A Systematic Review of Adherence to Cardiovascular Medications in Resource-Limited Settings

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BACKGROUND: Medications are a cornerstone of the prevention and management of cardiovascular disease. Long-term medication adherence has been the subject of increasing attention in the developed world but has received little attention in resource-limited settings, where the burden of disease is particularly high and growing rapidly. To evaluate prevalence and predictors of non-adherence to cardiovascular medications in this context, we systematically reviewed the peer-reviewed literature.

METHODS: We performed an electronic search of Ovid Medline, Embase and International Pharmaceutical Abstracts from 1966 to August 2010 for studies that measured adherence to cardiovascular medications in the developing world. A DerSimonian-Laird random effects method was used to pool the adherence estimates across studies. Between-study heterogeneity was estimated with an I^2 statistic and studies were stratified by disease group and the method by which adherence was assessed. Predictors of non-adherence were also examined.

FINDINGS: Our search identified 2,353 abstracts, of which 76 studies met our inclusion criteria. Overall adherence was 57.5% (95% confidence interval [CI] 52.3% to 62.7%; I^2 0.98) and was consistent across study subgroups. Studies that assessed adherence with pill counts reported higher levels of adherence (62.1%, 95% CI 49.7% to 73.8%; I^2 0.83) than those using self-report (54.6%, 95% CI 47.7% to 61.5%; I^2 0.93). Adherence did not vary by geographic region, urban vs. rural settings, or the complexity of a patient's medication regimen. The most common predictors of poor adherence included poor knowledge, negative perceptions about medication, side effects and high medication costs.

INTERPRETATION: Our study indicates that adherence to cardiovascular medication in resource-limited countries is sub-optimal and appears very similar to that observed in resource-rich countries. Efforts to improve adherence in resource-limited settings should be a priority given the burden of heart disease in this context, the central role of medications in their management, and the clinical and economic consequences of non-adherence.

KEY WORDS: cardiovascular medications; cardiovascular disease; compliance; cardiovascular risk reduction.
J Gen Intern Med
DOI: 10.1007/s11606-011-1825-3

Received November 8, 2010
Revised June 2, 2011
Accepted June 27, 2011

Non-infectious chronic diseases have long been thought to primarily affect affluent populations. However, these conditions are responsible for more deaths, both in absolute numbers and relative proportions, in resource limited settings.[1] Cardiovascular disease imposes a particular burden and is the leading cause of death in all age groups in virtually all low and middle income nations. Its prevalence in these regions is increasing at more than twice the rate observed in resource-rich countries.[1] Thus, the prevention and management of cardiovascular illness has become a major focus of healthcare providers worldwide.[1]

Medications are a cornerstone of cardiovascular risk reduction.[2] In resource-rich settings, substantial effort has been devoted to improving appropriate prescribing.[2] However, longer-term adherence to evidence-based medications remains suboptimal.[2] For example, only half of patients who experience an acute coronary event are adherent to their prescribed statin two years after starting therapy.[3,4]

Despite its disproportionate share of disease burden, much less is known about medication adherence in resource-limited regions. Access to healthcare, cultural beliefs, education about chronic disease and the role of medication, the nature of patient-physician interactions and social supports, among many other factors, are very different in resource-limited countries and may profoundly affect rates of adherence.[5,6] A greater understanding of these factors will help in the development of quality improvement activities in this context. Accordingly, we systematically reviewed the published literature in order to evaluate prevalence and predictors of non-adherence to cardiovascular medications in resource-limited settings.

METHODS

We performed an electronic search of Ovid Medline, Embase and International Pharmaceutical Abstracts from January 1, 1966 to August 19, 2010 for studies that reported adherence to cardiovascular medications in resource-limited regions of the world.

Search Strategy

Our electronic search strategy included medical subject headings (MESH) and keywords related to medication adherence (e.g. "adherence", "compliance", "non-adherence", "non-compliance", "treatment refusal"), cardiovascular disease (e.g. "hypertension", "hyperlipidemia", "anti-diabetic", "anti-

Published online: 20 August 2011

atherosclerosis"), adherence measures (e.g. "medication monitoring", "pill count"), cardiovascular medication classes (e.g. "ACE inhibitor", "metformin", "HMG CoA reductase inhibitors", and "statins"), and resource-limited countries. Our list of resource-limited countries was based upon the International Monetary Fund list of "emerging and developing economies", which include 153 countries in Africa, Southeast Asia, Eastern Europe, the Former Soviet states, Central and South America.[7]

Study Selection

Using pre-defined inclusion and exclusion criteria, two investigators (ADKB, JLL) independently reviewed the electronic search results to identify potentially relevant articles. Disagreements were resolved by consensus. We retrieved the published version of candidate articles and reviewed their reference lists to identify other studies that our search strategy may have missed.

We included studies that evaluated adherence to one or more cardiovascular medications. We excluded studies that: (1) did not present original data, (2) did not evaluate medications for the treatment of prevention of cardiovascular disease, (3) did not present quantitative adherence measures or (4) were not conducted in a resource-limited region. Included studies were not restricted to the English language and were translated accordingly.

Data Extraction

Data on patient and study characteristics, outcomes and study quality were independently extracted from each article by two investigators (ADKB, JLL) using a standardized protocol and reporting form. Specific information collected included study design (i.e. cohort, cross-sectional, randomized control trial), setting (i.e. country and rural or urban environment), patient demographics (including age and gender), the disease and drug evaluated and the method by which adherence was measured. Study quality was assessed with the Newcastle Ottawa Quality Assessment Scale[8] for observational studies, the Agency for Healthcare Research and Quality (AHRQ)[9] tool for rating cross-sectional studies and Jadad[10] assessment for randomized control trials. A study quality score from each scale was calculated as a proportion of total points that each paper received. We also recorded information on predictors of adherence if any were reported.

Studies were categorized into four mutually exclusive categories based on the disease being treated: (1) diabetes, (2) hypertension, (3) congestive heart failure or (4) coronary artery disease. Studies that evaluated more than one disease (e.g. diabetes and hypertension) and presented these results separately were included in their appropriate category. Studies that did not report results disaggregated by disease sub-type or that did not specify the type of heart disease that patients had were included in the coronary artery disease category.

