BARRIERS TO THE MANAGEMENT OF CARDIOVASCULAR DISEASE

BARRIERS TO THE MANAGEMENT OF CARDIOVASCULAR DISEASE:

A FOCUS ON AVAILABILITY AND AFFORDABILITY OF MEDICATIONS IN 17 COUNTRIES

By

RASHA KHATIB, B.A., MHS

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TITLE: Barriers to the Management of Cardiovascular Disease: A Focus on Availability and Affordability of Medications in 17 Countries

AUTHOR: Rasha Khatib, B.A., MHS

SUPERVISOR: Dr. Salim Yusuf

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ABSTRACT

Background: The use of evidence-based medications for the management of cardiovascular disease (CVD) is low worldwide. A key strategy to improving use of medications is to understand the barriers to their use. This thesis aims to identify barriers that may influence use of these medications in high, middle, and low income countries. Data on barriers in low and middle income countries are especially lacking. We postulate that in those settings lack of availability and affordability of proven medications are key barriers to medication use.

Methods: We initially systematically reviewed the literature on barriers to medication use. Since data on these barriers for the management of CVD are sparse, the review included studies focused on hypertension, because it is the leading risk factor for CVD. Baseline data from the PURE study were then used to investigate whether availability and affordability of medications influence their use for secondary prevention of CVD. PURE is a prospective study that recruited adults between the ages of 35 to 70 years from 17 high, middle, and low income countries. Availability and affordability of medications were documented for each country income group, and the associations between these two potential barriers and medication use was explored after accounting for other factors that may influence medication use.

Results: The review showed that in high income countries, non-healthcare system related factors, such as lack of knowledge and motivation, were more commonly reported as barriers, whereas in low and middle income countries healthcare system factors were most commonly reported as barriers to hypertension management. However, very few studies were conducted in low and middle income countries and so there is limited information on whether availability and affordability of medications affect their use. Results from the PURE study indicate that medications recommended for the secondary prevention of CVD were often not available and

when available, they were not affordable for a high proportion of individuals in low and middle income countries. Lack of availability and low affordability were strongly associated with medication use in these settings.

Conclusions: Barriers to medication use are context specific and interventions to improve use should be tailored to barriers depending on the setting. In high income countries where the medications are usually available and affordable interventions should target knowledge and motivation barriers. In low and middle income countries, the focus should be on healthcare system interventions to improve the availability and affordability of medications.

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LIST OF ABBREVIATIONS (alphabetical order)

ACE-inhibitors	Angiotensin Converting Enzyme Inhibitor
ALLHAT trial	Antihypertensive And Lipid-Lowering Treatment To Prevent Heart Attack Trial
ARBs	Angiotensin II Receptor Blockers
CHD	Coronary Heart Disease
CCBs	Calcium Channel Blockers
CPI	Consumer Price Index
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EML	Essential Medication List
EPOCH	Environmental Profile Of Community Health
FDC	Fixed-Dose Combination Medications
GAP	Global Action Plan
GDP	Gross Domestic Product
GNI	Gross National Income
HIC	High Income Countries
HOPE trial	Heart Outcomes Prevention Evaluation
HR	Hazard Ratio
JNC 8	8th Joint National Committee
LDL-c	Low-Density Lipoprotein Cholesterol
LIC	Low Income Countries
LMIC	Lower Middle Income Countries
LPGW	Lowest Paid Government Unskilled Worker
MDG	Millennium Development Goals
MI	Myocardial Infarction
MIC	Middle Income Countries
NPHW	Non-Physician Health Worker
OR	Odds Ratio
oPt	Occupied Palestinian Territory
PPP	Purchasing Power Parity
PURE	Prospective Urban Rural Epidemiology
RR	Relative Risk
SAGE	Study On Global Ageing And Adult Health
SBP	Systolic Blood Pressure
TIPS	The Indian Polycap Study

UAE	United Arab Emirates
UMIC	Upper Middle Income Countries
UMPIRE	Use Of A Multidrug Pill In Reducing Cardiovascular Events Trial
WHO	World Health Organization
WHO/HAI	World Health Organization/ Health Action International
95% CI	95% Confidence Interval

DECLARATION OF ACADEMIC ACHIEVEMENT

I was the primary person responsible for the research conducted in this thesis. My contributions included conception of the research idea and study design of this work. I also acquired and analyzed the data, created all the figures and tables, interpreted the results, and drafted and prepared the chapters.

Dr. Salim Yusuf, Dr. Harry Shannon, and Dr. Amiram Gafni supervised me during this work.

Co-authors of the systematic review participated in the data collection, screening, data abstraction, and review of the manuscript for publication.

Chapter 1

Introduction

1.1 Background

Cardiovascular disease (CVD) is the leading cause of death and a major cause of disability worldwide[1]. It is estimated that 17 million people died from CVD in 2002[2]. Projections suggest that by 2030 mortality due to CVD will reach 23 million with the majority of deaths occurring in low and middle income countries (LIC and MIC). High blood pressure is the leading risk factor for CVD mortality and is responsible for 13% of deaths globally[2]. Blood pressure control is associated with a lower risk of CVD events and mortality even among people without prior CVD[3,4].

Evidence-based recommendations for the secondary prevention of CVD and the management of hypertension have been developed in several clinical guidelines[5-10]. All guidelines recommend the use of angiotensin converting enzyme inhibitors (ACE-inhibitors) or Angiotensin II Receptor Blockers (ARBs), beta blockers, statins, and aspirin for the secondary prevention of CVD. Despite these recommendations, the rates of use of proven medications for secondary prevention and the proportion of individuals with hypertension whose blood pressure levels are controlled (i.e. to levels below 140/90 mm Hg) is low[11,12,6, 13]. The aim of this thesis is to identify barriers to medication use in secondary prevention, and to investigate whether the lack of availability and low affordability of medications recommended for the secondary prevention of CVD, influence their use in LIC and MIC countries where such data are currently lacking.

The thesis first reviews the literature to identify barriers that patients and healthcare providers report to influence medication use. Because the literature on barrier assessment for the secondary prevention of CVD is limited, we focused our review on barriers to the management of hypertension, as we expect substantial similarity with barriers for medication use in secondary prevention (for example the medications used have substantial overlap and the co-morbidities are similar between the two conditions). Results from the review indicated that availability and affordability of medications were commonly reported as barriers to medication use. However, the literature in LIC and MIC countries is sparse and inference on whether these factors affect medication use in these populations is not available in the literature. Therefore, the remaining chapters aim to fill this gap in the literature by first documenting the availability and affordability of medications recommended for CVD using data from the PURE study in 17 high,

middle and low income countries. We then investigate whether the lack of availability and affordability affects medication use among patients with a history of CVD.

The remaining sections of this introduction chapter describe the evidence-practice gaps to the secondary prevention of CVD. Given that the systematic review in this thesis included barriers to hypertension management, the evidence-practice gaps for the management of hypertension for the prevention of CVD is also described in this chapter.

1.2 Evidence-practice gap for the secondary prevention of CVD

Secondary prevention of CVD refers to measures taken to reduce the risk of recurrent vascular events in patients who have a history of CVD. Survivors of a myocardial infarction (MI) or stroke, and patients with coronary heart disease (CHD) are at high risk of a recurrent MI or stroke. Mortality rates are also high in these patients if they experience a recurrent event.

Robust evidence exists for the effectiveness of four medications (ACE-inhibitors or ARBs, beta-blockers, statins and anti-platelet medications) to prevent death, MI and stroke in those with prevalent CVD. Results from the Heart Outcomes Prevention Evaluation (HOPE) trial indicated a 26% risk reduction of CVD deaths in patients with CVD who were taking ACE-inhibitors (ramipril) compared to placebo, as well as reductions in MI, strokes, and any deaths[14]. An overview of clinical trials indicated that using beta-blockers after an MI resulted in a 20% reduction in mortality and a 25% reduction in recurrent MI[15]. Similarly, statin therapy can safely reduce the 5-year risk of major coronary events, coronary revascularisation, and stroke by about 20% for every one mmol/L reduction in LDL cholesterol[16]. A systematic review of randomized trials showed that the use of anti-platelet therapy following a CVD event reduced non-fatal MIs by 34%, non-fatal strokes by 25% and vascular deaths by 17%[17].

Given this evidence on the effectiveness of these medications, practically all clinical guidelines for the prevention of secondary CVD recommend the use of these four medications[7]. In addition it is recommended that individuals with CVD stop smoking, eat a healthy diet, and be physically active[7]. Controlling blood pressure levels and lowering glucose, either with medications or with lifestyle, is also recommended, although the evidence for the benefits of the latter approach is not clear[18].

Despite the overwhelming evidence for benefit, adherence to these recommendations among patients with CVD is low. Data from the Prospective Urban Rural Epidemiology (PURE) study conducted in 17 countries indicate low use of medications among patients with CVD, with only 25% of individuals receiving aspirin, 17% beta-blockers, 20% ACE-inhibitor or ARB, and 15% receiving statins[13]. The rates of use of these medications were particularly low in individuals from LIC. Adherence to a healthy lifestyle was also low among those known to have CVD; only 47% of these patients were not current smokers, 39% reported being physically active (undertook high levels of work- or leisure-related physical activities), and 35% consumed a healthy diet (measured using the Alternative Healthy Eating Index- AHEI)[19]. The proportion of individuals with CVD using medications and adhering to a healthy lifestyle greatly varied between countries of different incomes[13,19].

1.3 Evidence-practice gap in hypertension management for the primary prevention of CVD

The 8th Joint National Committee (JNC 8) on hypertension guidelines define hypertension as a systolic blood pressure (SBP) higher than 140mmHg or diastolic blood pressure (DBP) higher than 90 mmHg[9]. High blood pressure is independently associated with an increased risk of MI, heart failure, stroke, and renal disease[20]. Lowering blood pressure in individuals with at least moderate hypertension has been shown to reduce CVD events[21].

Several medications have been shown to effectively lower blood pressure in clinical trials. Major pharmacologic classes of blood pressure lowering medications include: thiazide diuretics, ACE-inhibitors, ARBs, beta-blockers, and calcium channel blockers (CCBs). A meta-analysis of 29 randomized clinical trials comparing the effects of the different blood pressure lowering medications showed no significant differences in major cardiovascular events between regimens based on thiazide type diuretics, ACE-inhibitors, CCBs, or beta-blockers[22]. Moreover, irrespective of the blood pressure lowering medication used, greater reductions in systolic and diastolic blood pressure were associated with larger reductions in CVD events[23].

Clinical trials have shown that most patients diagnosed with hypertension need at least two blood pressure lowering medications to lower blood pressure effectively. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) indicated that 60% of patients required two or more medications to achieve blood pressure control (defined as SBP<140 mmHg and DBP<90mmHg)[24]. Given that thiazide-type diuretics are inexpensive, safe, and effective, they are often the recommended initial treatment for most patients diagnosed with hypertension, either alone or in combination with one of the other classes (ACE-inhibitors, ARBs, beta-blockers, CCBs)[25]. Addition of a second medication from a different class is recommended when the use of a single medication in adequate doses fails to achieve the goal[25]. Alternatively fixed-dose combinations (FDC) of two or more medications at low doses may be the preferred initial approach in patients with hypertension[26].

Hypertension management at the population level involves several strategies, and does not depend on medication use only. First, individuals with high blood pressure must be identified and made aware of their diagnosis (detection). Second, individuals diagnosed with hypertension must be treated to lower blood pressure with either medications, lifestyle changes, or both. Third,

they must be followed up to ensure adherence to treatment and adequate blood pressure control[9,27]. Evidence-practice gaps can occur at each of these levels.

The PURE study documented this gap among 57,840 participants with elevated blood pressure (SPB>140 or DBP>90mmHg) from high, middle, and low income countries. Only 47% were aware of their diagnosis, and 31% of individuals who are aware of their hypertension diagnosis used two or more blood pressure lowering medications[12]. The proportion of individuals with hypertension using medications greatly varied between countries of different incomes in the PURE study[12]. Adherence to a healthy lifestyle is also low among patients with hypertension. Data from high income countries (HIC) report heavy alcohol intake, low physical activity, and high obesity rates among patients with hypertension[28,29]. Adherence to a healthy lifestyle in MIC and LIC has not been investigated in the literature.

Understanding the barriers to these evidence-practice gaps is essential to improve hypertension management at the population level. Similar to hypertension treatment, the secondary prevention of CVD also requires long term use of medications. Lessons learned from barriers to long term management of hypertension can, to some extent, be generalized to the long term use of medications in those with known CVD (secondary prevention).

1.4 Thesis rationale and objectives

The use of medications recommended for the secondary prevention of CVD is low. Knowledge translation models suggest that success in implementing evidence is greater if strategies are informed by and tailored to an assessment of potential barriers[30].The overall goal of this thesis is to describe barriers that may influence medication use for secondary prevention of CVD in high, middle, and low income countries. It is postulated that the lack of availability and affordability are key barriers to medication use in LIC and MIC. Such data are currently

lacking. This will be explored using baseline data from the PURE study from 17 high, middle, and low income countries.

We initially reviewed the literature on barriers to medication use reported by patients and providers (chapter 2). Since data on barriers to medication use for the secondary prevention of CVD are lacking in the literature, our review focused on barriers to the management of hypertension, the leading risk factor for CVD. Such an approach is justified as some of the medications used for hypertension control are also used for secondary prevention. Additionally, the prevalence of hypertension among patients with CVD is high[31] and therefore many of the included studies likely included patient groups that also had a history of CVD. Therefore, lessons learnt from studies in hypertension can, at least in part, be applied to secondary prevention.

Very few studies were conducted in LIC and MIC, and therefore inference on barriers in these settings was limited from our review in hypertension. However, in the few studies from these settings, the lack of availability and affordability of medications were commonly reported as barriers among patients and providers. Barriers in the included studies were self-reported and definitions of the lack of availability and affordability were not clearly stated. The included studies asked patients if the medications were affordable, without any specific measure or definition. This made comparisons across studies and settings difficult because affordability can be interpreted by participants in different ways. To fill this gap in the literature, the remaining chapters focus on two potential barriers: the availability and affordability of medications for the secondary prevention of CVD, with a particular focus on MIC and LIC.

Chapter 3 describes the methods that have been employed in the literature to measure the availability and affordability of medications. Studies in the systematic review in hypertension asked patients whether or not they find medications to be available and affordable, without an

objective measure or definition. Availability and affordability of medications may have been interpreted by participants in different ways. Therefore, objective methods and definitions to define availability and affordability of medications will be reviewed in chapter 3.

Chapters 4 and 5 provide an overview of the PURE study and describe the key variables that will be used in the analyses. Chapter 6 employs the methods described in chapter 3 to assess the availability and affordability of CVD medications in 17 high, middle, and low income countries. Chapter 7 discusses methodological issues related to data collection in the PURE study and proposes recommendations to improve the availability and affordability of CVD medications at the healthcare system level.

Chapter 2*

Patient and healthcare provider barriers to hypertension awareness, treatment and follow up: A systematic review and meta-analysis of qualitative and quantitative studies

***Note: This chapter has been published:**
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Author's contribution: RK contributed to study conception & design, screening & selection, data extraction & coding, statistical analysis, and drafted the manuscript. J-D S and RN contributed to study conception & design, and data extraction & coding. MK assisted in screening & selection and data extraction & coding. SY, BH and MM assisted in interpretation of results and provided critical input for the manuscript. All authors did critical reading and modification of drafts and approved the final manuscript.

2.1 Background

Hypertension is the leading global risk factor for mortality worldwide, responsible for 13% of deaths globally[32]. However, hypertension awareness (detection), medication use and control are low worldwide[33]. Blood pressure control at the population level involves several steps. First, those at risk must be identified. Second, patients with hypertension must be treated appropriately, whether with medication, lifestyle changes, or both. Third, they must be followed up to ensure that their blood pressure is controlled[9]. These recommendations are based on established research evidence yet their implementation in practice is suboptimal. Implementation can fail because of an inability to surmount barriers that relate to the patient, the healthcare provider, or the health system[34,35]. Barriers to each of these stakeholders have been subject to previous research but, to our knowledge, their role, importance, and generalizability have not been examined systematically thus far.

Barriers can be assessed by investigating how certain characteristics such as region, socio-economic status, age, sex or co-morbidities affect hypertension management, or by asking stakeholders such as patients and providers about the barriers they face. Patient characteristics are often non-modifiable and do not elucidate the actual reasons for subgroup disparities. Therefore we seek to address the gap in the literature of barriers to hypertension management by providing a systematic literature review of barriers as reported by patients and healthcare providers. Specifically, we go beyond much previous research that focused on medication use as the major barrier to blood pressure control. There is a need for a more nuanced approach to understanding blood pressure control, taking account of complex interactions at different levels of care and the roles of the different stakeholders involved[36]. The conceptual frameworks used in this work have been limited in scope and are often not linked to theories that can explain

processes of behavior change designed to achieve optimal implementation and thereby blood pressure control.

The aim of this chapter is to systematically review the literature on barriers reported by patients diagnosed with hypertension as well as population groups at risk for hypertension (together referred to as patients from here on) and healthcare providers (referred to as providers from here on) that may impede optimal hypertension awareness (detection), use of medications, or follow up with a provider (Figure 2.1). This review focuses on individual level barriers, whereby barriers related to the healthcare system are addressed only as they are reported by individuals, whether providers or patients. We included qualitative data to gain a better understanding of which barriers are perceived to be important from the patients' and providers' perspective, and quantitative data to assess their prevalence and their clinical importance in managing hypertension.

2.2 Methods

2.2.1 Protocol and registration

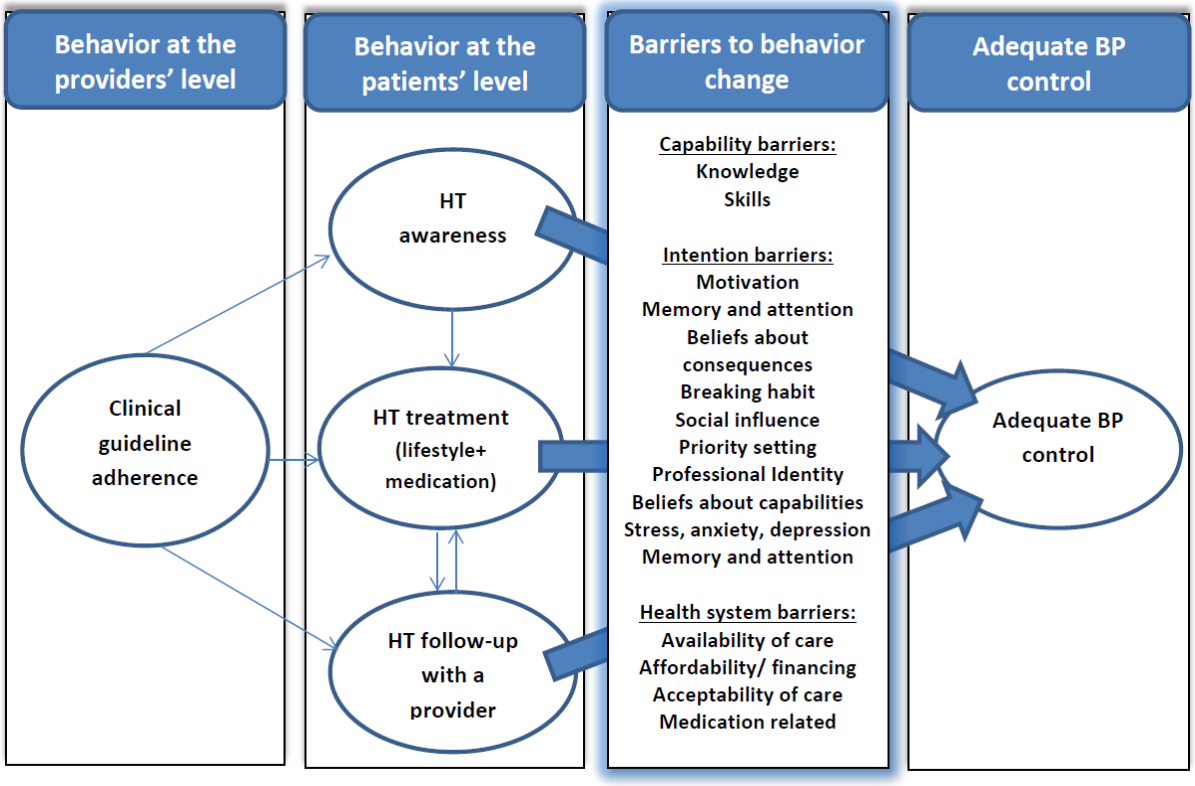
Methods of the systematic review were specified in advance and documented in a published protocol in the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42011001617.

2.2.2 Behavior change theoretical framework

Definition of barriers

Barriers to hypertension management in this systematic review were defined as any factor limiting the performance of a required behavior by patients or providers[36] to achieve optimal hypertension awareness (detection), treatment (medication or lifestyle) or follow up care. As indicated, non-modifiable patient characteristics such as age, race, and sex were not considered. In keeping with best practice, we begin with a theoretical framework that encapsulates the barriers and makes it possible to explore mediating pathways and moderators that influence the management of hypertension[37]. The framework used in this review draws on theories from implementation research[38] and behavior change[39]. Michie et. al. (2004) proposed 12 subthemes to describe barriers to the implementation of evidence based practice[38] (Figure 2.1). These subthemes are organized under three main themes suggesting that a change in behavior requires: 1. a strong commitment for change (intention barriers), 2. the necessary skills and abilities to perform the behavior (capability barriers), and 3. no health system constraints[39]. The qualitative studies that were identified in this review were used to adapt these subthemes to behaviors related to hypertension management. Barriers identified in the included qualitative studies were then grouped under these subthemes. Separate groups were created for barriers reported by patients and by providers.

Figure 2.1: Theoretical framework depicting barriers to hypertension management, modified from Michie et al (2004) and Fishbein et al (2000)



Definition of themes

Capability barriers relate to the knowledge of behaviors required to achieve blood pressure control, or the capacity to perform these behaviors. Intention barriers relate to attitudes or motivations towards actions necessary to achieve control and may be mediated by several behavioral characteristics (Figure 2.1). Healthcare system barriers include barriers that are external to patients' or healthcare providers' control[40]. These include availability of resources (inputs), financing and affordability, and the mode of delivery and acceptability of health services. These barriers also extend beyond the healthcare system to the wider health environment, and include other facilities required for a healthier lifestyle. In addition, medication

related barriers for patients, such as side effects, were included under health system barriers as they are also out of patients' and providers' control.

2.2.3 Information sources and search strategy

Studies were identified by searching electronic databases, scanning reference lists of included articles and consultations with experts in the field. No limits were applied with respect to language and those in languages other than English were translated. The search was applied to MEDLINE (1948 to January, 2013), EMBASE (1980 to 2013 Week 09) and Global Health (1973 to January 2013). An experienced librarian helped in developing the search strategy to identify studies (Appendix 2.1). Controlled vocabulary and keywords focused on "hypertension", "barriers", and "obstacles". No limits to study design were imposed.

2.2.4 Eligibility criteria, study selection, and data extraction

Box 1 describes the eligibility criteria of included studies. Two reviewers independently assessed studies identified by the search for eligibility based on the title and abstract. Selected full text papers were then assessed independently by the two reviewers using a standardized form that was designed to describe the characteristics of studies to be included based on recommendations in the Cochrane Handbook section 5.1.0[41]. Disagreement was resolved by a third author. The unweighted kappa for the second screening phase (calculated using PC-AGREE software; version 2.5) to assess agreement between the two reviewers was 0.87 (95% CI: 0.69-1.0)[41]. Finally, two reviewers independently extracted data from included studies using a form that was piloted on four studies, randomly selected from included studies.

Box 1: Eligibility criteria

Types of participants:

- Patient populations of any age, with a hypertension diagnosis or at risk for hypertension.
- Healthcare provider populations were considered without restrictions to the type of healthcare provider (physician, nurse, other), level of practice (primary care vs. hospital level), or the population they cater to.

Study outcome/focus:

- Hypertension awareness; detection, screening.
- Medication use: use, uptake, adherence, clinic visits
- Lifestyle change: diet, physical activity, alcohol intake, weight loss
- Follow up with a healthcare provider for hypertension management
- Clinical guideline adherence, medication prescription
- Studies that focused on blood pressure control in general, without specifying an outcome leading to control as specified above were excluded.

Types of studies:

- Qualitative and quantitative observational studies assessing barriers to hypertension awareness, treatment (medication and lifestyle), or follow-up care.
- Effectiveness (randomized clinical trials) and comparison (cohort, case-control) studies were included only if a barrier assessment was assessed within the study.
- Studies were included regardless of study quality
- No language or publication date restrictions were imposed.
- Conference abstracts and non- peer review studies were excluded.

2.2.5 Study quality assessment

Following the Cochrane Collaboration recommendations to present potential biases for each study instead of using scores to rate quality, a set of quality appraisal items relevant to the type of studies included was applied (Appendices 2.4, 2.5). Quality of included qualitative studies was assessed using an existing instrument[42]. This instrument was selected for this review due to its applicability among the different types of included studies and ease of presentation. For quantitative studies, biases in sample selection, quantification of barriers, measures of the outcome, and appropriateness of statistical analyses (i.e adjusting for confounders when applicable) were described.

2.2.6 Data synthesis and analysis

Studies were classified as qualitative or quantitative from the authors' description, and were organized according to the theoretical framework separately for patients and providers. Qualitative data investigates why and how certain barriers affect the outcome of interest[43]. Consequently we used these data to modify and explain themes according to the framework. We then used quantitative data to quantify how common these barriers are. Classification of barriers into the framework's subthemes was done independently by two reviewers; discrepancies were resolved by a third reviewer.

Qualitative data analysis

Qualitative data analysis was used to further clarify each subtheme in the framework. The number of studies and an example of a barrier were reported for each subtheme.

Quantitative analysis

Once barriers from each quantitative study were organized into the framework, the proportion of participants reporting each barrier was extracted (when reported). This generated a measure of how frequently each barrier was studied within the included studies. The extracted proportions were then pooled in order to identify how prevalent these barriers were across the different study populations included in this review. When the same study had more than one question or statement assessing the same barrier, the median prevalence was calculated. This was done in order to prevent pooling of duplicate results from the same study, which would result in an overestimation of the pooled proportion[44]. This method of organizing barriers and grouping their prevalence has been previously used to study barriers of medication adherence for highly active antiretroviral therapy (HAART)[45].

The inverse variance method was used to pool proportions presented in each study. Review manager 5 was utilized to conduct these calculations. The proportion of study participants reporting the barrier (p) and the study sample size (n) were used to calculate the standard error (SE(p)), using the following formula: SE (p) = square root [(p)(1-p) / n][43].

Association measures for barriers with the outcome of interest were also pooled and stratified by the frameworks subthemes. Four of the five studies that provided effect measures used odds ratios (OR), the remaining study used hazard ratios (HR)[46]. Risk was assumed similar for these two measures and they were pooled together, sensitivity analysis was conducted by excluding the study reporting hazard ratios. Only adjusted effect measures were pooled.

Due to expected heterogeneity in the included studies the random effects model was used to pool the data, making an adjustment to the study weights according to the extent of variation of proportions from each study. Using a random effects model does not explain or justify heterogeneity, yet it provides wider confidence intervals around pooled estimates[41]. Pooled proportions and pooled effect measures are presented using forest plots depicting the 95% confidence interval, the I^2 statistic, and the number of pooled studies. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)[41].

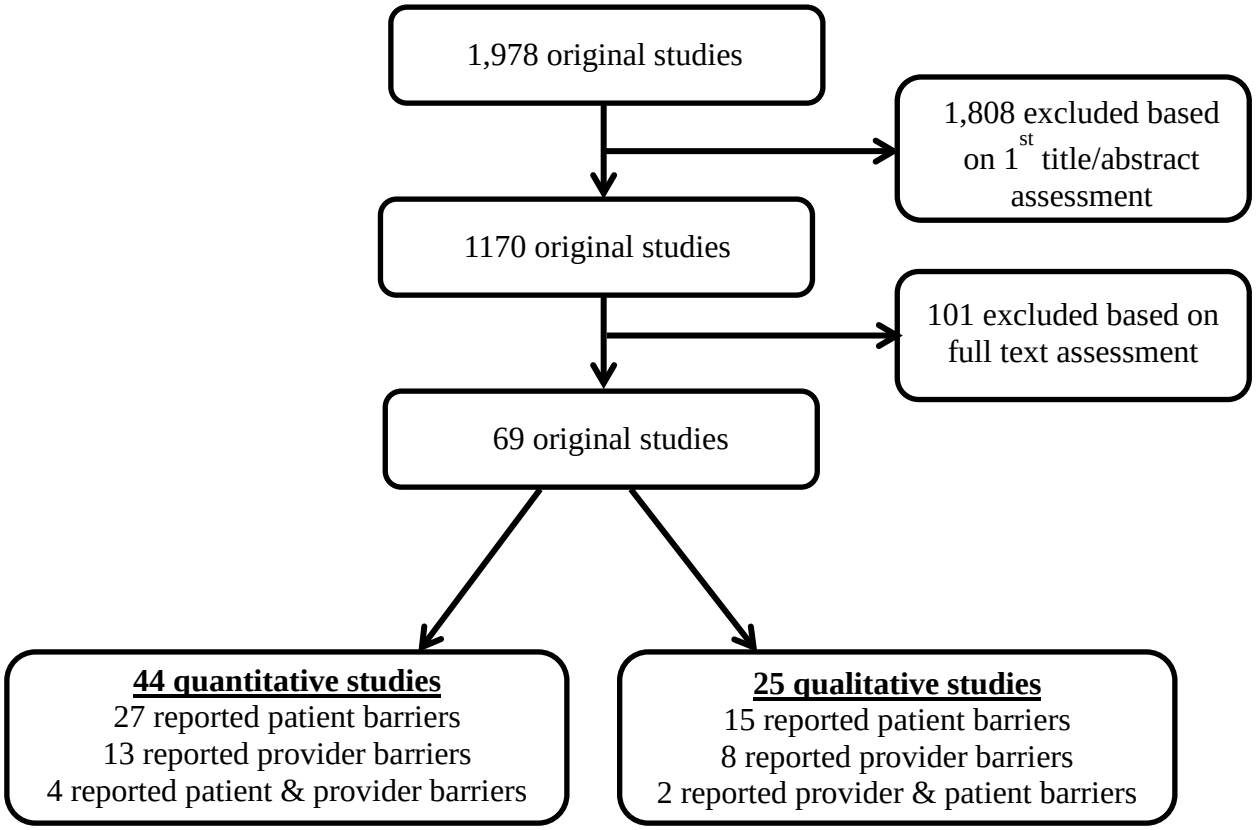
2.3 Results

2.3.1 Study selection

The search identified a total of 1,978 articles (Figure **2.2**). Of these, 1,808 articles were excluded in the first screening based on title/abstract reviews. The full texts of the remaining 170 citations were examined in more detail in the second screening, of which 69 studies (25

qualitative, 44 quantitative) were included in the review. Three included studies were translated from Russian[47], Portuguese[48], and Korean[49] into English.

Figure 2.2: Flow diagram of included studies



2.3.2 Review statistics

Eight qualitative and 13 quantitative studies reported provider barriers. Fifteen qualitative and 27 quantitative studies reported patient barriers. Two qualitative and 4 quantitative studies reported both patient and provider barriers. Table 2.1 presents a summary of study characteristics. The majority of studies were conducted in high income countries (HIC), mainly in the USA, with only 14 (20%) in low and middle income countries (LMIC). Among studies describing patient barriers, 28% sampled participants from households, while the remaining studies recruited patients from clinic or hospital settings. Among studies describing provider

barriers, 33% (n=7) included non-physician health workers in their sample (nurses, pharmacists, social workers, etc…) (Appendices 2.2 and 2.3).

Table 2.1: Characteristics of included studies (n=69)

	Number of studies		
	Qualitative	**Quantitative**	**Total**
High income countries (HIC)			
USA	15	22	37
UK	2	2	4
Canada	0	3	3
Other[1]	5	6	11
Low and middle income countries[2]	3	11	14
Setting			
Selected from hospitals/clinics	19	35	54
Selected from communities (household sampling)	6	9	15
Study type			
Focus groups	16	NA	16
In depth interviews	7	NA	7
Focus groups and interviews	2	NA	2
Cross sectional	NA	41	41
RCT baseline	NA	1	1
RCT follow up	NA	2	2
Study population			
Only hypertensive patients	12	26	38
Other chronic disease patient or general community	5	5	10
Physicians only	3	11	21
Other healthcare workers (nurses, pharmacists…)	5	2	
TOTAL	25	44	69

1. Australia, Republic of Korea, Israel, Netherlands, Kuwait, Switzerland, Ireland, Singapore, Europe, Croatia
2. India , South Africa, Brazil, Malaysia, Nigeria, Trinidad & Tobago, China , and Russian Federation
NA= Not Applicable

2.3.3 Study quality assessment

Risk of bias for each study is presented in Appendices 2.4 and 2.5. For qualitative studies, only 1 of the 25 studies explicitly assessed the likely impact of the authors own personal characteristics on the data obtained (reflexivity). The context or setting of the study was inadequately described in 40% (n=10) of studies, and 68% (n=17) of studies failed to support

their methods or results to a theoretical framework or a wider body of knowledge. As for quantitative studies 84% (n=37) reported a response rate lower than 85%, and 68% (n=30) did not use a validated tool/instrument to assess barriers.

2.3.4 Synthesis of results from qualitative studies- provider reported barriers

Appendix 2.6 presents the number of qualitative studies in which barriers were reported, according to the framework of behaviour change.

a. Capability barriers

Knowledge barriers were discussed in two studies that were conducted by the same group[50,51]; providers reported that lack of knowledge regarding hypertension management was not a barrier to hypertension control but there were reports of unfamiliarity in how best to manage certain subgroups like the elderly with comorbidities. Skills barriers mainly included difficulty in keeping up with new clinical information[51], educating and counselling patients[52] and addressing prehypertension[53].

b. Intention barriers

Motivation barriers pertained to the intention to perform the action. Providers reported difficulties and repeated failures in addressing healthy behaviors and achieving a controlled blood pressure resulting in the lack of motivation to continue to attempt to lower blood pressure [52-54]. Beliefs about consequences were related to concerns about medications, clinical guidelines, and other recommendations. Providers doubted the efficacy of certain medications[55] or were reluctant to initiate aggressive blood pressure lowering medications due to possible side effects[54]. Some providers doubted whether following clinical guidelines would improve outcomes[56]. Providers raised concerns about the accuracy and representativeness of individual blood pressure readings during the visit as well as concerns regarding white coat effect when taking these

readings[50,51]. Breaking habit was another barrier, where providers reported satisfaction with their current performance[56], and reluctance to change their habits or routines to manage hypertension (clinical inertia).

