase of lisinopril, [†]end of the first phase with lisinopril to the second phase of placebo, ^{||}end of the first phase with placebo to the second phase of lisinopril
AER, albumin excretion rate; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; CM, cardiomyopathy; DMD, Duchenne muscular dystrophy; ERPF, effective renal plasma flow; EF, ejection fraction; FF, filtration fraction; CFR, glomerular filtration rate; LA, left atrium; LAV, left atrium volume; LVH, left ventricular hypertrophy; MR, Mitral valve regurgitation; NS, non-significant; SD, standard deviation; SEM, Standard Error of the Mean; UAE, urine albumin excretion; UACR, urine albumin: creatinine ratio; UPCR, urine protein: creatinine ratio

GFR $> 90 \text{ ml min}^{-1}$ [19, 21]. For example, Ranieri *et al.* demonstrated that lisinopril significantly increased GFR ($116.94 \pm 11.11 \text{ ml min}^{-1}$ to $127.27 \pm 18.89 \text{ ml min}^{-1}$; $P < 0.01$) [19]. This could possibly be due to more efficient renal compensatory mechanisms in higher levels of GFR [29].

Lisinopril was compared with different drugs or placebos regarding their effects on proteinuria and GFR within included studies:

- **Lisinopril vs. placebo:** Studies in normotensive patients with diabetes [21, 28] highlighted a significant regression rate from macroalbuminuria to microalbuminuria with administration of lisinopril compared to a placebo (15% in lisinopril vs. 4% in placebo, $P < 0.001$) and a significant reduction of the risk of progression to macroalbuminuria [mean risk reduction 49.1%; 95% confidence interval (CI): 26.8–63.4, $P < 0.03$]. The decrease in the albumin excretion rate was also significantly more in lisinopril than in the placebo [geometric mean (interquartile range) of the albumin excretion rate $8 (4.7\text{--}14)$ to $9.4 \mu\text{g min}^{-1}$ in placebo vs. $8 (4.4\text{--}14.8)$ to $7.3 \mu\text{g min}^{-1}$ in lisinopril, $P = 0.03$]. Another study in nondiabetic normotensive patients showed that lisinopril significantly reduced exercise-urine albumin excretion when compared to a placebo [geometric mean (tolerance factor) $150.1 (3.7)$ to $213.6 (6.9) \mu\text{g min}^{-1}$ in placebo vs. $96.8 (1.8)$ to $48.3 (3.1)$ in lisinopril, $P = 0.04$] [25] (Tables 3 and 4).
- **Lisinopril vs. angiotensin receptor blockers:** Lisinopril in comparison to angiotensin receptor blockers (ARBs; e.g. irbesartan, valsartan, losartan, candesartan) [17, 18, 20, 23] showed different results. Its effects on proteinuria (or albuminuria) and GFR were similar to irbesartan and valsartan [mean rate of reduction of GFR per year; 3.8 ml min^{-1} (95%CI 1.8–6.3) in lisinopril vs. 3.3 ml min^{-1} 1.73 m^{-2} (1.8–4.7) in irbesartan) but they were significantly superior when compared to losartan and candesartan [adjusted geometric mean reduction of urine albumin to creatinine ratio 39 (95%CI 20–54) in lisinopril vs. 24 (0–43) in candesartan] (Tables 3 and 4).
- **Lisinopril vs. calcium channel blockers:** Studies on both diabetic and nondiabetic, hypertensive and normotensive patients (Table 3) demonstrated that although calcium channel blockers (CCBs; e.g. nisoldipine, amlodipine and nifedipine) [16, 19, 21, 26, 27] conversely increased albuminuria, lisinopril significantly reduced it (Table 4). Tarnow *et al.* showed that nisoldipine increased albuminuria by 12% (95%CI –10 to 40) but lisinopril decreased albuminuria by 52% (14–73) [27]. Similarly, Ranieri *et al.* demonstrated that amlodipine significantly increased albuminuria (44.7 ± 9.5 to $69.3 \pm 6.4 (\text{mg } 24\text{-h}^{-1})$; $P < 0.01$) but lisinopril significantly decreased albuminuria (71.7 ± 7.5 to 54.3 ± 3 ; $P < 0.01$) [26]. There were controversies about the effect of lisinopril on GFR and creatinine clearance in comparison with CCBs; however, those studies with greater sample sizes and longer duration showed similar effects (Tables 3 and 4).
- **Lisinopril vs. β -blockers:** Nielsen *et al.* [24] conducted a study on diabetic patients with diabetic nephropathy comparing lisinopril with atenolol. They highlighted the fact that lisinopril significantly decreased albuminuria better

