Introduction:

Aspirin, statins, angiotensin-converting enzyme inhibitors, and beta-blockers are cardiovascular medications that have been shown to reduce the risk of death, myocardial infarction and stroke in patients with cardiovascular disease (CVD)[1-4]. The Prospective Urban Rural Epidemiology (PURE) study demonstrated that the use of these medications for CVD secondary prevention is low worldwide, with rates of use of 40-66.5% in high-income countries, 11.8-30.0% in upper-middle income countries, 4.3-21.9% in lower-middle income countries, and 3.3-9.7% in low-income countries[5].

The reasons for the sub-optimal use of evidence-supported medications are likely to be multifactorial and context-specific. The patient-level factors shown to be associated with low adherence include pill load[7], health literacy[8], age[9], ethnicity, education level, cognitive function, and employment status[10-11]. Additionally, the number of medications, side effects and the relationship with healthcare professionals (HCPs) are treatment-related and patient-provider related factors that may influence medication use[11]. Appropriate medication use is affected by all levels of the health system including the HCPs, the organization of hospitals, pharmacies and clinics, and the health policies and economic conditions under which the patients live and the HCPs work. A limited number of studies have examined health system barriers and facilitators associated with cardiovascular medication adherence, particularly in low and middle-income countries where rates of use are poorest[12]. Of the studies conducted, the use of combination pills[13], subsidized medication costs through co-payments[14,15], and physician, nurse or pharmacist counseling improved adherence in secondary prevention patients[16-18]. Given the absence of data in low-income countries, and the multifactorial causes of decreased adherence, additional

research is needed. Quantitative methodologies may be inadequate to capture the complexities and relationships among stakeholders of a healthcare system. Therefore, the objective of this paper is to explore the major obstacles and facilitators to the use of evidence-supported medications for secondary prevention of CVD using qualitative analysis in two diverse countries across multiple levels of their healthcare systems. These together may help strategize future major researches and policy.

Methods:

We conducted a qualitative descriptive study to explore the barriers and facilitators to CVD medication adherence in two settings, Hamilton, Canada and Delhi, India. We selected these two settings because they reflect a balance between contrasting economic status and health system structures and the feasibility of successfully carrying out the study. The units of analyses were the stakeholder groups involved in the study, which include: a) patients; b) physicians: family physicians, cardiologists, nurse practitioners, AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy) physicians and c) non-physician healthcare workers (NPHWs): pharmacists, pharmaceutical companies, social workers, NGOs, nurses, hospital administrators, policy makers. In Canada, nurse practitioners complete additional educational training and have authority to prescribe medications. Given their advanced knowledge and responsibilities, we present the findings for physicians and nurse practitioners as one stakeholder group.

The sampling methodologies used were specific to each context and stakeholder group (Table 1). In Canada, patients were sampled through purposeful sampling. The patients were identified

from the research investigators' patient lists and patient referrals from other HCPs, and invited to participate in the study. Purposeful and snowball sampling were used to recruit physicians, pharmacists, social workers and policy makers. We identified these stakeholders through college referrals and invited potential respondents to participate by telephone and email. Additionally, we used the snowball sampling technique which involved asking the participants to refer other stakeholders with knowledge and experience that may be relevant to the study.

In India, purposeful sampling was used to sample cardiologists, AYUSH physicians, and pharmacists. Hospitals in New Delhi and the National Capital Region with Cardiology and AYUSH departments were identified and contacted via email and telephone to recruit participants. Similarly, pharmacists within the region were contacted personally. Snowball sampling was used to recruit patients, nurses and hospital administrators. The participating cardiologists were asked to refer secondary prevention patients, administrators working within the hospital, and nurses on their service. Lastly, the policy makers working in the Department of Non-Communicable Disease within the Ministry of Health and Family Welfare, Government of India were contacted via email and telephone.