Social influence barriers included the lack of coordination with colleagues as well as social pressure and conflicting roles in clinical practice settings. Providers described their reluctance to initiate treatment for 'someone else's patient' despite repeated recording of high blood pressure[50]. Poor coordination between different general practices and lack of consensus in standardization of measurements were also reported[51,53,57]. Problems with Priority setting may sometimes prevent better control of blood pressure levels. For example, other acute medical conditions competed for attention with hypertension during the consultation[56,57] making it harder to prioritize the management of hypertension. Professional identity was commonly discussed in terms of lack of trust in the evidence on which guidelines were based upon[50,56]. Providers reported that guidelines may not always be practical and do not necessarily translate to everyday[54]. One study invoked beliefs about capabilities, suggesting that providers cannot adequately perform according to the guidelines[56]. Emotional barriers, which include issues relating to stress or burn-out due to high workloads, or to anxiety/depression, and Memory and attention barriers were not reported by providers.

c. Health systems related barriers

Health system barriers were the most commonly reported barriers among providers. Barriers relating to Availability of healthcare resources included lack of consultation time[52,53] which may impair the ability to follow guidelines, resulting in poor control of blood pressure levels. The lack of space, equipment, and shortage of staff were also reported[52]. In atypical settings, disruption of treatment due to severed supply channels and inoperable pharmacies

following disasters were also reported[58]. Providers also reported difficulties in locating guidelines[50,52]. Affordability barriers included insufficient financial reimbursement or incentives to apply the recommended hypertension care[51,53,54,56,57]. None of the providers reported any barriers due to providers' acceptability of the guidelines or medications side effects.

It is important to note that provider-focused studies also reported the patient to be a barrier to managing hypertension; for example providers stated that patients were reluctant to take more medications[50] and they wanted to try changing their lifestyle before starting a medication regimen[50], thus creating a barrier for providers seeking to follow clinical guidelines. Providers also reported patients' resistance to improve their lifestyle, as well as patient stress and comorbidities[56] as barriers to the control of blood pressure levels. Since these barriers were patient-specific and are external to providers they were not coded under provider barriers.

2.3.5 Synthesis of results from qualitative studies- patient reported barriers

a. Capability barriers

Knowledge of hypertension risk factors varied by study and within study; some participants were aware that a poor diet, high salt and fat intake, and lack of physical activity might be a risk factor for hypertension[59], whereas others reported less knowledge of such risk factors[55,59]. Alcohol was addressed as risk factors for hypertension in one study only[48]. Some patients were not familiar with blood pressure readings and their meaning[60]. Gaps in understanding risk factors to and consequences of hypertension were reported[48,55,59-62]. Patients reported the need for better education regarding hypertension management and prevention[59,60,63], and suggested that, in comparison with hypertension, they receive more information regarding the management and prevention of diabetes[64]. In one study, not knowing about the existence of screening service was reported as a barrier to awareness[65]. Skills were discussed in terms of

communication between patients and providers, such as not feeling guilty about asking questions and knowing what questions to ask[66]. Lack of skills to check blood pressure at home was also discussed[60].

b. Intention barriers

Motivation barriers refer to intention to change and were reported in terms of exercise, where patients described being too lazy or too tired to exercise[67]. Lack of motivation was also reported as barrier to medication use, patients admitted to not putting enough effort or thought to taking their medication as prescribed[64]. Beliefs about consequences of taking medications were commonly discussed; participants believed that they did not need blood pressure lowering medications because they have no symptoms[66,68], they denied the diagnosis and viewed it as a reaction to stressful events and not necessarily a chronic disease[64]. Patients also expressed fear of "dependence" on blood pressure lowering medications if they continue to take them[66,69] and preferred modifying their lifestyle over taking medication[70]. Beliefs about the consequences of a healthy lifestyle were also discussed[61], for example, African American patients, reported that a hypertension diagnosis is inevitable[62]. Similarly, some patient groups displayed a fatalistic perspective suggesting that "it is all in God's hands"[63]. Therefore improving diet or exercising might not make any difference. Breaking habit barriers were mostly reported in terms of adapting to a healthier lifestyle, whereby patients mainly expressed difficulty in changing dietary habits[52,63]. Difficulties with long term commitments to using medications were also identified[55,67].

Social influence was reported as both a barrier and a facilitator of improved hypertension control. Lack of social support, mainly from the family, affected medication use[55,66] and improving lifestyle[67]. Studies also reported that having to cook for oneself differently from the

rest of the family (due to fat or sodium restrictions) was perceived as a barrier[52,61,62,67]. In terms of utilizing healthcare services and screening for hypertension, participants stated that they are more likely to attend sessions aimed at increasing health awareness and screening if they were organized in groups rather than one-on-one sessions[65]. Social pressure was also reported as a barrier to a healthier lifestyle[63,70]. Inability to prioritizing one's health was also reported as a barrier. Participants found it hard to prioritize clinic visits, diet and exercise over needs of family members[52,62,64,70,71] and work obligations[65,67,71]. Patients reported that stress and anxiety affect hypertension management; such emotions maybe related to lack of money and jobs, single parenting, and living in unsafe neighbourhoods[61,62,64,67,69]. Memory or forgetting to take one's medication played an important role in medication use[60,66]. Beliefs about capabilities were not discussed in any of the included studies.

c. Healthcare system barriers

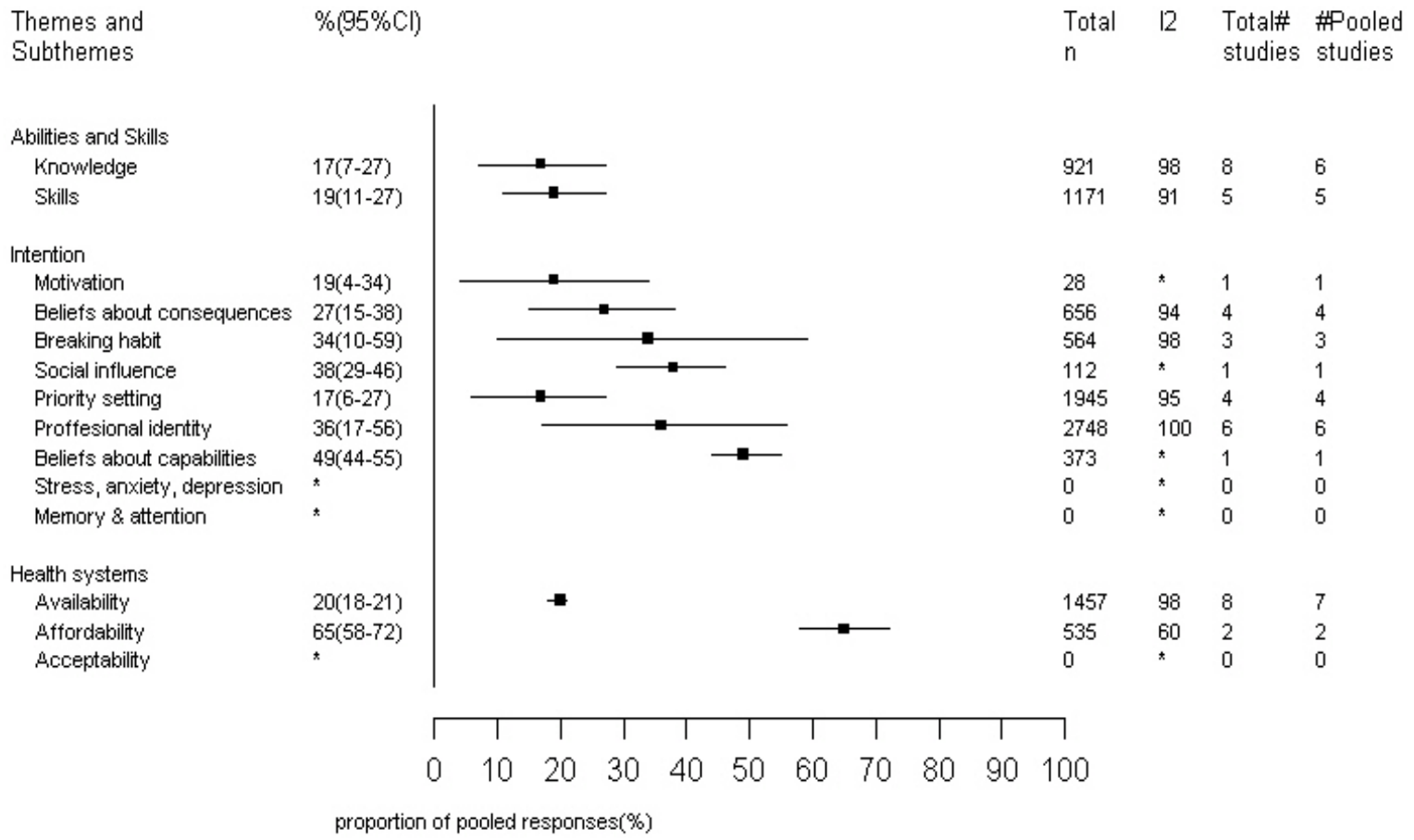
Availability barriers were relevant to improving lifestyle behaviours as well as to utilizing healthcare services. Patients reported the lack of facilities, bad weather, and safety issues as barriers to physical exercise[63,67]. Barriers to following a healthy diet included absence of nearby stores that sell healthy foods[69], limited healthy food choices when eating out[52], and lack of dietary counselling from clinicians[61]. In terms of utilizing care, patients reported absence of or inaccessible healthcare facilities[55,63]. Patients also reported difficulties with transportation to these facilities[59,60,71], inappropriate hours for screening services that conflict with working hours[65], and difficulties in getting clinic appointments[66]. Other availability barriers included the lack of interpreter services in provider offices[59], the lack of information targeting population subgroups such as African Americans on managing hypertension[62], and short duration of consultations with providers[55].

Affordability of care barriers included lack of insurance and high costs of medications[60,68,70] resulting in patients seeking care only for acute problems[55,58,59,62,71]. Cost issues also limited the ability to follow a healthy diet[61,62,67] and to exercise[63] . Acceptability of available care included poor provider-patient communications[66], patients' distrust in the services provided[63,71], lack of respect for the poor[55], and lack of attention to minorities[60,71]. Medication related barriers mainly included side effects experienced from blood pressure medications[64,66-69], as well as dosing frequency, taste, and large pill size[66].

2.3.6 Synthesis of results from quantitative studies- provider reported barriers

In terms of capability barriers, 19% (95%CI: 11-27%) of providers reported that their lack of skills contributed to suboptimal levels of blood pressure. 17% (95%CI: 7-27%) reported either directly or indirectly (by means of some measure of their knowledge) lack of knowledge regarding hypertension management as a barrier. Beliefs that one's capabilities to manage and control blood pressure levels was the most commonly reported subtheme under the Intention barriers theme (49%, 95%CI: 44-55%), although it was only assessed in one study. This was followed by social influence from peer providers (38%, 95%CI: 29-46%) and providers' disagreement with guidelines (36%, 95%CI: 17-56%). In terms of health system barriers, low salaries and lack of reimbursements were most often reported as barriers among providers (65%, 95CI: 58-72%) (Figure 2.3).

Figure 2.3: Pooled prevalence of barriers to hypertension management reported by providers (percent and 95%CI) (n=13 studies)

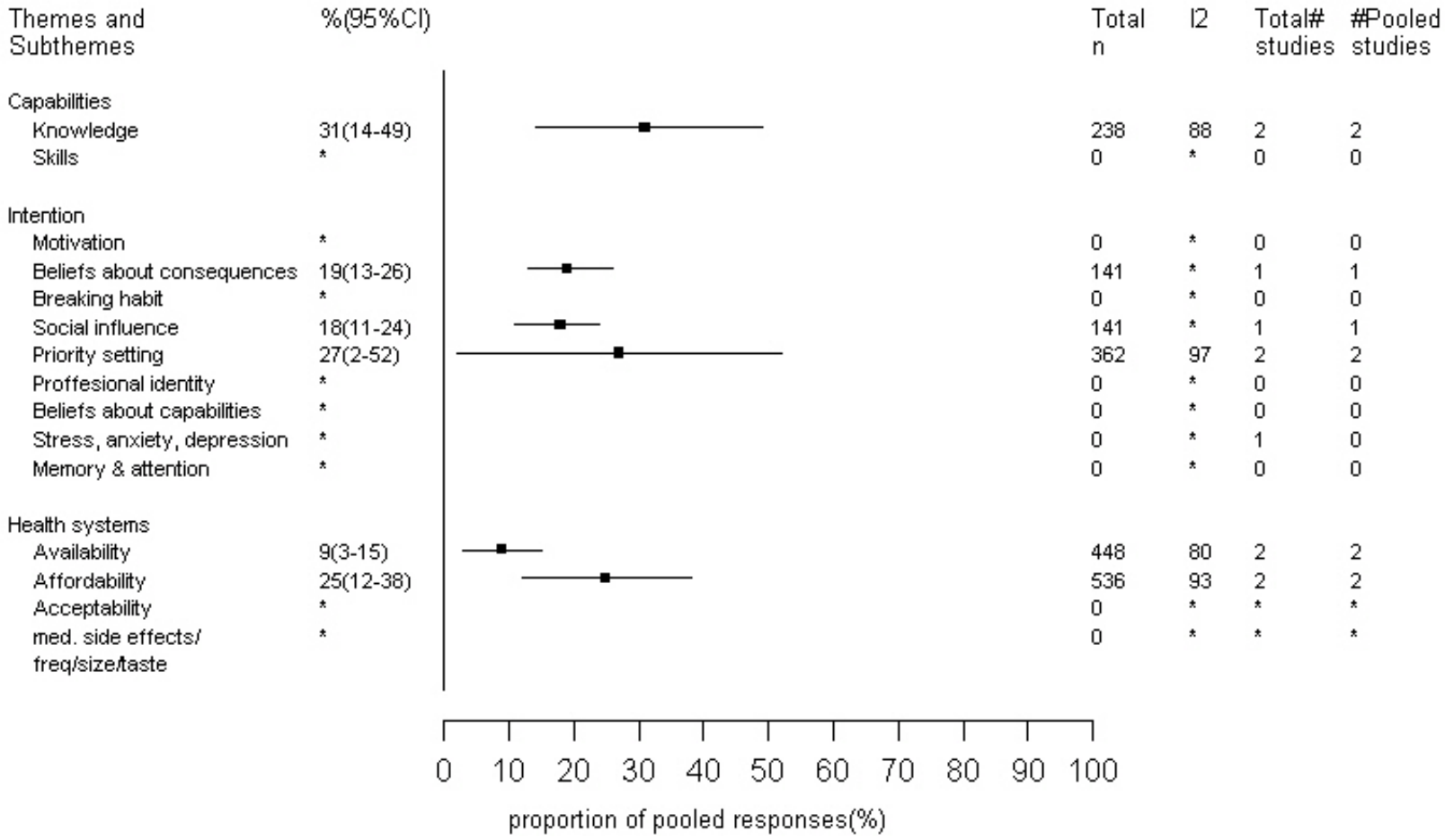


- When more than one statement was used in the same study to measure the same barrier subtheme, the median prevalence was used in the pooling of the total prevalence.
- In some cases the study assessed a barrier, but did not provide prevalence for that barrier. In those cases, the study was included in the "total # of studies" but not in the "pooled studies".
- 95% CI= 95% Confidence Interval

2.3.7 Synthesis of results from quantitative studies- patient reported barriers

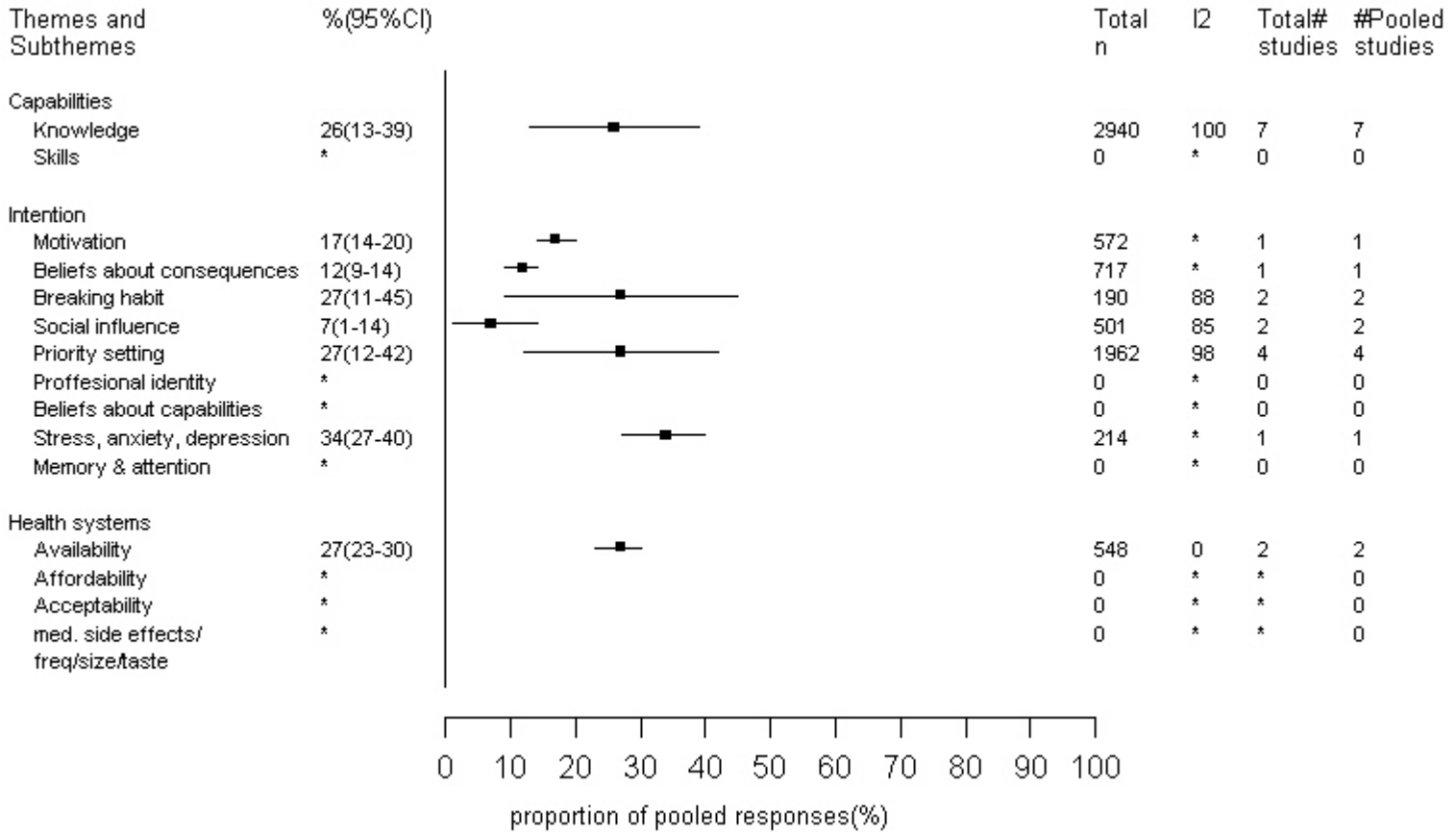
Figures 2.2 to 2.7 present the pooled prevalence of barriers reported by patients to each of the stages of hypertension management organized by subthemes of the framework of behavior change. Of the two capability subthemes, only knowledge was assessed, and was mostly reported as a barrier to adhering to blood pressure lowering medications (reported as a barrier by 46% (95%CI: 24-64%) of patients). In terms of Intention barriers, memory and attention barriers were of most important to patients in terms of medication use (55%, 95%CI: 35-75%). In terms of changing lifestyle, stress/anxiety was mostly reported (34%, 95%CI: 27-40%), but results were based on one study only. Priority setting (27%, 95%CI: 12-42%) and breaking habit (27%, 95% CI: 9-45%) were more commonly assessed and also appeared to be prevalent barriers to lifestyle change. Priority setting was again the most commonly reported barrier to hypertension screening and follow up with a provider (38%, 95%CI:32-44%). As for healthcare system barriers, availability (29%, 95%CI:17-41%) of medication and side effects (29%, 95%CI: 9-49%) were the most common barriers to medication use. For seeking hypertension screening, affordability barriers (28%, 95%CI: 25-53%) were more commonly reported than availability barriers. And finally in terms of following up with a provider, availability barriers had the highest prevalence (33%, 95%CI: 9-58%).

Figure 2.4: Pooled prevalence of barriers to hypertension awareness (detection) reported by patients (percent and 95%CI) (n=4 studies)



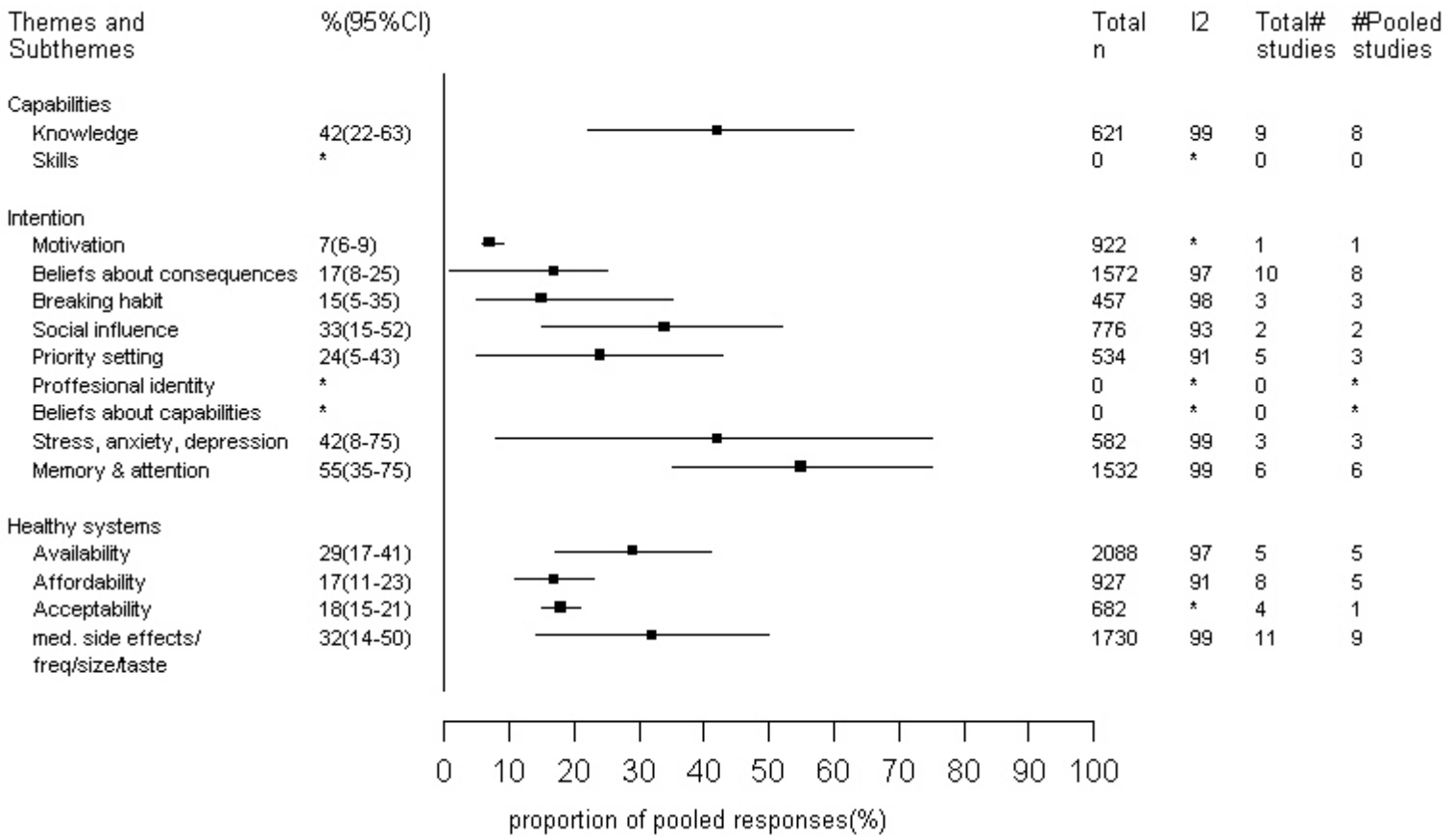
- When more than one statement was used in the same study to measure the same barrier subtheme, the median prevalence was used in the pooling of the total prevalence.
- In some cases the study assessed a barrier, but did not provide prevalence for that barrier. In those cases, the study was included in the "total # of studies" but not in the "pooled studies".
- 95% CI= 95% Confidence Interval

Figure 2.5: Pooled prevalence of barriers to lifestyle change reported by patients (percent and 95%CI) (n=4 studies)



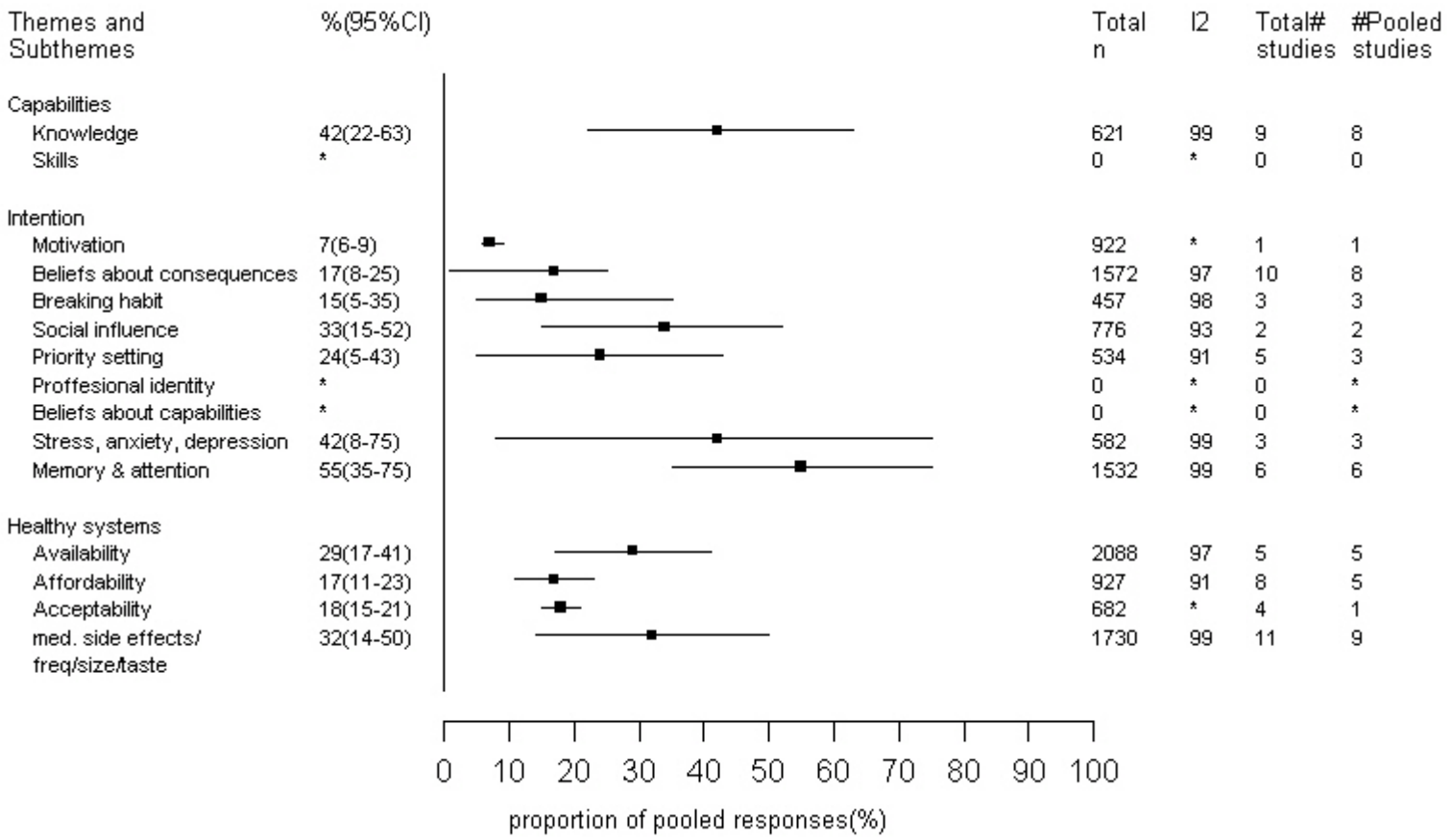
- When more than one statement was used in the same study to measure the same barrier subtheme, the median prevalence was used in the pooling of the total prevalence.
- In some cases the study assessed a barrier, but did not provide prevalence for that barrier. In those cases, the study was included in the "total # of studies" but not in the "pooled studies".
- 95% CI= 95% Confidence Interval

Figure 2.6: Pooled prevalence of barriers medication use reported by patients (percent and 95%CI) (n=15 studies)



- Medication use included measures of persistence and adherence
- When more than one statement was used in the same study to measure the same barrier subtheme, the median prevalence was used in the pooling of the total prevalence.
- In some cases the study assessed a barrier, but did not provide prevalence for that barrier. In those cases, the study was included in the "total # of studies" but not in the "pooled studies".
- 95% CI= 95% Confidence Interval

Figure 2.7: Pooled prevalence of barriers to following up with a provider reported by patients (percent and 95%CI) (n= 9 studies)



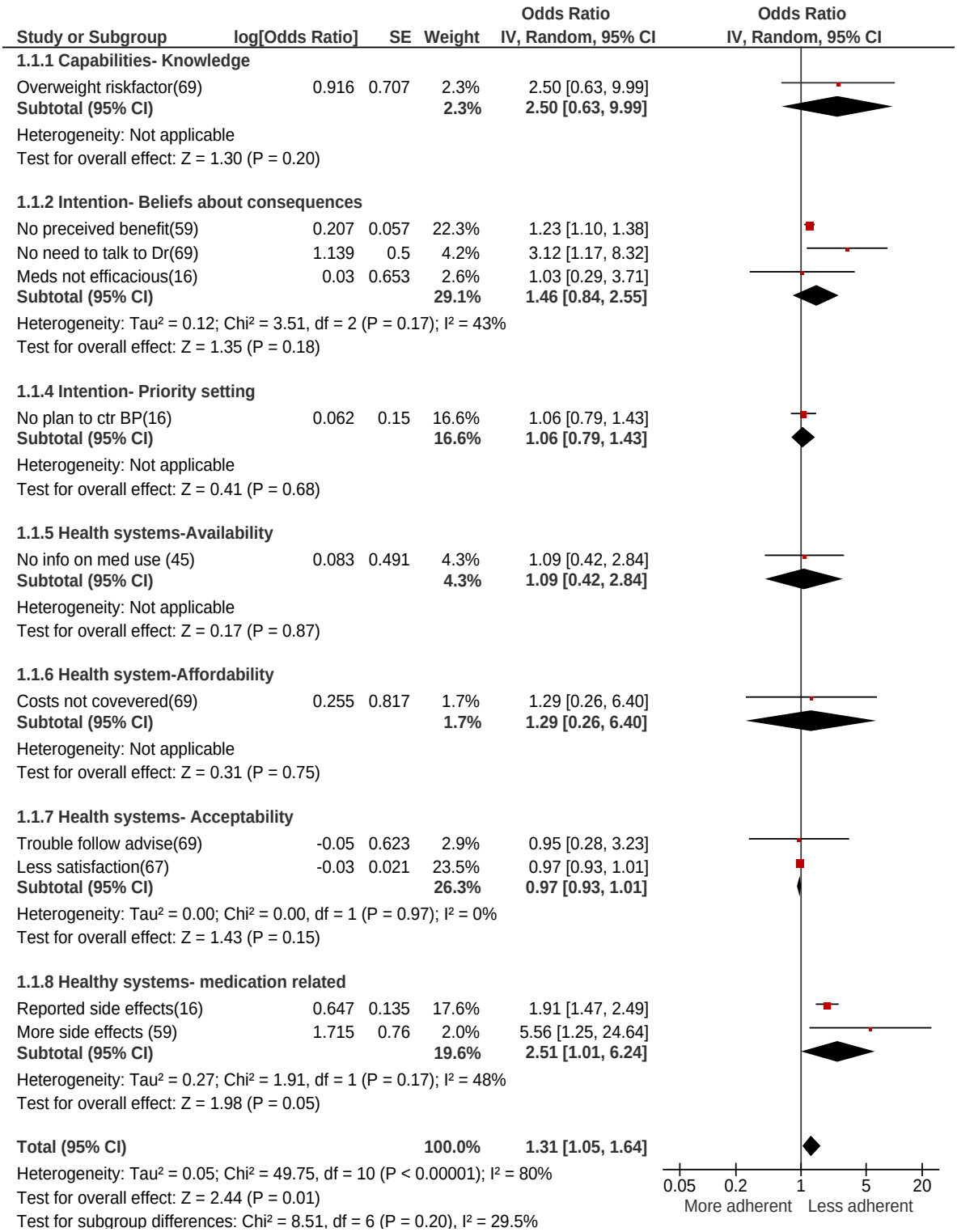
- When more than one statement was used in the same study to measure the same barrier subtheme, the median prevalence was used in the pooling of the total prevalence.
- In some cases the study assessed a barrier, but did not provide prevalence for that barrier. In those cases, the study was included in the "total # of studies" but not in the "pooled studies".
- 95% CI= 95% Confidence Interval

2.3.8 Clinical importance of barriers

None of the studies that described barriers reported by providers reported effect measures of how the barriers influence hypertension management. For patient reported barriers, it was possible to assess the association of barriers with use of blood pressure lowering medications based on five studies that provided an adjusted effect measure[46,72-75]. Overall reporting of at least one barrier was associated with an increased risk of non-use (OR: 1.27, 95%CI: 1.00- 1.58). Heterogeneity was very high (I^2= 78%), and excluding the one study that reported hazard ratios instead of odds ratios did not explain heterogeneity (OR: 1.28, 95%CI: 1.03- 1.60), 1^2= 80% (Figure 2.8).