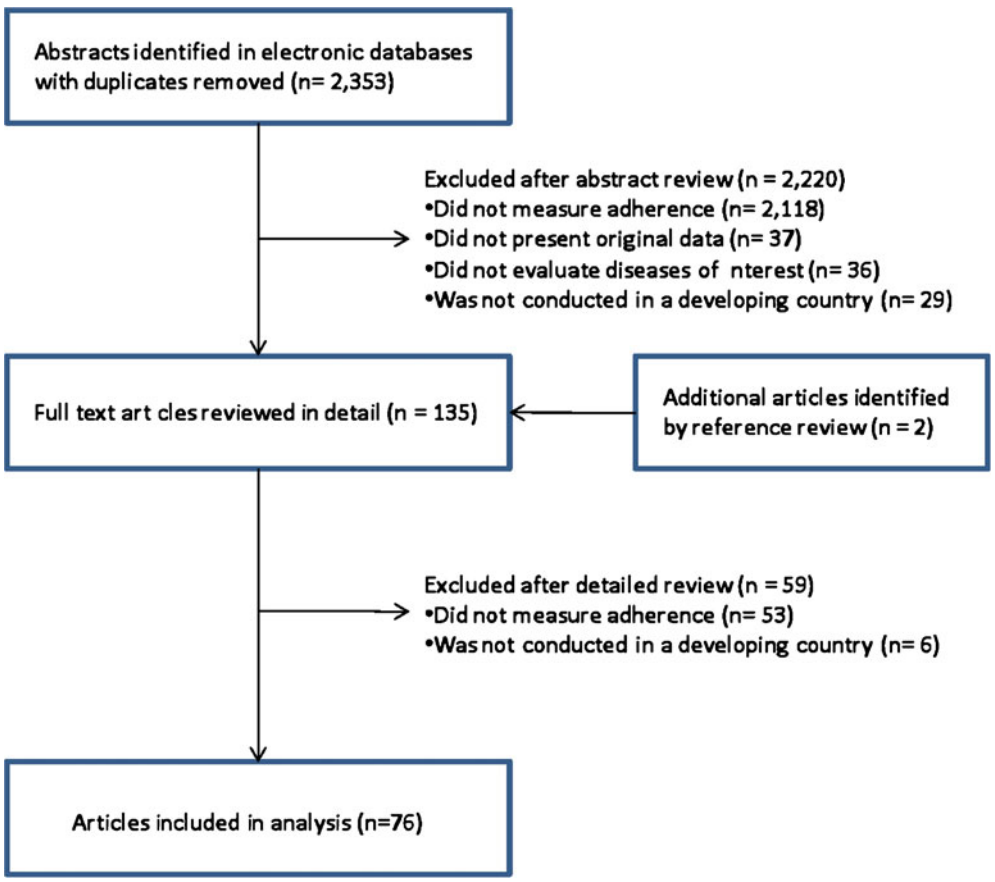

Figure 1. Flow diagram of study selection.

Table 1. Study Characteristics

Source	Patient Population	Sample Size	Country	Rural/ Urban	Design	Adherence Measure	Definition of Adherence	Adherence Rate (%)	Quality Score (%)
Diabetes									
Venter, 1991[65]	Randomly selected diabetes clinic patients	68	South Africa	Urban	Cross sectional	Urine test	Drug detected in urine	35	50
Garay-Sevilla, 1995[71]	Sample of diabetic patients not previously on treatment at "diabetes clubs"	200	Mexico	Urban	Cross sectional	Self report	Regular medication use	92	88
Kaur, 1998[74]	Diabetic patients in resettlement colony	35	India	Urban	Cross sectional	Self report	Regular medication use	63	13
Khattab, 1999[75]	All registered diabetic patients at a health center	142	Saudi Arabia	Urban	Cohort	Pill Count	Regular medication use	98	11
El-Shazly, 2000[70]	Random selection of diabetic patients with complete health service insurance records	1000	Egypt	Urban	Cross sectional	Self report	...	89	100
Duran, 2001[69]	Adults with type 2 diabetes not taking insulin	150	Mexico	Urban	Cross sectional	Pill Count	≥80% pills taken	54	38
Yousuf, 2001[78]	All eligible hospital patients with diabetes	163	Pakistan	Urban	Cross sectional	Self report	Regular medication use	41	38
Srinivas, 2002[77]	Population-based sample of registered diabetics on medication for >1 year	111	India	Rural	Cross sectional	Self report	No interruption of more than 1 month within the last year	43	50
Hernandez 2003[73]	Consecutive clinic patients with type 2 diabetes	58	Mexico	Urban	Cross sectional	Pill Count	...	59	50
Cui, 2005[67]	Hospital inpatients with diabetes	144	China	Urban	Cross sectional	Self report	...	74	50
Zhang, 2005[79]	Hospital inpatients with diabetes	176	China	Urban	Cross sectional	Self report	Regular medication use	53	50
Babwah, 2006[66]	Consecutive patients at medical and diabetes clinics	360	Trinidad	Urban	Cross sectional	Self report	Regular medication use	71	75
Duff, 2006[68]	Randomly selected clinic patients with diabetes	86	Jamaica	Urban	Cross sectional	Self report	Regular medication use	45	75
Hanko, 2007[72]	Patients with diabetes from randomly selected pharmacies	211	Hungary	Mix	Cross sectional	Self report	Regular medication use	53	75
Roaeid, 2007[76]	Diabetes clinic patients with diabetes for >1 year	805	Libya	Urban	Cross sectional	Self report	Regular medication use	73	50
Coronary artery disease									
Olubodun, 1990[89]	Hypertensive patients referred to hospital cardiac unit	37	Nigeria	Urban	Cohort	Self report	Regular medication use	0	63
Wiseman, 1991[91]	Sample of patients attending cardiac clinic outpatients	137	South Africa	Urban	Cross sectional	Serum drug titers	Serum concentration differs from measured by<50%	60	38
Chizzola, 1996[85]	Sample from outpatient cardiology referral center	185	Brazil	Urban	Cross sectional	Self report	Regular medication use	41	75
Dantas, 2002[86]	Hospital inpatients who had undergone CABG surgery in the prior 5 months	17	Brazil	Urban	Cohort	Self report	Regular medication use	65	22
Rotchford, 2002[90]	Patients with diabetes presenting for clinic follow up	253	South Africa	Rural	Cross sectional	Self report	Taking medication in previous 24 hours	94	50

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Table 1. (Continued)