In both contexts, in-depth, semi-structured interviews were conducted to explore the perceptions of cardiovascular medication use in secondary prevention, and the health system factors that influenced medication uptake. The interviews were undertaken by research assistants at a private location selected by the participants in New Delhi, and at the David Braley Research Institute, Hamilton General Hospital, Hamilton, ON, or by telephone. A total of 61 interviews were conducted in person and 8 were conducted via telephone. The interviews lasted between 30 and

60 minutes and consent was obtained for the interviews to be audio recorded. A final sample (n=69) of 23 patients, 10 physicians, 5 AYUSH physicians, 11 pharmacists, 2 nurse practitioners, 3 nurses, 4 hospital administrators, 1 social worker, 3 non-governmental organization (NGO) workers, 2 pharmaceutical company representatives and 5 policy makers participated in the study. Table 2-5 illustrates characteristics of the stakeholder groups.

Data collection and analysis were completed concurrently from December 2014 to November 2015. The interviews were transcribed verbatim with directed content analysis[19] guiding initial coding and analysis to organize, summarize and categorize the data. Data analysis was completed by VM in Canada, and LN and MS in India by deriving codes, organizing the codes into broader categories, and collapsing the categories into themes and sub-themes. LN, MS and VM compared the emergent themes between the two countries to identify similarities and differences. Detailed theme summaries were written for each of the stakeholder groups in both countries.

We used Guba and Lincoln's (1994) criteria (credibility, transferability, confirmability, and dependability) to ensure trustworthiness in the qualitative findings[20]. Table 6 shows the strategies used. Research ethics approvals were obtained from the Hamilton Integrated Research Ethics Board and Institutional Ethics Committee, Public Health Foundation of India. Participants provided written consent for in-person interviews and verbal consent for telephone interviews.

Results:

We present our findings under six main themes identified from analysis of the stakeholder groups' responses. These themes encapsulate responses across the stakeholder groups and demonstrate the agreement or contrast among the groups. Additionally, the themes described within each stakeholder group are presented in the Appendix (Tables S1-12).

Medication Counseling

In Canada, physicians, nurses and pharmacists provided medication counseling to patients, while in India counseling was exclusively provided by physicians. The information provided during counseling included: the purpose of the medication, dosage, frequency, contraindications, side effects, adverse effects, instructions on how to take the medication and medication benefits. The physicians, nurse practitioners and pharmacists in Canada reported providing thorough medication counseling. In India, the physicians did not extensively discuss the purpose, benefits, or side effects of medications with patients due to time constraints. Additionally, they felt that notifying patients about potential side effect may decrease adherence. The primary mode used to communicate information about medications was exclusively verbal, except the Canadian pharmacist group who provided patients with written drug fact sheets for each prescription.

The patients in India stated that they felt they lacked adequate information about medication side effects and they often attributed a multitude of physical discomforts to side effects of their medications.

The physicians and nurse practitioners in Canada, and AYUSH practitioners in India included patients in the decision making when developing their treatment plan. Conversely, the physicians

in India indicated that joint-decision making does not regularly occur due to low patient education level and lack of desire to be included in treatment planning.

"90% of [patients] are not involved and don't want to get involved. They only want a remedy. They think doctor knows the best; that is the kind of wisdom they have which is not right but that is how they are brought up in their villages that if you have this problem go to the doctor he will give you the medicine and no questions. That is the kind of patients we deal with." **(Physician 4, female, 31 years of work experience, 730 patients /month, India)**

Monitoring Adherence

In Canada and India, the physicians (allopathic and AYUSH) and nurses monitored patient medication adherence by asking the patient, checking biological markers (blood pressure, blood lipid levels), and examining the patient's prescription history. The HCPs who reported discussing adherence with the patient included physicians, nurse practitioners, nurses and pharmacists. Additionally, the patients in Canada stated that their physicians regularly inquired about their medication adherence, whereas in India this was seldom reported.

The physicians in Canada addressed poor adherence by providing the patient with additional information on the purpose and benefits of the medication, discussing the health implications of non-adherence, making recommendations to assist the patient with establishing a medication routine, involving family members to reinforce the importance of being adherent and trying to understand the factors affecting adherence.

Medication availability

In India, several patients stated that the nearest healthcare facility (public or private) and pharmacy were at considerable distance from their residence, particularly those residing in

rural areas. Many patients expressed distrust of private facilities and felt that better treatment was provided at government-funded hospitals, which required travelling further to receive treatment. The longer commute to access care and fill prescriptions resulted in considerable expenditure from lost wages, travel expenses, and older patients relied heavily on family members to procure their medications. The patients who were entitled to government subsidized medications indicated that they were required to commute to specific dispensaries and their medications were frequently unavailable.