Stratifying the barriers by subthemes of our framework explained most of this heterogeneity. Only one study reported a measure for capability barriers, suggesting a non-statistically increased risk of non-use among those with lower hypertension knowledge. Data were available on only two of the intention subthemes and suggested a non-statistically significant trend towards higher non-use among patients reporting barriers. Finally, all four health systems subthemes were assessed in terms of their effect on non-use, three of which (availability, affordability, acceptability) indicated a non-statistically significant trend towards higher non-use among patients reporting barriers. Patients reporting medication side effects had a statistically significant two fold increased risk of non-use (OR: 1.92, 95%CI: 1.47-2.49, I^2=0%).

Figure 2.8: Pooled effect of barriers to medication use (n=5)



- **Medication use included measures of persistence and adherence**

2.3.9 Comparison between barriers reported in HIC and LMIC

Provider barriers

Only three studies reported qualitative data from LMIC (India[55], Brazil[76], and South Africa[52]). Unlike barriers reported by providers from HIC, providers in LMIC reported shortages of space, equipment and staff as barriers to managing hypertension[52,55]. These barriers were not reported in HIC. These differences were also observed in data from the four quantitative studies conducted in LMIC (Nigeria[77], Russian federation[47]), Trinidad[78] and China[79]. These studies were more likely to assess and report lack of equipment, medication, time[78], and specialists[47] as barriers to care. The studies from HIC focused more on issues of availability of guidelines[80] and organization of follow up care[81].

Patient barriers

Qualitative studies reporting patient barriers in HIC focused on lack of exercise facilities and healthy food choices, patients in LMIC on the other hand, were more likely to report lack of healthcare facilities[55]. In terms of acceptability, LMIC[55] reported barriers similar to those reported by ethnic minorities in HIC[60,71].

Among quantitative studies that provided enough data on the prevalence of patient barriers, only seven were from LMIC; two from South Africa[82,83], and one from each of Malaysia[75], Egypt[84], Singapore[85], Trinidad[86], and India[87]. Only one study assessed barriers to screening[84], two studies assessed barriers to medication use[82,85], and two assessed barriers to following up with a healthcare provider[84,85].

2.4 Discussion

Among qualitative studies, health system barriers, specifically availability barriers, were most commonly discussed as barriers to hypertension management for patients and providers. For providers, availability barriers included lack of resources and time, and a high workload. For patients, availability barriers were related to distance and transportation to primary healthcare centres and pharmacies, as well as proximity of physical activity facilities and grocery stores that sell fresh fruits and vegetables. This was different from quantitative studies, where researchers focused on assessing barriers related to knowledge and professional identity/agreement with guidelines. Among studies assessing patient barriers, researchers focused on assessing intention barriers such as patients' beliefs about consequences of using medications.

The prevalence of the barriers in quantitative studies varied. This may reflect the heterogeneity of study populations and methodologies of the quantitative studies. However, with these caveats, it was possible to make some inferences on which barriers were most prevalent in terms of hypertension management. Barriers related to beliefs about capabilities were most common among providers, although on the basis of only one study. Social influence and disagreement with guidelines were also commonly reported as barriers to hypertension management by providers.

For patients, very few studies assessed barriers to awareness (detection), likely because such studies require sampling participants at the household level which is more difficult to mount compared to clinic based studies of populations with known hypertension. Knowledge barriers regarding the importance of hypertension and blood pressure screening were the most common barriers to hypertension awareness (detection). Stress, anxiety and depression barriers were most commonly reported in terms of lifestyle change, followed by breaking habit and priority setting

problems. In terms of use of blood pressure lowering medications, patients mainly reported forgetting to take their medication or were unsure if they had already taken their medication. Finally, priority setting for regularly scheduling visits to their healthcare provider was often reported by patients.

Our review suggests that knowledge barriers were commonly assessed, yet they were not always the most prevalent barrier. Similar observations can be made about intervention studies to improve blood pressure control. A Cochrane review identified 72 clinical trials, of which 30 assessed education interventions directed either at patients or providers but they were not effective at improving blood pressure control[88]. The same review reported that self-monitoring and appointment reminders may be useful but require further evaluation[88]. These programs likely affect intention barriers which, based on our review, require further study. Understanding these barriers may help develop more effective interventions for improving blood pressure control.

Previous reviews have identified possible barriers to hypertension management[36,89], yet none have done so systematically. These reviews acknowledge that different factors affect control of blood pressure levels, whether patient related or provider related. Our review systematically reviewed the literature and indicates that barriers are different for different stakeholders, settings and at different stages of hypertension management.

Knowledge translation models suggest that success is more likely if strategies are informed by and tailored to an assessment of possible barriers and facilitators[30]. This review provides a framework to help in this process. The framework also offers a means for future researchers to present their results in ways that provide greater conceptual clarity on the nature of interventions, increasing the chances of designing more effective implementation interventions and translating evidence into improved hypertension control[90].

2.5 Limitations

The methodological quality of both qualitative and quantitative studies was modest. Surveys were rarely validated and their development was usually not explicitly based on theory or previous qualitative analyses. Other reviews in the literature of barriers to medication use support these findings[91]. Further, studies mainly focused on providing prevalence of reported barriers and very few studies measured how these barriers actually might affect the control of blood pressure levels by assessing measures of association. The majority of included studies were conducted in HIC, mainly the USA, and therefore results may not be applicable to other settings with different resources and structures of the healthcare system. Although the literature acknowledges that poor blood pressure control is determined not only by barriers at the patient level but also at the provider level[36], this review indicates that research is still focused on assessing barriers at the patient level, rather looking at other stakeholders. Further, included studies focused mostly on barriers to use of blood pressure lowering medications, and very few focused on other aspects of hypertension management, such as barriers to awareness of the diagnosis, improving patients' lifestyles, and regular follow up with healthcare providers.

The I^2 statistic was high even though pooled proportions were stratified by stage of hypertension management (detection, lifestyle change, medication use and following up with providers). Studies were heterogeneous in terms of the study population, study setting, use of theory, and barrier assessment methods and tools. We pooled prevalence of each barrier primarily for illustration, and the pooled results should therefore be interpreted with caution. Considerable heterogeneity has been observed in previous studies that used similar methods of pooling proportions of reported barriers, reflecting the nature of the underlying research[45].

A more systematic way of measuring barriers, using standardized and validated methods, is necessary. Very few studies actually assessed the three main themes of the proposed theoretical framework, and none incorporated aspects from all 12 subthemes. Using a theoretical framework to measure all the barriers, with the same methodology, might provide a more reliable way to compare the prevalence and clinical importance of these barriers between different settings.

2.6 Conclusions

To improve the management of hypertension, interventions should overcome capability barriers, intention barriers, and health system barriers. These barriers should be targeted at the provider and the patient levels. More methodologically rigorous studies that consider all the different barriers and that include data from LMIC are required in order to improve our confidence in determining the most important modifiable barriers, to compare them among regions and populations, and to develop interventions tailored to different settings and types of patients to improve hypertension management.

The small number of studies from LMIC in this review indicated that the lack of availability and affordability of medications was commonly reported among patients and providers in these settings. However, how these barriers influence use of medications could not be assessed due to the small number of studies from these settings and due to the lack of consistent definitions and methods to measure these terms. The next chapter presents methods that can be used to systematically measure these barriers in order to investigate how they influence medication use.

Chapter 3

Factors associated with the rates of use of cardiovascular disease medications

3.1 Introduction

Treatment of chronic illnesses commonly includes the long-term use of medications. Although medications, when used appropriately, are effective in improving outcomes in those with specific conditions, epidemiological studies frequently report that their use is suboptimal[13,33]. Suboptimal use of chronic disease medications may result in limited clinical benefits[92,93], which in turn can lead to increased mortality[94] and healthcare costs[95,96].

The use of medications proven to be effective in those with known cardiovascular disease (CVD) is low. This is worse in low income countries (LIC) compared to high income countries

(HIC). For example, the Prospective Urban Rural Epidemiology study (PURE) involving 17 countries, showed that only 3% of patients known to have CVD in LIC reported using a statin, compared to 4% in lower middle income countries (LMIC), 18% in upper middle income countries (UMIC), and 67% in HIC[13]. Similar differences have been documented in the use of other medications recommended for patients with CVD in the PURE study[13,33].

The differences in rates of medication use between high, middle, and low income countries may be partly due to the lower availability and affordability of these medications in poorer countries, which in turn may reflect differences in the healthcare systems between countries. For example, patients in some HIC may be covered by some form of health insurance that provides coverage for part or all of their medication costs, whereas patients in many LIC are required to pay directly (i.e. out-of-pocket) to cover the costs of the medications[97].

There is no widely accepted definition of availability and affordability of medications in the literature. Additionally, methods of measuring affordability of medications reported in studies have not been consistent. The literature on this topic is mostly based on the World Health Organization/Health Action International (WHO/HAI) project, which currently has the largest database on costs and availability of medications collected systematically from a wide range of countries representing HIC, UMIC, LMIC, and LIC settings. This chapter describes how the WHO/HAI measures medication availability and affordability. The chapter also describes two additional methods that have been developed in the literature to measure medication affordability. Limitations to these methods are described.

The methods used in the literature account only for the availability and affordability of the medications. Recording the availability of a medication does not account for other factors which may affect their use, such as the availability of a healthcare provider to examine the

patient and prescribe medications. The WHO/HAI methodology of documenting if particular medications are available, does so for pharmacies that are within one day's walk from the community, however, whether the hours of operation of the pharmacy are convenient to patients or not and whether patients are able to make this walk or have other means of transportation is not accounted for.

Similarly, the methods of measuring affordability do not include costs of the healthcare provider's fees to write a prescription, costs for diagnostic tests, transportation costs and costs due to taking time off work. This is because these items are different in nature from medications, and they have to be measured in a different manner and so are generally not considered when the affordability of medications is described. For example, fees to the healthcare provider may not be made as frequently as purchasing the medications. Visits to a physician may be less frequent than renewals of prescriptions and in some countries, medications may be "self-prescribed" or continued by the pharmacist once they have been initiated. Additionally, these costs may be harder to capture in population studies as they may greatly vary by patient, they may even vary with time for the same patient. However, even if the costs of these items are not accounted for, it is still important to consider these items when interpreting the results of how available and how affordable medications are. Physician costs, and costs related to diagnostic tests or those related to transportation have not been collected in the PURE study and will not be considered further in this thesis.

This chapter also discusses other factors (e.g. patient characteristics, years since CVD diagnosis) that could potentially influence medication use. These factors will be adjusted for in the remaining analyses of the thesis to investigate the association between the availability and affordability of medications and their use in the PURE study.

3.2 Medication availability

Clinical guidelines recommend the use of four medications for the prevention of secondary CVD (an Angiotensin Converting Enzyme Inhibitor (ACE-inhibitor) or an Angiotensin II Receptor Blockers (ARB), a beta-blocker, a statin, and aspirin) [5-10]. Collectively, these medications could potentially reduce the risk of recurrent events and death by about 75%[98]. It is therefore important to assess the availability of all these medications in a given community. The WHO/Health Action International (HAI) project was developed to collect data on 30 core medications in a standardized manner from all WHO regions[97]. The project defined medication availability as the proportion of pharmacies where the medication was physically present in the pharmacy on the day of data collection[97]. Results from 36 countries indicate that the lowest brand generics of CVD medications (defined by the WHO/HAI as atenolol, captopril, hydrochlorothiazide, losartan, and nifedipine) were available in 26% of the public sector, and 57% of the private sector pharmacies from 36 high, middle, and low income countries included in the survey. In both sectors, CVD medications were more commonly available in HIC than in LIC[99].

This method only refers to availability on the day of data collection and does not provide information on how continuous the supply of medications is over time. Collecting data on the stored quantity of the available medications can give an indication of how long the supply will last. However, this information was not collected in the WHO/HAI project.

3.3 Medication affordability

Affordability of medications partly depends on the financing structure of the healthcare system and the coverage (e.g., full or partial) for the prescribed medications. Estimates suggest that in LIC, up to 90% of healthcare costs, (including costs of medications), may be directly

incurred by patients[100]. It is therefore important to investigate how affordable CVD medications are based on their purchasing price to the patient.

The available literature defining affordability of medications has been adapted from approaches to describe estimates of rent for affordable housing. The literature on housing defines affordability in terms of how much the household has to forgo in order to obtain a certain commodity. A commodity is not affordable if its price imposes an unreasonable burden on the household. An unreasonable burden may result in pushing the household below some poverty standard[101]. To operationalize the concept of affordability, three items are required: the cost of the commodity, in this case, the medications recommended for CVD; the household income; and a threshold for an unreasonable burden[100].

Given that clinical guidelines recommend the use of four medications for the prevention of secondary CVD, affordability should be calculated in terms of costs of a basket of these medications. The dose and frequency should also reflect the way the medications are meant to be used when calculating how affordable the medications are.

Information on household income can be obtained either by directly asking a knowledgeable household member about the total income earned by all household members or by estimating it based on total household expenditures. Households may prioritize subsistence needs over purchasing medications, and therefore the literature recommends subtracting expenditures on subsistence needs from the households' income before evaluating how affordable medications are[102,103]. The amount of income remaining after subsistence needs is referred to as the households' capacity-to-pay[102]. Capacity-to-pay has been generally used as the household's budget available for purchasing specific commodities (and in our case recommended medications) when calculating their affordability.[102].

Studies have used expenditure on food to estimate subsistence needs because of the assumption that food is a basic need that every household has to spend part of its income on to survive[102]. However, subsistence needs may also include expenditures on shelter, education, clothing, and other items that the household deems necessary. Similarly, a household might prioritize healthcare expenditures of diseases other than CVD or healthcare needs of another household member over expenditures on CVD medications. Subsistence needs will vary by household, and by setting, and should be carefully accounted for when calculating a household's capacity-to-pay. These expenditures have not been commonly included when calculating subsistence needs to measure affordability. This might be because determining whether or not each of these items is considered to be truly a subsistence need, depends on the setting and the household. Additionally it is difficult to obtain such information on each of these household expenditures in large population surveys involving many different countries. If these are not accounted for, affordability of medications will be underestimated for households that deem such expenditures more essential than the medications recommended for CVD.

Niens et al (2012) proposed two ways to measure an unreasonable economic burden[104]: 1. By calculating the proportion of households that fall below a poverty threshold after subtracting the cost of the medications from capacity-to-pay, referred to as the impoverishment payment approach. 2. By calculating the ratio of medication costs to the household's capacity-to-pay, referred to as the catastrophic payment approach. These methods are described and examples of how they have been used in the literature are presented.

The impoverishment approach is based on the assumption that medications are not affordable if purchasing them pushes the household into poverty[104]. The threshold in this approach is set in reference to a defined poverty line that is appropriate to the country. A

household is poor if its income is not sufficient to secure basic needs required for survival. The income required to secure these needs is referred to as the poverty line. Households with an income lower than the poverty line are considered poor. There are different methods of identifying the basic needs required for survival (i.e. the poverty line), the methods usually vary by country and therefore national poverty lines cannot be compared between countries. The literature measuring affordability of medications using the impoverishment approaches uses an international poverty line developed by the World Bank as an attempt to facilitate such comparisons[103,105]. This international poverty line is arbitrarily set at $2.00 international dollars a day and is based on 2008 purchasing power parity prices. This value is the median national poverty line of all middle and low income countries in 2008. Poverty lines of $1.00 and $1.25 international dollars per day have also been used in the literature[100].

Calculating the prevalence of households who cannot afford medications recommended for CVD involves identifying households that are already poor, using the international poverty line (for example $2 international dollars per day) and identifying the additional number or proportion of households in a community or country that would become poor (or are pushed into poverty) if they were to purchase these medications. Adding the two groups together provides an estimate of the households that are unable to afford the medications. This method focuses on the poorer portion of society because the closer a household is to the poverty line, the more likely it is that expenditures on medications will move the household below the poverty line[104].

Data from the WHO/HAI project and the Household Final Consumption Expenditure (HHFCE) from the World Bank on 16 low and middle income countries indicated that purchasing medications for CVD could lead to the impoverishment of large proportions of households. For example, purchasing a month's standard treatment of atenolol (50mg per day for

30 days) increased the proportion of impoverished households in Pakistan (using a poverty level of $2 international dollars per day) from 8% to 12%[105]. These results indicate that in Pakistan, 8% of the households are already too poor (ie. live under $2 international dollars per day) to afford a month's standard treatment of atenolol. An additional 4% of the households would become poor if they were to purchase a months' standard treatment of atenolol. By definition these 4% also cannot afford the medications. Therefore 12% of the households in Pakistan would be unable to afford a months' standard treatment of atenolol.

A major limitation to this approach is the choice of a threshold to define poverty. The international poverty line defined by the World Bank is based on data from LIC and MIC and would be inappropriate to assess affordability of medications in HIC, where $2 international dollars per day is well below the poverty line. Additionally, the impoverishment approach ignores patients who are not pushed below the poverty line, but who nonetheless experience a substantial income drop if they were to purchase the medications[103]. These patients may consider the medications to be unaffordable even if the remaining household income is above the poverty line. This approach may therefore underestimate the proportion of patients who are unable to afford the medications.

The catastrophic payment approach indicates that CVD medications are not affordable if purchasing them results in an unreasonable burden to the household[104]. The idea is that if a household spends a large portion of its income on medications, it will have to reduce consumption on other goods and services[103]. This method has been previously used to assess the affordability of total healthcare expenditures and considers total health expenditure payments to be "catastrophic" if they exceed 40% of households' capacity-to-pay[102,106]. Costs of medications can take up to 50% of total healthcare expenditures, especially in low and middle income

countries[97]. Niens et al. (2012), therefore, suggests a threshold equivalent to half of that used for total health expenditures, when assessing the affordability of medications (i.e., 20% of capacity-to-pay).[104]

The catastrophic payment approach has not been used in the literature to assess affordability of medications for the secondary prevention of CVD. Analysis of the monthly cost of one of the common diabetes medications, glibenclamide, indicated that when a threshold of 20% or higher is considered to be unaffordable, 66% of the population in Indonesia cannot afford this medication. In India, the proportion that cannot afford glibenclamide using this approach would be 79%[100].

The choice of the threshold to determine when the medications are affordable is arbitrary and studies have used different thresholds. Comparisons of medication affordability across different studies are therefore not possible[103]. Additionally, it is not clear if any particular threshold chosen over or underestimates the prevalence of households who can afford the medications. To overcome this limitation, previous studies conducted sensitivity analyses using a range of thresholds when describing the affordability of medications.

Other methods of measuring affordability: The WHO/HAI project used a third approach to evaluate medication affordability. This method expresses the cost of the medications in terms of the number of days the lowest paid government unskilled worker (LPGW) has to work to be able to pay for the monthly standard course of treatment[104]. An analysis of data from six middle and low income countries indicated that affordability of medications varied widely between countries. In Pakistan, for example, the monthly cost of the four recommended CVD medications (aspirin, atenolol, statin, ACE-inhibitor) approximates 4.7 day's wage compared to 18.4 day's wage in Malawi[107].

This method uses a standard LPGW for each country and does not require data collection of household income, and is a more feasible approach to calculating affordability, when data at the household level are not available. However, the authors acknowledge that this method tends to overestimate affordability because a large proportion of the population earns less than the LPGW. Additionally the unemployed do not earn any wages [107]. Further, this method does not provide a cutoff for the number of days of LPGW wage that makes a medicine unaffordable and therefore it is not possible to identify the households that can actually afford these mediations[104].

3.4 Other factors that influence medication use

Medication use can be influenced by factors other than the availability and affordability of medications. Investigating how these two factors affect use should therefore account for these other factors. These factors may include factors related to the healthcare system, or they may include other factors related to the patient:

3.4.1 Healthcare system factors

The availability and affordability of CVD medications represent one of the building blocks of a well- functioning healthcare system. The WHO suggests additional building blocks to identify a well-functioning healthcare system: human resources which includes trained healthcare providers who are capable of properly diagnosing and prescribing medications; physical resources and infrastructure including healthcare facilities and diagnostic equipment; information and research that can deliver statistics on services and medications that are needed; a sustainable financing structure; and good leadership and governance[108]. A well-functioning healthcare system requires the integration and alignment of all of these building blocks[109]. For example, the availability and affordability of medications are only relevant if human resources include knowledgeable healthcare providers who can prescribe these medications and only if

these providers and the pharmacy are within reach to the patient. Further, the continuous supply of affordable medications at a pharmacy depends on the health information system that can forecast the type and quality of medications required within the healthcare system. Financing and leadership and governance are also important for effective oversight and provision of appropriate regulations within the healthcare system[109].

3.4.2 Non-healthcare system factors

The medication adherence model, developed by the WHO, suggests that in addition to the healthcare system, there are other factors that also affect medication use[110]. The WHO model has been developed specifically for chronic diseases requiring lifetime medication use. This model suggests that patient factors such as patient characteristics and behaviors, social and economic factors, comorbidities, years since CVD diagnosis, and side effects of medications are factors that influence medication use[110]. Additionally, this model acknowledges that healthcare system factors, including access to medications, also influence medication use[110]. The next section describes how each of these factors may influence the use of CVD medications.

Patient characteristics

Patient characteristics are important factors that may influence medication use. For example, patients who did not refill their prescriptions in the Medicare Currency Beneficiaries Survey tended to be younger, female, and nonwhite[111]. Data on discontinuation or non-use of medications in LIC are limited. Results from the Prospective Urban Rural Epidemiology (PURE) study, which included high, middle, and low income countries indicated that patients with CVD who were younger (less than 60 years old), female, more educated, and current smokers, were less likely to use CVD medications[13].

Patient behaviors

Suboptimal medication use may be further attributed to patient behaviors and attitudes towards using medications. These behaviors have been described in the systematic review in chapter 2 using a framework of behavior change. It identified behavioral barriers that impaired patients from using blood pressure lowering medications. Clinical guidelines may recommend the use of CVD medications even in the absence of clinical symptoms, and therefore patient motivation and attitudes are especially important for the use of these medications[112]. Lack of motivation to take the medication may be due to lack of knowledge or lack of belief in the efficacy of medication; it might also be due to social and cultural beliefs discouraging patients from taking medications long term when they are feeling well. Social support from family members has been linked to higher rates of medication use[113], whereas depression, anxiety and stress are associated with lower rates of medication use[114].

Socioeconomic factors

Poverty, low education levels, unemployment, unstable living conditions, and insurance status can also influence the use of medications. Some studies suggest lower medication use among patients with low socioeconomic, although results have been inconsistent and may depend on the severity of disease and whether or not a particular health system covers the costs of medication. In Ontario, Canada, a study of 38,945 stroke patients showed no effect of socioeconomic status (measured by median neighborhood income) on medication use, though socioeconomic status was related to the rates of use of other health services and mortality[115]. These results can be explained by the financial protection provided by the healthcare system in Ontario, Canada. Results might differ in other countries where such financial protection is not available.

Comorbidities

The influence of comorbidities on medication use is more complex and is especially important among patients with CVD who also tend to suffer from other conditions which require medications such as diabetes, hypertension, and hypercholesterolemia. Given the older age of this population, patients also tend to suffer from other conditions such as arthritis and depression. Patients with comorbidities may have higher rates of medication use[116] if these comorbidities lead to more contact with healthcare providers. Further, patients with CVD and other comorbidities tend to have more severe symptoms which may increase their likelihood of taking their medications. On the other hand, comorbidities may force patients to choose between taking certain medications, as costs may become a limiting factor. For example, they may prefer to use the medications that are essential for symptom relief over those for asymptomatic conditions or prevention. Depression, which is another common comorbidity among patients with CVD, is associated with decreased overall medication use[114].

Years since CVD diagnosis

As the number of years since a myocardial Infarction (MI) or stroke increases, the risk of a subsequent event decreases[117]. Therefore, the interval after an event may be used as a surrogate for the severity of the prognosis of a given patient. Patients with CVD show lower rates of medication use as the number of years since their event increases[116]. A retrospective observational study of patients hospitalized for an MI in the United States indicated that the discontinuation rates of ACE-inhibitors were high: 7% stopped within 1 month, 22% at 6 months, 32% at 1 year and 50% at 2 years. The study showed similar discontinuation rates for beta-blockers[118]. This is likely because patients with CVD experience fewer symptoms with time than they did earlier when the event first took place. Patients who recently had an event are also

more likely to be in contact with a healthcare provider and may thus be more likely to use medications compared to patients who had an event more than one year ago. Further, the patient's perception of "vulnerability" may decrease with increasing interval since an event such as a myocardial infarction (MI).

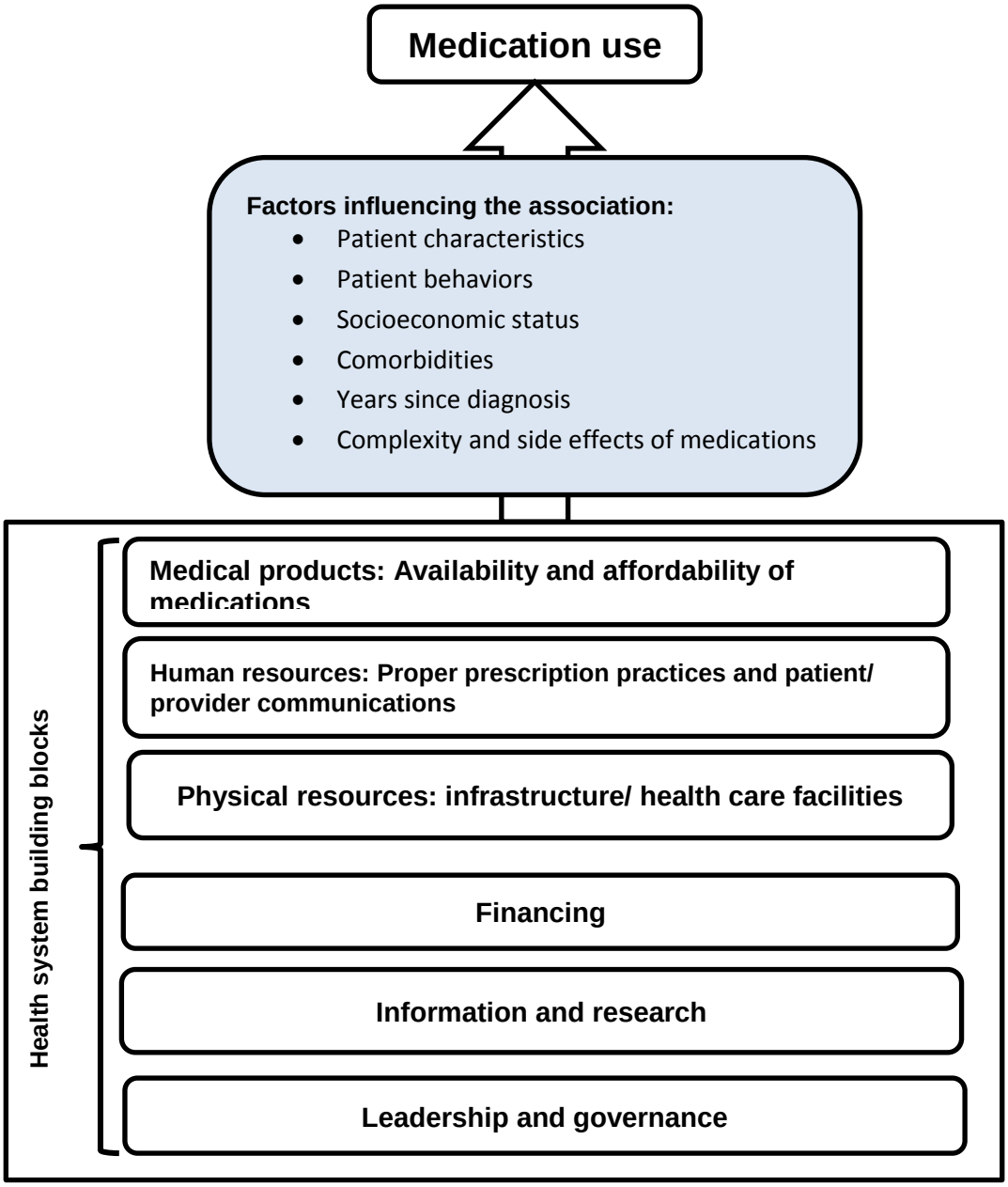
Side effects of medications

Patients often report side effects of medications as the main reason for not using the prescribed medications[119]. Patients' perceptions of side effects of medications contribute significantly to decisions regarding continuing to use medications[120].

3.5 Understanding how availability and affordability affect medication use

In examining the association of availability or affordability to the use of medications, one needs to consider additional factors such as the ones described above. Figure 3.1suggests that the availability and affordability of medications affect medication use. The figure also indicates that certain factors could influence this association. Additionally the figure indicates that the availability and affordability of medications depends on other building blocks of the healthcare system. Availability and affordability of healthcare services and knowledgeable healthcare providers who can prescribe the proper medications should be in place in order for the medications to be used. Appropriate financing, leadership and governance, and a health information system are additional building blocks that can facilitate the availability and affordability of medications[121].

Figure 3.1: Theoretical framework of factors associated with medication use, adapted from the WHO model of medication use and the health system's building blocks model



3.6 Conclusions

A number of factors need to be considered in understanding influences on the use of medications among patients with CVD. This chapter has summarized the approaches used to measuring how available or how affordable medications are. The limited literature on this topic has found low availability and affordability of medications in low and middle income countries regardless of the methods used. The chapter also describes other factors that should be considered in order to understand reasons for low rates of medication use.

Two limitations in the literature on the availability and affordability of medications are noteworthy. First, comparisons across high, middle, and low income countries were limited due to the lack of consistency in the methods used to measure these factors. Second, none of the studies investigated the association between availability and affordability of medications and their use by patients with CVD, because the existing studies collected only pharmacy level data and did not have information on rates of medication use among the patients attending these pharmacies. The Prospective Urban Rural Epidemiology (PURE) Study collected this information at the community (availability and costs of medications), household (income), and individual (medication use) levels. Chapters 4 and 5 provide more details on the aims and methods of the PURE study and addresses how certain variables collected in the study can be used to document availability and affordability of CVD medications.

Chapter 6 presents the analyses of the PURE data relating availability and affordability of medications to their use. The costs and availability of the medications are presented for each medication separately and also for a basket of the four medications recommended for the secondary prevention of CVD accounting for the appropriate dose and frequency per day. Medications are considered to be available if they are all present at the pharmacy on the day of

data collection. Medications are considered to be affordable if their costs do not result in an unreasonable burden to the household (set at >20% of the household's income after subtracting household expenditures on food). This approach uses actual household income rather than the lowest wage set by the government and may therefore provide a closer estimate to how affordable medications for CVD really are. This approach has been more commonly used in the literature on total healthcare expenditures compared to the impoverishment approach, and is therefore easier to interpret. Additionally, the impoverishment approach requires identifying one poverty line for all countries involved in the analyses which is only possible in countries with similar country incomes, whereas the PURE study includes data from HIC, MIC, and LIC.

Chapter 4

Overview and goals of the PURE study

4.1 Introduction

The remaining chapters of this thesis use data from the Prospective Urban Rural Epidemiology (PURE) study to investigate whether the availability and affordability of medications affects use among patients with cardiovascular disease (CVD) in high, middle and low income countries. The methods, rationale, and characteristics of the baseline PURE cohort have been previously published[13,122-124]. This chapter describes the aims, sampling methods, and data collection of the study as they pertain to the analyses in the chapters that follow.

4.2 Study goals

The Prospective Urban Rural Epidemiology (PURE) study is a large scale study that initially enrolled 155,875 people between 35 and 70 years of age from 628 communities in 17 high, middle and low income countries on five continents[13]. It has since expanded to four additional countries and is targeting a total of about 200,000 individuals. The aim is to examine the relationship of societal influences on health behaviors, cardiovascular risk factors, and the incidence of cardiovascular and other chronic diseases[122]. At baseline, data collection included medical history, health behaviors (tobacco and alcohol use, physical activity and dietary intake), blood and urine collection and storage for future analyses, electrocardiogram, blood pressure and anthropometric measures. In addition, detailed information was collected on the built environment, nutrition and associated food policy, and tobacco environment[122]. The study expects to follow participants for up to 10 years (current median follow up is 4.0 years) for incident events.

4.3 Sample selection

The selection of countries included in the PURE study reflected a balance between including a heterogeneous group of countries, in terms of country income levels and social and economic circumstances, and the feasibility of collecting high quality data and achieving long-term follow[122]. Initial recruitment included three high income countries (HIC): Sweden, Canada, United Arab Emirates (UAE); seven upper middle income countries (UMIC): Poland, Chile, Turkey, Brazil, Malaysia, South Africa, Argentina; three lower middle income countries (LMIC): Colombia, Iran, and China; and four lower income countries (LIC): India, Pakistan, Bangladesh, and Zimbabwe. The classification of countries by economic groups is based on the World Bank classification at the beginning of the study (2006), which has been retained in all

analyses. The World Bank classifies countries based on different cutoff points of per capita Gross National Income (GNI). GNI is the total domestic and foreign output claimed by residents of a country, consisting of gross domestic product (GDP) plus incomes earned by foreign residents, minus income earned in the domestic economy by nonresidents[125].

The study has expanded to four more countries: Saudi Arabia- classified as HIC, Philippines and occupied Palestinian territory (oPt)- classified as LMIC, and Tanzania- classified as LIC. Data collection from the oPt has been completed and will be included in the analyses of the data for this thesis in the subsequent chapters. Data collection from the other new countries has not been completed, and therefore they are not included in the analyses.