than atenolol [geometric mean reduction 55% (95%CI 29–72) in lisinopril vs. 15% (–13 to 34) in atenolol, $P < 0.01$] [24]. The effects of these drugs on GFR were similar (decrease in means \pm antilog standard error of GFR: $0.67 \pm 0.10 \text{ ml min}^{-1}$ for lisinopril vs. $0.60 \pm 0.11 \text{ ml min}^{-1}$ for atenolol, $P = 0.63$; Tables 3 and 4).

- **Lisinopril vs. other ACE inhibitors:** One single study compared lisinopril with another ACE inhibitor fosinopril. The result demonstrated a similar nonsignificant reduction in GFR (mean \pm standard error of the mean of GFR 46 ± 6 to $42 \pm 6 \text{ ml min}^{-1}$ in lisinopril vs. 56 ± 5 to $53 \pm 7 \text{ ml min}^{-1}$ in fosinopril, $P > 0.05$) [22] (Tables 3 and 4).

Atrial fibrillation

Nonsignificant results were reported for using lisinopril for atrial fibrillation (AF). Van Den Berg *et al.* [30] assessed the effects of daily lisinopril in patients with congestive heart failure and chronic AF. Monitoring the heart rates for 6 weeks showed that reduction of the mean heart rate was not significant in the lisinopril group. However, a minor reduction of the median number of isolated premature ventricular beats h^{-1} was demonstrated in the lisinopril group [34 (range = 2–228) to 27 (4–335) beats h^{-1} , P (lisinopril vs. placebo) = 0.04]. Additionally, the effect of lisinopril on the maintenance of sinus rhythm after an electrical cardioversion was 71% in the lisinopril group and 36% in the placebo group ($P > 0.05$). Haywood *et al.* evaluated the incidence of new AF cases in patients who received lisinopril, amlodipine, doxazosin, or chlorthalidone. The results of this study showed that treatment with lisinopril as well as other antihypertensive drugs did not affect AF incidence when compared with usual care (odds ratio 0.987, $P = 0.9$ in the univariable logistic model) [31] (Tables 3 and 4).

Cardiomyopathy in patients with Duchenne muscular dystrophy

A multicenter double-blind prospective study compared the efficacy and safety of lisinopril versus losartan in the treatment of cardiomyopathy (CM) on 22 Duchenne muscular dystrophy (DMD) patients with newly diagnosed CM. Although the ejection fraction after 1 year was significantly improved in each treatment group, the difference was not statistically significant [32] (Tables 3 and 4).

Left ventricular hypertrophy

The effect of lisinopril on left ventricular hypertrophy (LVH) was assessed using two different diagnostic tools. An American study randomized 26 376 subjects into three groups: lisinopril, amlodipine and chlorthalidone, and used electrocardiography to examine LVH and its prevalence (defined as Cornell voltage $>2200 \mu\text{V}$ in women and $> 2800 \mu\text{V}$ in men). After 4 years, the mean Cornell voltage was increased in the lisinopril group; however, LVH prevalence was not changed [33]. Another study recruited 35 hypertensive patients with LVH to be treated with either lisinopril or hydrochlorothiazide and evaluated the outcome using echocardiography. Results of this study demonstrated no significant treatment effect of lisinopril on the left ventricular mass index after a 6-month follow-up [34] (Tables 3 and 4).

Mitral valve regurgitation

Wong *et al.* [35] conducted an RCT on 23 patients with mitral regurgitation. A significant reduction in mitral regurgitation fraction occurred during the 1-year follow-up with lisinopril. Both maximum and minimum left atrium volumes were reduced in the lisinopril group (88 ± 33 ml reduced to 75 ± 23 ml as compared to 46 ± 20 ml reduced to 38 ± 16 ml for placebos; $P < 0.01$; Tables 3 and 4).