Medication affordability and drug coverage

In Canada, physicians and pharmacists reported asking patients about medication affordability and coverage. Medication cost was the largest barrier to adherence reported by physicians, healthcare administrators and policy makers in India. However, the physicians in India stated that they did not overtly ask patients about medication affordability unless the patient explicitly stated that they were unable to afford their medications. Conversely, the physicians in Canada indicated that the minority of their patients experienced difficulties affording cardiovascular medications.

Most patients in India stated that they received medication coverage through the central or state government scheme and they accessed the subsidized medications from government-funded hospitals monthly. Many patients chose to pay out of pocket to purchase medications from private sector pharmacies to ensure consistent access to medications.

"We are poor people. If we really were to buy medicines from outside, we would die. Thankfully we get free medicines from the government. We get free medicines from the hospital itself. We come here once in a month. Get all the medicines from the hospital itself." **(Patient 8, 62 years old, male, India).**

Within Canada, patients reported having medication coverage through employer health benefits programs, private insurance or government programs. The cost of medications was a barrier for 3 of the 9 Canadian patients. These patients reported spending $40.00 to $300.00 per month on medications, including dispensing fees.

"The biggest problem that I told [my cardiologist] is that I lost all my health coverage this February. I told him that what I am going to do to, to save money is skip my pill one day and take them every other day." **(Patient 1, 59 years old, male, Canada).**

Within Canada, the physicians and pharmacists were aware and referred patients to several government programs to subsidize medication cost for patients with financial difficulties. The Canadian social worker reported regularly seeing patients with difficulties affording cardiovascular medications and recommended patients apply to the Ontario Trillium Benefit Plan, Ontario Works, and the Ontario Disability Support Program for assistance. She indicated that many patients are not aware of programs offered by the government to improve affordability, and approval for these programs could take several months.

Additional strategies that were used by these stakeholder groups to improve medication affordability included: modifying the dose and frequency, and limiting the number of medications. Further, prescribing generic medications was a common practice used by the Canadian physicians. However, the physicians in India indicated that they based their prescribing practices on the information obtained from medical representatives which resulted in a greater

preference for prescribing branded medications. The use of poly-pills to reduce pill burden and improve medication affordability was not widely supported by the physicians in India because they felt that poly-pills could not be tailored to the specific patient.

Within India, the pharmacists stated that many patients attempt to negotiate the cost of medications with the pharmacist, but high taxes, drug licenses, and permits prevented pharmacies from being able to offer medication discounts and rebates to patients. The pharmacists reported adhering to the prescriptions written by physicians even if generic medications were available as a more cost-effective option.

Time Restrictions

In both contexts, physicians (allopathic and AYUSH), nurses and healthcare administrators indicated that high patient workloads and time constraints affected the physician's ability to spend an adequate amount of time counseling patients on their medication usage and adherence. The number of patients seen per day ranged from 75-185 for physicians in India and 7-55 for physicians in Canada. Further, the healthcare administrators in India stated that 160 to 1000 patients were seen per day in the cardiology department.

The Canadian patients were dissatisfied with the wait times to schedule appointments and short appointments durations. Many indicated that they were not able to spend an adequate amount of time with their physician to discuss their medical concerns.

Task Shifting

In Canada, the physicians discussed the importance of patients' receiving follow-up by NPHWs as a means of reinforcing counseling on medication use. In addition to physicians and nurse practitioners, patients regularly interacted with residents/medical students, nurses, and hospital/community pharmacists.

The physicians and pharmacists in Canada were also supportive of NPHWs taking on new roles and responsibilities in relation to renewing and modifying prescriptions, provided they completed training and certification. Further, the pharmacists felt comfortable prescribing medications for patients with stable cardiovascular conditions.