Within each country, a number of communities were selected to represent urban and rural locations within the country. The community was defined as "a group of people who have common characteristics and reside in a defined geographic area" [122]. The selection of communities varied by country and reflected a balance between heterogeneity in social and economic circumstances balanced against the capacity of local investigators to carry out the study[122].

Within each community, the selection of households aimed for a sample that is representative of adults aged between 35 and 70 years intending to reside at the same address for the next four years so that long-term follow up is feasible. Methods of approaching households varied by country, for example, households in Canada were contacted by mail followed by telephone inviting eligible members of the households to a central clinic. In rural India and China households were approached door-to-door and the data were collected during household visits[13]. In all countries, at least three attempts were made to contact household members[122]. All household members between 35 and 70 years of age, who provided written informed consent,

were enrolled in the study. If a household refused to participate, a non-respondent form with basic demographic characteristics and risk factors was completed, when possible. Approvals for this study were obtained from the appropriate institutional ethics committee of each country[122].

4.4 Data collection

A comprehensive operations manual was developed and used to ensure standardized data collection. The operations manual included detailed instructions on the study objectives, sampling frame, recruitment methods, and data collection methods. The manual also included a definition of each question in the data collection forms to ensure that interviewers in different countries were consistently asking the same questions. A training session was conducted for key staff in each country by a project office staff person ensuring the same training in all countries using centrally created manuals and training videos. Collected data were entered into a customized database programmed with range and consistency checks and transmitted electronically to the central project office[122].

The study collected data at the individual, household, and community levels:

4.4.1 Individual level

Individual level information included demographic characteristics, history of CVD, risk factors for CVD and other diseases, and lifestyle behaviors. Data were self-reported by each participant. Self-reported history of CVD was centrally adjudicated in a sample of 455 reported events. Verification with medical or hospital records indicated a confirmation rate of 89%[13]. The names of all medications taken by each participant were recorded. Medication use was defined as taking the medication at least once per week in the past month. To ensure reliable data collection, interviewers asked to see the medications during home visits. If data collection was conducted during a clinic visit, participants were asked to bring their medications to the clinic so that they

could be reviwed[13]. The medications were coded centrally by trained project office staff from generic formulation or originator brand names into broad groups of medications (e.g. Aten and Betacard were coded as Atenolol; Lipitor was coded as Atorvastatin).

4.4.2 Household level

Household level information was collected from one knowledgeable member of the household. It included total monthly household income and expenditures on food, collected in the local currency. A checklist of household amenities and living conditions was also administered to assess household wealth.

4.4.3 Community level

The Environmental Profile of Community Health (EPOCH) instrument was used to collect community level data in each of the PURE countries. This instrument was administered only in communities that included at least 30 PURE participants. EPOCH is an audit tool that was developed for the PURE study to directly observe and systematically record physical aspects of the environment that were expected to influence CVD risk factors. The main aim was to create an instrument that was applicable in diverse cultural, socio-economic and regional (urban/rural) settings[124].

Trained researchers directly observed and systematically recorded the physical aspects of the environment using the EPOCH instrument. The audit included visiting a number of health facilities in the community, including a pharmacy to collect information on availability and costs of CVD and other medications[124]. To ensure a standardized method of selecting the pharmacy, researchers were instructed to select the pharmacy closest to the centre of the community.

The audit included collecting information on the availability and costs of CVD and other medications from the pharmacy. The EPOCH instrument included a list of predefined medications for CVD and other diseases. The selection of the CVD medications audited was based on proven effectiveness in preventing secondary events and death[7] and included ACE-inhibitors (captopril 20 mg, enalapril 5 mg, ramipril 5mg) beta-blockers (metoprolol 25 mg, atenolol 50 mg), statins (simvastatin 20 mg, atorvastatin 40 mg), and aspirin (aspirin 100 mg or nearest available dose). The types and doses of each recommended medication are not comprehensive but include the most common types and doses used in the PURE countries based on discussions with local investigators.

One pharmacy was visited in each community and information was collected on whether the medication was available at the time. Information on the total cost of the box (retail purchase price to the patient) and the number of tablets per box were also recorded. If the medication was available in a dose different from the one specified in the EPOCH instrument, the available dose was noted along with its cost and the number of tablets per box. If more than one medication type was available at the pharmacy (eg. Aceten and Angiopril both of which are brands of Captopril), information was collected on the most commonly used medication based on discussions with the pharmacy personnel.

4.5 The PURE cohort

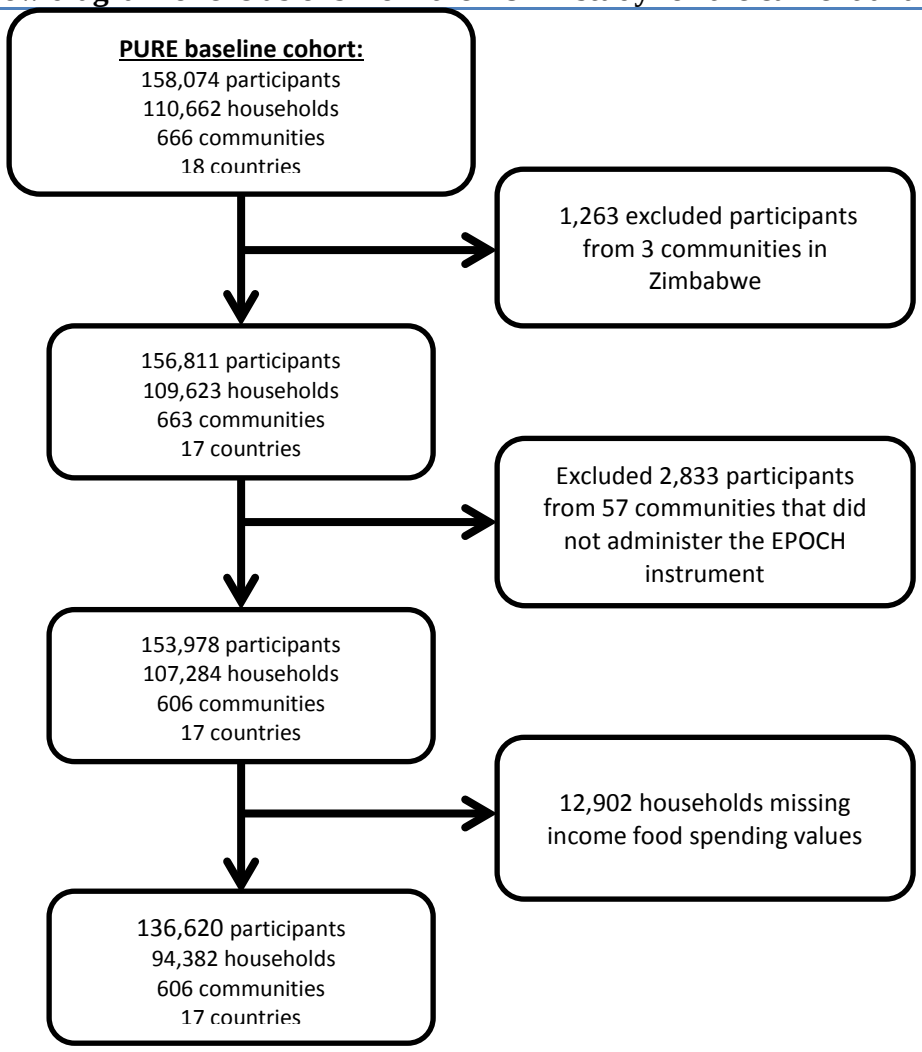
A total of 197,332 individuals were eligible to participate in the PURE study during the initial recruitment from the 17 countries. Of those eligible, 22% did not agree to participate in the study resulting in a sample size of 155,875 PURE participants from 628 communities. Measured baseline characteristics were similar across participants and non-participants[13]. Analyses for this

thesis are based on recruitment by December, 2013 which included data from one additional LMIC country; the occupied Palestinian territory (oPt).

The addition of data from the oPt as well as some additions in the recruitment from the original 17 countries increased the size of the baseline cohort to 158,074 participants from 667 communities representing 18 countries. Figure 4.1 presents a flow diagram of exclusions from the baseline cohort for the purposes of this thesis. Data collection in Zimbabwe coincided with the collapse of the country's economy resulting in the devaluation of the Zimbabwean dollar. Zimbabwe was excluded from the current analyses because inflation rates for that period are not available. The EPOCH instrument was only administered in communities that had at least 30 PURE participants and therefore an additional 2,833 participants from 57 communities where also excluded from the analyses. Finally, 17,358 participants (12,902 households) did not provide data on household income or on food expenditures. The final sample for the remaining analyses of this thesis included 136,620 participants (94,382 households) from 606 communities in 17 countries (Table 4.1).

The remaining chapters use data from the PURE study to address the aims of this thesis: document the availability and how affordability of medications recommended for CVD are, in high, middle, and low income countries, and investigate whether availability and affordability affect medication use.

Figure 4.1: Flow diagram of exclusions from the PURE study for the current analyses



- **57 communities were not eligible to administer the EPOCH instrument because less than 30 participants were recruited from the community**

Table 4.1: Number of communities, households, and participants by country and by country income group (n=136,620)

	Communities (#)	Households (#)	PURE study participants (#)
All countries	606	94,382	136,620
High income countries (HIC)	**84**	**9,922**	**13,382**
Sweden	23	2,415	3,215
Canada	58	6,554	8,803
United Arab Emirets (UAE)	3	953	1,364
Upper middle income countries (UMIC)	**120**	**24,536**	**34,249**
Poland	4	1,499	2,031
Chile	5	2,223	3,307
Turkey	38	2,642	4,185
Brazil	14	3,702	4,876
Malaysia	33	9,896	13,753
South Africa	6	2,416	3,078
Argentina	20	2,158	3,015
Lower middle income countries (LMIC)	**225**	**40,049**	**58,573**
Colombia	58	5,120	6,665
Iran	20	2,993	4,434
China	108	30,383	45,904
occupied Palestinian territory (oPt)	39	1,553	1,570
Low income countries (LIC)	**87**	**19,875**	**4,633**
Pakistan	4	1,043	1,713
Bangladesh	83	1,997	2,920
India	90	16,835	25,787

- Countries are ranked in order from highest to lowest per capita GNI

Chapter 5

Descriptive statistics of capacity-to-pay and costs of medications in the PURE study and agreement with other data sources

5.1 Introduction

This chapter provides descriptive statistics of the variables that will be used to calculate the availability and affordability of medications recommended for cardiovascular disease (CVD). Additionally this chapter compares values of household income and costs of medications collected from the PURE study with other sources of data collected in the PURE countries as a measure of validity for the data collected in the PURE study. A gold standard for these values does not exist in the literature, and therefore face validity of the data is assessed.

5.2 Methods

Household income, expenditures on food, and costs of medications from the PURE study were collected in the local currency between 2003 and 2013 (Table 5.1). These values were adjusted for inflation to 2010 values using consumer price index (CPI) values. CPI measures the change in price levels of a market basket of consumer goods and services purchased by households[126]. These values were also converted to international dollars using purchasing power parity (PPP) rates from 2010. PPP is the number of units of a country's currency required to buy the same amounts of goods and services in the domestic market as one US dollar would buy in the United States. To remove outliers (either implausible or extreme values) income and expenditures on food were set at the 5^{th} and 95^{th} percentiles. If the reported expenditure on food was more than the total reported household income, capacity-to-pay values were set to zero.

The results section presents countries ranked in order from highest to lowest per capita Gross National Income (GNI) in 2010 (PPP adjusted). Countries are also grouped based on World Bank 2006 classifications of country income into high (HIC), upper middle (UMIC), lower middle (LMIC) and low income countries (LIC). The results are presented using country level median values and interquartile ranges. Data in the tables and figures are presented in international dollar (PPP) values. Data in the appendices (Appendices 5.1- 5.5) are presented in local currencies.

Table 5.1: Currency and years of data collection for each of the PURE countries

Income group	Country	Currency of data collection	Year of data collection	
			Cost of medications	**Income**
High income countries	Sweden	Krona	2010-2011	2005-2009
	Canada	Canadian dollar	2009-2013	2006-2009
	UAE	Dirham	2009-2010	2005-2009
Upper middle income countries	Poland	Zloty	2009	2007-2009
	Chile	Peso	2010	2006-2009
	Turkey	Lira	2010	2008-2009
	Brazil	Real	2010	2005-2010
	Malaysia	Ringgit	2009-2010	2007-2010
	South Africa	Rand	2009-2010	2005-2010
	Argentina	Peso	2009-2010	2006-2009
Lower middle income countries	Colombia	Peso	2010	2006-2009
	Iran	Toman	2010	2006-2009
	China	Renminbi	2010	2005-2009
	oPt	New Israeli Shekel (NIS)	2011-2013	2012-2013
Low income countries	India	Rupee	2009-2010	2003-2007
	Pakistan	Rupee	2010	2008-2009
	Bangladesh	Taka	2009	2007-2008

- Countries are ranked in order from highest to lowest per capita GNI
- Costs of medications were collected at the community level; income was collected at the household level
- UAE= United Arab Emirates; opt= occupied Palestinian territory

5.2.1 Capacity-to-pay

The health economics literature recommends using total household expenditures to estimate capacity-to-pay rather than asking about the total household income earned, as the latter might be under or over reported[127]. Self-employed participants may under report their total income earned, especially in rural and lower income countries where self-employment is common. Participants may also choose to conceal other sources of income such as government stamps and other non-monetary income sources. On the other hand some households may report higher earnings for social acceptability during an interview. The PURE study collected data on household income earned rather than household expenditures. This was done because of the

complexity of recording household expenditures accurately in such a large study. As a check on the validity of the information collected in the PURE study, we compared the extent of agreement between values of household income earned from the PURE study and information on household expenditures collected from other sources that have used standardized methods.

5.2.2 Face validity of variables in the PURE study

It was expected that households with higher wealth index scores would have higher capacity-to-pay values. The wealth index score was developed for the PURE study based on a list of household amenities (appendix 5.1). As a measure of face validity, we compare the median household income across quintiles of the wealth index score. It was also expected that countries with a higher per capita GNI would have a higher median household capacity-to-pay. We compared the rank of countries by their median capacity-to-pay versus their per capita GNI.

5.2.3 Agreement with other data sources

Capacity-to-pay values obtained from the PURE study were compared with data from the Study on Global Aging and Adult Health (SAGE). These surveys were conducted by the WHO in 2003 for nine of the 17 PURE countries: Sweden, UAE, Brazil, Malaysia, South Africa, China, India, Pakistan, and Bangladesh. Standardized questionnaires were used to collect total monthly household expenditures and total monthly expenditures on food from households representing each country[128]. We calculated the median capacity-to-pay from the WHO data for these countries by subtracting expenditures on food from total household expenditures.

Costs of medications from the PURE study were compared to costs obtained from the WHO/ Health Action International (WHO/HAI) project. Though this database collected costs for a range of medications, we compared agreement of the costs of atenolol 50mg collected from the PURE study versus that obtained from the WHO/HAI project. This decision was made because

atenolol costs in the WHO/HAI project were available for more PURE countries than any of the other CVD medications. The cost of atenolol 50mg from the WHO/HAI project was available for eight of the PURE countries: South Africa, Brazil, Colombia, Iran, Pakistan, UAE, Malaysia, and, India[129].

Results are presented using correlation plots and Spearman correlation coefficients. A correlation coefficient of 0.70 is considered to show good agreement. Bland & Altman plots are also presented as another measure of agreement. These plots have the advantage of providing the mean of the two measures being compared against their difference as well as a 95% Confidence Interval (CI) around the difference[130]. Bland & Altman plots provide a visualization of whether or not the two measures provide similar estimates or whether one is over or underestimating the other measure.

5.3 Results

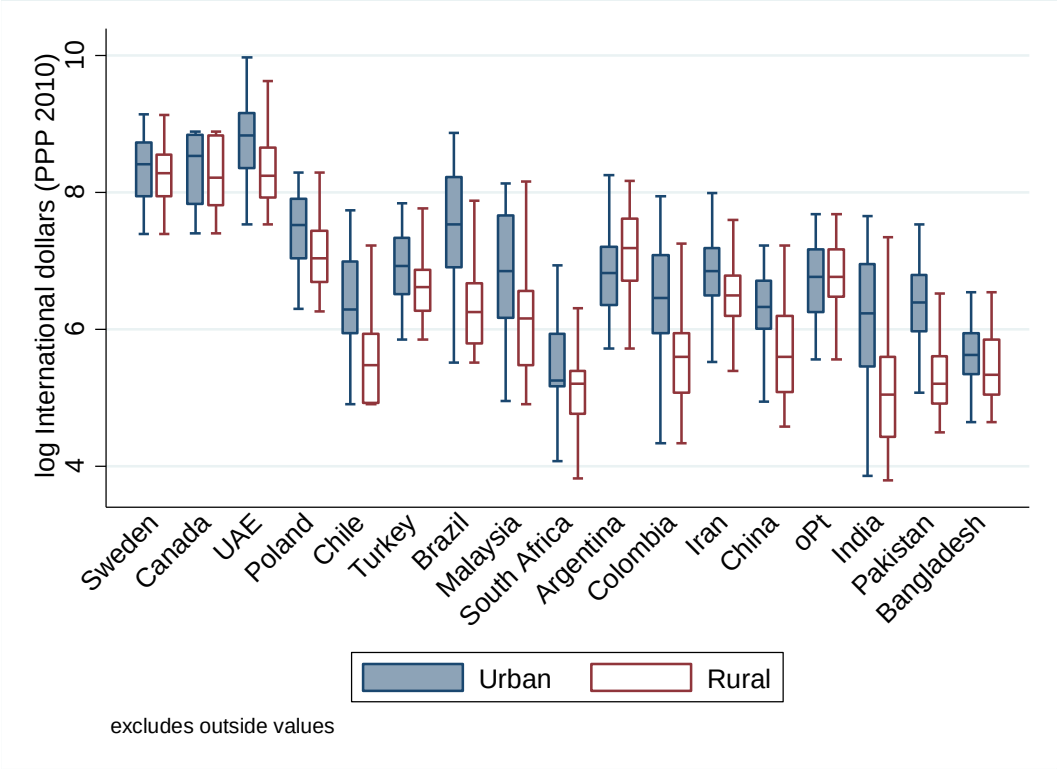
5.3.1 Capacity-to-pay

Distribution of income from the PURE study

Figure 5.1 and Figure 5.2 present box plots depicting household income for each of the PURE countries in international dollars. Each box plot presents the country median value, upper and lower interquartile range (IQR), and minimum and maximum values. Countries are presented in order of per capita GNI and separately for urban and rural locations (see Appendix 5.2 for income and expenditures on food in local currency). Total household income was available for 95,943 (90%) of households enrolled in the PURE study. Figure 5.1 indicates that the median total household income was lower in rural locations than in urban locations with the

exception of Argentina. The figure also shows that household income in Sweden, Canada, and the UAE, was much larger than in the remaining countries with lower per capita GNI.

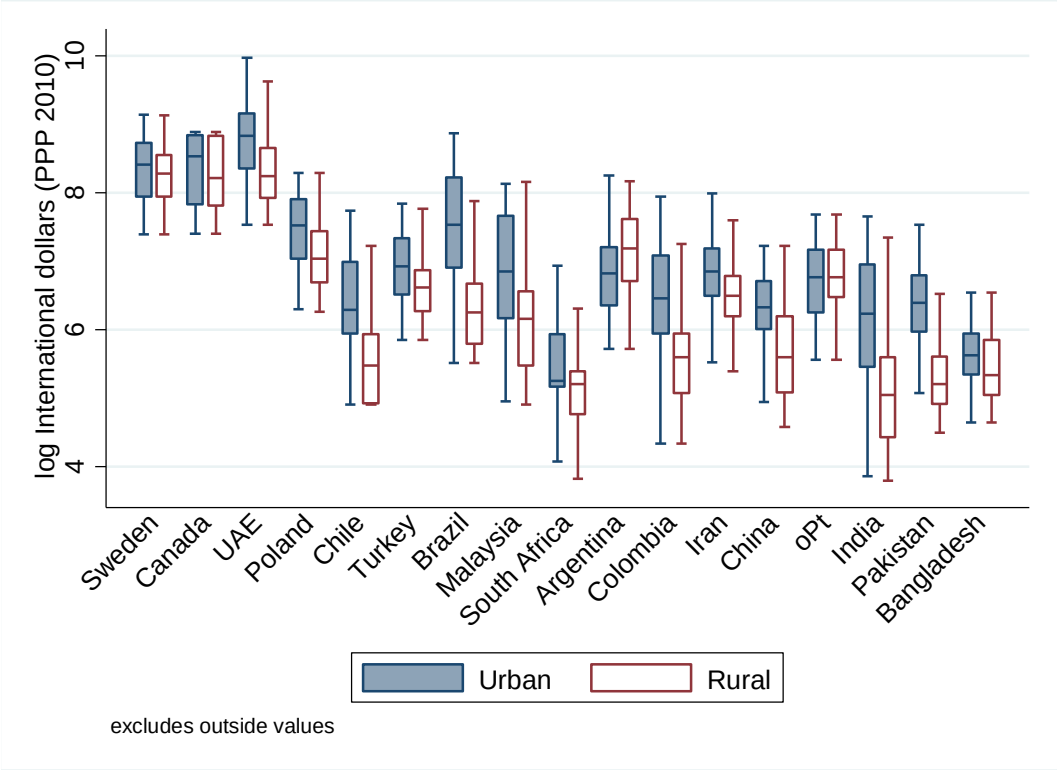
Figure 5.1: Monthly household income for urban and rural locations in each of the PURE countries, international dollars (n=95,943 households)



- **Countries presented in order from highest to lowest per capita GNI**
- **Household income values are presented on a logarithmic scale**
- **Box plots present the median values, upper and lower interquartile ranges, and minimum and maximum values for each location**

Information on expenditures on food was available for 95,943 (92%) of the households enrolled in the PURE study. Figure 5.2 indicates that expenditure on food was higher in urban locations than in rural locations for all of the PURE countries, with the exception of Argentina. Similar to results on household income, this figure shows the large difference in expenditure on food between Sweden, Canada, and the UAE, and the remaining countries with lower per capita GNI.

Figure 5.2: Monthly expenditures on food for urban and rural locations in each of the PURE countries, international dollars (n= 95,943 households)

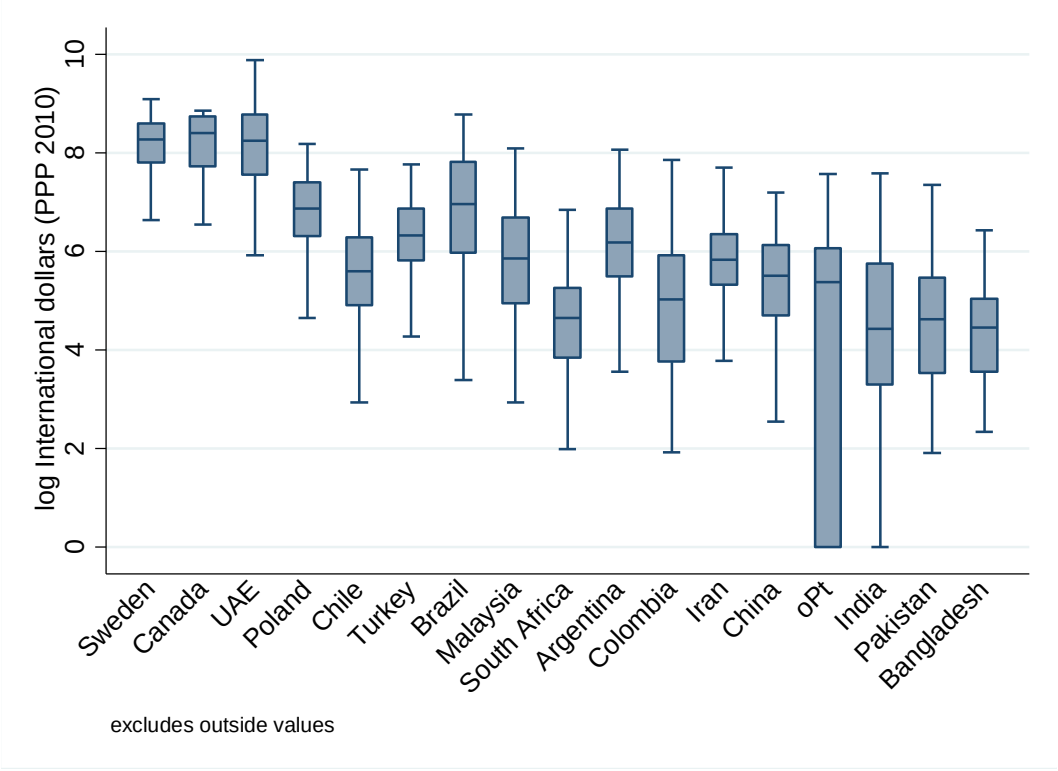


- **Countries presented in order from highest to lowest per capita GNI**
- **Expenditure on food values presented on a logarithmic scale**
- **Box plots present the median values, upper and lower interquartile ranges, and minimum and maximum values for each location**

Calculating capacity-to-pay

Capacity-to-pay was calculated by subtracting expenditure on food from total household income. Data on capacity-to-pay were available for 94,382 households (89%). Figure 5.3 presents households' monthly capacity-to-pay in international dollars. PURE countries were ranked from highest to lowest per capita GNI. The figure indicates that the median households' capacity-to-pay is high in countries with high per capita GNI, and that it decreases for countries with low per capita GNI.

Figure 5.3: Households' capacity-to-pay, international dollars (n= 94,382 households)



- **Countries presented in order from highest to lowest per capita GNI.**
- **Capacity-to-pay values were set at zero when reported expenditures on food exceeded household income.**
- **Box plots present the median values, upper and lower interquartile ranges, and minimum and maximum values for each location.**

Table 5.2 presents the proportion of households with missing capacity-to-pay values in each country, ranked from highest to lowest per capita GNI. Data were missing for less than one percent of households in Poland, Turkey, and Bangladesh but were missing in 60% in Argentina. Participants living in households with missing information were less educated. Other measured characteristics were similar across the two groups (see appendix 5.3).

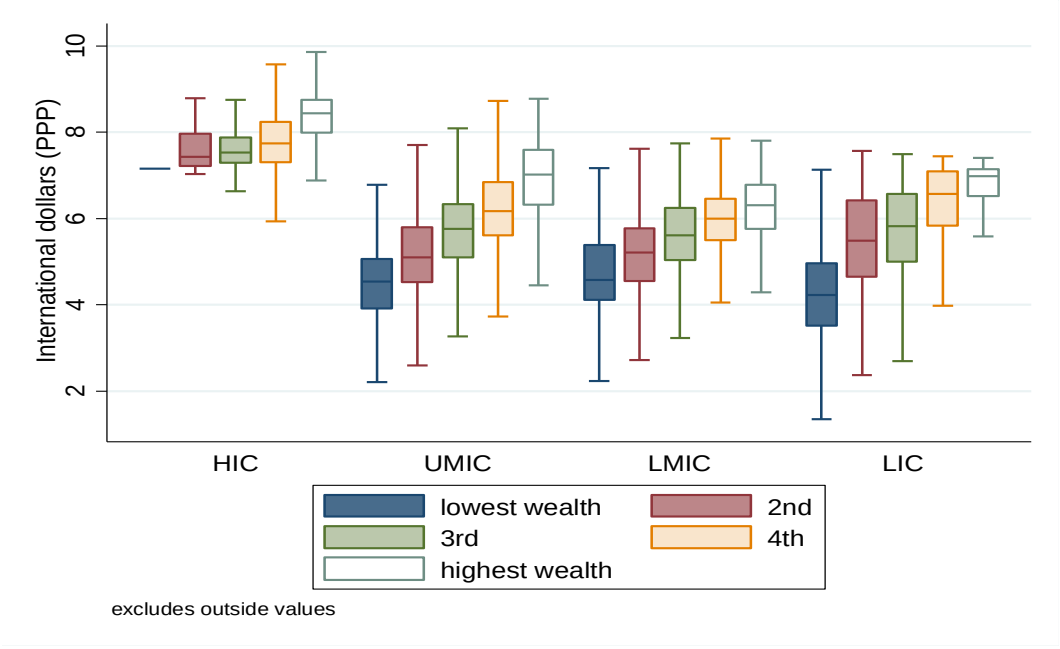
Table 5.2: Proportion of households that did not report enough information to calculate capacity-to-pay values by country (n=107,284 households)

Country	missing data % (n)	Country	missing data % (n)
Sweden	17% (504)	**Argentina**	60% (3,173)
Canada	12% (882)	**Colombia**	9% (521)
UAE	10% (109)	**Iran**	27% (1,106)
Poland	0.33% (5)	**China**	3% (991)
Chile	8% (184)	**oPt**	6% (95)
Turkey	1% (26)	**India**	13% (2,451)
Brazil	18% (822)	**Pakistan**	2% (23)
Malaysia	9% (1,006)	**Bangladesh**	0.1% (2)
South Africa	29% (998)		

Face validity of income data

Figure 5.4 presents box plots of capacity-to-pay values at different levels of household wealth index categorized by country income group. The figure highlights the difference in the median income between HIC and the remaining countries. The figure also indicates that within each country income group, households with higher capacity-to-pay scored higher on the household wealth index.

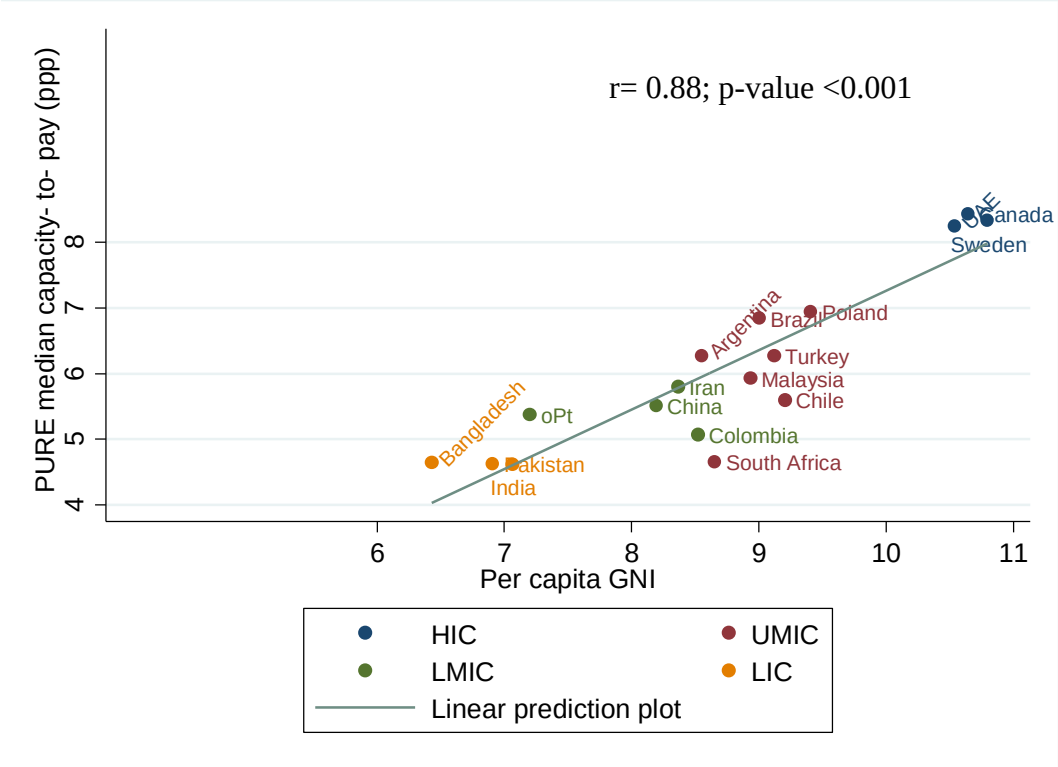
Figure 5.4: Households' capacity-to-pay at different levels of household wealth stratified by country income group, international dollars (n=94,382 households)



- **Capacity-to-pay values were set at zero when reported food expenditure exceeded household income.**
- **Capacity-to-pay presented on a logarithmic scale**
- **Box plots present the median values, upper and lower interquartile ranges, and minimum and maximum values for each location.**
- **HIC=high income countries; UMIC= upper middle income countries; LMIC= lower middle income countries; LIC= low income countries.**

The median households' capacity-to-pay was positively correlated with the country's per capita GNI, with a correlation coefficient of 0.88. Figure 5.5 presents countries by their income group and shows that LIC reported a smaller median capacity-to-pay compared to HIC.

Figure 5.5: County median capacity-to-pay in relation to per capita GNI, international dollars (n=17 countries)

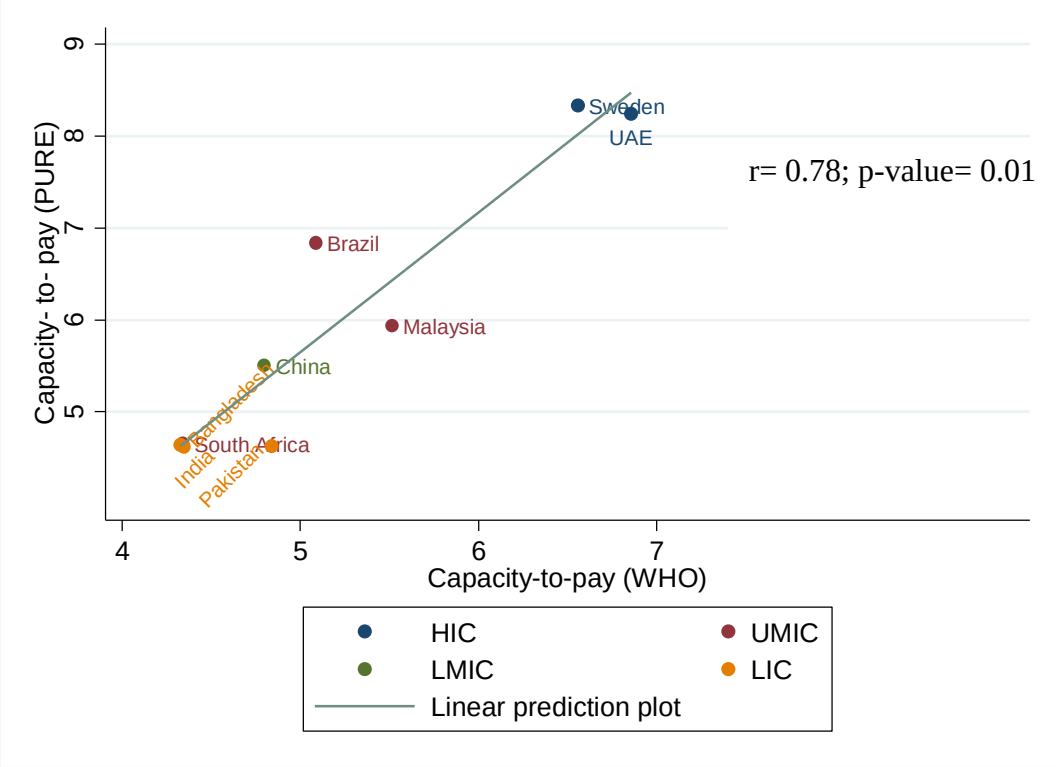


- **Capacity-to-pay and per capita GNI values presented on a logarithmic scale.**
- **HIC=high income countries; UMIC= upper middle income countries; LMIC= lower middle income countries; LIC= low income countries.**
- **r= Spearman rho correlation.**

Agreement between capacity-to-pay obtained from PURE and other data sources

Data on capacity-to-pay values from the WHO were available for nine of the PURE countries. Agreement between the two sources of data was high with a Spearman rho correlation of 0.78 (Figure 5.6).