Source	Patient Population	Sample Size	Country	Rural/ Urban	Design	Adherence Measure	Definition of Adherence	Adherence Rate (%)	Quality Score (%)
El-Gatit, 2003[87]	Clinic patients post aortic valve replacement surgery	62	Libya	Urban	Cohort	MEMS	Regular medication use	93	11
Asefzadeh, 2005[84]	Randomly selected clinic patients with cardiovascular disease	56	Iraq	Urban	Cross sectional	Self report	Regular medication use	59	50
Kocer, 2006[88]	Clinic patients at risk for stroke	612	Turkey	Urban	Cross sectional	Self report	Regular medication use	56	50
Moodley, 2006[83]	Medical scheme beneficiaries on lipid reducing medications	100,691	South Africa	...	Prospective cohort	Pharmacy claims	...	87	63
Heart failure									
Joshi, 1999[81]	Consecutive inpatients with congestive heart failure	125	India	Urban	Cross sectional	Pill Count	≥80% pills taken	55	50
Bhagat, 2001[80]	Patients with clinically stable heart failure from 4 general practice clinics	22	Zimbabwe	Urban	Cross sectional	Self report	Regular medication use and knowledge	73	38
Sadik, 2005[82]	Hospital in- and outpatients with heart failure	208	UAE	Urban	Randomized controlled trial	Self report	Regular medication use	33	60
Hypertension									
Buchanan, 1979[23]	Sample of black diabetic and hypertensive clinic patients	100	South Africa	Urban	Cohort	Home visits	≥85% pills taken	38	75
Unterhalter1979[55]	Sample of black diabetic clinic patients	50	South Africa	Urban	Cross sectional	Pill Count	≥85% pills taken	38	50
Supramaniam, 1982[54]	Random sample of armed force personnel with hypertension	102	Malaysia	Rural	Cross sectional	Self report, visit records	...	41	25
Marshall, 1988[43]	Random sample of women not previously receiving treatment	88	South Africa	Rural	Cross sectional	Self report	Regular medication use	73	0
Roy, 1990[48]	Hospital inpatients with hypertension who had a prior stroke	66	Bangladesh	Urban	Cohort	Self report	Regular medication use	12	22
Stein, 1990[53]	Sample of hypertension clinic patients	18	Zimbabwe	Urban	Open cross-over	Pill Count	Correct number of pills returned	97	75
Saunders, 1991[51]	Consecutive clinic patients with hypertension	20	South Africa	Urban	Randomized controlled trial	Pill count	≥80% pills taken	15	20
Lim, 1992[39]	Consecutive hospital outpatients with hypertension	168	Malaysia	Urban	Cohort	Pill count, self report	≥80% pills taken	74	63
Hungerbuhler, 1995[34]	Consecutive clinic patients with uncontrolled hypertension	187	Seychelles	...	Cohort	Urine test	Pills taken "concordant" with pills prescribed	56	50
Joshi, 1996[35]	Consecutive new clinic patients with hypertension	139	India	Urban	Cohort	Pill Count	≥80% pills taken	66	63
Khalil, 1997[62]	Random sample of health centers patients with hypertension	347	Saudi Arabia	Urban	Cohort	Pill Count	≥80% pills taken	47	63
Maro, 1997[42]	Cardiac clinic patients starting antihypertensive treatment	146	Tanzania	Urban	Cohort	Self report or pill count	≥75% pills taken	90	44
Lunt, 1998[41]	Community health center patients with hypertension	889	South Africa	Urban	Cohort	Drug pick up	Collected drugs on≥75% of visits	77	33
Salome Kruger, 1998[50]	Outpatients attending clinic for at least 1 year	132	South Africa	Urban	Cross sectional	Self report	Regular medication use	38	50
Zdrojewski, 1999[60]	Elderly patients with hypertension	198	Poland	...	Cross sectional	Self report	Regular medication use	71	50

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Table 1. (Continued)

Source	Patient Population	Sample Size	Country	Rural/ Urban	Design	Adherence Measure	Definition of Adherence	Adherence Rate (%)	Quality Score (%)
Elzubier, 2000[29]	Consecutive clinic patients with hypertension	198	Sudan	Urban	Cross sectional	Pill Count	≥80% pills taken	60	75
Bovet, 2002[21]	Random sample of patients with sustained hypertension	50	Seychelles	Rural	Cohort	MEMS	≥86% pills taken	46	44
Jiang, 2002[61]	Clinic patients with hypertension from general hospitals in 8 cities	4510	China	Urban	Cross sectional	Self report	…	44	38
Youssef, 2002[57]	Random selection of hypertensive patients at health insurance clinics	316	Egypt	Urban	Cross sectional	Records, self report	≥90% pills taken	74	50
Bharucha, 2003[20]	Random population sample of patients with hypertension	453	India	Urban	Cross sectional	Self report	…	64	38
Li, 2003[38]	Clinic patients with hypertension from 8 cities	3112	China	Urban	Cross sectional	Self report	Regular medication use	44	75
Salako, 2003[49]	Consecutive clinic patients with hypertension	422	Nigeria	Urban	Cross sectional	Self report	…	80	25
Buabeng, 2004[22]	All new clinic patients with hypertension	128	Ghana	Urban	Cross sectional	Self report	≥80% pills taken	7	38
Chen, 2004[25]	Sample of patients with hypertension on medication	312	China	Urban	Cross sectional	Self report	Regular medication use	43	50
Hadi, 2004[32]	All eligible patients with hypertension who attended clinic consultation	250	Iran	Urban	Cross sectional	Self report	≥90% pills taken	40	100
Lu, 2004[40]	Sample of patients with hypertension	1831	China	Urban	Cross sectional	…	…	74	63
Naddaf, 2004[44]	Randomly selected clinic patients with hypertension	100	Jordan	Urban	Cross sectional	Self report	No missed doses in prior 30 days	58	38
Peltzer, 2004[46]	Consecutive clinic patients with hypertension for >1 year	100	South Africa	Mix	Cross sectional	Self report	Regular medication use	65	75
Sookaneknun, 2004[52]	Pharmacy and primary care patients with hypertension	217	Thailand	Mix	Randomized controlled trial	Pill Count	≥80% pills taken	61	49
Akpa, 2005[16]	Consecutive cardiology clinic patients with hypertension	100	Nigeria	Urban	Cross sectional	Self report	≥75% pills taken	60	25
Coelho, 2005[26]	Randomly selected clinic patients with hypertension	245	Brazil	Urban	Cohort	Self report	…	87	22
Feng, 2005[30]	Hospital inpatients with essential hypertension	164	China	Urban	Cross sectional	Self report	Regular medication use	65	75
Fodor, 2005[31]	All hypertensive employees at workplace	359	Austria, Hungary, Slovakia	Urban	Cross sectional	Self report	Regular medication use	54	75
Xiao, 2005[56]	Hospital inpatients with hypertension	119	China	Urban	Cross sectional	Self report	…	41	50
Yusuff, 2005[59]	Clinic outpatients presenting with hypertension	200	Nigeria	…	Cohort	Record	Regular medication use	83	44
Almas, 2006[17]	Outpatients with hypertension	200	Pakistan	Urban	Cross sectional	Self report	Did not miss dose for 6 months	57	63