"Many times a treatment is very algorithmic and a lot of cardiovascular medications do not have many risks so, I think someone can be easily trained in managing the first step such as blood pressure control or optimizing cardiovascular medication without too much risk; if they are presented with an algorithm or strategy to do so in a setting where a physician can be alerted. I think it has to be in a controlled environment then it's a reasonable thing to do." **(Physician 4, male, 5-10 patients per day, Canada).**

In contrast, in India, physicians were not supportive of NPHWs prescribing, modifying and renewing medications and they indicated a lack of clinical experience and expertise as the deterrent. However, the nurses indicated that short-term certification would be sufficient to provide them with the necessary knowledge to prescribe medications.

Discussion:

This qualitative study yielded several important findings. First, we found that the barriers to medication adherence did not differ substantially between the two contexts. The barriers that

were present in both Canada and India included: high patient loads, time constraints, medication affordability, and the absence of written counseling. Instead, limited medication counseling, adequate availability and accessibility to healthcare services and resistance to task shifting were barriers that were exclusive to India.

Second, both contexts reported that monitoring adherence promoted better medication compliance. However, additional facilitators unique to Canada included adherence monitoring by NPHWs, inquiry and referral to programs to improve medication affordability, and task shifting medication renewal to NPHWs. Medication affordability was consistently recognized as a strong barrier to adherence across the stakeholder groups despite drug coverage availability in both countries. This finding is in line with previous research which has shown that lower out-of-pocket medication expenses are associated with greater levels of adherence[21-22] and adherence can be modestly improved when patients are provided with full medication coverage[23]. Within Canada, many adults do not have medication coverage and must pay out-of-pocket to cover some portion of their medication expenses[24,25]. Despite the availability of government drug programs, very few Canadian patients reported being familiar with these programs which suggests that public health agencies and HCPs should work to increase patient awareness and facilitate higher utilization rates. In India, the affordability of medications is heavily dependent on access to hospital formularies. Many patients chose to purchase medications out of pocket from private, community pharmacies to avoid long commutes, lost wages, and the unavailability of medications from hospitals formularies. Although the patients included in the study did not report medication unaffordability, this finding may be reflective of social stigma related to

disclosing financial information. Policies that extend the government-funded drug coverage to community-based pharmacies may address unaffordability and access to medications in India.

We also demonstrated that the depth of counseling varied between Canada and India. In India, physicians regularly failed to discuss critical information with a patient when prescribing a medication. Medication indication[9] and possible adverse effects[26] may influence the patient's adherence, both of which were not regularly discussed. A greater emphasis on counseling patients in India on the efficacy and effectiveness of generic medications may reduce self-alteration of medication and improve the use of affordable generic drugs. In Canada and India, verbal information was the primary mode of counseling provided by HCPs and written materials were not routinely used. The duration of time spent counseling patients and a trusting physician-patient relationship has been shown to be positively associated with adherence[27-29]. However, the HCPs in Canada and India indicated that time constraints inhibited their abilities to provide thorough medication counseling to patients.

Third, in Canada, physicians were supportive of the redistribution of medication renewal and modification to NPHWs. Conversely, physicians in India stated that NPHWs lack the clinical expertise to manage cardiovascular medications. Several studies have demonstrated improved adherence[30], health outcomes[31], treatment concordance between physicians and NPHWs, and the cost-effectiveness of task shifting for chronic disease management[32-33]. Further, Adeyemo et al. showed that nurse-led follow up, counseling and medication prescription resulted in high rates of adherence in Nigerian hypertensive patients[34], suggesting that it is a suitable intervention in middle and low-income countries.

Strength and Limitations:

Our study has some limitations. First, the sample sizes for some of the stakeholder groups were small and may not reflect the perspectives of these groups, and the stakeholders included do not represent an exhaustive list of groups relevant to the health system. A limited number of individuals occupy these healthcare roles which reduced the potential pool of participants for these groups. Extensive efforts were made to recruit participants from each of the stakeholder groups and colleague referral was predominantly used in Canada to improve the feasibility of recruitment. Second, the study sampled participants from two cities in Canada and India, and the findings may not be transferable to other settings or contexts. However, in-depth descriptions of the sampling and data collection methods enable readers to determine whether the findings are transferable to other contexts. Lastly, social desirability bias may influence participants to present their experiences positively. Participant confidentiality and anonymity were emphasized prior to beginning the interviews. Further, the HCPs responsible for referring participants were not involved in the data collection and analysis, and patients were informed that their quality of care would not be influenced by study participation.