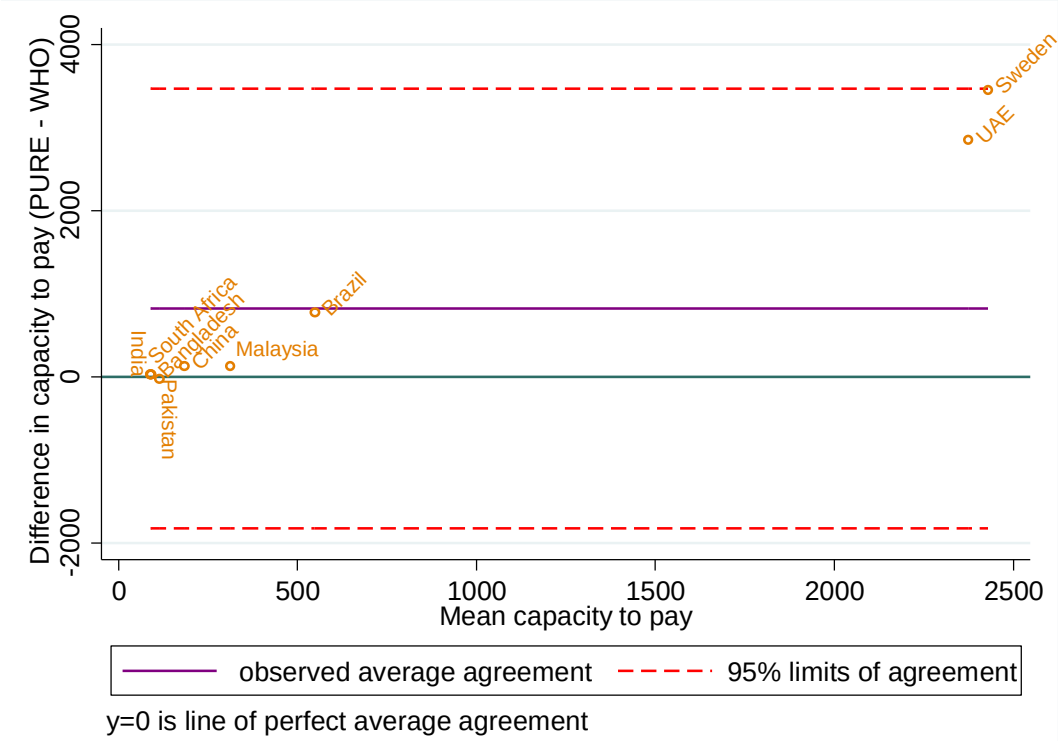
Figure 5.6: Country median capacity-to-pay- correlation between data obtained from PURE and from the WHO



- **Data from the WHO was available for 9 of the 17 PURE countries.**
- **WHO data were obtained from the Study on Global Aging and Adult Health survey (SAGE).**
- **Capacity-to-pay values presented on a logarithmic scale.**
- **HIC=high income countries; UMIC= upper middle income countries; LMIC= lower middle income countries; LIC= low income countries.**
- **r= Spearman rho correlation.**

Figure 5.7 shows that capacity-to-pay values calculated from the PURE study were higher than values reported by the WHO by 820 international dollars (95% CI: -3,469 to 1,828). This difference was mostly due to variations reported by HIC (Sweden and UAE). Excluding these countries results in higher agreement between PURE and WHO data; reducing the difference to 171 international dollars (95%CI: -336 to 678) (data not presented in figures).

Figure 5.7: Country median capacity-to-pay- agreement between data obtained from PURE and from the WHO



- **WHO data obtained from the Study on Global Aging and Adult Health survey (SAGE)**
- **Data from the WHO was available for 9 of the 17 PURE countries**
- **Bland Altman plot presents the difference in values between data obtained from PURE and the WHO against the mean capacity –to- pay values, the 95% CI around the difference is also presented**

5.3.2 Costs of Medications

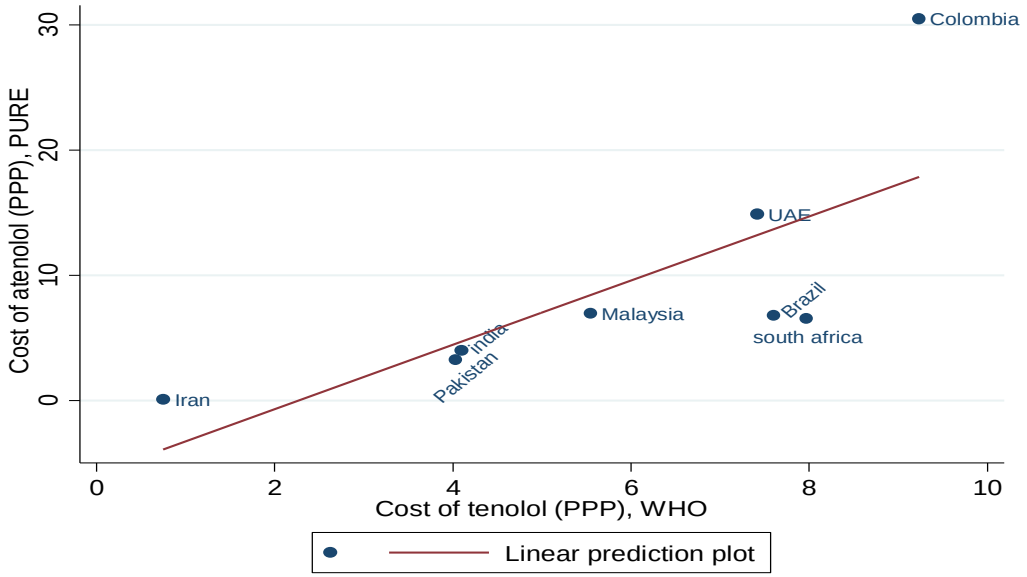
Data on medications for CVD were collected for 606 of the PURE communities, 327 (54%) of which were urban, and 279 (46%) were rural. Data were collected on more than one type of medicine for each of the four CVD medications (box 1). If the same community had more than one of the medication types collected (eg. if both captopril and enalapril were available), we used the medication type with the lower cost. When the medication was not available in the community, a cost was estimated from other communities in the country based on the lowest cost of the same medication, accounting for urban and rural variations. Appendices 5.4- 5.7 presents the costs of each medication type in the local currency for each country.

Box 1: Type and dose of CVD medications collected in the PURE study
Three types of ACE-inhibitors:
Captopril (25mg)
Enalapril (5mg)
Ramipril (5mg)
Two types of beta blockers:
Metoprolol (25mg)
Atenolol (50mg)
Two types of statins:
Simvastatin (20mg)
Atorvastatin (40mg)
Aspirin (100mg)

Agreement between PURE and other data sources

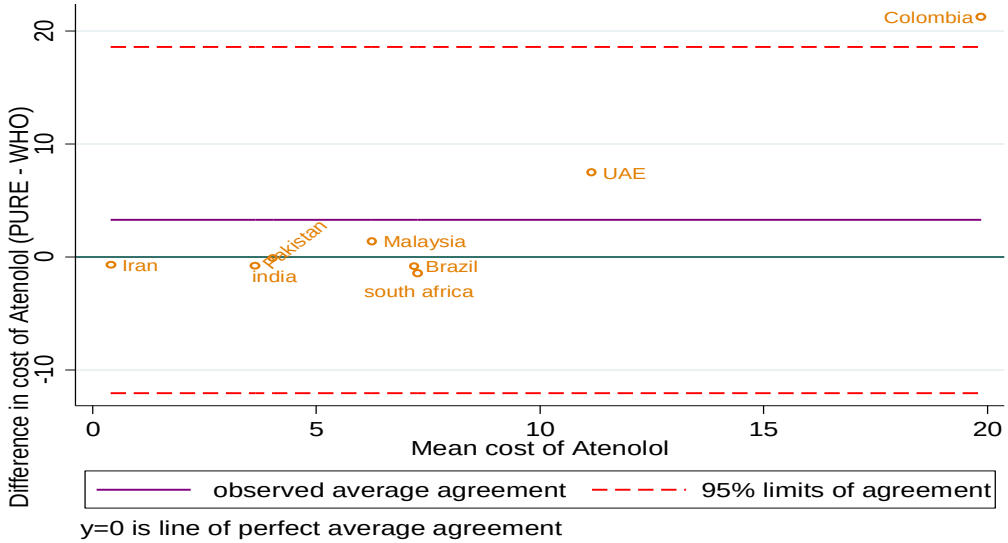
Costs of atenolol from the WHO were available for eight of the PURE countries. The monthly cost of atenolol correlated well between data from PURE and from the WHO with a Spearman correlation of 0.79 (Figure 5.8). The costs obtained from PURE were slightly higher than those obtained by the WHO. Figure 5.9 indicates that atenolol's monthly cost (50mg per day) collected from PURE was three international dollars (95%CI -12 to 19) higher than the cost collected by the WHO.

Figure 5.8: Country median monthly cost of atenolol- correlation between data obtained from PURE and from the WHO



- **WHO data obtained from the Health Action International/WHO project**
- **Data from the WHO was available for 8 of the 17 PURE countries**

Figure 5.9 : Country median monthly cost of atenolol- agreement between data obtained from PURE and from the WHO



- **WHO data obtained from the Health Action International/WHO project**
- **Data from the WHO was available for 8 of the 17 PURE countries**
- **Bland Altman plot presents the difference in values between data obtained from PURE and the WHO against the mean capacity –to- pay values, the 95% CI around the difference is also presented**

5.4 Conclusions

Analyses presented in this study indicated that capacity-to-pay derived from the PURE study correlated well with other data sources. As expected, the capacity-to-pay estimates were higher among households with higher wealth index scores. Ranking countries by per capita GNI indicated that the countries with a lower per capita GNI had a lower median capacity-to-pay than countries with higher per capita GNI. Further, results indicate good correlations of country level capacity-to-pay and medication cost values between data obtained from the PURE study and data collected by the WHO.

Data on household income were obtained from the PURE study by directly asking participants about their income, whereas the WHO obtained household income by asking households about their total expenditures (ie. effective income). The effective income method maybe a more accurate reflection of purchasing power compared to the income method[127]. However, our results indicated good agreement between the two methods, with slightly higher capacity-to-pay values in PURE compared to the WHO. Costs of medications collected from the PURE study were also slightly higher than those obtained by the WHO. Other baseline characteristics of the PURE sample have been previously compared to other sources that have used standardized methods and similarly showed good agreement for sex, urban/rural residence, education, and mortality profiles[123].

A limitation to these analyses is that data from the WHO or other statistics may not necessarily represent the "gold standard" and uncertainty remains even in these estimates. Further, capacity-to-pay values from the WHO were available for nine of the 17 PURE countries, and cost of medications were available for eight of the PURE countries only, so agreement of the data from the remaining countries with other sources that have used standardized methods

remains unknown. However, since the methods of sampling households and data collection in PURE were standardized across all countries, we expect that had we been able to measure agreement in the other countries, it would have been as good as for those countries where we could assess agreement.

Taken overall, our results indicate that the information obtained from the PURE study on capacity-to-pay and medication costs have face validity and that they are comparable to data collected by other sources that have used standardized methods.

Chapter 6

Availability and affordability of medications for secondary prevention of cardiovascular disease in high, middle, and low income countries

6.1 Introduction

An estimated 17 million people die of cardiovascular diseases (CVD) every year[131]. Beta-blockers[15], angiotensin-converting-enzyme (ACE-inhibitors)[14] or angiotensin II receptor blockers (ARBs), statins[16], and aspirin[17], have been proven to reduce mortality and recurrent cardiovascular events after a myocardial infarction (MI) or a stroke. These medications are widely recommended for the management of patients with CVD and their risk factors[7], yet their use is low[13]. Although individual level factors such as age, sex, and education status show strong associations with medication use, data from studies representing countries of different income

groups indicate that country level factors are more strongly associated with the use of these medications [13].

The availability and affordability of medications recommended for the management of CVD may vary by country income group leading to variations in their use across countries. One of the targets of the Global Action Plan (GAP) proposed by the World Health Organization (WHO) is to achieve 80% availability of affordable essential medications to combat non-communicable diseases, including CVD, globally[132]. Increasing the availability of affordable essential medications in developing countries is also a target of the Millennium Development Goals (MDG)[133]. Data on rates of availability and affordability of medications are lacking, especially in low and middle income countries (LIC and MIC) where population level data are limited.

Describing to what extent these medications are available and affordable among different country income groups is the initial step to achieving these goals. This chapter uses data from the PURE standardized collaborative study to describe the availability and affordability of medications recommended for the secondary prevention of CVD. Associations between the effects of availability and affordability on rates of use are then described.

6.2 Methods

6.2.1 Study design

The PURE study initially enrolled 155,875 individuals between 35 and 70 years of age from 628 communities in 17 low, middle, and high income countries on five continents and is currently expanding to include four additional countries targeting a total of 200,000 individuals. Details on the study methods and sampling selection were provided in chapter 4. The PURE study was approved by the ethics committee in all participant centres.

The current analyses use data from the World Bank in 2006[125] to classify the 17 countries into three high income countries (HIC): Sweden, Canada, United Arab Emirates (UAE); seven upper middle income countries (UMIC): Poland, Chile, Turkey, Brazil, Malaysia, South Africa, Argentina; four lower middle income countries (LMIC): Colombia, Iran, China, and the occupied Palestinian territory (oPt); and three low income countries (LIC): Pakistan, Bangladesh, and India[13]. The PURE study collected data from Zimbabwe, however it was excluded from these analyses because information on inflation rates were not available for the time period of data collection.

In the presentation of results, information from India is presented separately from other LIC, because of the unique nature of its domestic pharmaceutical industry. Unlike other LIC, many local generic versions of each medication are produced in the Indian local market[97]. Descriptive data are presented by country income group (HIC, UMIC, LMIC, LIC excluding India, and India separately). Results are also presented for each country against per capita Gross national Income (GNI). Income and medication costs were collected in the local currency for each country between 2003 and 2013. To allow for comparisons across countries, income and medication costs were adjusted for inflation using consumer price index (CPI) for 2010 from the World Bank[126].

The analyses in this chapter are restricted to participants living in the 606 PURE communities where information on availability and costs of medications is available. The final study sample for these analyses comprised 94,382 households who reported income data.

6.2.2 Data collection

CVD diagnosis and medication use

CVD diagnosis in the PURE study refers to self-reported history of stroke or Coronary Heart Disease (CHD) which included myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary angioplasty or angina. Self-reported history of CVD was centrally adjudicated in a sample of 455 reported events. Verification with medical or hospital records indicated a confirmation rate of 89%[13]. The names of all medications taken by each participant were recorded. Medication use was defined as taking the medication at least once per week in the past month. The medications were coded centrally by trained staff at the Project Office, based on the names of the individual medication names into four broad classes (ACE-inhibitors, beta blockers, statins, or aspirin) of medications (e.g. Aten and Betacard were coded as atenolol; Lipitor was coded as atorvastatin).

Capacity-to-pay

The PURE study collected information on household income by directly asking a knowledgeable household member about the total earnings of the household. Information on expenditures on food was also collected. Capacity-to-pay was defined as the household income remaining after expenditures on food. This definition is consistent with the literature, indicating that expenditures on food are a basic necessity that households have to spend a portion of their income on.

Availability and costs of medications

The PURE study used the Environmental Profile of Community's Health (EPOCH) instrument to collect information on the built environment from the PURE communities that enrolled at least 30 participants into the study (a total of 606 communities). EPOCH is an audit tool developed for the PURE study to directly observe and systematically record physical aspects of the environment that were expected to influence CVD risk factors. Procedures included

visiting a number of health facilities in the community, including a pharmacy to collect information on CVD and other medications[124]. To ensure a standardized method of selecting the pharmacy, researchers were instructed to select the pharmacy closest to the centre of the community. The selection of the CVD medications audited was based on proven effectiveness in preventing secondary events and death[7] listed in Table 6.1. The types and doses of each recommended medication are not comprehensive but include the most common types and doses used in the PURE countries as determined from communications with local investigators.

Table 6.1: Type, dose and frequency of CVD medications collected in the PURE study

	Target dose (trial reference)	Dose collected in PURE	Standard dose (used in analyses)	Recommended frequency per day
ACE- inhibitors				
Captopril	50mg (SAVE trial)[134]	25mg	25mg	3
Enalapril	10mg (SOLVD trial)[135]	5mg	5mg	2
Ramipril	10mg (HOPE trial)[136]	5mg	5mg	1
Beta-blockers				
Metoprolol	100mg (MERIT-HF trial)[137]	25mg	50mg	2
Atenolol	100mg (ISIS trial)[138]	50mg	50mg	1
Statins				
Simvastatin	40mg (HPS trial)[139]	20mg	20mg	1
Atorvastatin	10mg (ASCOT trial)[140]	40mg	20mg	1
Aspirin	75-150mg (Antiplatelet trialists systematic review)[17]	100mg	75-150 mg	1

- **If the cost was not available for the specified standard dose, cost was adjusted based on the assumption that doubling the dose increases the cost by one and half times.**
- **SAVE= Survival and Ventricular Enlargement Trial; SOLVED=Studies Of Left Ventricular Dysfunction; HOPE= Heart Outcomes Prevention Evaluation Trial; MERIT-HF= Metoprolol cr/xl Randomized Intervention Trial in Congestive Heart Failure; ISIS-1= First International Study of Infarct Survival; HPS= Heart Protection Study; ASCOT= Anglo Scandinavian Cardiac Outcomes Trial.**

6.2.3 Definitions

Medication use

Use of the four medications recommended for the secondary prevention of CVD was very low. Therefore, the primary outcome in these analyses was use of at least three out of the four of the medications recommended for secondary prevention of CVD. As secondary outcomes, the rates of use of each of the four recommended CVD medications are also presented. Medication use was defined in the PURE study as using a medication at least once per week in the past month.

Availability of medications for CVD

Availability was defined as the presence of the medication in the pharmacy on the day of data collection. Availability data were presented based on availability of any dose of each medication. In communities that did not have a pharmacy it was assumed that none of the CVD medications were available. Clinical guidelines recommend the use of all four CVD medications (ACE-inhibitor, beta-blocker, statin, and aspirin) to optimize clinical benefits[7]. The primary analyses present the availability and affordability of medications as a basket of the four medications. For descriptive purposes, the availability of each medication is also presented.

Affordability of medications for CVD

Affordability is a function of the cost of the medication, and the total household budget[104]:

Costs were calculated for one month's supply based on the standard dose of each medication and accounting for the number of pills per day recommended by clinical guidelines (Table 6.1). If the medication was not available in the community (and therefore no cost was reported for it) the cost was imputed by assigning a cost equal to the lowest cost of the same type of medication in neighboring communities in the country, accounting for urban and rural

variations. This approach assumes that if a medication is not available in the community, patients can purchase it from an adjacent community where it is available.

The total budget refers to the household's capacity-to-pay, defined as the household income remaining after expenditure on food. This definition of capacity-to-pay is consistent with previous analyses used to assess expenditures on health[102,104].

The costs of the medications are presented as a percentage of households' capacity-to-pay. To operationalize the concept of affordability it is important to identify a cutoff point after which the household is no longer able to afford the medications. Affordability is a subjective concept that depends on the households' subsistence needs and on other expenditures (e.g. education or clothes) that they deem necessary. Consistent with the literature we categorize CVD medications to be affordable if they cost less than 20% of households' capacity-to-pay[104]. We also present sensitivity analyses for thresholds ranging from 10%-50% of households' capacity-to-pay. Additionally we present the data as a continuum of affordability, we assume that medications are affordable if they cost up to 10% of households' capacity-to-pay; marginally affordable if they cost more than 10% up to 20%; and unaffordable if they cost more than 20% of households' capacity-to-pay.

It is important to note that our analyses only include the cost of CVD medications. To procure these medications, patients have to incur fees for the healthcare providers' consultation and any diagnostic tests or transportation costs to the clinic or to the pharmacy. Therefore, the capacity-to-pay may be even lower than what is presented in our analyses. In addition to food, households may consider expenditures on shelter or clothing, to be more important than purchasing medications for CVD, especially if the condition is stable and asymptomatic. Given these additional expenditures, it is likely that having to spend 20% or higher on these

medications long term, will result in households forgoing other expenditures making the medications unaffordable[103].

6.2.4 Statistical analyses

Medication availability is presented at the community level as the proportion of communities that had the medication in the pharmacy that was visited (summarized as n (%)). Medication affordability is presented at the household level and calculated as a ratio of medication costs to households' capacity-to-pay (summarized as median and interquartile range).

The effect of availability and affordability on medication use is restricted to participants who reported a history of CVD and is presented at the participant level. Multilevel logistic regression models, accounting for clustering at the community level and the household level, were used to assess the adjusted effects of availability and affordability (presented separately) on use. The statistical models adjusted for variables that may affect the association the availability and affordability of medications and their use based on a framework of medication use proposed by the WHO[110]. These variables included age, sex, education level (primary education or no education, secondary school or high school, trade school, college or university), and community location (urban, rural), years since CVD diagnosis, use of other medications (for diabetes or relief of pain), cancer diagnosis, smoking status (current, non-current), and number of household members (less than five members, five or more members). Country income group (HIC, UMIC, LMIC, and LIC) was not adjusted for in the model, however, we stratified the analyses by country income group to assess whether it modified the associations of interest. The modifying effects of smoking and the size of the household on the association between medication affordability and use were also assessed. Results were reported as Odds Ratios (OR) and 95% confidence intervals (95% CI). All statistical analyses were done using STATA version 13.0.

6.3 Results

The current analyses included data from 94,382 households, from 606 communities representing 17 countries. Table 6.2 describes the number of communities, the overall number of PURE participants and the number of participants with a history of CVD for each country income group and for India.

Table 6.2: Number of communities, households, and study participants by country income group

	Communities (#)	Households (#)	Participants with CVD (#)
Total	**606**	**94,382**	**7,014**
High income countries (HIC)	84	9,922	691
Upper middle income countries (UMIC)	120	24,536	1,523
Lower middle income countries (LMIC)	225	40,049	3,918
Low income countries (LIC) excluding India	87	3,040	197
India	90	16,835	685

6.3.1 Availability of medications for CVD

Data on medication availability are presented at the community level in Table 6.3 . The table presents the availability of each class of CVD medication as well as the availability of all four medications. Of the 606 communities, 45 (7%) did not have a pharmacy. Medications were most commonly available in HIC and least commonly available in LIC excluding India, however availability varied in UMIC and LMIC. Availability of medications in India was higher than that of other LIC, and was almost as high as in HIC. Medication availability was higher in urban compared to rural communities, especially in LIC excluding India. Overall, aspirin was the most commonly available and statins were the least commonly available CVD medications.

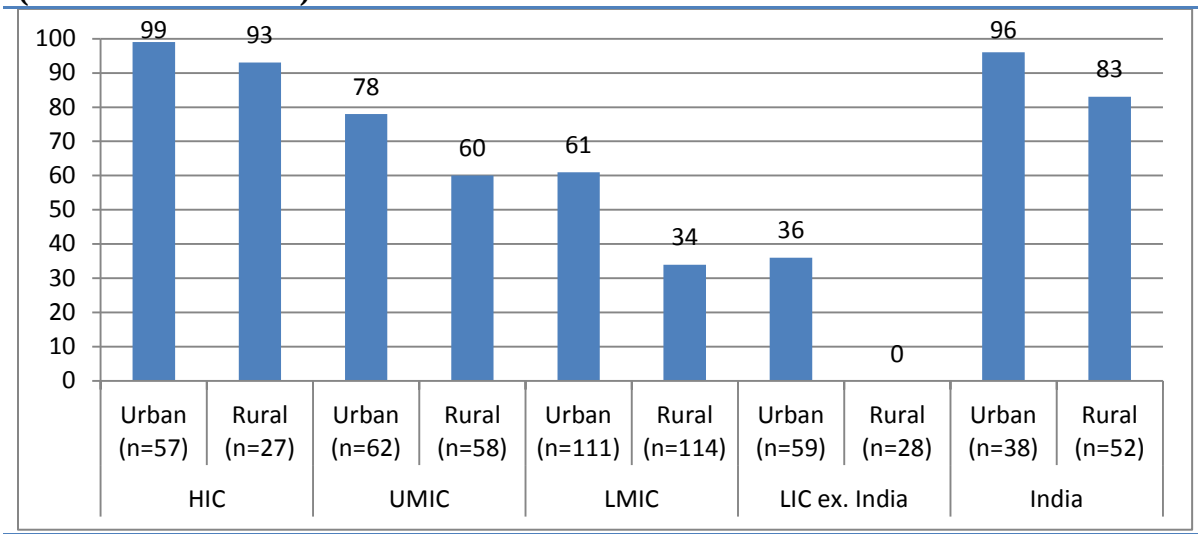
Table 6.3: Availability (%) of each CVD medication in PURE communities (N=606 communities)

	HIC		UMIC		LMIC		LIC ex. India		India	
	urban	rural	urban	rural	urban	rural	urban	rural	urban	rural
Communities (n)	**57**	**27**	**62**	**58**	**111**	**114**	**59**	**28**	**38**	**52**
Any ACE-inhibitor (%)	100	97	87	79	91	68	29	11	97	94
Any beta-blocker (%)	100	96	95	84	79	58	97	86	97	94
Any statin (%)	100	85	95	79	76	40	75	46	92	81
Aspirin (%)	95	85	92	79	97	79	93	68	95	94

HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India; ACE-inhibitor= angiotensin-converting-enzyme inhibitor

Availability of all four CVD medications (at least one type of each of ACE-inhibitors, beta-blockers, statins or aspirin at any dose) varied across different country income groups. Availability was highest in HIC (99% of urban and 93% of rural communities) and lowest in LIC excluding India (36% of urban and 0% of rural communities). Availability in India was similar to what was reported in HIC (96% and 83%, respectively) (Figure 6.1).

Figure 6.1: Availability (%) of the four CVD medications in the PURE communities (N=606 communities)

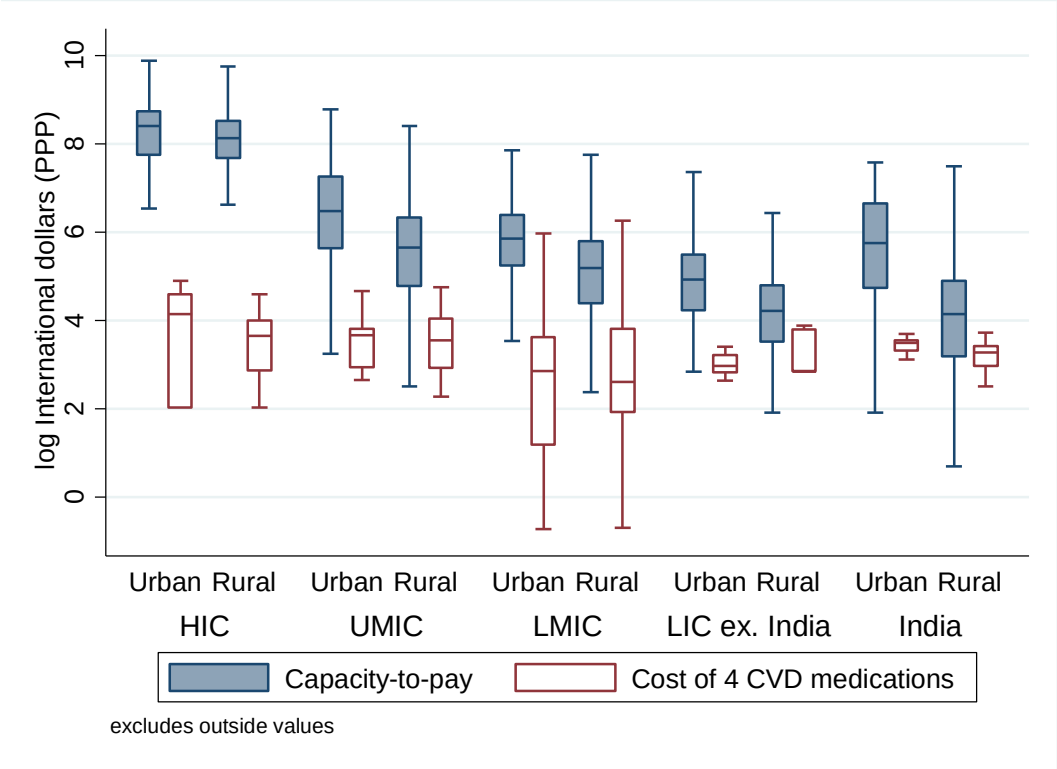


- **"n" refers to the total number of communities in each location of each country income group**
- **HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India.**
- **The 4 CVD medications include: at least one ACE-inhibitor (angiotensin-converting-enzyme inhibitor), one beta blocker, one statin, and one aspirin**

6.3.2 Costs of medications for CVD

Figure 6.2 presents the costs of the four CVD medications as well as household's capacity-to-pay in international dollars using purchasing power parity (PPP) adjustments. The figure indicates that costs of medication are roughly similar across the different country income groups, although large variations in households' capacity-to-pay were observed.

Figure 6.2: Box plots of monthly households' capacity-to-pay and cost of the four CVD medications in international dollars by country income group for urban and rural locations (n=94,382 households)



- **Capacity-to-pay values and costs of medications converted from the local currency in each country to international dollars using purchasing power parity (PPP) values from 2010**
- **Capacity-to-pay values and costs of medications presented on a logarithmic scale**
- **Box plots present the median values, upper and lower interquartile ranges, and minimum and maximum values for each location.**
- **IQR= interquartile range; HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India**

The costs of each CVD medication as a proportion of households' capacity-to-pay varied by country income group (Table 6.4). Each medication cost less than 1% of households' capacity-to-pay in HIC. Medications were less affordable in UMIC and LMIC, and were least affordable in LIC. Affordability in India was low and resembled affordability in other LIC. Statins were the least affordable medications, in HIC a household has to spend 0.7% of its capacity-to-pay to purchase a statin in urban communities and 0.4% in rural communities. In LIC, a household has to spend 13% of its capacity-to-pay in urban communities, and 39% in rural communities in order to purchase a statin. In India, a household has to spend 6% and 25% of its capacity-to-pay to purchase a statin, in urban and rural communities, respectively.

Based on results from Figure 6.2 (above), the observed variations in affordability across country income groups are due to the household's capacity-to-pay which was different in each group, rather than due to the costs of the medications were similar across the different country income groups.

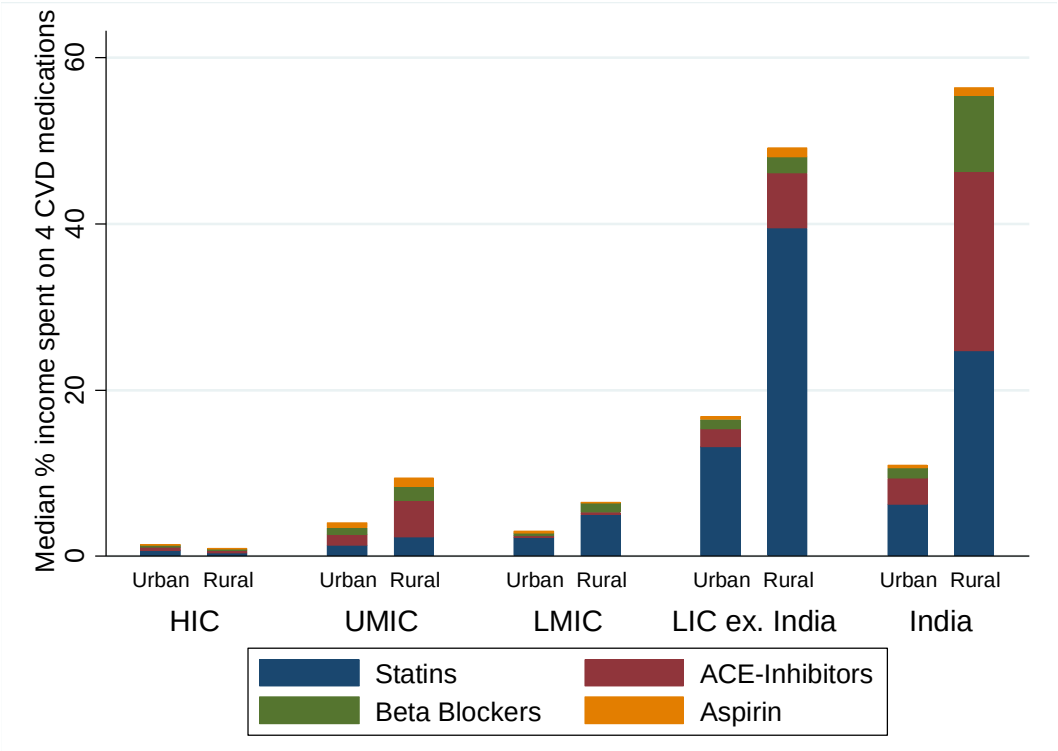
Table 6.4: Median costs and IQR of each CVD medication as a percentage of household's capacity-to-pay (%) (n=94,382)

	HIC		UMIC		LMIC		LIC ex. India		India	
	urban	rural	urban	rural	urban	rural	urban	rural	urban	rural
ACE-inhibitor	0.4 (0.2- 0.6)	0.3 (0.1-0.5)	1 (0.5-3)	4 (2-14)	0.2 (0.08-0.9)	0.3 (0.1-1)	2 (1-5)	7 (2-13)	3 (1-9)	21 (7-57)
Beta-blocker	0.2 (0.1-0.4)	0.1 (0.07-0.3)	0.7 (0.3-2)	2 (0.3-6)	0.3 (0.06-4)	1 (0.3-32)	1 (0.5-3)	2 (0.7-5)	1 (0.5-6)	9 (3-27)
Statin	0.7 (0.1-1)	0.4 (0.1-1)	1 (0.6-4)	2 (0.9-7)	2 (0.5-10)	5 (2-15)	13 (6-19)	39 (13-79)	6 (2-20)	25 (8-87)
Aspirin	0.1 (0.05-0.2)	0.06 (0.04-0.1)	0.6 (0.02-0.2)	1 (0.04-3)	0.2 (0.02-1)	0.1 (0.04-0.7)	0.4 (0.3-0.8)	1 (0.4-2)	0.4 (0.09-0.9)	1 (0.3-9)

IQR= interquartile range; HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India; ACE-inhibitor= angiotensin-converting-enzyme inhibitor

Following the recommended clinical guidelines (i.e. using all four CVD medications) indicates that a patient with CVD would have to spend 1% of the household's capacity-to-pay in HIC, 6% in UMIC, 8% in LMIC, 24% in LIC other than India, and 26% in India to be able to purchase the four recommended medications. Figure 6.3 presents the median proportion of a household's capacity-to-pay required to purchase the four medications for rural and urban communities. The figure indicates that the majority of the cost is due to statins and ACE-inhibitors. The figure also indicates that the proportion of the household's capacity-to-pay required to purchase these medications was consistently higher in rural compared to urban communities across all country income groups.