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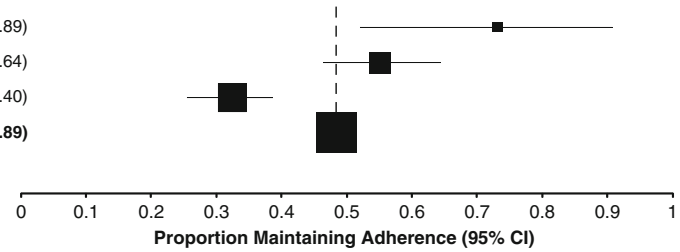
Table 1. (Continued)

Source	Patient Population	Sample Size	Country	Rural/ Urban	Design	Adherence Measure	Definition of Adherence	Adherence Rate (%)	Quality Score (%)
Ben Abdelaziz, 2006[19]	Representative sample of hypertensive patients in regional health care facilities	292	Tunisia	Urban	Cross sectional	Healthcare assessment	Pharmacy contacts	59	38
Hassan, 2006[33]	Clinic patients with hypertension on medications for at least 3 months	242	Malaysia	Urban	Cross sectional	Self report	≥80% pills taken	44	100
Lambert, 2006[37]	Convenience sample of hypertension clinic patients	98	South Africa	Urban	Cross sectional	Self report	Regular medication use	24	63
Amira, 2007[18]	Consecutive clinic patients with hypertension	225	Nigeria	Urban	Cross sectional	Self report	Regular medication use	65	75
Castro, 2007[24]	Consecutive patients with hypertension from a family health program	66	Brazil	Urban	Cross sectional	Self report	Regular medication use	67	63
de Souza, 2007[27]	Consecutive patients at a cardiovascular pharmacology clinic	48	Brazil	Urban	Cohort	Pill count	≥80% pills taken	64	44
Dennison, 2007[28]	Black patients with hypertension at local primary care clinics	403	South Africa	Urban	Cross sectional	Self report	…	48	88
Konin, 2007[36]	Consecutive clinic patients who were hypertensive	200	Ivory Coast	Urban	Cross sectional	Self report	…	13	50
Prado, 2007[64]	Random sample of health center patients with mild to moderate hypertension	120	Brazil	Urban	Cross sectional	Pill count	≥80% pills taken	38	75
Qureshi, 2007[47]	Patients in the control arm of a hypertension health education trial	100	Pakistan	Urban	Randomized controlled trial	MEMS	Regular medication use	48	60
Yusuff, 2007[58]	Random sample of hypertension clinic patients	400	Nigeria	Urban	Cross sectional	Healthcare assessment	…	49	63
Nugmanova, 2008[45]	Sample of patients with hypertension	227	Kazakhstan	Urban	Randomized controlled trial	Self report	Medication taken on the morning of interview	38	40

a

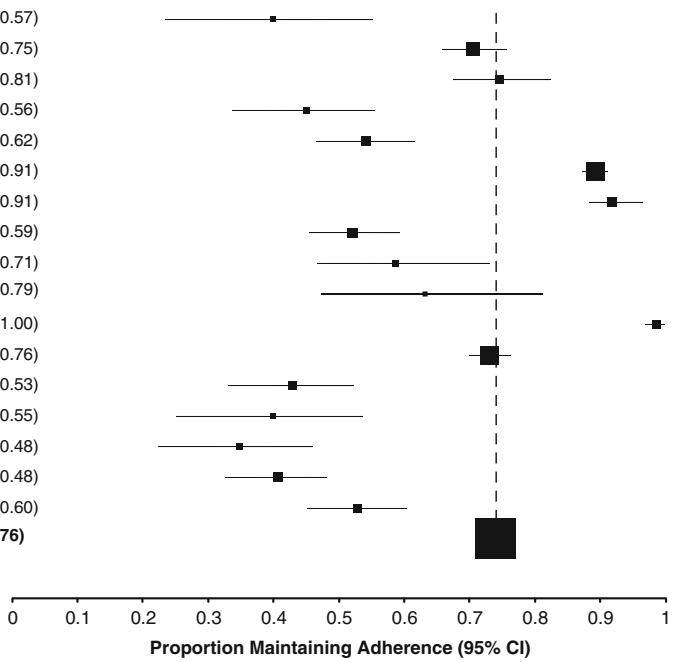
Vientiane

Author, Year	Country	Adherence
Bhagat, 2001	Zimbabwe	0.73 (0.50-0.89)
Joshi, 1999	India	0.55 (0.46-0.64)
Sadik, 2005	UAE	0.33 (0.26-0.40)
Congestive Heart Failure		**0.48 (0.09-0.89)**



b

Author, Year	Country	Adherence
Buchanan, 1979	South Africa	0.40 (0.25-0.57)
Babwah, 2006	Trinidad	0.70 (0.65-0.75)
Cui, 2005	China	0.74 (0.66-0.81)
Duff, 2006	Jamaica	0.45 (0.35-0.56)
Duran, 2001	Mexico	0.54 (0.46-0.62)
El-Shazly, 2000	Egypt	0.89 (0.87-0.91)
Garay-Sevilla, 1995	Mexico	0.92 (0.87-0.91)
Hanko, 2007	Hungary	0.52 (0.45-0.59)
Hernandez, 2003	Mexico	0.59 (0.45-0.71)
Kaur, 1998	India	0.63 (0.45-0.79)
Khattab, 1999	Saudi Arabia	0.98 (0.94-1.00)
Roaeid, 2007	Libyan Arab Jamahiriya	0.73 (0.70-0.76)
Srinivas, 2002	India	0.43 (0.34-0.53)
Unterhalter, 1979	South Africa	0.40 (0.26-0.55)
Venter 1991	South Africa	0.35 (0.24-0.48)
Yousuf, 2001	Pakistan	0.41 (0.33-0.48)
Zhang, 2005	China	0.53 (0.45-0.60)
Diabetes Mean		**0.74 (0.66-76)**



c

Author, Year	Country	Adherence
Asefzadeh, 2005	Iraq	0.59 (0.45-0.72)
Chizzola, 1996	Brazil	0.41 (0.34-0.49)
Dantas, 2002	Brazil	0.65 (0.38-0.86)
El-Gatit, 2003	Libyan Arab Jamahiriya	0.93 (0.84-0.98)
Kocer, 2006	Turkey	0.56 (0.52-0.60)
Moodley, 2006	South Africa	0.87 (0.87-0.87)
Olubodun, 1990	Nigeria	0.00 (0.00-0.10)
Rotchford, 2002	South Africa	0.94 (0.90-0.97)
Wiseman, 1991	South Africa	0.60 (0.51-0.68)
Coronary Artery Disease Mean		**0.59 (0.28-0.86)**