Myocardial fibrosis

A double-blind RCT compared the effect of lisinopril and hydrochlorothiazide on patients with primary hypertension, LVH and LV diastolic dysfunction investigating myocardial fibrosis. After 6 months of treatment, myocardial fibrosis significantly regressed with lisinopril [34] (Tables 3 and 4).

Diabetic retinopathy

Mehlsen *et al.* [36] recruited 25 normotensive diabetic patients with mild retinopathy and randomized them to receive lisinopril, placebo or amlodipine. To show the perfusion disturbances that occur in retinopathy, the diameter response of retinal arterioles during an acute increase in the blood pressure induced by isometric exercise, during flicker stimulation and stimulus conditions simultaneously were studied before and through the treatment period. The results revealed that lisinopril did not significantly change the diameter response of retinal vessels ($P = 0.11$). However, the study of Chaturvedi *et al.* [37] assessed the effect of lisinopril on retinopathy in patients with insulin-dependent diabetes mellitus. Retinopathy was evaluated by retinal photographs. They showed that retinopathy progression was halved in the lisinopril group compared to the placebo group (OR 0.50, $P = 0.02$) and progression to proliferative retinopathy was also reduced significantly (OR 0.18, $P = 0.03$; Tables 3 and 4).

Prevention of diabetes

Previous studies using lisinopril raised new hopes for the prevention of diabetes. Fogari *et al.* [38] compared the effects of the lisinopril and losartan on insulin sensitivity. They involved 25 nondiabetic patients with mild to moderate hypertension and randomized them to receive lisinopril or losartan for 12 weeks. They found that the glucose infusion rate – used as an indicator of insulin sensitivity – was significantly increased by lisinopril but not by losartan (P value for lisinopril vs. losartan < 0.05). Also, total glucose requirement (defined as the total amount of exogenous glucose required to maintain a steady-state blood glucose level in response to a defined increase in plasma insulin concentration) was increased by lisinopril, whereas losartan did not significantly modify it. Another study [39] compared chlorthalidone with lisinopril, doxazosin and amlodipine in a large sample size. This study, after a mean 5 years of follow-up, demonstrated a significant reduction in the risk of developing diabetes in the lisinopril group vs. chlorthalidone ($P < 0.001$; Tables 3 and 4).

Inflammatory cystoid macular oedema

Kooij *et al.* [40] designed a randomized control trial to analyse the effect of lisinopril on inflammatory cystoid macular oedema and visual acuity. They included 40 patients with

inflammatory cystoid macular oedema then randomized them to receive lisinopril or placebo. Lisinopril had no effect on cystoid macular oedema, visual acuity, papillary leakage, retinal vasculitis or choroidal leakage [40] (Tables 3 and 4).

Migraine

One RCT randomized 60 patients with migraine to receive lisinopril or placebo for a treatment period of 12 weeks. The lisinopril group had a 20% reduction of hours suffering with a headache, a 21% reduction of days with migraine, and a 20% reduction of the headache severity index as compared with the placebo group [41]. Side effects were not significantly different compared to placebo ($P = 0.7$; Tables 3 and 4).

Oligospermia and infertility

In a crossover RCT, 33 men with idiopathic oligospermia were randomized to receive either lisinopril or placebo. Lisinopril was found to cause a normalization of seminal parameters in 53.6% of the participants. Although the mean ejaculate volume was unchanged, the total sperm cell count and the percentage of motile sperm cells increased, whereas the percentage of sperm cells with abnormal morphology decreased [42] (Tables 3 and 4).

Prevention of pneumonia

One RCT randomized 93 patients with dysphagia from cerebrovascular diseases, who were on tube-feeding, to receive lisinopril or placebo for 26 weeks. No difference in the incidence of pneumonia or fatal pneumonia was noted between these groups [43] (Tables 3 and 4).