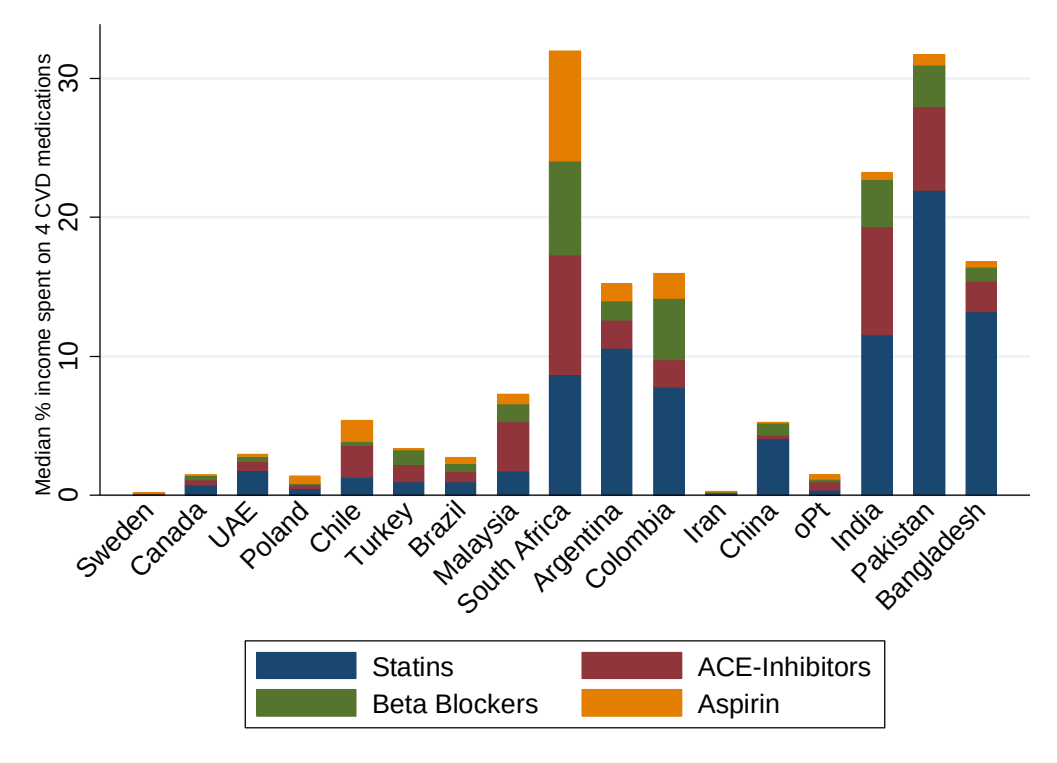
Figure 6.3: Monthly cost of the four CVD medications as a percentage of a household's capacity-to-pay, median % (n=94,382 households)



- **HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India.**

Figure 6.4 presents the households' capacity-to-pay for all four recommended CVD medications in each PURE country. The proportion ranges from less than 1% in Sweden and Iran, to 37% in South Africa.

Figure 6.4: Monthly cost of the four CVD medications as a percentage households' capacity-to-pay for each country, median % (n=94,382 households)

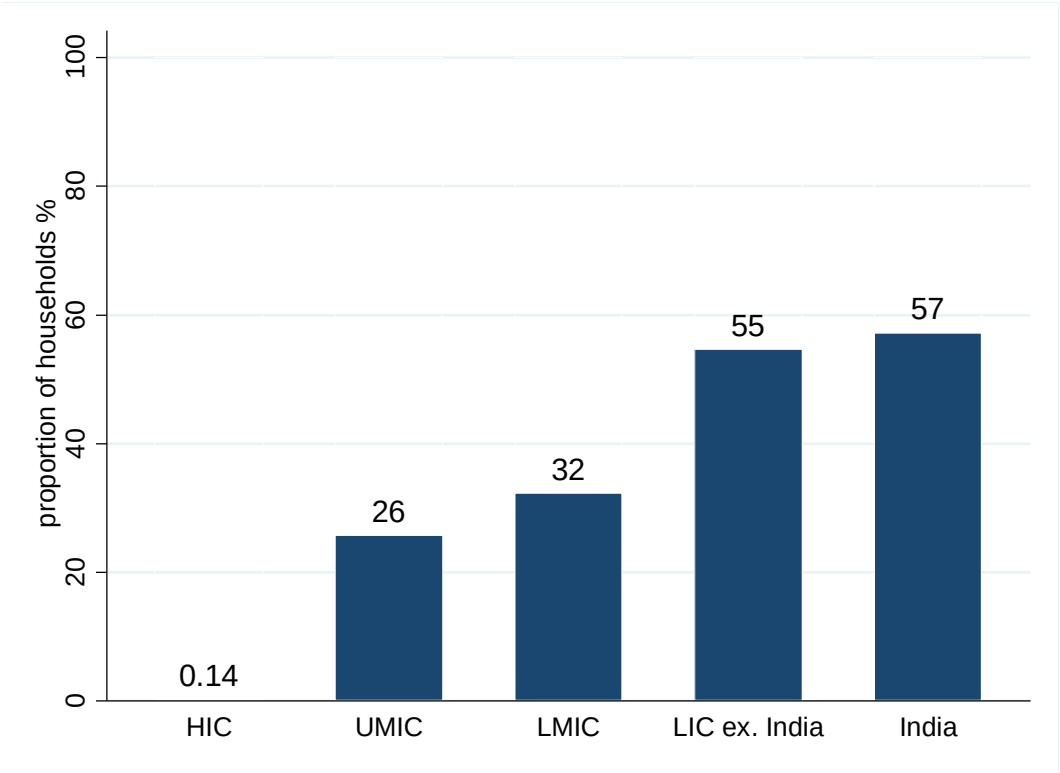


- **UAE= United Arab Emmirates; oPt= occupied Palestinian territory**

6.3.3 Affordability of medications for CVD

Using 20% of households' capacity-to-pay as a threshold to describe what is unaffordable, 26% and 32% of households in UMIC and LMIC, respectively, would not be able to afford the medications. These proportions increase to 55% and 57% in LIC other than India and in India, respectively (Figure 6.5). In HIC only 0.14% of households would not be able to afford the medications.

Figure 6.5: Proportion of households who cannot afford the CVD medications (n=94,382 households)



- **Households cannot afford the medications if their total costs exceed 20% of capaty-to-pay**
- **HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India.**

Table 6.5 illustrates the proportion of households that would not be able to afford the four CVD medications using different thresholds to define lack of affordability, ranging from 10% to 50% of a household's capacity-to-pay. 1% of the households in HIC and 78% of households in LIC, excluding India, would be unable to afford the medications, if lack of affordability is defined as the medications using 10% or more of a household's capacity-to-pay. If the lack of affordability is defined as the medications using 50% or more of a household's capacity-to-pay, less than 1% of households in HIC would be unable to afford the medications, however, 25% of households in LIC would still not be able to afford these medications. This sensitivity analysis (i.e. using different thresholds to define lack of affordability) indicates that even when the definition of lack of affordability is restricted to those who have to spend 50% or more of their income to afford the medications, many households (25%) in LIC are still not able to afford these medications.

Table 6.5: Proportion of households who cannot afford the CVD medications at different thresholds to define what is unaffordable, % n

% of household's capacity-to-pay	HIC	UMIC	LMIC	LIC ex. India	India
10% or more	1% (127)	40% (9,858)	44% (17,701)	78% (2,365)	71% (11,906)
20% or more	0.14% (14)	26% (6,320)	32% (12,935)	55% (1,662)	57% (9,630)
30% or more	0.08% (8)	19% (4,654)	27% (10,957)	41% (1,237)	49% (8,229)
40% or more	0.01% (1)	14% (3,509)	25% (9,969)	35% (1,069)	43% (7,277)
50% or more	0.01% (1)	11% (2,799)	23% (9,163)	25% (756)	38% (6,389)
Total n	**9,922**	**24,536**	**40,049**	**3,040**	**16,835**

- **HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India.**

6.3.4 Rates of medication use for CVD

The remaining analyses are restricted to patients with known CVD which includes 7,014 individuals (refer to Table 6.2 of results section). The analyses start with a description of factors that may be associated with use of medications recommended for CVD in the PURE sample based on the World Health Organization (WHO) model of medication use[100], and then focuses on whether the availability and affordability of each medication (and all four together) affect their use.

Determinants of medication use

Statins were the least commonly used medication in patients with CVD (13%), and aspirin was the most commonly used (20%). ACE-inhibitors and beta blockers were used by 14% and 15% of patients, respectively (Table 6.6).

Table 6.6: Percent (n) of patients with a history of CVD who reported the use of CVD medications

	Proportion of PURE participants (%)	Number of PURE participants (n)
ACE-inhibitors	14%	942
Beta-blockers	15%	1,044
Statins	13%	921
Aspirin	20%	1,376
3 or 4 medications	8%	575
4 medications	2%	154
Total n	**100%**	**7,014**

Fully adjusted analyses indicate that patients using three to four of the recommended CVD medications (n=575) were more likely to be older than 50 years and males. Patients using three to four CVD medications were also more educated, and lived in urban localities. Further, patients were more likely to use these medications if they were diagnosed with CVD in the past year compared to those diagnosed more than one year earlier, used other medications (insulin, other diabetes medication, or chronic pain medication), and if they were non- current smokers.

Lack of availability of all four medications in the community was associated with lower use. If the four medications were unaffordable (using 20% of households' capacity-to-pay as the threshold), patients were less likely to use the medications. Being diagnosed with cancer (another life-threatening condition) or the size of the household (less than five members versus five or more) were not statistically significantly associated with rates of medication use for CVD (Table 6.7).

Table 6.7: Factors that may affect the use of at least three of the recommended CVD medications among patients with a history of CVD (n=7,014)

	no. in group	% (n) using medication	OR and 95%CI of using at least three medication	
Age:			**Unadjusted**	**Adjusted**
Less than 50 years (ref)	1,470	4% (56)	1.00	1.00
50+ years	5,535	9% (519)	2.61 (1.97-3.46)	2.01 (1.33-3.06)
Sex:				
Females (ref)	3,531	5% (178)	1.00	1.00
Males	3,442	12% (397)	2.46 (2.04-2.95)	2.67 (1.94-3.69)
Education level:				
Primary education or no education (ref)	3,164	6% (184)	1.00	1.00
Secondary school or high school	2,413	8% (185)	1.34 (1.09-1.66)	1.42 (1.01-1.99)
Trade school, college or university	1,419	15% (206)	2.75 (2.23-3.39)	1.30 (0.89-1.86)
Years since CVD diagnosis:				
1 year or less since diagnosis (ref)	1,125	9% (101)	1.00	1.00
> 1 year to 5 years since diagnosis	2,465	9% (232)	1.05 (0.82-1.35)	0.91 (0.64-1.29)
> 5 years since diagnosis	3,424	7% (242)	0.77 (0.60-0.98)	0.62 (0.43-0.89)
Comorbidities:				
No history of Cancer (ref)	6,506	8% (543)	1.00	1.00
History of Cancer	492	7% (32)	0.76 (0.53-1.10)	0.94 (0.53-1.67)
Use of other medications:**				
Not using other medications (ref)	6,079	7% (427)	1.00	1.00
Using other medications	935	16% (148)	2.48 (2.04-3.04)	1.42 (1.05- 1.91)
Smoking status:				
Nonsmokers (ref)	5,470	9% (514)	1.00	1.00
Smokers	1,226	5% (61)	0.50 (0.38-0.66)	0.37 (0.24-0.56)
Number of household members:				
Less than 5 members (ref)	4,887	9% (455)	1.00	1.00
5 or more members	1,599	7% (114)	0.75 (0.60-0.93)	1.03 (0.75-1.42)
Community location:				
Urban (ref)	4,184	10% (423)	1.00	1.00
Rural	2,830	5% (152)	0.50 (0.42-0.61)	0.56 (0.33-0. 93)
Country income group:				
HIC (ref)	691	43% (296)	1.00	NA*
UMIC	1,523	13% (293)	0.19 (0.16-0.24)	
LMIC	3,918	2% (66)	0.02 (0.02-0.03)	
LIC ex. India	197	0.5% (1)	0.007 (0.0009-0.05)	
India	685	3% (19)	0.04 (0.02-0.06)	
Availability:				
All four available (ref)	4,940	12% (538)	1.00	1.00
Fewer than 4 available	2,911	1% (37)	0.10 (0.07-0.14)	0.07 (0.03-0.15)
Affordability (using the 20% threshold):				
Affordable (ref)	5,111	11% (537)	1.00	1.00
Not affordable	1,903	2% (38)	0.17 (0.12-0.24)	0.26 (0.15-0.47)

***NA= Country income level not adjusted for to avoid colinearity with clustering at community level**

****Other medications included insulin, other diabetes medications, or pain medication**

- **Adjusted: age, sex, education, years since diagnosis, cancer diagnosis, use of other medications, smoking status, number of household members, community location, availability, and affordability; clustered at the community and household levels**
- **OR= Odds Ratio; 95%CI= 95% Confidence Interval; HIC= high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC ex. India= lower income countries excluding India**

Medication availability and their use

Lack of availability of medications in the community was statistically significantly associated with lower medication use in univariate analyses (Table 6.8). In the fully adjusted models, the association was slightly attenuated but remained statistically significant, for all medications except for aspirin. Having fewer than four CVD medications available in the community was associated with lower rates of use of at least three medications (OR: 0.07, 95%CI: 0.03-0.15).

Table 6.8: Effect of lack of availability on use of each CVD medication (n=7,014)

	Total n	% (n) using medication	OR and 95%CI of using each medication	
			Unadjusted model	Adjusted model
ACE-inhibitors:				
Available	5,786	15% (862)	1.00	1.00
Not available (ref)	1,228	7% (80)	0.40 (0.31-0.50)	0.39 (0.22-0.68)
Beta-blockers:				
Available	5,430	18% (974)	1.00	1.00
Not available (ref)	1,584	4% (70)	0.21 (0.16-0.27)	0.14 (0.08-0.25)
Statins:				
Available	5,882	17% (1,019)	1.00	1.00
Not available (ref)	1,969	2% (31)	0.07 (0.05-0.11)	0.04 (0.02-0.12)
Aspirin:				
Available	6,949	21% (1,483)	1.00	1.00
Not available (ref)	902	11% (98)	0.47 (0.37-0.59)	0.66 (0.34-1.28)
All medications:				
All four available (ref)	4,940	12% (538)	1.00	1.00
Fewer than 4 available	2,911	1% (37)	0.10 (0.07-0.14)	0.07 (0.03-0.15)

- **Adjusted for: age, sex, education, years since diagnosis, cancer diagnosis, use of other medications, smoking status, number of household members, community location, and affordability; clustered at the community and household levels**
- **OR= Odds Ratio; 95%CI= 95% confidence interval; ACE-inhibitors= angiotensin-converting-enzyme inhibitors**

Medication affordability and their use

The use of each CVD medication was lower when the cost of each medication was not affordable (using a threshold of 20% to define what is affordable) in univariate analyses. In multivariate analyses results remained statistically significant for all medications expect for the effect of lack of affordability of ACE-inhibitors which was no longer statistically significant, however it showed a trend for lower use of medications when the medications was not affordable (Table 6.9). Patients who are not able to afford the four CVD medications were significantly less likely to use at least three of the medications (OR=26, 95% CI: 0.15-0.47).

Table 6.9: Effect of lack of affordability (using the 20% threshold of capacity-to-pay) on use of each CVD medication (n=7,014)

	Total n	% (n) using medication	OR and 95%CI of using each medication	
			Unadjusted model	Adjusted model
ACE-inhibitors:				
Affordable (ref)	6,327	14% (897)	1.00	1.00
Not affordable	687	7% (45)	0.42 (0.31-0.58)	0.70 (0.43-1.13)
Beta-blockers:				
Affordable (ref)	6,158	17% (991)	1.00	1.00
Not affordable	856	5% (53)	0.34 (0.26-0.46)	0.58 (0.37-0.92)
Statins:				
Affordable (ref)	5,807	15% (892)	1.00	1.00
Not affordable	1,207	2% (29)	0.14 (0.09-0.20)	0.34 (0.19-0.61)
Aspirin:				
Affordable (ref)	6,625	20% (1,345)	1.00	1.00
Not affordable	389	8% (31)	0.34 (0.23-0.49)	0.44 (0.24-0.81)
All medications				
Affordable (ref)	5,111	11% (537)	1.00	1.00
Not affordable	1,903	2% (38)	0.17 (0.12-0.24)	0.26 (0.15-0.47)

- **Adjusted for: age, sex, education, years since diagnosis, cancer diagnosis, use of other medications, smoking status, number of household members, community location, and availability; clustered at the community and household levels**
- **OR= Odds Ratio; 95%CI= 95% confidence interval; ACE-inhibitors= angiotensin-converting-enzyme inhibitors**

Table 6.10 illustrates the effect of different levels of affordability on medication stratified by country income group. UMIC and LMIC showed similar trends in terms of medication affordability, and so did LIC, including India. Given the small number of participants that reported medication use within each country income group, UMIC, LMIC, LIC, and India where grouped under one group (lower and middle income countries- LMIC) so that more reliable estimates are possible. A trend for lower use with lower affordability was observed in HIC although the results were not statistically significant due to the very small number of patients who could only marginally afford the medications in HIC. In LMIC, a trend for lower use with lower affordability in LMIC was observed, however, results were only statistical significant for the unaffordable group, where patients were 62% less likely to use the medication if it was unaffordable compared to being affordable (OR=0.38; 95%CI: 0.22-0.66).

Table 6.10: Effect of different levels of affordability on using at least three CVD medications stratified by country income (n=7,014)

	Total n	% (n) using medication	OR and 95% CI of using at least three medications	
			Unadjusted model	Adjusted model
HIC				
Affordable	675	43% (290)	1.0	1.0
Marginally affordable	14	42% (6)	0.98 (0.34-2.90)	0.54 (0.13-2.25)
Unaffordable	2	0	NA	NA
P-value for trend				**0.316**
LMIC				
Affordable	3,475	6% (222)	1.0	1.0
Marginally affordable	773	3% (19)	0.39 (0.24-0.63)	0.58 (0.32-1.06)
Unaffordable	1,901	2% (38)	0.31 (0.22-0.45)	0.38 (0.22-0.66)
p-value for trend				**< 0.001**

- **Adjusted for: age, sex, education, years since diagnosis, cancer diagnosis, use of other medications, smoking status, number of household members, community location, and availability; clustered at the community and household levels.**
- **Affordable= up to 10% of households' capacity-to-pay**
- **Marginally affordable= >10-20% of households' capacity-to-pay**
- **Unaffordable= >20% of households' capacity-to-pay**
- **OR= Odds Ratios; 95%CI= 95% Confidence Interval; LMIC=lower and middle income countries, including India**

Subgroup analyses

The effect of lack of affordability on medication use appeared to be similar among current smokers compared to nonsmokers, but appeared to be stronger among patients who have a larger households (five or more members), compared to patients with smaller households (less than five members). However, the difference between those with larger and smaller families was not statistically significant (p value for interaction > 0.05). Table 6.11 presents the OR and 95%CI as well as the numbers of participants in each subgroup.

Table 6.11: Subgroup analyses of the effects of different levels of affordability on using at least 3 CVD medications (n=7,014)

	Total n	% (n) using medication	OR and 95%CI of using at least three medications	
			Unadjusted model	Adjusted model
Current smoking status				
Smokers				
Affordable	712	8% (55)	1.00	1.00
Marginally affordable	136	1% (1)	0.09 (0.01-0.64)	0.03 (0.00008-10.55)
Unaffordable	378	1% (5)	0.16 (0.06-0.40)	0.6 (0.00007-4.44)
P-value for trend				<0.001
Non smokers				
Affordable	3,449	13% (457)	1.00	1.00
Marginally affordable	623	4% (24)	0.26 (0.17-0.40)	0.52 (0. 29-0.93)
Unaffordable	1,398	2% (33)	0.16 (0.11-0.23)	0.22 (0.12-0. 40)
P-value for trend				0.001
Household size				
Less than five household members				
Affordable	3,158	13% (414)	1.00	1.00
Marginally affordable	517	3% (14)	0.18 (0.11-0.32)	0.40 (0.20-0.80)
Unaffordable	1,212	2% (27)	0.15 (0.10-0.22)	0.25 (0.13-0.48)
P-value for trend				<0.001
Five household members or more				
Affordable	943	10% (93)	1.00	1.00
Marginally affordable	196	6% (11)	0.54 (0.29-1.04)	0.46 (0.17-1.27)
Unaffordable	460	2% (10)	0.20 (0.10-0.39)	0.12 (0.03-0.54)
P-value for trend				<0.001

- **Adjusted for: age, sex, education level, community location (urban, rural), years since CVD diagnosis, cancer diagnosis, use of other medications, smoking status, availability of 4 CVD medications; clustered at the community level.**
- **P-value for interaction >0.05 for all subgroups.**
- **Affordable= up to 10% of households' capacity-to-pay**
- **Marginally affordable= >10-20% of households' capacity-to-pay**
- **Unaffordable= >20% of households' capacity-to-pay**
- **LMIC include UMIC, LMIC, and LIC including India**
- **OR= Odds Ratio; 95%CI= 95% Confidence Interval**

6.4 Discussion

6.4.1 Main findings

Each of the four recommended CVD were more commonly available in HIC compared to LIC. None of the communities in LIC, excluding India had all four medications available. The cost of the four medications used up a higher proportion of households' capacity-to-pay in LIC compared to HIC. The four CVD medications were unaffordable (using a threshold of 20% of households' capacity-to-pay) for 26%, 32%, 55%, and 57% of households living in UMIC, LMIC, LIC other than India, and India, respectively. The four medications were unaffordable for less than one percent of the households in HIC, indicating that lack of affordability is not an important barrier in patients in HIC. Medications were more likely to be available and affordable in urban compared to rural communities especially in MIC and LIC including India. The difference in affordability between the two locations was largely due to differences in capacity-to-pay between households in urban and rural communities, rather than differences in the price of medications.

Analyses restricted to patients with known CVD indicate low rates of use of three to four of the recommended CVD medications (8%) and even lower rates for use of all four medications (2%). The effects of lack of availability and affordability of medications on their use were large even after adjusting for other factors relevant for medication use (patient factors, socioeconomic status, and disease specific factors). As suggested by the WHO model of chronic disease medication use[110], our data showed that patient factors (age, sex), socioeconomic status (education, and community location), and using other medications (insulin, other diabetes medication, or pain medication) were also associated with medication use. However, the impact was much stronger for availability and affordability compared to these other variables.

Although some methods of measuring medication affordability have been described in the literature there is no consensus on a standardized definition. We used methods of measuring affordability that have been described by Nien's et al (2012)[104]. Our results support the general findings in the literature indicating that medication affordability is low in MIC and LIC[104]. Our analyses are unique because we obtained standardized data from 17 countries making it possible to make comparisons across countries and communities (urban and rural). Our study also provides new information by linking availability and affordability to rates of medication use in patients with CVD in these communities. This gives validity to the methods we used by showing that if the medications are not affordable patients are less likely to use them even after controlling for patient or community level factors.

6.4.2 Limitations

The PURE study did not collect data on the availability of insurance to cover the costs of medications at the individual level and therefore it was not possible to identify separately the group of patients in PURE that are insured and do not pay the full costs of the medications charged by the pharmacies. This might have affected the observed associations between rates of medication use and how affordable they were. Unlike HIC, large proportions of patients in lower income countries pay directly for their healthcare costs, including costs of medications[100].

To measure affordability we subtracted expenditures on food as a minimum necessity for subsistence of households. Taking the households' other spending into consideration, such as other healthcare costs, expenditures on education and rent, might also be necessary before assessing whether CVD medications are affordable or not. We used different thresholds of what is "affordable" (ie. 10% to 50% of capacity-to-pay) to assess whether lower or higher thresholds to define what is "affordable" influences the results .We observed consistent results regarding the

trends of affordability irrespective of the different thresholds used. Further, costs such as physician consultation fees, time off work to visit healthcare providers and the pharmacy, and transportation costs to the healthcare facility or the pharmacy (which are indirect costs associated with use of the medications) were not collected and so we could not consider these in our analyses. Therefore, our results may overestimate how affordable these medications are, and in reality even fewer patients may be able to afford these medications once these expenditures are also considered.

Information was collected regarding the most commonly used medication types (eg. simvastatin and atorvastatin as types of statins). However, these types might not reflect the cost of the actual medication type used by individual participants. The PURE study did not collect information on combination medications, which may be used by some patients. The costs of such medications may be lower or higher than the cost of individual medications. Also, patients could be using ARBs (which are generally more expensive) instead of ACE-inhibitors, for which we did not collect costs for.

If the medication was not available in the pharmacy visited, patients could purchase their medications from another pharmacy in the same community or from an adjacent community that has the medications. If the costs of the same medication varied substantially between pharmacies in adjacent communities, this could affect the observed associations between availability and rates of use. However, results indicated that the driving factor of lack of affordability is the household's capacity-to-pay which greatly varied by country, rather than the cost of the medications which were more consistent across countries. The availability of aspirin was not associated with its use (unlike ACE-inhibitors, beta- lockers and statins) because it could be

purchased from locations other than pharmacies, and thus its availability in pharmacies might not be a true reflection of how available it is in the community.

6.4.3 Implications

Our results indicate that healthcare system level interventions are required to improve the availability and affordability of CVD medications, especially in MIC and LIC where the majority of CVD burden exists. Medication affordability is a function of the total cost of the four CVD medications and households' capacity-to-pay. Given that increasing households' capacity-to-pay requires sustained economic changes over several decades, especially in MIC and LIC where poverty levels are high, interventions should focus on reducing the costs of CVD medications incurred by patients to improve their use. Such interventions could include provision of essential medications at no or subsidized costs especially to poorer individuals, or further reductions in the price charged to patients in lower income countries.

Although not assessed in our study, the literature indicates that availability of CVD medications is usually lower in the public sector, although costs of medications are lower, compared to the private sector[97]. Healthcare system interventions aimed at improving the availability of medications in the public sector, at low cost, can improve their use. Medications can be made more available through an efficient medication supply chain that can forecast the appropriate amounts of medications needed and by avoiding spoilage through appropriate storage (e.g. temperature controlled and safe storage environment). A well-managed distribution system is also essential to ensure continuous and reliable availability of medications in the pharmacies[141]. Increasing the affordability of these medications can also be achieved through efficient medication supply chains. Selecting generic formulations of high quality, as opposed to originator brands can result in lower patient prices[107]. Similarly, introducing fixed dose

combinations (FDC) could result in lower procurement costs, as well as reducing storage and distribution costs, which can translate into lower costs at the patients' end. Reducing excessive mark-ups between procurement and patient prices as well as tariff and tax exemptions can further lower prices[107].

6.4.4 Conclusions

The medications assessed in this chapter have been proven to prevent recurrent CVD events and to reduce mortality, and all clinical guidelines recommend their use. Our results indicating the relatively low availability and affordability in MIC and LIC compared to HIC, are of concern, and should stimulate efforts to make CVD, and other essential, medications more available and affordable, through policy and health systems approaches.

Chapter 7

Discussion

7.1 Overview of main findings

Numerous evidence-based guidelines for prevention and management of cardiovascular disease (CVD) and hypertension have been published. However, substantial gaps exist between recommendations and their implementation[142]. Exploring the barriers that contribute to these gaps is essential for designing interventions to improving care [142].

The findings from the systematic review included in this thesis (chapter 2) showed that suboptimal control of hypertension may be due to barriers related detection, lifestyle change,

medication use, or follow up with a healthcare provider. Barriers were contextual and varied by study setting. Barriers to hypertension management in high income countries (HIC) were mostly related to patients' attitudes and motivation. For example, the commonest barrier to following up with a healthcare provider was inability to set it as a priority to do so. Because 80% of the studies included in this review were conducted in HIC, the results are mostly applicable to those settings. The limited data that were available from low income (LIC) and middle income (MIC) countries showed that the main barriers to hypertension management were predominantly related to the lack of healthcare facilities and inability to afford care.

Given the limited data on barriers to care in MIC and LIC in the literature, the remaining chapters of this thesis analyzed data from the Prospective Urban Rural Epidemiology (PURE) study from 17 countries to describe the availability and affordability of medications recommended for the secondary prevention of CVD, and their associations with rates of their use. Due to potential variations in barriers to medication use by context or setting (e.g. economic level of the country), results are presented separately for HIC, upper middle income countries (UMIC), lower middle income countries (LMIC), and LIC. Data from India, an LIC country, are presented separately, due to the unique nature of its pharmaceutical industry. Unlike other LIC, a large number of locally manufactured medications are available in India[97].

The results showed that the four medications recommended for patients with CVD (Angiotensin Converting Enzyme Inhibitors (ACE-inhibitors), beta-blockers, statins, and aspirin) are often not available in the PURE communities. Although these medications were almost always available in HIC, they were less frequently available in UMIC, LMIC, and LIC other than India, with lower availability in rural compared urban communities. Unlike other LIC, availability in India was high, with rates close to those of HIC. While medication affordability is

high in HIC, it was much lower in UMIC, LMIC, and LIC, including India. Medications were considered affordable if their total monthly cost did not exceed 20% of a households' capacity-to-pay. Using this threshold, CVD medications were not affordable for 26%, 32%, 55%, and 57% of households in UMIC, LMIC, LIC other than India, and India, respectively. By contrast, the four medications were unaffordable for less than one percent of the households in HIC. These results are based on the total cost of the medications; however if these medications were covered by private or government insurance systems these medications would be more affordable. Paradoxically, insurances and medication coverage by governments are more common in HIC compared to LIC where the majority of healthcare costs or met directly by the patient [97].

The PURE study previously demonstrated the low use of CVD medications, especially in MIC and LIC[13]. Results from the present analyses indicate that the lack of availability and affordability are important factors that contribute to the low rates of medication use. In fact, multivariable analyses demonstrated that availability and affordability were strongly associated with medication use even after adjusting for other factors that may influence medication use.

7.2 Methodological issues

Proper interpretation of research findings depends on the validity of the data and on the generalizability of results. This section discusses the internal validity of the findings reported in this thesis by considering how the participants were selected, how the explanatory variables and outcomes were measured, and how possible confounding was accounted for. Subsequently this section discusses the extent to which the findings are externally valid. Methodological issues related to effect modifiers and statistical analyses are also addressed.

7.2.1 Internal validity

Threats to internal validity can occur due to three types of bias: selection bias, information bias, and confounding.

1. Selection bias

Selection bias is a systematic error due to differences in characteristics that could modify the results between those who take part in the study and those who do not. It can occur in any type of epidemiologic study. For instance, selection bias can occur if certain individuals or population subgroups systematically refuse to participate in the study more often or choose to volunteer into the study more so than other individuals or groups. In cohort studies selection biases can also occur if the outcome of interest is not determined in a significant proportion of individuals initially selected for study (eg, due to loss to follow-up or withdrawal) [143]. The subjects that remain to be analyzed may no longer represent the source population from which the original sample was selected. If this distorts the direction or magnitude of the association of interest, then the observed results may be biased.

Findings from the systematic review: The likelihood of selection bias in the systematic review was assessed in terms of how representative the study sample was of the source population. Most studies adequately selected study participants from the source population (84% of included studies). However, the participation rate was low to moderate in most of the included studies. Only 16% of the studies reported a response rate higher than 85%, and therefore the possibility of selection bias cannot be ruled out. None of the studies compared the characteristics of participants and non-participants and therefore whether those who were excluded from the study differed systematically from those who were included could not be assessed.

Findings from the PURE study: Given the prospective design of the PURE study, the selection of countries and communities reflected a balance between involving a large number of urban and rural locations from different country income groups with substantial heterogeneity in social and economic characteristics and the feasibility of centres to successfully achieve long-term follow up. Households were selected from geographically identified communities. Common and standard approaches were applied to enumerate the households and identify eligible household members. The method of approaching households differed between countries, but was designed to avoid biases based on levels of risk factors or prevalence of any disease[19]. Among eligible participants, the inclusion rates were high (78%) and there were no systematic biases between those included and the overall eligible population[146]. The selection of communities as well as households and study participants was conducted prior to knowledge about medication use (the outcome of interest), and so medication use could not have influenced how subjects were selected into the study.