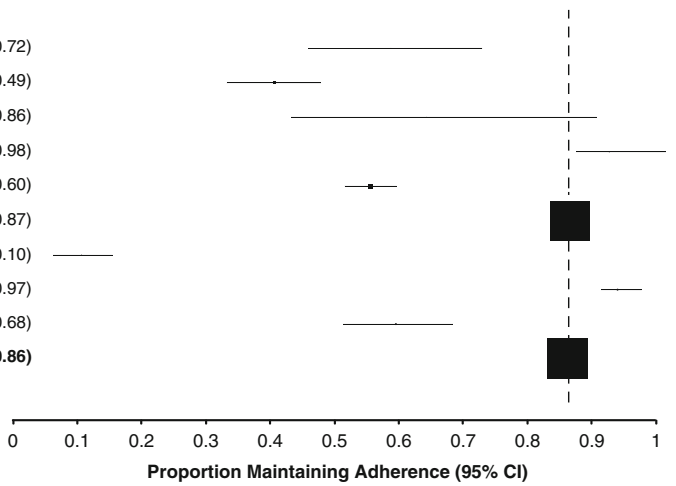


Figure 2. a Adherence to medications for congestive heart failure. b Adherence to medications for diabetes. c Adherence to medications for coronary artery disease. d Adherence to medications for hypertension.

Author, Year	Country	Adherence
Akpa, 2005	Nigeria	0.60 (0.50-0.70)
Almas, 2006	Pakistan	0.57 (0.50-0.64)
Amira, 2007	Nigeria	0.66 (0.59-0.72)
Ben Abdelaziz, 2006	Tunisia	0.59 (0.53-0.65)
Bharucha, 2003	India	0.64 (0.59-0.68)
Bovet, 2002	Seychelles	0.46 (0.32-0.61)
Buabeng, 2004	Ghana	0.07 (0.03-0.13)
Buchanan, 1979	South Africa	0.38 (0.28-0.48)
Castro, 2007	Brazil	0.67 (0.54-0.78)
Chen, 2004	China	0.43 (0.38-0.49)
Coelho, 2005	Brazil	0.87 (0.83-0.91)
Dennison, 2007	South Africa	0.48 (0.43-0.53)
de Souza, 2007	Brazil	0.64 (0.49-0.78)
Elzubier, 2000	Sudan	0.60 (0.52-0.66)
Feng, 2006	China	0.65 (0.57-0.72)
Fodor, 2005	Austria, Hungary, Slovakia	0.54 (0.48-0.59)
Hadi, 2004	Iran	0.40 (0.33-0.46)
Hassan, 2006	Malaysia	0.44 (0.38-0.51)
Hungerbuhler, 1995	Seychelles	0.56 (0.49-0.63)
Jiang, 2002	China	0.44 (0.42-0.45)
Joshi, 1996	India	0.66 (0.58-0.74)
Khalil, 1997	Saudi Arabia	0.47 (0.42-0.52)
Konin, 2007	Ivory Coast	0.13 (0.08-0.18)
Lambert, 2006	South Africa	0.24 (0.15-0.33)
Li, 2003	China	0.44 (0.42-0.46)
Lim, 1992	Malaysia	0.74 (0.60-0.80)
Lu, 2004	China	0.74 (0.72-0.76)
Lunt, 1998	South Africa	0.77 (0.74-0.80)
Maro, 1997	Tanzania	0.90 (0.84-0.94)
Marshall, 1988	South Africa	0.73 (0.62-0.82)
Naddaf, 2004	Jordan	0.58 (0.48-0.68)
Nugmanova, 2008	Kazakhstan	0.38 (0.32-0.45)
Peltzer, 2004	South Africa	0.65 (0.55-0.74)
Prado, 2007	Brazil	0.38 (0.29-0.47)
Qureshi, 2007	Pakistan	0.48 (0.38-0.58)
Roy, 1990	Bangladesh	0.12 (0.05-0.22)
Salako, 2003	Nigeria	0.79 (0.75-0.83)
Salome, Kruger 1998	South Africa	0.38 (0.30-0.47)
Saunders, 1991	South Africa	0.15 (0.03-0.38)
Sookaneknun, 2004	Thailand	0.61 (0.54-0.68)
Stein, 1990	Zimbabwe	0.97 (0.73-1.00)
Supramaniam, 1982	Malaysia	0.41 (0.32-0.51)
Toprak, 2007	Turkey	0.76 (0.65-0.86)
Unterhalter, 1979	South Africa	0.38 (0.25-0.53)
Xiao, 2005	China	0.41 (0.32-0.51)
Youssfef, 2002	Egypt	0.74 (0.69-0.79)
Yusuff, 2005	Nigeria	0.83 (0.77-0.87)
Yusuff, 2007	Nigeria	0.49 (0.44-0.54)
Zrojewski, 1999	Nigeria	0.71 (0.64-0.77)
Hypertension Mean		**0.55 (0.49-0.61)**