Discussion

In furtherance of conducting a reliable and comprehensive review of off-label uses of lisinopril for physicians, an extensive search in seven prominent databases was executed and 28 RCTs were acquired. Twenty-four off-label uses for lisinopril were identified in our review, but 12 lacked supporting RCT. The overall risk of bias across the studies was moderate. *Other bias*, *selective reporting* and inadequate details on *random sequence generation* were the most prevalent problems of the included studies. We were not able to perform meta-analysis due to: the heterogeneity of inclusion criteria for patients; dosage of lisinopril, placebos or drugs being compared; variables reported within different RCTs; and the differences in the duration of administration and follow-ups. However, this heterogeneity somehow helped our review to assess the effects of lisinopril examined in different aspects: for example, the effect of lisinopril on left ventricular hypertrophy was assessed using both electrocardiography and echocardiography in two separate studies.

Among the remaining 12 off-label uses with RCT support (Table 2), proteinuric kidney disease was the most prominent use. The renoprotective effect of ACE/ARBs have been demonstrated in meta-analyses [44, 45] but the specific effect of lisinopril was not designated. The result of our systematic review showed a clear benefit from lisinopril for proteinuria and albuminuria as defined by the albumin excretion rate, total proteinuria, total albuminuria, urine

protein/creatinine ratio and urine albumin/creatinine ratio. This positive effect was noticed in a variety of underlying diseases such as diabetic nephropathy, essential hypertension, membranous glomerulopathy, chronic pyelonephritis, membranoproliferative, glomerular nephropathy, IgA nephropathy, hypertensive glomerulosclerosis, adult polycystic kidney disease, focal glomerulosclerosis and hereditary nephritis. Lisinopril is approved for hypertension. Treatment of proteinuria in patients with hypertension can be considered as an off-label use since it has not been specified in any of the FDA approval letters. That said, lisinopril has some positive effects on proteinuria, which are beyond its antihypertensive effects as not all antihypertensive drug can improve proteinuria (e.g. calcium channel blockers) [16, 19]. The included studies were primarily aiming at patients with proteinuria, although some of them were conducted on hypertensive or diabetic patients (see Table 3). It should be noted that no included studies determined the proportion of patients with hypertension.

A small yet statistically significant decrease in GFR and creatinine clearance was demonstrated in patients using lisinopril; however, increase in serum creatinine of up to 30% (up to about 23% reduction in GFR) is generally considered not to be clinically significant and is a function, and not an adverse effect, of its mechanism of action in diminishing angiotensin II mediated efferent glomerular arteriolar constriction, thus reducing glomerular filtration pressure [46]. This slight reduction of GFR was not seen in those studies which were conducted on patients with $\text{GFR} > 90 \text{ ml min}^{-1}$. Furthermore, lisinopril, in comparison to other standard treatments of diabetic nephropathy including CCB, ARBs and β -blockers [47], demonstrated better outcomes; however, its effects on decreasing GFR and creatinine clearance were similar to the others.

Among other off-label uses of lisinopril, the included RCTs highlight the positive effects of lisinopril for migraine, prevention of diabetes, myocardial fibrosis and mitral valve regurgitation, CM in patients with DMD, and oligospermia and infertility. However, lisinopril appeared to be ineffective for atrial fibrillation, LVH, inflammatory macular oedema and prevention of pneumonia. Moreover, the results of two studies into the effects of lisinopril on retinopathy were contradictory: different methods were used in these studies [36, 37]; however, Chaturvedi *et al.* using retinal photographs (96% sensitivity and 89% specificity [48]), larger sample size and longer duration of follow-up, reported more reliable positive results for lisinopril. Moreover, regarding the effect of lisinopril on LVH, one of the studies had a very short follow up of only 6 months [34]. As it is not expected to see the effect of this drug on LVH in such a short period, the result of this study may not clearly represent lisinopril's efficacy for LVH. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study with 4 years of follow up could put forward more reliable evidence that lisinopril cannot be considered very effective for LVH [33]. Some other off-label uses (mitral valve regurgitation, CM in patients with DMD, inflammatory cystoid macular oedema and oligospermia and infertility) were investigated with RCTs of small sample sizes, making their results less trustworthy.