Restricting enrolment to communities and individuals where long-term follow-up was feasible, may result in under representation of some settings or some individuals in which such follow-up was not possible (e.g. nomadic populations, displaced populations, less keen or 'busy' individuals). However, previously published assessments of the characteristics of participants in the PURE sample showed substantial similarities with national data[123]. For example, 59.3% of PURE participants lived in urban communities, compared to an average of 63.1% of participating countries national statistics data. The PURE study had generally similar representation of men and women (sex ratio 95.1 men per 100 women versus 100.3) when compared to national statistics. Households in the PURE study also had a similar level of education compared to the average national statistics data (ie, 37.8% of PURE household

members completed secondary education compared to 31.3% in the national data). These findings indicate that the PURE sample reflects the population in the communities sampled in each of the PURE countries with reference to demographic characteristics. Additionally, the mortality rates in the communities studied from each country in PURE was similar to mortality data for each country obtained from independent sources, such as World Health Organization (WHO) statistics[123].These analyses additionally suggest that the information obtained in PURE can be a reasonable reflection of the country.

In prospective cohort studies, the long term commitment to the study can influence participation rates and the characteristics of individuals selected for the study. In the PURE study 22% of eligible individuals refused to participate in the study[13]. Participants and non-participants had similar measured characteristics and therefore the non-response rate is unlikely to have affected the accuracy of the findings[13]. Eleven percent of enrolled households did not report household income or spending on food and were subsequently excluded from the analyses of this thesis. Exploring characteristics of participants with missing household income data indicated that participants excluded from the analyses were less educated in UMIC, LMIC, and LIC and therefore our study sample may have overrepresented more educated households. , who were more likely to wealthier. Other measured characteristics were similar between included and excluded households.

2. Information bias

Information bias is a systematic error in the study arising from measurement error (ie, misclassification), or incorrect information obtained on one or more variables in the study. There are two types of misclassification errors in the context of examining the relationship between an exposure and outcome. Differential misclassification occurs when the error rate or probability of

being misclassified differs across groups of study subjects, which may magnify or dilute study estimates.[143] Non-differential misclassification occurs when all classes, groups, or categories of a variable (whether exposure, outcome, or covariate) have the same error rate or probability of being misclassified for all study subjects. This type of error is random and usually leads to diluted parameter estimates toward the null[144].

Findings from the systematic review: With a majority of studies (68%) not using validated instruments to assess the barriers to hypertension management, there is uncertainty as to the accuracy in assessing these variables. Among the studies that reported estimates of the effect of reported barriers on medication use (five studies), it is unlikely that the estimates of association were differentially biased, since the information on barriers was obtained using the same instrument among all participants without knowledge of the outcome (medication use). Therefore errors in the ascertainment of the barriers were likely random, which would dilute rather than magnify associations. In the estimates of prevalence of reported barriers to hypertension management, random measurement error in the instruments assessing barriers may under or overestimate the true prevalence depending on the direction of bias in the assessment tools which have not been validated.

Findings from the PURE study: Differential misclassification is unlikely to occur in the PURE study because data on the exposure (availability and costs of medications) were collected independent of knowledge of study outcome (medication use). If the methods used to collect information on the availability and costs of medications over or underestimated the actual availability and costs, this would occur similarly among all participants regardless of their medication use. Therefore it is likely to result in non-differential misclassification and dilute any observed associations towards the null.

Non-differential misclassification could have occurred during the data collection of the PURE study. Information on availability and costs of the medications was collected systematically by trained researchers using the Environmental Profile of Community's Health instrument (EPOCH). Researchers were instructed to identify one pharmacy at the centre of each community and inquire about medication availability and costs. If the pharmacy visited was atypical of the pharmacy in which the study participants purchase their medications, the assessment is done independently of information on medication use in the community, so the error in assessing cost and availability is likely to be non-differential, and so the estimates of association between availability and affordability and medication use are likely to be attenuated. However, there is little reason to believe that there are marked variations in costs of medications within the same community. Additionally, the results indicated that the variations in lack of affordability across country income groups was likely due to the large variations observed in household's capacity-to-pay rather in the cost of the medication.

Data on household income were also collected systematically for all participants in the PURE study. However, income data are prone to measurement error because participants may choose to conceal sources of income such as government stamps and other non-monetary income sources. Self-employed participants may also underreport their total income, especially in rural and lower income countries where self-employment is common. The literature therefore recommends using effective income (defined as total household expenditures) rather than directly asking about household earnings. Information on total household expenditures was not available in the PURE study and therefore household income was used in the analyses as a proxy measure. Comparisons between self-reported income with household expenditure data collected using standardized forms by the World Health Organization (WHO) from nine of the PURE

countries indicates good agreement between the two data sources suggesting that self-reported household income is reasonable robust to be used in the analyses conducted in this thesis. The positive correlation observed between the median values of household's capacity-to-pay collected in the PURE study and the country's per capita GNI further validates the information on capacity-to-pay.

3. Confounding bias

Confounding bias concerns how a measure of effect may change in value depending on whether variables other than the exposure variable are controlled for in the analysis[144]. Proper assessment of the association between an exposure variable and the outcome of interest requires identifying and statistically adjusting for potential confounders.

Findings from the systematic review: effects of barriers on medication use were pooled for studies that adjusted for at least age and sex in the original studies. Other potential confounders such as socioeconomic status were not necessarily adjusted for. Further, the data on the prevalence of barriers that were pooled across studies did not necessarily standardize the proportion of patients reporting barriers by age or sex which may further confound the pooled proportions.

Findings from the PURE study: The analyses of the PURE study examined the association between CVD medication availability and affordability and medication use. The analyses were adjusted for possible confounders based on a theoretical framework of determinants of medication use adapted from the WHO [110]. Variables adjusted for included age, sex, education level, years since CVD diagnosis, cancer diagnosis, use of other medications (glucose lowering or pain medications), smoking status, and size of the households (five or more members versus less than five). Our analyses showed a strong and statistically significant

association between medication use and its availability and affordability independent of these other factors. Data on patient knowledge and attitudes and on knowledge and communication skills of healthcare providers, which also affect medication use, were not collected in the PURE study and could not be accounted for in our analyses.

7.2.2 External validity

External validity pertains to the process of generalizing the findings of the study from the study population to other populations[145].

Findings from the systematic review: Most of the studies included in the systematic review sampled patients who attend a clinic to manage their hypertension (78% of studies). Such a study design is more feasible compared to a community based design because the population is sampled from a defined location (ie. clinic) rather than having to visit widely scattered households. Although more feasible, the barriers reported by patients in this systematic review may not be applicable to populations who do not have regular access to healthcare facilities. Additionally, only 20% of the studies included in the systematic review were conducted in MIC and LIC and therefore information on the reported barriers was applicable mostly to HIC.

As an attempt to overcome these limitations, the search strategy of the systematic review included terms such as “household” and “population” as an attempt to include household based studies. Further, studies written in any language were eligible for the review and not only those conducted in the English language. In fact three of the included studies were not written in the English language and were translated into English. To further ensure the inclusion of studies from LMIC the database “Global Health” was searched in addition to the more traditional databases such as “Embase” and “Pubmed”.

Results from the PURE study*:* The PURE study aimed to create a cohort of participants that is diverse in terms of country income (HIC, UMIC, LMIC and LIC), community location (urban and rural), social and economic circumstances policies, and participant socioeconomic status. To assess the external validity of the PURE study, it is important to determine whether or not the findings from the PURE countries could be generalized to other countries in the same geographic regions or similar economic status. The selection of the PURE countries depended on previous collaborations between researchers rather than probability sampling of countries around the world[122]. The need to restrict enrolment to those countries for which long-term follow-up was feasible, may also limit the ability to generalize the findings to other countries or communities where follow up is more difficult. However, the countries were selected from five continents and represented a broad range of country per capita GNI covering HIC, UMIC, LMIC, and LIC. Therefore results from the PURE study are likely to be reflective of these different country income groups.

7.2.3 Effect modification

Given the small number of studies that provided effect measures in the systematic review (n=5), stratifying the pooled analyses by subgroups was not possible. However, the barriers reported by HIC and other LMIC were qualitatively compared this indicated that the types of barriers reported varied by country income. Patients from HIC were more likely to report barriers related to knowledge and intentions. Patients from MIC and LIC reported barriers that were related to access to healthcare facilities.

In assessing the association between the affordability of CVD medications and their use in the PURE study, analyses were stratified by country income groups (HIC versus LMIC) current smoking status and by size of the household. These analyses for effect modification were

exploratory in nature. The lack of statistically significant interaction terms could be due to the absence of a true difference in the associations across the different subgroups, or alternatively it could be due to a lack of adequate power to examine effects within subgroups, given the relatively small sample size of patients using medications in each subgroup. In a larger study it may be expected that the effect of affordability will be stronger among patients who are current smokers as these patients may choose to spend their budget on cigarettes rather than on medications for CVD. Further, a patient living in a larger household but earning an income similar to that of a smaller household might be more sensitive to the cost of the medications; the effect of affordability on use might therefore be stronger among patients living in larger households.

7.2.4 Statistical analysis

In the systematic review, the proportion of participants who reported a barrier from each study were pooled under subthemes of the barriers to behavior change framework in order to identify how prevalent these subthemes of barriers were across the different study populations included in this review. This method of pooling the prevalence rates of barriers has been previously used in the literature on barrier assessment[45]. The prevalence of barriers representing the same subtheme was pooled from all studies primarily for illustration, and the pooled results should therefore be interpreted with caution due to the considerable heterogeneity observed in the results. Heterogeneity has been observed in previous studies that used similar methods of pooling proportions of reported barriers, reflecting a limitation in this research[45]. The random effects model was used to pool the data given the expected heterogeneity. A random effects model does not explain heterogeneity, but it provides wider confidence intervals around pooled estimates to account for the heterogeneity[41]. The systematic review highlighted that

heterogeneity across the reported barriers was high and indicated that a more systematic way of measuring barriers, using standardized and validated methods, may be necessary.

The PURE study sampling design included clusters of communities and selection of participants within each cluster. A multilevel logistical regression model was used to account for the homogeneity across participants within households and within communities. Adjusting for clusters does not influence the estimate but results in a wider confidence interval around the estimate to account for the clustering effect.

7.3 Policy implications

Our results indicate that the four medications recommended for patients with CVD are often not available in communities in MIC and LIC. When available, a high proportion of individuals would find them to be not affordable in these countries. The WHO acknowledged that access to CVD medications is an important barrier to care and has aimed for an 80% availability of affordable medications to combat non-communicable diseases globally by the year 2025[132]. However, the WHO did not define how available and how affordable these medications are currently or how they or countries would make such medications more available and affordable. Methods of documenting whether this goal has been reached in 2025 have not been identified either. Our results propose one method of measuring change in this goal. The strong association observed between our approach to measure affordability and medication use illustrates the validity of this method. Our results obtained from more than 600 communities also indicate that this measure is feasible across countries at different economic levels.

Additionally, our results indicate that healthcare system level interventions are needed to improve the availability and affordability of CVD medications. The secondary prevention of CVD requires lifelong treatment and following up with healthcare providers. Health insurance

that partially or fully covers out-patient medications can improve the affordability of medications. The best approach for the type of health insurance will depend on each country's healthcare system. Additionally, an efficient medication supply system can improve the availability and affordability of medications. The WHO suggests five steps to improving the management of medication supply at the healthcare system level[141]. This starts by developing a list of medications for the healthcare system to invest in. This can be achieved by developing an essential medication list (EML) that is tailored to the medication needs of the country. This is followed by forecasting medication quantities based on needs. Once medication types and quantities are identified, medications are procured through managing tenders, obtaining best prices, and assuring medicines quality. Medications are then properly stored in a way to prevent spoilage. Finally, medications are distributed to be used in medicine outlets[141].

Measures can be taken at each of these steps to improve the availability and affordability of CVD medications. Selecting fixed-dose combination medications (FDC) in the EML can lower procurement prices. FDC are formulations that include two or more active pharmaceutical ingredients combined in a single dosage form. Similarly, endorsing high quality generic medications as opposed to originator brand medications into the EML can help lower procurement prices[97]. Ensuring proper forecasting methods can prevent medication shortages and therefore improve availability. It can also prevent over-stocking which may lead to losses due to expiration or lack of storage space and therefore lead to inefficient use of resources. Proper storage practices can prevent medication loss due to spoilage. Finally, a well-managed distribution system is essential for constant supply of medications to outlets where patients can receive these medications. Again, using FDC medications rather than traditional medications can result in further savings in storage and distribution through reduced packaging and storing costs

due to the smaller number of pills, as well as more efficient distribution strategies and lower marketing costs.

CVD medications tend to cost less at public medication outlets compared to private outlets, although availability is considerably lower in public outlets[97]. Measures to improve medication supply at the healthcare system level can improve medication availability and affordability at public outlets. Further efforts to improve affordability from private outlets can be achieved by laws and regulations to avoid excessive mark-ups between procurement costs and the consumer price.[97]

CVD poses a large burden worldwide and although effective medications exist they are not available and not affordable at the community level. This calls for global innovative approaches that can be implemented at different settings and utilizing limited resources[34]. As discussed earlier, the use of FDC medications is one approach that can improve the management of medication supply at the healthcare system level and improve the availability and affordability of medications. Results evaluating several different types of FDC medications, referred to as polypills, indicate that a single pill of four or five active compounds can lower risk factors to a substantial extent, and that these pills are safe and tolerated[146].

Although methods of improving medication supply may result in increasing the availability and affordability of CVD medications they will not necessarily optimize their use. This is because other barriers to medication use exist. Using FDC medications that combine the four recommended CVD medications can result in benefits beyond those expected at the medication supply level. These benefits include increasing the ease of prescribing, and avoiding multiple steps for dose titration of each medication[147]. The effects of FDC on adherence were assessed in the Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE) trial,

which was conducted in India and three European countries. The UMPIRE trial randomized 2004 patients with established CVD or at risk of CVD to FDC delivery of aspirin, statin, and two blood pressure lowering medications versus usual care. After 15 months of follow-up the FDC group had improved adherence versus usual care with a 1.33 relative risk (RR) of being adherent (95% confidence interval (CI), 1.26-1.41). The FDC group also showed statistically significant improvements in systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-C) levels compared to the usual care group[148].

When combined with new models of healthcare delivery, such as non-physician health workers (NPHW), the use of FDC medications may lead to more widespread and cost-effective management of CVD. Given the ease of prescribing these medications with no need for titration, trained NPHW who may be more available and less costly compared to physicians can provide the medications without the need to travel to a healthcare facility to consult with a physician or the need to visit a pharmacy[147]. Trained NPHW can also advise patients on the importance of using and adhering to the medications as well as provide lifestyle advice[147]. These methods of care delivery have been effective in the management of other diseases such as HIV and maternal care on LMIC[149]; similar results are expected in the management of CVDs although further implementation research is needed in this area.

7.4 Conclusions

Numerous barriers to the management of hypertension and secondary prevention of CVD exist. We described many of the barriers to hypertension management in a systemic review of the literature. In addition, detailed analyses of the large PURE study from 17 countries indicate that the availability and affordability of the medications recommended for the secondary prevention of CVD substantially influences their use. Therefore healthcare system strategies to make these

medications more available and more affordable are essential for improving the rates of use of proven medications for secondary prevention.

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Appendices

Appendix 2.1: Search strategy for the systematic review (Medline)		
	Searches	**Results**
1	exp hypertension/	197869
2	hypertens$.tw.	284429
3	exp blood pressure/	233640
4	(blood pressure or bloodpressure).tw.	197506
5	1 or 2 or 3 or 4	554665
6	exp Guideline Adherence/ or exp Nurse Practitioners/ or exp Evidence-Based Medicine/ or exp Family Practice/ or exp Adult/ or exp Group Processes/ or facilitator*.mp. or exp Diabetes Mellitus, Type 2/	5259880
7	"healthcare facilities, manpower, and services"/ or advance directive adherence/ or guideline adherence/ or "healthcare quality, access, and evaluation"/ or "delivery of healthcare"/ or health services research/	98872
8	exp Medication Adherence/	3491
9	concordance.mp.	21649
10	exp Health Knowledge, Attitudes, Practice/ or exp Attitude to Health/ or exp "Attitude of Health Personnel"/	337276
11	exp Evidence-Based Medicine/	45306
12	exp Health Education/ or exp Access to Information/	127977
13	exp Health Behavior/ or exp Attitude to Health/	270858
14	exp Health Promotion/	44829
15	exp Health Behavior/ or exp Health Education/	196397
16	exp Health Services Accessibility/	73251
17	exp "Attitude of Health Personnel"/	107170
18	exp Physician's Practice Patterns/	34408
19	exp guideline/ or practice guideline/	22013
20	exp "Delivery of Healthcare"/	694729
21	exp Access to Information/	3431
22	exp Health Services Accessibility/ or accessibility.mp.	92630
23	exp Polypharmacy/ or exp Drug Combinations/ or polypill.mp.	56142
24	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	5817930
25	barrier*.mp.	140834
26	facilitator.mp.	2757
27	obstacle.mp.	9666

Appendix 2.1: Search strategy for the systematic review (Medline)		
28	25 or 26 or 27	152556
29	24 and 28	47232
30	5 and 29	1120
31	exp Policy/ or exp Organizational Policy/ or exp Nutrition Policy/ or exp Policy Making/ or exp Health Policy/	118195
32	exp Legislation, Medical/ or exp Legislation/ or exp Legislation as Topic/ or exp Legislation, Drug/	136128
33	organizations/ or exp government/ or exp government agencies/ or exp health planning organizations/ or exp international agencies/ or exp organizations, nonprofit/	164593
34	31 or 32 or 33	364850
35	24 or 34	6033781
36	28 and 35	48556
37	5 and 36	1126

Appendix 2.2: Detailed study characteristics of included qualitative studies

Study, year, Participants	Country	Recruitment site	Study focus	Population
Anthony, 2012 Patients	Israel	Large publicly financed health organization	to gain a deeper understanding of the beliefs, attitudes and coping mechanisms of patients with HT	Diagnosed with HT, with and without diabetes
Aroian, 2012 Patients	USA	Hispanic professional organization and a food service worksite	To explore attitudes and beliefs related to prevention and control of high BP among a diverse group of Hispanics living in Orange County, central Florida.	Not specific to HT patients
Barnes, 2012 Patients	USA	two primary care clinics utilized by immigrants and Mexican Americans	Describe knowledge of Mexican immigrants and Mexican Americans and their experiences with a diagnosis of hypertension as they lived with and engaged in care for high blood pressure	Diagnosed and treated for HT
Horowitz, 2004 Patients	USA	Harlem hospitals	Explore patients' perceptions of their condition, and the role of certain factors, in causing and controlling HT	Diagnosed and treated for HT
Fongwa, 2008 Patients	USA	Routine clinic visits	Identify factors associated with adherence to HT treatment in African American women	Diagnosed and treatment for HT
Ford, 2009 Patients	USA	Local churches of urban communities	To describe the perceptions of hypertensive Southern, rural African American women regarding factors that affect HT	Diagnosed with HT
Greer, 2010 Patients	USA	Outpatient clinic	To examine African American patient perceptions of racial discrimination in clinical encounters	Diagnosed with HT; kept 2 appointments
Machado, 2012 Patients	Brazil	Centre of reference in cardiovascular diseases (CRDC)	To understand perceptions of hypertensive patients regarding risk factors and experiences with high BP in the city of Salvador.	Diagnosed with HT
Murimi, 2010 Patients	USA	Local organizations, schools, and churches	Investigate personal, cultural, and external barriers that interfered with participating in a community preventive outreach program	Not specific to HT patients
Ogedegbe, 2003 Patients	USA	Two primary care practices	Perspectives of hypertensive African American patients regarding the factors they perceived as barriers or facilitators to adherence	HT patients taking at least 1antihypertensive
Park, 2012 Patients	Republic of Korea	local health centre in Seoul	to develop an effective education program for hypertension based on health belief model	hypertensive or pre-hypertensive patients
Peters, 2006 Patients	USA	Schools and churches	To explore the behavioral, normative, and control beliefs of African Americans relative to initiating and maintaining self-care behaviors necessary to control BP and prevent HT	Healthy community dwellers
Pham, 1999 Patients	USA	Organizations, local leaders, churches	Awareness and understanding of chronic conditions, healthcare barriers, and cultural beliefs in Philadelphia Vietnamese community	Not specific to HT patients
Schafheutle,2002 Patients	UK	Three community pharmacies	How charges for medicines incurred by patients influence their decisions for managing acute or chronic conditions	Not specific to HT patients
Wexler2, 2009 Patients	USA	The Ohio State University	Identify barriers and understand beliefs and attitudes of African American patients as they relate to HT	Diagnosed with HT

Appendix 2.2: Detailed study characteristics of included qualitative studies				
Cranney2, 2001 HCP	UK	Practice-based educational visits	To identify what is impeding GPs from implementing evidence-based guidelines in management of HT in the elderly (for an RCT)	GPs from nine practices in Merseyside
Crosson, 2010 HCP	USA	Outpatient primary care clinics	To assess how primary care physicians caring for patients with diabetes perceive barriers to achieving good BP control	Primary care physicians
Hernandez, 2012 HCP	USA	Urban, rural and suburban primary care clinics	To characterize the meaning nurse practitioners ascribed to provider/patient experiences and the NP role in health promotion and disease prevention of prehypertension	NPs caring for pre hypertensive patients
Howes, 2010 HCP	Australia	Southern Division of General Practice	Identify and explore barriers to initiating medication and treating elevated BP to target levels in the general practice setting	GPs and registrars
Howes 2, 2012 HCP	Australia	Southern Division of General Practice	Identify strategies to improve the management of hypertension in general practice	GPS
Hysong, 2012 HCP	USA	Veterans Affairs hospital outpatient clinics	To qualitatively identify participants' planning and improvement strategies in hypertension care	Primary care physicians
Kasje, 2002 HCP	Netherlands	1 Non-teaching and 2 university hospitals	To identify factors that may hinder or facilitate specialists use of joint treatment guidelines for primary and secondary care	Specialists
Parker, 2012 HCP	South Africa	Primary healthcare facilities	Barriers preventing the optimal utilization of health promotion	Physicians, nurses, and health educators
Kusuma, 2010 HCP & patients	India	Community dwellers	Perceptions of socio- economically disadvantaged migrants in Delhi regarding treatment seeking behavior for HT	Key informants, migrants from rural areas
Arrieta, 2009 HCP & patients	USA	Local organizations	Elicit challenges and solutions in the provision of healthcare to those with chronic diseases after Hurricane Katrina	Key informants, chronic diseases patients
HT= Hypertension BP= Blood pressure				

Appendix 2.3: Detailed study characteristics of included quantitative studies

Study, year, Participants	Country	Study aim	Population
Al-Ali, 2012 HCP	Egypt	To understand family physicians' reasons for not implementing WHO/ISH guidelines.	Family physicians
Cornuz, 2000 HCP	Switzerland	Importance of identified barriers to preventative interventions	General physicians
Flynn, 2012 HCP	Ireland	To quantify the use of clinical guidelines for hypertension and identify the role of ABPM in General Practice and barriers to its use	General practitioners
Henegan, 2007 HCP	UK	GPs' awareness of current HT guidelines and their self-reported implementation of them in clinical practice	General practitioners
Holland, 2008 HCP	USA	Role of clinical inertia in the treatment of patients with HT was assessed	Physicians and support staff
Lin, 2006 HCP	USA	Factors contributing to low adherence of clinical guidelines based on clinician feedback on recommendations displayed at the point of care	Physicians and nurses caring for HT patients
Mahabir, 1997 HCP	Trinidad	Providers' views and barriers to their practice of measuring BP, deciding the need for treatment, and selecting therapeutic drugs	Medical practitioners
Oliveria1, 2002 HCP	USA	Identify barriers to primary care physicians' willingness to increase the intensity of treatment among patients with uncontrolled HT	Physicians treating patients with uncontrolled BP
Reiner, 2010 HCP	Croatia	To examine physicians' knowledge and perception of CVD risk factors and barriers to guideline implementation	GPs and specialists
Roumie, 2007 HCP	USA	Provider responses to computer alerts regarding guideline recommendations for patients with suboptimal HT care	Physicians, nurses, and physician assistants
Schmieder, 2012 HCP	Europe	To understand attitude of physicians towards clinical guidelines for CVD prevention, cardiovascular risk assessment tools, and patient management in Europe	Primary care physicians, cardiologists, endocrinologists, diabetes specialists, and internal medicine specialists
Wang, 2004 HCP	China	Investigate the levels of understanding and implementation of current HT guidelines	Cardiologists
Waxler1, 2004 HCP	USA	Patient and physician barriers to HT treatment and physician decision making in the management of HT	family medicine and internal medicine physicians
Coleman, 2000 Patients &HCP	USA	Case study reemphasizes the importance of a holistic, integrated approach to any continuous quality improvement	Diagnosed with HT and uncontrolled BP
Dean, 2007 Patients &HCP	UK	To examine potential barriers to adequate BP control in patients with poorly controlled HT	Uncontrolled HT patients and their physicians
Kobalava, 2007 Patients &HCP	Russia	Problems of physician-patient cooperation and physician related barriers to target BP achievement	Diagnosed with NTH
Mendis, 2004 Patients &HCP	Nigeria	Capacity of health-care facilities in a low-resource setting to implement the absolute risk approach assess CVD risk among HT patients	Patients diagnosed with HT, Physicians, Non-physician health-care providers

Appendix 2.3: Detailed study characteristics of included quantitative studies			
Ahluwalia, 1997 Patients	USA	To identify correlates of controlled HT in a largely minority population of treated hypertensive patients	Inner city HT patients who previously filled an HT prescription
Bovet, 2008 Patients	Switzerland	To determine proportion of persons who utilized health services after being diagnosed as hypertensive	Population survey participants who had raised BP but untreated for HT
Cummings, 1982 Patients	USA	Examines the relationship of health beliefs, knowledge, and barriers to receiving care and drug treatment maintenance	HT patients previously or currently on HT treatment
Dennison, 2007 Patients	South Africa	To examine determinants of HT care and control among peri-urban hypertensive Black South Africans	Patients diagnosed HT, attended a clinic within previous 12 months
Edelman, 2008 Patients	USA	To assess follow-up practices among individuals found to have elevated cardiovascular disease (CVD) risk factors	HT, pre HT, sub optimal lipids, or abnormal blood glucose participants of the (FIT Heart) RCT
Gee 1, 2012 Patients	Canada	Self-reported adherence to antihypertensive medications, and reasons for not using and occasionally missing doses of antihypertensive drugs.	Self-reported HT patients from 2008 Canadian Community Health Survey &2009 Survey on Living with Chronic Diseases in Canada
Gee 2, 2012 Patients	Canada	Prevalence of Canadian adults with HT who use lifestyle changes to control blood pressure. And barriers to self-managing elevated blood pressure	Self-reported HT patients from the 2008 Canadian Community Health Survey
Gregoire, 2002 Patients	Canada	Examine the effects of potential predisposing, enabling and reinforcing factors on the discontinuation of initial HT medication	HT patients newly prescribed an antihypertensive monotherapy
Hassan, 2006 Patients	Malaysia	To identify the predictors of medication noncompliance among HT patients	HT patients who had been on treatment for at least 3 months
Hill, 1999 Patients	USA	examining barriers to being in care and having adequate control of BP among African American men	HT patient participating in an RCT
Hong, 1006 Patients	USA	Barriers to adherence to anti-hypertensive medication	USA veterans diagnosed with HT
Hsu, 2010 Patients	USA	HT medication adherence in relation to the demographic attributes and the perception of need, effectiveness and safety.	Chinese American elders diagnosed with HT
Joyner-Grantham, 2009- Patients	USA	Assessed and identified gaps related to “patient inertia” factors and the control of BP	Hypertensive emergency department (ED) patients
Krousel-woods, 2008 Patients	USA	Examining barriers in post disaster situations which may reduce adherence	hypertensive patients receiving care at a multispecialty group practice
Mochari, 2007 Patients	USA	Assess BP and cholesterol knowledge, awareness of CVD risk, and factors associated with non-adherence to CVD medications and lifestyle goals.	racial/ ethnic minorities visiting Ambulatory Care in Harlem
Nelson2, 1978 Patients	USA	Examined the relationships between patients' perceptions of health, disease, medical treatment and medication compliance	HT patients on treatment
Oliveria2, 2005 Patients	USA	To assess HT knowledge, awareness, and attitudes related to SBP	HT patients from a primary care setting
Peltzer, 2004 Patients	South Africa	Examine the relationships between health beliefs variables and the use of both HT medications and alternative healing agents	HT patients attending an out-patient clinic in rural South Africa

Appendix 2.3: Detailed study characteristics of included quantitative studies

Serour, 2007 Patients	Kuwait	To measure adherence and barriers of complying with lifestyle recommendations among patients with high cardiovascular risk factors	HT or type 2 diabetes patients, diagnosed for at least 1 year
Shulman, 1986 Patients	USA	Associations between education, socioeconomic class and economic barriers to HT medication adherence	Population survey; analysis included those with raised BP only
Thomas, 2011 Patients	India	To assess medication adherence in hypertensive patients and to identify the main barriers associated with medication adherence	HT patients treated for at least 6 months
Turner, 2009 Patients	USA	To examine the effect of antihypertensive adherence on BP and barriers to adherence in racially diverse elderly patients	HT patients with prescribed medication
Thrope, 2006 Patients	USA	To measure the association between psychological distress and adherence to USPSTF-recommended preventive care services among older adults in the	Community-dwelling elderly
Vawter, 2008 Patients	USA	To characterize the reasons for antihypertensive medication non adherence	Healthy Styles survey respondents who received prescriptions for HT medications
Wee, 2012 Patients	Singapore	To determine hypertension awareness, treatment and control, in a multi-ethnic urban lower and higher SES Asian communities in same geographic location.	General population of 2 communities with different SES status
Williams, 1998 Patients	USA	Relationship between functional health literacy level of patients and knowledge of their chronic disease and treatment	Patients with HT or diabetes presenting to general medicine clinics
Youssef, 2002 Patients	Egypt	Impediments to pharmacological and non-pharmacological compliance among patients with HT	HT patients attending health insurance clinics for prescription refills

HT= Hypertension
BP= Blood pressure

Appendix 2.4: Quality appraisal of qualitative studies

	Question/ objective sufficiently described?	Study design evident and appropriate?	Context for the study clear?	Connection to a theoretical framework / wider body of knowledge?	Sampling strategy described, relevant and justified?	Data collection methods clearly described and systematic?	Data analysis clearly described & systematic?	Use of verification procedure(s) to establish credibility?	Conclusions supported by the results?	Reflexivity of the account?
Anthony, 2012 Patients	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No
Aroian, 2012 Patients	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No
Barnes, 2012 Patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Horowitz, 2004 Patients	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Fongwa, 2008 Patients	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Ford, 2009 Patients	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
Greer, 2010 Patients	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Machado, 2012 Patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Murimi, 2010 Patients	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Ogedegbe, 2003 Patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Park, 2012 Patients	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No
Peters, 2006 Patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Pham, 1999 Patients	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Schafheutle, 2002Patients	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Wexler2, 2009 Patients	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Cranney2, 2001	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No

Appendix 2.4: Quality appraisal of qualitative studies										
HCP										
Crosson, 2010 HCP	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No
Hernandez, 2012 HCP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Howes, 2010 HCP	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No
Howes 2, 2012 HCP	Yes	No	No		Yes	No	Yes	Yes	No	Yes
Hysong, 2012 HCP	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No
Kasje, 2002 HCP	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No
Parker, 2012 HCP	Yes	Yes	Yes	No	No	No	No	No	Yes	No
Kusuma, 2010 HCP & patients	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No
Arrieta, 2009 HCP & patients	No	Yes	No	No	Yes	No	Yes	No	Yes	No

Appendix 2.5: Quality appraisal of quantitative studies

Study, year population	Study sample represents population of interest on key characteristics, sufficient to limit potential bias to results	Response rate (%)	Exposure measures well defined and robust to misclassification bias? i.e used a validated tool	Outcome measures well defined and robust to misclassification bias? i.e objective and not self-reported, or validated if self-reported	Controlled for confounding (if applicable)
Al-Ali, 2012	No	73	No	No	N/A
Cornuz, 2000 HCP	yes	72	no	yes	N/A
Flynn, 2012 HCP	No	68	No	No	No
Henegan, 2007 HCP	no	50	yes	no	N/A
Holland, 2008 HCP	yes	Not stated	no	yes	N/A
Lin, 2006 HCP	yes	Not stated	yes	yes	N/A
Mahabir, 1997 HCP	yes	64	no	yes	N/A
Oliveria1, 2002 HCP	yes	86	yes	yes	N/A
Reiner, 2010 HCP	yes	Not stated	no	no	N/A
Schmieder, 2012 HCP	Yes	Not stated	no	N/A	No
Wang, 2004 HCP	yes	71	no	yes	N/A
Waxler1, 2004 HCP	no	Not stated	yes	N/A	N/A
Dean, 2007 Patients &HCP	Yes	Not stated	No	Yes	No
Coleman, 2000 Patients &HCP	Yes	Not stated	No	Yes	No
Kobalava, 2007 Patients &HCP	Yes	71	No	Yes	N/A
Mendis, 2004 Patients &HCP	Yes	51	No	Yes	N/A
Ahluwalia, 1997 Patients	Yes	51	No	No	Yes
Bovet, 2008	Yes	77	No	Yes	yes