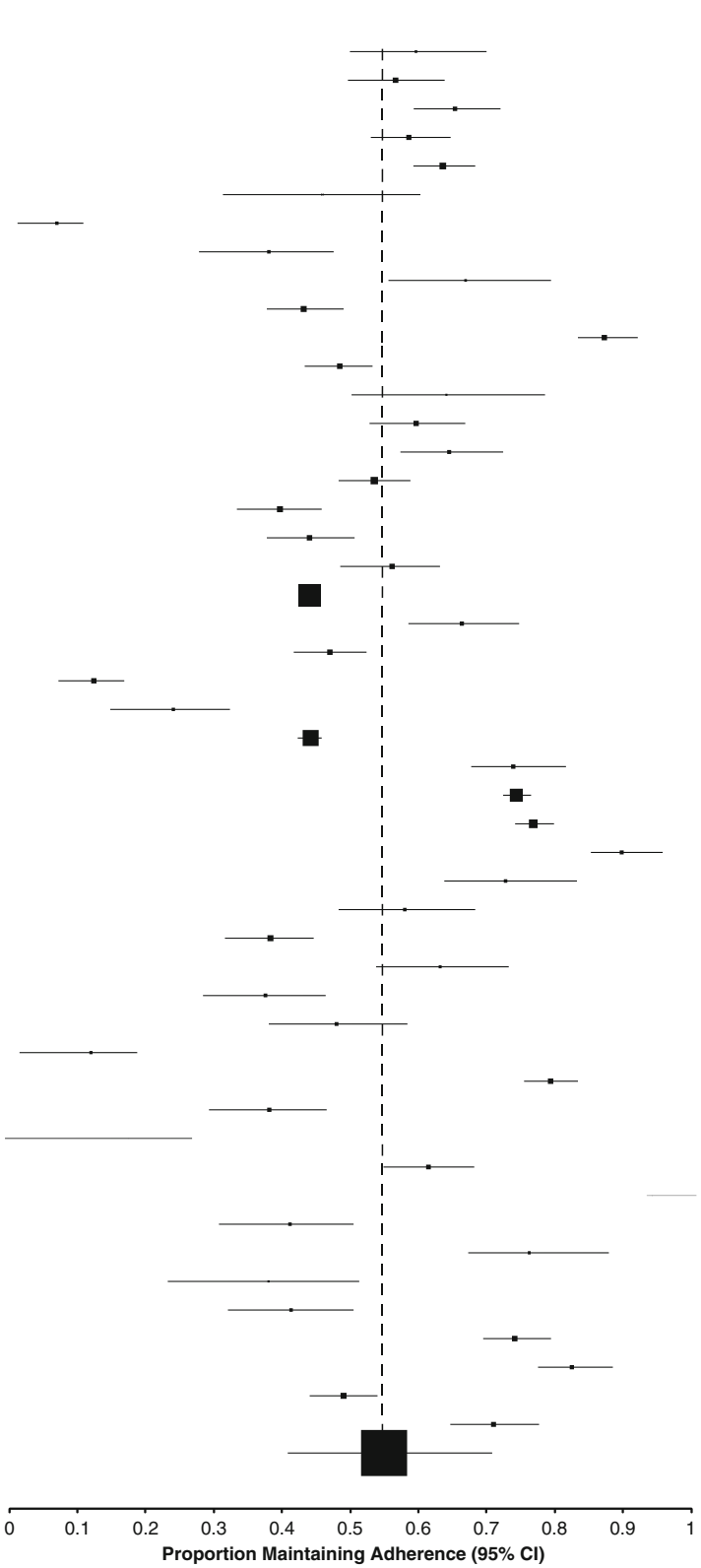


Figure 2. (Continued)

We also classified studies based on the method by which adherence was assessed: (1) pill counts, (2) self-report or (3) other. The latter category included studies that used electronic pill-bottles (e.g. medication event monitoring system [MEMS]), assessments by healthcare professional, reviews of health records and biochemical assays. In post-hoc analyses, we also evaluated subgroups based upon the complexity of medication regimens, the care setting, the use of drugs for primary as compared with secondary prevention,

whether or not medications were provided to patients for free, age, gender and study quality.

Data Analysis

The main outcome measure of our study was a summary estimate of medication adherence. In order to pool studies, the variances of the raw proportions from individual studies (variance[r]) were stabilized using a Freeman–Tukey-type arcsine square root transformation: y=arcsine [$\sqrt{(r/n+1)}$+arcsine[$\sqrt{(r+1)/(n+1)}$] with a variance of 1/(n+1), where n represents the sample size of the study.[11,12] A DerSimonian-Laird random effects method was then used to pool the transformed proportions.[3,13,14] Our results are reported as summary estimates with 95% confidence intervals. All statistical analyses were conducted using SAS v9.2 (Cary, NC).

Between-study heterogeneity was explored in several ways. First, we visually inspected the plot of overall adherence proportions to look for outliers. Second, the proportion of the overall variation in adherence that was attributable to between-study heterogeneity was estimated with an I^2 statistic.[15] Third, heterogeneity was re-evaluated after influential studies were excluded. Finally, pooled adherence was calculated for each of our pre-specified study sub-categories. Pooling was only performed in subgroups with three or more studies.

Predictors of medication adherence were evaluated from those studies that reported empirical results about factors affecting adherence. Included studies either presented adherence rates stratified by a given predictor (e.g. men vs. women) or regression parameters (or correlation coefficients) for the association between adherence and a