One of the studies compared lisinopril with chlorthalidone in reducing the of risk of diabetes and

concluded a significant superior effect of lisinopril [39]. Although, chlorthalidone can slightly increase blood glucose, it cannot make a patient diabetic as it cannot induce an fasting blood sugar level of $\geq 126 \text{ mg dl}^{-1}$ (7 mmol l^{-1}). Moreover, the other study comparing lisinopril with losartan confirmed the positive effect of lisinopril for diabetes prevention [38]. Therefore, it is more likely that lisinopril can reduce the risk of diabetes.

While the exact mechanism of lisinopril for its off-label uses are yet to be fully determined, some possible mechanisms have been suggested. It is stated that lisinopril can alter sympathetic activity, inhibit free radical activity, increase prostacyclin synthesis, and block the degradation of bradykinin, enkephalin and substance P, resulting in improvement of migraine [41]. Moreover, activated angiotensin has been shown to stimulate fibrosis in both renal and cardiac tissues and similar findings have been demonstrated for hepatic fibrosis through pharmacological inhibition and genetic knockdown of angiotensin I, evidenced by reduced collagen deposition, accumulation of myofibroblasts, inflammation and procollagen $\alpha 2(\text{I})$ gene expression. Therefore, lisinopril, by inhibiting angiotensin II formation, can reduce this fibrogenesis effect [49]. ACE-inhibitors can modulate the actions of sex hormones, cytokines, growth factors and leptins, thereby improving oligospermia and infertility [42]. Studies show that ACE is produced locally by vascular endothelial cells, which may have direct detrimental effects on retinal flow and vascular structure (independent of changes in systemic blood pressure). Therefore, lisinopril, by inhibiting ACE, may play a role in prevention and improvement of diabetic retinopathy [37].

Previous reviews discussing the effects of the class of ACE inhibitors including lisinopril reported findings similar to ours for some of the off-label uses [49–54]. ACE inhibitors are reported to have significant effects on diabetic retinopathy and might even perform better than ARBs [50]. We only found one RCT discussing the positive effect of lisinopril on myocardial fibrosis but previous reviews showed therapeutic effects of lisinopril on hepatic fibrosis [49] and fibrosis in the course of chronic pancreatitis [51]. Although we found unsuccessful results about the effect of lisinopril on atrial fibrillation, previous reviews on ACE inhibitors demonstrated significant positive effects; however, they also mentioned that the follow-up and sample size of the studies were not large enough to recognize AF episodes properly [52, 55]. ACE inhibitors were recommended as the second- or third-line migraine preventative. They were not considered as first-line due to the insufficiency of evidence [53]. Also, similar to our findings, ACE inhibitors were shown to reduce the incidence of new-onset diabetes [54].

Conclusion

Among 24 off-label uses obtained in our search, proteinuric kidney disease constituted the largest number of studies. We found lisinopril highly effective for proteinuria from a wide range of underlying pathologies, although it resulted in a minor and inconsiderable decrease in GFR in those

patients with $\text{GFR} < 90 \text{ ml min}^{-1}$. Lisinopril, compared to other standard treatments of diabetic nephropathy including ARBs, CCBs and β -blockers, achieved better outcomes. Our review showed that a few studies reported the effect of lisinopril in other off-label uses. These studies showed the positive effects of lisinopril for migraine, prevention of diabetes, myocardial fibrosis, mitral valve regurgitation, CM in patients with DMD, oligospermia and infertility, and diabetic retinopathy. Still, we do not recommend considering lisinopril as the first choice for these off-label uses until more RCTs confirm these positive effects. Conversely, the studies reported that lisinopril was ineffective for atrial fibrillation, LVH, inflammatory macular oedema and prevention of pneumonia. While we did not find any RCTs for some of the off-label uses of lisinopril as mentioned in Table 2, we are monitoring the development of proper RCTs for future updates to this review.

Competing Interests

There are no competing interests to declare.

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Contributors

S.-R.S.-E., conceived of and designed the study, performed the research, analysed the data, and wrote the paper. N.P., conceived of and designed the study, performed the research, analysed the data, and wrote the paper. N.V., performed the research and analysed the data. H.B., designed the study and wrote the paper. M.G., analysed the data and wrote the paper. S.T., analysed the data and wrote the paper. A.A., designed the study, performed the research, analysed the data, and wrote the paper.

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