Appendix 2.5: Quality appraisal of quantitative studies					
Patients					
Cummings, 1982 Patients	No	66	No	Yes	no
Dennison, 2007 Patients	No	Not stated	Yes	No	yes
Edelman, 2008 Patients	Yes	Not stated	No	Yes	yes
Gee1, 2012 Patients	Yes	NA	No	No	Yes
Gee2, 2012 Patients	Yes	78	No	Yes	N/A
Gregoire, 2002 Patients	Yes	98	No	Yes	yes
Hassan, 2006 Patients	Yes	98	Yes	Yes	yes
Hill, 1999 Patients	Yes	Not stated	Yes	Yes	N/A
Hong, 1006 Patients	Yes	Not stated	yes	Yes	no
Hsu, 2010 Patients	Yes	94	Yes	Yes	no
Joyner-Grantham, 2009- Patients	Yes	87	Yes	No	no
Krousel-woods, 2008 Patients	Yes	90	No	No	yes
Mochari, 2007 Patients	Yes	Not stated	No	Yes	yes
Nelson2, 1978 Patients	Yes	77	No	No	yes
Oliveria2, 2005 Patients	Yes	72	No	No	yes
Peltzer, 2004 Patients	Yes	Not stated	No	No	no
Serour, 2007 Patients	Yes	Not stated	No	Yes	no
Shulman, 1986 Patients	Yes	86	No	Yes	N/A
Thomas, 2011 Patients	Yes	Not stated	Yes	No	no
Thrope, 2006 Patients	Yes	Not stated	Yes	No	N/A

Appendix 2.5: Quality appraisal of quantitative studies					
Turner, 2009 Patients	Yes	67	Yes	No	yes
Vawter, 2008 Patients	No	63	No	No	yes
Wee, 2012 Patients	Yes	78	No	No	N/A
Williams, 1998 Patients	Yes	71	No	Yes	no
Youssef, 2002 Patients	Yes	Not stated	No	No	yes

Appendix 2.6: Counts and examples of barriers per theme among qualitative studies			
	Number of studies	**Examples of patient barriers (n=17)[1]**	**Examples of provider barriers (n=10)[1]**
capability	**Knowledge** N=9 patient studies N=2 provider studies	- HT is a temporary disease (Anthony) - Service availability (Murimi) - Consequences and risk factors of HT (Pham, Kusuma, Barnes, Carol, Waxler2(Anthony) (Mochado) - BP readings and normal levels (Barnes) - The need for HT education classes (Pham) and diet programs to manage and prevent HT (Barnes) (Peters)	- Dealing with elderly comorbidities (Howes 1). - Guidance on home BP monitoring (Howes 2)
	Skills N=2 patient studies N= 3 provider studies	- Patient communication skills (Ogedebe) - Checking BP at home (Barnes)	- Keeping up with new clinical information (Howes) - Training in education and counseling (Parker) - Addressing pre hypertension (Hernande)
Intention	**Motivation and goals** N=2 patient studies N=3 provider studies	- Too lazy and too tired to exercise (Ford) - Not putting enough effort or thought into treatment (Anthony)	- "I'm sure that at 6 o'clock on Friday, I'm not that fussed whether its 160 or 164- I just want to go home" (cranny 2) - ". . .as a caregiver you get tired of saying the same thing over and over and over again" (Parker) - Difficulties and failures in addressing health promotion and lifestyle changes (Hernande)
	Beliefs about consequences N=7 patient studies N=5 provider studies	- No need for medications if no symptoms (Schaufleid, Ogedegbe, Aroian) - Dependence on medication (Fongwa, Ogedegbe) - Doubts over association between challenging lifestyle and HT (Carol, Waxler2) - Denial of hypertension diagnosis (Anthony) - Preference of lifestyle modifications over medical treatment (Aroian) - Fatalistic perspective: "It's all in God's hands" (Peters) or "it runs in the family there is nothing I can do about it" "(Waxler2)	- Uncertainty regarding accuracy and representativeness of individual BP readings (Howes) - Doubted the efficacy of certain medications (Kusuma) - Reluctant to initiate aggressive blood pressure lowering medications due to possible side effects (Cranny2) - Following guidelines will not improve outcomes (Kajse) - Accuracy and representativeness of individual BP readings during the visit (Howes) (Howes2)
	Nature of behavior (Breaking habit) N=7 patient studies N= 1 provider study	- Difficulty changing dietary habits "change is hard," "habits are hard to break," (Fongwa, Greer, Waxler2, Carol, Park, Peters). - Difficulty of long term medication adherence (Ford, Ogedegbe, Kusuma).	- Routine and satisfaction with current behaviour (Kasje)
	Social influence N=6 patient studies N= 3 provider studies	- Lack of family support as a barrier to eating healthy food (Ford) and to clinical care (Ogedegbe)(Kusuma) (Murimi) - Having to cook for oneself differently from the rest of the family (Ford, Carol, Waxler2, Park) - Spending time with other Hispanics created fairly regular opportunities for unhealthy eating (Aroian) - Social pressure: Healthy behaviors, including exercise may not be socially acceptable (Aroian, Peters) - Being overweight viewed as preferable or "healthy" in some cultures (Aroian, Peters)	- Reluctance to initiate treatment in 'someone else's patient' (Howes), - Poor coordination between different practices (Crosson) (Hernande) (Howes2) - Achieving consensus in practice 'Standardization of measurement (Howes2)

Appendix 2.6: Counts and examples of barriers per theme among qualitative studies			
	Behavioral regulation (Priority setting) N= 8 patient studies N= 2 provider studies	- Work schedule and family obligations interfered with exercise, diet, attending clinic visits and overall HT control HT (Murimi, Schafelid, Greer, Waxler2, Ford, Aroian, Park) - Changing diet, quitting smoking and exercise disrupts lifestyle (Anthony)	- Acute medical conditions compete with HT during the visit (Crosson, Kasje)
	Professional identity/ agreement with guidelines N= 3 provider studies	NA	- Lack of trust in guidelines (Howes) (Kajse) - Impracticality of guidelines (Cranny2) - Ambiguous role identity, and nurses not differentiated from physician assistants (Herande)
	Beliefs about capabilities N=1 provider study	NA	- Beliefs that providers cannot perform according to the guidelines (Kasje)
	Emotion (Stress and anxiety) N= 4 patient studies	- Stress is a major cause to non-adherence and lack of HT control (Carol, Fangwa, Ford, Waxler2, Anthony)	NA
	Memory and attention N= 4 patient studies	- Forgetting to take medication (Greer) (Ford) (Ogedegbe) (Barnes)	NA
Healthcare system	**Availability** N= 13 patient studies N= 9 provider studies	- Lack of exercise facilities (Ford, Peters), grocery stores with healthy foods (Fongwa), dietary counselling (Carol), and healthcare facilities (Kusuma, Peters) - Limited food choices when eating out (Park) - Transportation difficulties affecting clinic visits (Pham, Barnes) and medication refills (Greer, Barnes) - Timing of screening services conflict with working ours (Murimie) - Difficulties getting clinic appointments (Ogedegbe) - Short duration of consultation time (Kusuma) - Lack of interpreter services (Pham) and information targeted specifically to African American health (Waxler2). - Commercials only encourage bad eating habits (Peters)	- Lack of consultation times (Cranny2, Crosson, Kasje, Kusuma, Parker, Herande) - Lack of space and equipment and shortage in staff (Parker) - Disruption of treatment due to severed supply channels and inoperable pharmacies after disasters (Martha). - Difficulties in locating guidance to providing care (Howes) - Guidelines are available but inaccessible (Parker) - Need simpler guidelines that are practical at the general practice (Howes 2)
	Affordability/ financing N= 9 patient studies N= 5 provider studies	- lack of insurance, out of pocket payments, and high costs of treatment (Shawfild, Aroian, Barnes), resulting in seeking care only in acute problems (Pham, Ford, Greer, Waxler2, Martha, Kusuma) - Healthy food (Waxler2, Ford, Carol, Aroian, Peters) and exercise facilities (Peters) are too costly	- Insufficient financial reimbursement and incentives (Crosson, Kasje, Cranny2, Hernande, Howes2)
	Acceptability N= 6 patient studies	- Lack of respect (Kusuma), lack of attention (Barnes), and unfair treatment (Greer). - Provider- patient communications (Ogedegbe) - Lack of trust in the services provided (Greer, Peters)	NA
	Medication Related N= 5 patient studies	- Medication side effects (Schawfil, Fangwa, Ford, Ogdegbe, Anthony) - Dosing frequency, taste, and large pill size (Ogedegbe).	NA
1 The two studies with providers and patient barriers are included in both columns - HT = hypertension- NA= not available			

Appendix 5.1: list of amenities included in the wealth index score developed for the PURE study
Electricity
Car
Other four wheeler
Computer
Television
Motor bike
Livestock
Fridge
Washing machine
stereo
bike
kitchen
mixture phone
land
kitchen window

Appendix 5.2: Median (IQR) income in local currency (CPI, 2010), n=107,284 households

Country	Currency	N*	Household income	Household expenditure on food	Household capacity-to-pay
Sweden-Urban	Krona	1,937	42069 26029-57265	4,257 3,020-5,726	37,482 22,648-52,342
Sweden-Rural	Krona	478	37243 26029-48311	3,725 3,020-5,033	33,318 23,010-43,729
Canada-Urban	Canadian dollar	4,801	6,593 4,665-8,932	510 357-763	5,962 2,986-8,115
Canada-Rural	Canadian dollar	1,753	4,892 3,266 – 8,905	510 407 - 679	4,475 2,875-7,888
UAE – Urban	Dirham	630	19,551 11,500-25,613	5,123 3,074-6,147	13,319 7,172-20,490
UAE-Rural	Dirham	323	10,245 7,479-15,368	4,098 3,026-5,123	6,147 3,074-10,245
Poland-Rural	Zloty	912	3,618 2,226-5,332	1,113 890-1,669	2,226 1,280-3,626
Poland-Rural	Zloty	587	2,226 1,558-3,338	1,027 640-1,335	1,335 779-2,179
Chile – Urban	Peso	1,759	200,000 140,000-400,000	100,000 60,000 - 150,000	120,000 70,000-250,000
Chile-Rural	Peso	464	88,099 50,705-140,000	50,000 35,000-70,000	526 326-760
Turkey-Urban	Lira	1,784	1,154 760-1,730	434 326-577	728 434-1,194
Turkey-Rural	Lira	858	859 597-1,086	326 217-434	526 326-760
Brazil-Urban	Real	2,831	3,305 1,763- 6,610	661 441-1,102	2,699 1,212-5,188
Brazil-Rural	Real	871	914 582-1,432	349 233-466	578 296- 965
Malaysia-Urban	Ringgit	4,229	2,034 1,023 - 4,068	512 407-1,017	1,526 712-3,560
Malaysia-Rural	Ringgit	5,667	1,017 512 – 1,526	407 254-512	509 203-1,017
South Africa-Urban	Rand	1,387	1,089 1,010-2,178	500 349-700	700 461-1,536
South Africa-Rural	Rand	1,029	1,043 698-1,251	521 349-834	391 100-680
Argentina-Rural	Peso	1,259	1,391 904- 2,046	767 511-1,060	575 278-1,108
Argentina-Rural	Peso	899	1,994 1,177-3,102	942 589-1,413	997 471-1,790
Colombia - Urban	Peso	2,585	852,615 505,254-1,598,654	409,113 251,053-639,461	409,113 191,838-982,974
Colombia-Rural	Peso	2,535	361,068 213,154-511,391	228,068 153,417-342,102	102,278 22,807-228,068

Appendix 5.2: Median (IQR) income in local currency (CPI, 2010), n=107,284 households

Iran-Urban	Toman	1,645	4,956,172 3,311,276-7,158,915	275,3429 1,875,089 - 3,750,179	2,000,095 1,101,372-3,311,276
Iran-Rural	Toman	1,348	3,304,114 2,500,119 - 4,405,486	1,652,057 1,101,371-2,354,172	1,569,448 784,724-2,354,172
China – Urban	Renminbi	15,683	2,360 1,706-3,463	1033 693-1,303	1,365 683-2,309
China – Rural	Renminbi	14,700	1,138 683-2,078	410 231-616	750 341-1,365
oPt-Urban	NIS	911	2,000 1,200 - 3,000	1,500 1,000 - 2,000	500 0-1,000
oPt – Rural	NIS	642	2,000 1,500 - 3,000	1,500 1,000 - 2,000	750 0-1,300
India-Urban	Rupee	7,798	10,764 4,930-22,176	4,557 2,862-6,823	6,011 1,643-15,611
India-Rural	Rupee	9,037	3,287 1,781-5,725	2147 1431-3287	822 317-2,279
Pakistan-Urban	Rupee	572	20,000 13,666 - 30,748	12000 8935-17082	6,000 3,416-15,000
Pakistan-Rural	Rupee	471	6,097 4,555-9,110	4555 3416-6833	1,139 1,000-2,278
Bangladesh-Rural	Taka	1,052	10,259 6,839 - 13,679	5700 4560-7979	3,420 1,710-5,700
Bangladesh-Urban	Taka	945	6,839 5,130-11,399	4560 3420-6839	2,280 1,140-4,560

***numbers refer to PURE participants missing income, expenditure on food, or both**

Appendix 5.3: Measured characteristics of participants included in the this analysis (study sample) versus excluded participants

	HIC		UMIC		LMIC		LIC	
	Excluded participants	**Study sample**	**Excluded participants**	**Study sample**	**Excluded participants**	**Study sample**	**Excluded participants**	**Study sample**
N	1,738	13,382	8,434	34,245	3,729	58,573	3,426	30,418
Mean age (years)	54	53	51	51	52	51	49	48
% Females	56	54	61	59	62	58	58	56
% Current Smokers	16	13	25	22	17	21	27	23
% Low education	12	12	65	49	59	39	57	51
% CVD	6	5	4	4	7	7	3	3

- **Excluded participants are those who did not report enough information to calculate capacity-to-pay values**
- **Information on years since diagnosis and use of CVD medications were compared across participants with a history of CVD only**
- **HIC=high income countries; UMIC=upper middle income countries; LMIC=lower middle income countries; LIC=low income countries**

Appendix 5.4: Availability and median (IQR) cost, local currency (CPI, 2010) of ACE-inhibitors, n=606 communities (monthly recommended standard dose)

		Captopril		Enalapril		Ramipril		Lowest cost of ACE-inhibitors		
Country	**N**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
Sweden-Urban	20	100% (20)	115 115- 115	100% (20)	34 34 - 34	100% (20)	21 21 - 21	100% (20)	21 21- 21	21 21- 21
Sweden-Rural	3	100% (3)	115 115- 115	100% (3)	34 34 - 34	100% (3)	21 21 - 21	100% (3)	21 21- 21	21 21- 21
Canada-Urban	36	88% (32)	62 37- 67	97% (35)	53 44- 70	100% (34)	36 17 - 30	100% (36)	36 17 -30	36 17 -30
Canada-Rural	22	60% (12)	38 36- 42	93% (20)	49 40 -52	100% (21)	18 18 - 20	100% (21)	18 18 - 20	18 18 - 20
UAE-Urban	1	100% (1)	102	100% (1)	63	100% (1)	114	100% (1)	63	63
UAE-Rural	2	50% (1)	103	50% (1)	67	50% (1)	114	100% (2)	85 67 -103	85 67 -103
Poland-Urban	1	100% (1)	21	100% (1)	9	100% (1)	4	100% (1)	4	4
Poland-Rural	3	100% (3)	21 11-22	100% (3)	9	100% (3)	6 4 -13	100% (3)	6 3 - 9	6 3 - 9
Chile-Urban	2	100% (2)	8,655 8,430 – 8,880	100% (2)	3,135 2,970 – 3,300	0	NA	100% (2)	3,135 2,970 - 3,300	3,135 2,970- 3,300
Chile-Rural	3	100% (3)	6750	100% (3)	1,050 1,050 - 1,050	0	NA	100% (3)	1,050 1,050 -1,050	1,050 1,050 -1,050
Turkey-Urban	25	92% (23)	11 11 - 11	92% (23)	8 8 - 8	100% (25)	10 10 – 10	100% (25)	8 8 - 8	8 8 - 8
Turkey-Rural	13	100% (13)	11 11 - 11	100% (13)	8 8 - 8	100% (13)	20 20 – 20	100% (13)	8 8 - 8	8 8 - 8
Brazil-Urban	7	100% (7)	39 22-43	100% (7)	15 12 -24	71% (5)	41 36 -54	100% (7)	15 12 - 24	15 12 - 24
Brazil-Rural	7	100% (7)	4 4 - 29	100% (7)	3 3 -18	86% (6)	54 54 - 54	100% (7)	3 3 - 18	3 3 - 18
Malaysia-Urban	18	44% (7)	36 29 - 68	61% (11)	36 32 - 57	28% (5)	55 52 - 67	61% (11)	34 29- 42	18 18 - 24
Malaysia-Rural	15	20% (3)	45 42 - 54	33% (5)	45 43 -60	13% (2)	56 45 -179	33% (5)	49 35- 60	35 27 - 60

Appendix 5.4: Availability and median (IQR) cost, local currency (CPI, 2010) of ACE-inhibitors, n=606 communities (monthly recommended standard dose)

		Captopril		Enalapril		Ramipril		Lowest cost of ACE-inhibitors		
Country	**N**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
South Africa - Urban	3	33% (1)	NA	33% (1)	61	33% (1)	146	67% (1)	61	61
South Africa - Rural	3	33% (1)	34 34 - 34	33% (1)	73	33% (1)	144	33% (1)	34	34
Argentina-Urban	6	0	NA	100% (6)	22 22 - 22	67% (4)	10 10 – 10	100% (6)	10 10 - 22	10 10 - 22
Argentina-Rural	14	7% (1)	0	100% (13)	24 22- 37	21% (3)	24 9 -126	100% (13)	22 20 - 37	22 20 - 37
Colombia-Urban	35	94% (33)	7,200 6,000 - 9,000	97% (34)	4,800 3,800 – 6,000	0	NA	97% (34)	5,100 3,800 – 6,000	5,100 3,800 – 6,000
Colombia-Rural	23	83% (18)	8,250 4,800 - 18,000	83% (18)	6000 2,400 – 6,600	0	NA	83% (18)	4,800 2,400 – 6,000	4,320 2,000 - 6,000
Iran-Urban	11	100% (11)	1,386 1,386- 1,395	100% (11)	960 960- 960	0	NA	100% (11)	960 960 -960	960 960 - 960
Iran-Rural	9	100% (9)	1,386 1,350-1,395	100% (9)	960 960- 960	0	NA	100% (9)	960 924 - 960	960 924 - 960
China-Urban	44	84% (35)	4 2 - 8	0	NA	11% (5)	670 667 - 787	84% (35)	4 2 - 8	3 1 - 4
China-Rural	64	59% (33)	3 3 -11	0	NA	0	NA	58% (1)	3 3 - 11	3 1 -4
oPt-Urban	21	19% (4)	22 7 - 116	90% (18)	6 0 - 6	10% (1)	32	90% (18)	6 0 - 6	6 0 - 6
oPt-Rural	18	17% (3)	0	67% (12)	6 0 - 6	6% (1)	0	72% (13)	6 0 - 6	6 0 - 6
India-Urban	38	32% (12)	337 337- 341	95% (36)	187 183- 192	92% (35)	321 234 - 323	97% (37)	187 184 - 192	187 184 - 216
India-Rural	52	52% (27)	382 321-383	90% (47)	176 170-184	50% (37)	207 150 - 207	94% (33)	170 150 - 176	170 150 - 176
Pakistan-Urban	2	50% (1)	598	0	NA	50% (1)	180	50% (1)	180	180
Pakistan-Rural	2	50% (1)	599	50% (1)	300	50% (1)	321	50% (1)	300	300

Appendix 5.4: Availability and median (IQR) cost, local currency (CPI, 2010) of ACE-inhibitors, n=606 communities (monthly recommended standard dose)

		Captopril		Enalapril		Ramipril		Lowest cost of ACE-inhibitors		
Country	**N**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
Bangladesh-Urban	57	2% (1)	360	25% (14)	75 75 -76	18% (10)	150 150- 150	28% (16)	75 75 - 99	61 61 - 75
Bangladesh-Rural	26	100% (26)	NA	4% (1)	75	4% (1)	180	4% (1)	75	75

NA= Cost of medication not collected because the medication type is not available in the community
***estimated median= if a cost was not collected because the medication was not available, the cost of the medication was estimated based on the lowest cost in the country**

Appendix 5.5: Availability and median (IQR) cost, local currency (CPI, 2010) of beta-blockers, n=606 communities (monthly recommended standard dose)

		Metoprolol		Atenolol		Lowest cost of beta-blockers		
Country	**N**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
Sweden-Urban	20	100% (20)	103 103 - 103	100% (20)	15 15 - 15	100% (20)	15 15 - 15	15 15 - 15
Sweden-Rural	3	100% (3)	103 103 - 103	100% (3)	15 15 - 15	100% (3)	15 15 - 15	15 15 - 15
Canada-Urban	36	97% (33)	23 11- 29	100% (36)	21 12 24	100% (36)	21 12-24	21 12 - 24
Canada-Rural	22	100% (15)	12 10-14	100% (22)	14 14 16	100% (22)	12 10-14	12 10 - 14
UAE-Urban	1	0	NA	100% (1)	40	100% (1)	40	40
UAE-Rural	2	0	NA	100% (2)	40	100% (2)	40 40 – 40	40
Poland-Urban	1	100% (1)	8	100% (1)	3	100% (1)	3	3
Poland-Rural	3	100% (3)	9 9 - 48	100% (3)	3	100% (3)	3 3 - 3	3 3 - 3
Chile-Urban	2	0	NA	100% (2)	304 300 307	100% (2)	304 300 -307	304 300 - 307
Chile-Rural	3	0	NA	100% (3)	345	100% (3)	345	345
Turkey-Urban	25	100% (25)	28 28 - 28	100% (25)	6	100% (25)	6 6- 6	6 6- 6
Turkey-Rural	13	100% (13)	28 28 - 28	100% (13)	6	100% (13)	6 6- 6	6 6- 6
Brazil-Urban	7	71% (5)	23 23 -34	100% (7)	9 8 12	100% (7)	9 8 - 12	9 8 - 12
Brazil-Rural	7	71% (5)	34 34 - 34	100% (7)	12	100% (7)	12 12 - 12	12 12 - 12
Malaysia-Urban	18	33% (6)	46 42 - 52	89% (16)	21 13 30	89% (16)	21 13 - 30	15 10 - 30
Malaysia-Rural	15	20% (3)	43 15 - 43	53% (8)	10 8 21	53% (8)	10 8- 21	0.2 0.2 - 10

Appendix 5.5: Availability and median (IQR) cost, local currency (CPI, 2010) of beta-blockers, n=606 communities (monthly recommended standard dose)

		Metoprolol		Atenolol		Lowest cost of beta-blockers		
Country	**N**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
South Africa - Urban	3	0	NA	67% (1)	50	67% (1)	50	50 50 – 50
South Africa – Rural	3	0	NA	33% (1)	24	33% (1)	25	25 25 - 25
Argentina-Urban	6	67% (4)	46 37 - 54	100% (6)	10 10 - 10	100% (6)	10 10 - 10	10 10 - 10
Argentina-Rural	14	29% (4)	45 37 - 55	100% (14)	14 10 - 14	100% (14)	14 10 - 14	10 10 - 10
Colombia-Urban	35	89% (31)	9,240 60,00-12,000	37% (2)	40,850 7,300- 74,400	89% (31)	9,000 6,000 -10,200	9,000 6,000 -11,800
Colombia-Rural	23	78% (17)	11,000 9,000- 11,400	0	NA	78% (17)	11,000 9,000 -11,400	9,900 5,400-11,400
Iran-Urban	11	73% (8)	840 840 – 1,260	100% (11)	330 330 - 330	100% (11)	330 330- 330	330 330- 330
Iran-Rural	9	78% (7)	840 840- 900	100% (9)	330 330- 450	100% (9)	330 330 - 450	300 300- 300
China-Urban	44	50% (20)	87 24 -247	27% (12)	2 1 - 42	59% (24)	30 2 -78	1 1 - 1
China-Rural	64	38% (22)	570 39 - 630	3% (2)	3 3 - 3	38% (22)	444 39 - 570	3 3 - 39
oPt-Urban	21	0	NA	95% (19)	2 0 -2	95% (19)	2 0 -2	2 0 - 2
oPt-Rural	18	6% (1)	0	78% (14)	2 0 - 2	83% (15)	2 0 - 2	2 0 - 2
India-Urban	38	97% (37)	131 105 - 192	97% (37)	90 81- 90	97% (37)	90 81 -91	90 80 - 91
India-Rural	52	79% (41)	105 105 -128	94% (49)	84 77 - 90	94% (49)	84 77- 90	84 58 - 90
Pakistan-Urban	2	50% (1)	162	100% (2)	108 90 - 127	100% (2)	108 90 - 127	108 90 - 127
Pakistan-Rural	2	0	NA	100% (2)	117 51 -182	100% (2)	117 51 - 182	116 51 - 182

Appendix 5.5: Availability and median (IQR) cost, local currency (CPI, 2010) of beta-blockers, n=606 communities (monthly recommended standard dose)

		Metoprolol		Atenolol		Lowest cost of beta-blockers		
Country	**N**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Availability % (n)**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
Bangladesh-Urban	57	88% (49)	120 120 - 120	68% (39)	23 23 - 24	96% (54)	24 23 - 120	24 23 - 120
Bangladesh-Rural	26	81% (21)	120 120 - 120	73% (19)	23 23 - 24	85% (22)	23 23 -24	23 23 -24

NA= Cost of medication not collected because the medication type is not available in the community
***estimated median= if a cost was not collected because the medication was not available, the cost of the medication was estimated based on the lowest cost in the country**

Appendix 5.6: Availability and median (IQR) cost, local currency (CPI, 2010) of statins, n=606 communities (monthly recommended standard dose)

		Simvastatin		Atorvastatin		lowest statin cost		
Country	**N**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
Sweden-Urban	20	100%	17 17 - 17	100%	315 315- 315	100%	17 17 - 17	17 17 - 17
Sweden-Rural	3	100%	17 17 - 17	100%	315 315- 315	100%	17 17 - 17	17 17 - 17
Canada-Urban	36	100%	52 45 - 60	100%	56 37- 60	100%	54 44- 60	50 32 - 60
Canada-Rural	22	80%	44 33 - 48	80%	28 14 - 47	80%	31 28- 46	27 11 - 32
UAE-Urban	1	100%	240	100%	263	100%	240	240
UAE-Rural	2	100%	108 108 -108	100%	227 214 - 240	100%	108 108 -108	108 108 -108
Poland-Urban	1	100%	17	100%	10	100%	10	10
Poland-Rural	3	100%	13 5 - 29	100%	10 10 - 34	100%	10 5 -29	10 5 - 29
Chile-Urban	2	100%	8,430 8,430 - 8,430	100%	1,507 1,305 – 1,710	100%	1,507 1,305- 1,710	1,507 1,305- 1,710
Chile-Rural	3	0	NA	0	NA	0	NA	1,305 1,305 – 1,305
Turkey-Urban	25	96%	6 6 - 6	96%	36 34 -36	100%	6 6 - 6	6 6 - 6
Turkey-Rural	13	92%	6 6 - 6	100%	36 34 - 36	100%	6 6 - 6	6 6 - 6
Brazil-Urban	7	100%	22 10 - 35	86%	121 118- 127	100%	22 10 - 36	22 10 - 36
Brazil-Rural	7	100%	10 10 - 21	71%	83 83- 83	100%	10 10 - 21	10 10 - 21
Malaysia-Urban	18	89%	45 30 - 60	33%	126 108 - 133	89%	45 30 - 60	39 17 - 57
Malaysia-Rural	15	40%	17 11 - 36	20%	130 4 - 136	40%	17 11 - 36	4 4 - 17

Appendix 5.6: Availability and median (IQR) cost, local currency (CPI, 2010) of statins, n=606 communities (monthly recommended standard dose)

		Simvastatin		Atorvastatin		lowest statin cost		
Country	**N**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
South Africa – Urban	3	67%	58 58- 58	33%	133 133 - 133	67%	58 58- 58	58 58 - 58
South Africa – Rural	3	33%	45 45 - 45	0	NA	33%	45 45 - 45	45 45 - 45
Argentina-Urban	6	100%	73 73 - 73	100%	121 121 - 121	100%	73 73 - 73	73 73 - 73
Argentina-Rural	14	93%	84 73- 115	93%	112 71- 121	93%	74 67 - 88	74 67 - 88
Colombia-Urban	35	34%	25,925 24,700 – 27,150	80%	12,750 8,000- 18,000	80%	12,750 8,000 - 22,500	8,000 8,000 -8,000
Colombia-Rural	23	0	NA	39%	22,500 22,500 - 22,500	39%	22,500 22,500 - 22,500	22,500 22,500 - 22,500
Iran-Urban	11	100%	3,000 3,000 - 3,000	100%	2,800 2,800 – 2,800	100%	2,800 2,800 – 2,800	2,800 2,800 – 2,800
Iran-Rural	9	100%	3,000 3,000 - 3,000	100%	2,800 2,800 3,000	100%	2,800 2,800 – 3,000	2,800 2,800 – 3,000
China-Urban	44	68%	154 35 -324	27%	310 166 - 518	73%	139 33- 228	27 5 - 161
China-Rural	64	20%	420 74-1,566	6%	28 25- 32	22%	345 32 – 1,566	25 25- 25
oPt-Urban	21	19%	19 8 - 26	52%	3 3 - 3	62%	3 3 - 3	2 2 - 3
oPt-Rural	18	22%	0 0 - 2	61%	3 2 - 3	78%	3 0 - 3	2 0 - 3
India-Urban	38	87%	507 427 - 555	89%	404 348 - 451	92%	401 307- 450	390 280 -440
India-Rural	52	62%	296 296- 360	81%	330 188- 350	81%	295 188 - 350	295 132- 295
Pakistan-Urban	2	50%	960 960 -960	100%	600 500 - 700	100%	600 500 - 700	600 500 - 700
Pakistan-Rural	2	50%	1,110 1,110- 1,110	0	NA	50%	1,110	1,110 1,110 – 1,110

Appendix 5.6: Availability and median (IQR) cost, local currency (CPI, 2010) of statins, n=606 communities (monthly recommended standard dose)

		Simvastatin		Atorvastatin		lowest statin cost		
Country	**N**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**

Appendix 5.4(continued): Availability and median (IQR) cost, local currency (CPI, 2010) of statins, n=606 communities (monthly recommended standard dose)

		Simvastatin		Atorvastatin		lowest statin cost		
Country	**N**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Availability %**	**Cost Median (IQR)**	**Estimate cost* Median (IQR)**
Bangladesh-Urban	57	49%	450 450- 450	53%	450 450 - 450	74%	450 450 - 450	450 450 - 450
Bangladesh-Rural	26	38%	450 450- 450	31%	450 450 - 450	46%	450 450 - 450	450 450 - 450

NA= Cost of medication not collected because the medication type is not available in the community
***estimated median= if a cost was not collected because the medication was not available, the cost of the medication was estimated based on the lowest cost in the country**

Appendix 5.7: Availability and median (IQR) cost, local currency (CPI, 2010) of aspirin, n=606 communities (monthly recommended standard dose)

Country	N	Availability %	Cost Median (IQR)	Estimate cost* Median (IQR)
Sweden- Urban	20	100%	18 18 - 18	18 18 - 18
Sweden- Rural	3	100%	18 18 - 18	18 18 - 18
Canada- Urban	36	91%	5 3 - 13	5 3 13
Canada- Rural	22	80%	3 3 - 5	3 1 5
UAE- Urban	1	100%	20	20
UAE- Rural	2	100%	17 15 - 20	17 15 - 20
Poland- Urban	1	100%	10	10
Poland- Rural	3	100%	10 10- 10	10 10- 10
Chile- Urban	2	100%	1,826 1,492 – 2,160	1,826 1,492 – 2,160
Chile- Rural	3	100%	900 900 - 900	900 900 - 900
Turkey- Urban	25	100%	1 1 - 2	1 1 - 2
Turkey- Rural	13	100%	1 1 - 1	1 1 - 1
Brazil- Urban	7	100%	8 5 - 9	8 5 - 9
Brazil- Rural	7	100%	11 11- 11	11 11- 11
Malaysia-Urban	18	78%	11 10 -12	11 10- 12
Malaysia-Rural	15	33%	6 6 - 7	3 3 - 6

Appendix 5.7: Availability and median (IQR) cost, local currency (CPI, 2010) of aspirin, n=606 communities (monthly recommended standard dose)

Country	N	Availability %	Cost Median (IQR)	Estimate cost* Median (IQR)
South Africa - Urban	3	67%	55 55 - 55	55 55 - 55
South Africa – Rural	3	33%	32 32 -32	32 32 -32
Argentina- Urban	6	100%	15 15 - 15	15 15 - 15
Argentina- Rural	14	100%	5 5 - 15	5 5 - 15
Colombia- Urban	35	97%	6,000 5,100 – 6,000	6,000 4,500- 6,000
Colombia- Rural	23	91%	6,000 4,714 -6,000	5,400 600- 6,000
Iran- Urban	11	100%	225 210 - 360	225 210 - 360
Iran- Rural	9	100%	210 210- 210	210 210- 210
China- Urban	44	98%	2 1 - 14	2 1 - 14
China- Rural	64	70%	1 1 - 2	1 1 - 2
oPt- Urban	21	95%	3 0 - 3	3 0 -3
oPt- Rural	18	83%	3 0 - 3	3 0 - 3
India- Urban	38	95%	13 8 - 15	13 8 -15
India- Rural	52	94%	7 6 - 9	7 6 -9
Pakistan- Urban	2	100%	29 24- 33	29 24- 33
Pakistan- Rural	2	100%	24 24 - 24	24 24 - 24

Appendix 5.7: Availability and median (IQR) cost, local currency (CPI, 2010) of aspirin, n=606 communities (monthly recommended standard dose)

Country	N	Availability %	Cost Median (IQR)	Estimate cost* Median (IQR)
Bangladesh-Urban	57	93%	15 15 -15	15 15 -15
Bangladesh-Rural	26	73%	15 15 -15	15 15 -15

NA= Cost of medication not collected because the medication type is not available in the community
***estimated median= if a cost was not collected because the medication was not available, the cost of the medication was estimated based on the lowest cost in the country**