Table 2. Reported Adherence by Subgroup

Characteristic	Subgroup	N	Summary estimate (95%CI)	I^2 (95% CI)
Disease	Diabetes	17	0.74 (0.66 to 0.76)	0.94 (0.86 to 0.93)
	Coronary Artery Disease	9	0.59 (0.28 to 0.86)	0.96 (0.94 to 0.97)
	CHF	3	0.48 (0.09 to 0.89)	0.68 (0.11 to 0.91)
	Hypertension	49	0.55 (0.49 to 0.61)	0.91 (0.89 to 0.93)
Adherence Measure	Count	16	0.62 (0.5 to 0.74)	0.83 (0.73 to 0.89)
	Self report	48	0.55 (0.48 to 0.62)	0.93 (0.92 to 0.94)
	Other	14	0.63 (0.51 to 0.74)	0.96 (0.94 to 0.97)
Geographic Region	Africa	34	0.58 (0.48 to 0.68)	0.96 (0.95 to 0.97)
	Asia	26	0.54 (0.46 to 0.61)	0.91 (0.88 to 0.93)
	Central & South America	11	0.61 (0.36 to 0.83)	0.87 (0.73 to 0.93)
	Eastern Europe, Soviet Union	7	0.57 (0.46 to 0.67)	0.63 (0.15 to 0.84)
Study Design	Observational	73	0.59 (0.53 to 0.64)	0.98 (0.97 to 0.98)
	Randomized controlled trial	5	0.43 (0.25 to 0.61)	0.67 (0.15 to 0.88)
Proportion of male patients	> median	34	0.64 (0.64 to 0.64)	0.98 (0.97 to 0.98)
	< median	34	0.63 (0.64 to 0.64)	0.98 (0.97 to 0.98)
Age	> median	29	0.61 (0.53 to 0.69)	0.9 (0.87 to 0.92)
	< median	27	0.58 (0.48 to 0.69)	0.92 (0.89 to 0.94)
Journal Impact Factor	> median	28	0.53 (0.43 to 0.62)	0.9 (0.87 to 0.93)
	< median	13	0.54 (0.37 to 0.7)	0.96 (0.94 to 0.97)
	Unknown	37	0.62 (0.56 to 0.69)	0.98 (0.97 to 0.98)
Proportion of patients receiving study medication for free	1-49%	4	0.31 (0.02 to 0.74)	0.81 (0.49 to 0.93)
	50-99%	3	0.52 (0.26 to 0.78)	0.51 (0.69 to 0.86)
	Unknown	54	0.59 (0.53 to 0.65)	0.93 (0.91 to 0.94)
Proportion of patients taking medications more than twice daily	<50%	4	0.56 (0.32 to 0.78)	0.84 (0.59 to 0.94)
	>50%	4	0.71 (0.38 to 0.95)	0.85 (0.62 to 0.94)
	Unknown	70	0.57 (0.51 to 0.62)	0.98 (0.97 to 0.98)
Proportion of patients taking 2 or more medications	<50%	14	0.66 (0.57 to 0.76)	0.96 (0.94 to 0.97)
	>50%	13	0.54 (0.43 to 0.65)	0.75 (0.56 to 0.85)
	Unknown	51	0.55 (0.48 to 0.62)	0.94 (0.92 to 0.95)
Clinical setting	Primary care	14	0.52 (0.38 to 0.66)	0.9 (0.85 to 0.93)
	Secondary or tertiary care	43	0.59 (0.51 to 0.67)	0.93 (0.92 to 0.94)
	Primary, secondary or tertiary care	2	0.59 (0 to 1)	0.8 (0.12 to 0.95)
	Unknown	18	0.58 (0.49 to 0.67)	0.97 (0.96 to 0.97)
Patients taking medications for the first time (i.e. new users)	Yes	11	0.47 (0.28 to 0.67)	0.78 (0.62 to 0.88)
	No	19	0.59 (0.47 to 0.7)	0.9 (0.86 to 0.93)
	Unknown	48	0.59 (0.55 to 0.65)	0.98 (0.97 to 0.98)
Drugs being used for primary prevention	Yes	29	0.53 (0.44 to 0.62)	0.89 (0.85 to 0.91)
	No	4	0.58 (0.05 to 1)	0.9 (0.76 to 0.95)
	Unknown	45	0.6 (0.54 to 0.67)	0.98 (0.97 to 0.98)
Length of study follow-up	>6 months	26	0.54 (0.45 to 0.63)	0.89 (0.85 to 0.92)
	< 6 months	30	0.61 (0.51 to 0.71)	0.95 (0.93 to 0.96)
	Unknown	21	0.57 (0.48 to 0.66)	0.96 (0.95 to 0.97)
Overall		76	0.58 (0.52 to 0.63)	0.98 (0.97 to 0.98)

potential predictor. To maintain consistency across studies, predictors were reoriented, if necessary, to evaluate their association with rates of non-adherence rather than adherence. For example, if a study reported that lower medication costs were associated with higher rates of adherence, we report this as demonstrating a relationship between higher drug costs and higher rates of non-adherence. Because not all studies tested the statistical significance of the given predictor, we conservatively assumed that the associations of these predictors with adherence were not statistically significant.

RESULTS

Study Characteristics

Our search identified 2,353 abstracts, of which 76 studies met our inclusion criteria (Fig. 1). These studies included a total of 124,733 subjects (sample size range 17 to 100,691, median 157 subjects). Forty-nine studies evaluated adherence to antihypertensive medications[16–64] and an additional 17,[23,55,65–79] 3[80–82] and 9[83–91] studies assessed medications for diabetes, congestive heart failure and coronary artery disease, respectively. The studies were predominantly performed in urban settings and were mostly based in Africa (40%), Asia (34%) or Central and South America (14%). All studies were either cross-sectional or cohort studies, with the exception of 5 randomized control trials. The majority assessed adherence using pill counts (n=16) or self-report (n=49). Further details of the study designs and patient demographics are presented in Table 1.

Reported Adherence

The included studies reported adherence ranging from 0 to 98% (Fig. 2a-d). Only eighteen (23%) studies reported that, on average, patients were fully adherent to their prescribed therapy. Pooled across studies, overall adherence to cardiovascular drugs was 57.5% (95% confidence interval [CI] 52.3% to 62.7%; I^2 0.98).

Subgroups

Reported adherence was relatively consistent across study subgroups (Table 2), although adherence to medications for congestive heart failure was lower (48.4%, 95% CI 9.0% to 89.2%; I^2 0.68) than that for other disease categories. Studies using pill counts reported higher levels of adherence (62.1%, 95% CI 49.7% to 73.8%; I^2 0.83) than those using self-report (54.6%, 95% CI 47.7% to 61.5%; I^2 0.93) or other methods (63%, 95% CI 51% to 74.3%, I^2 0.96) to estimate adherence. Adherence did not vary by geographic region or urban vs. rural settings, but when assessed in the context of randomized controlled trials, adherence was lower (42.6%, 95% CI 25.3% to 60.9%; I^2 0.67) than in observational studies (59.0%, 95% CI 52.6% to 64.1%; I^2 0.98). Similarly, adherence did not significantly change according to gender, age, the complexity of medication regimens, by clinical setting or the integrity of the studies (Table 2).

Predictors of Adherence

Of the 76 papers included in our study, 29 reported factors associated with adherence. The most commonly and consistently reported predictors of non-adherence were poor knowledge (10 of 18 studies evaluating this factor reported a statistically significant association), negative perceptions about medications (11 of 15 studies evaluating this factor reported a statistically significant association), the occurrence of side effects (10 of 14 studies evaluating this factor reported a statistically significant association) and high medication costs (9 of 11 studies evaluating this factor reported a statistically significant association) (Fig. 3). All studies (n=4) reporting social

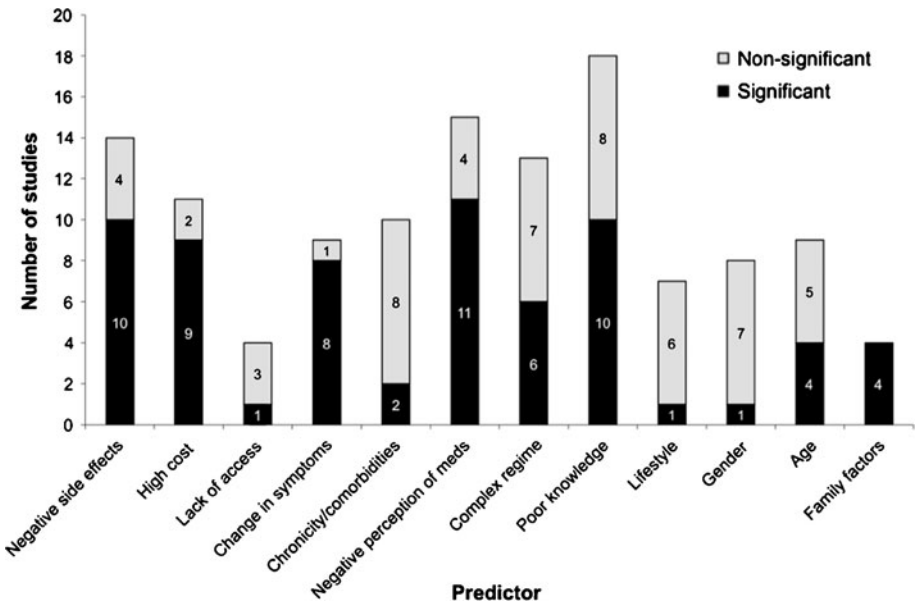


Figure 3. Factors predicting non-adherence to cardiovascular medication.

factors (e.g. lack of family support) as a predictor of non-adherence reported a significant association, as did the majority of studies (79%) evaluating a change (improvement or worsening) of symptoms. Patient factors such as age, gender, lifestyle factors, complex treatment regimens, and lack of access to health care services were not consistently associated with non-adherence. Restricting our analysis to studies that used significance testing to compare risk factors between adherent and non-adherent patients did not change our findings.

DISCUSSION

The role of medications in the management of cardiovascular disease is well recognized. While these conditions impose a greater burden in resource-limited than resource-rich countries, medication adherence in this context has received very little attention. Even the World Health Organization report[1] which highlights the global problem of non-adherence relies almost exclusively on studies data from the developed world. To fill this void, we systematically reviewed studies in the peer-reviewed published literature that evaluated adherence to cardiovascular medications in the developing world. We found that although there was substantial heterogeneity across studies, overall adherence was 58%. This rate is remarkably similar to that observed in resource-rich regions.[4,92,93] As such, our results highlight the quality improvement opportunity that exists worldwide from improving adherence to essential medications.

Given the scarcity of health resources available in resource-scarce countries, only quality improvement interventions that are cost-efficient are likely to be feasible.[94] As a whole, increasing adherence to evidence-based medications is likely to be a more efficient strategy for improving cardiovascular outcomes than increasing treatment initiation rates or developing and evaluating new cardiovascular medications.[95] Further, improved adherence has been shown to improve the effectiveness of interventions which target lifestyle modifications[96] and may represent an opportunity to not only improve health quality but also reduce health care spending.[1,2,4] This may be particularly true in resource-limited settings where the majority of cardiovascular medications are available as low-cost generic products.[97]

Unfortunately, the literature contains virtually no published reports of successfully implemented and rigorously evaluated cardiovascular medication adherence improvement strategies in resource-limited countries. Numerous strategies to improve adherence have been studied in the developed world. These include approaches that are "informational" (e.g. telephonic coaching, group classes, or the mailing of instructional materials), "behavioral" (e.g. pillboxes, mailed reminders, simplifying treatment regimens, or audit and feedback), "family and social focused" (e.g. support groups and family counseling), or some combination thereof.[6]

The studies we reviewed included a broad range of factors affecting adherence, with poor knowledge, negative perceptions about medications, the occurrence of side effects and high medication costs being evaluated most often and being most consistently associated with non-adherence. The literature evaluating reasons for non-adherence in resource-poor settings is extremely limited, and the most robust data comes from studies evaluating therapies for HIV. Mills et al. have found cost, complexity and perception of medications to be consistent reasons for non-adherence to medications in this context.[6,98] These factors have also been observed in resource-rich settings as well.[4,99] Thus, general approaches to non-adherence used in resource-rich settings may hold promise once translated into the developing world context.

We found adherence to be consistently poor across all of the disease subgroups we evaluated. The slightly worse adherence rates in studies of congestive heart failure medications may have been the result of the nature of the patient population or the severity of their disease, although these factors were not explored in any of the studies we evaluated. Interestingly, when assessed by pill count, adherence rates were better than when evaluated by self-report. This is somewhat different than studies in resource-limited settings where subjective measures tend to provide higher estimates of adherence than those provided by objective measures.[92] While the reason for our apparently contrary findings are unclear, it may be that patients' perceptions of medications and the social stigma associated with chronic disease may actually lead patients to under-report their true levels of adherence. Nevertheless, future adherence improvement in these resource-limited areas should pay particular attention to study design and the use of rigorous assessment methods.

Our study has several limitations. Although we have evaluated studies that have studied adherence rates in resource-rich countries, we did not directly compare adherence rates between the resource-rich and resource-limited countries, as no such studies exist. Although our search strategy included a wide range of electronic sources and our literature search sample was quite large, we may have missed some studies, especially if research conducted in resource-limited countries is less likely to be published. Furthermore, we did not include studies presented in abstract form at a scientific meeting but which were not subsequently published in the peer-reviewed literature. Due to the variation in trial size and methodology, there is significant heterogeneity between the studies, despite our having performed numerous subgroup analyses. It is possible that some of the between study differences in adherence we observed were due to differences in adherence patterns associated with different classes of medications to treat a single condition (for example, diuretics as compared to ACE inhibitors for hypertension).[100] The included studies do not provide sufficient detail to explore this further. While our study summarizes possible predictors of non-adherence to cardiovascular medications, in some cases, these predictors were only reported by a minority of studies. As such, we are only able to comment on the importance of these factors as a proportion of studies actually report on them.

In conclusion, adherence to cardiovascular medication in resource-limited countries is sub-optimal and appears similar to rates observed in the developed world. Greater attention to long-term adherence in resource-limited countries should be a priority given the burden of heart disease in this context, the central role of medications in their management, and the clinical and economic consequences of non-adherence.

Acknowledgement: *This work was not funded by any external sources.*

Conflict of Interest: *None disclosed.*

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