Qualitative research provides the opportunity to solicit rich information about the health system barriers to and facilitators of CVD medication adherence from patients and the key HCPs involved in patient care. Within this study, the selection of stakeholder groups was specific to the two contexts. For example, social workers are commonly employed by Canadian hospitals to refer financial and social resources to patients and their family members. Conversely, we did not include social workers in India because they were not referenced during interviews with the patients and HCPs. Further, the country of conduct influenced the type of sampling

methodologies used. In accordance with ethical standards in Canada, the recruitment of patients through physician's referral required the physicians to obtain patient consent prior to contact from study staff. This requirement was not stipulated by ethical review boards in India. Therefore, future qualitative research on health system barriers in other countries should consider the context, particularly when selecting key stakeholder groups and implementing sampling strategies.

To our knowledge this is the first study to examine the health system related barriers and facilitators of medication use in secondary prevention of CVD from the perspectives of key HCPs and patients. The strength of this paper is that it highlights the context-specific health system factors that influence adherence to cardiovascular medication and demonstrates the differences and similarities between the two countries. Another important strength of this study is that it provides information on obstacles and facilitators to medication use in India, a low-income country for which there is limited available literature to inform policy development on medication adherence.

Conclusion:

This study has identified several areas that should be addressed to improve medication adherence in secondary prevention of CVD. The barriers that we described herein included high patient loads, time constraints, medication availability and affordability, and the absence of written counseling. Additionally, monitoring adherence, adherence follow-up by NPHWs, inquiry and referral to programs to improve medication affordability, and task shifting were the facilitators referred by the stakeholder groups. Our findings provide vital information to HCPs,

administrators, and policy makers about the factors that influence medication adherence in both contexts.

Funding:

This work was supported by the World Heart Federation Emerging Leader Programme.

Table 1
Barrier and facilitators in Canada and India.

Barrier		**Facilitator**	
Canada	**India**	**Canada**	**India**
Mode of counselling	Mode of counselling	Monitoring adherence	Monitoring adherence
Time constraints	Time constraints	Family support	Family support
Medication cost	Medication cost	Addressing poor adherence	Inquiring about medication affordability
High patient loads	High patient loads	Inquiring about medication affordability	
	Uncomprehensive medication counselling	Adherence follow-up by NPHWs	
	Resistance to task-shifting	Supportive of task-shifting	

Table 2
Contrasting key themes between the stakeholders in Canada and India.

Theme	Canada	India
Medication counselling	Communicated verbally Written materials provided to patients by pharmacists Information communicated: medication purpose, benefits, dosage, frequency, side effects, adverse effects, contraindications, instructions on how to take Joint-decision making practiced by most physician/nurse practitioners	Communicated verbally Written materials not provided to patients by HCPs Information communicated: medication dosage, significant side effects Joint-decision making practiced by AYUSH physicians
Medication adherence	Medication adherence assessed by physician/nurse practitioners, pharmacists Methods used to check adherence: biological makers, prescription refill history, ask patient about medication use Methods to address non-adherence: additional counselling and education (purpose, benefits, health implications), involve family members, recommendation to establish a routine Patients reported being asked about adherence by their HCPs	Medication adherence assessed by physicians, nurses Methods used to check adherence: biological markers, ask patient about medication use The doctors mentioned that due to time constraint they were unable to ask about adherence during every single visit
Affordability and drug coverage	Medication coverage discussed with patient: physician/nurse practitioner, pharmacist, social worker HCPs were knowledgeable about resources available to patients with affordability issues (government programs, social worker consult) Tailors prescription to patient socioeconomic status: generic medication, modified dose and frequency, limit number of medications, combination pill	Tailors prescription to patient socioeconomic status: generic medication Medication costs not advertised or standardized across

	Medication dispensing fee: $10.50-12.00 per medication Medication costs not advertised or standardized across pharmacies Medication coverage through employer, private insurance, government (ODBP) One third of patients reported medications were unaffordable	pharmacies Medication coverage through government (Universal Health Coverage)
Time restrictions	Number of patients seen per day: 7-55 Appointment length: 5-30 minutes Long wait times to see specialists Patients dissatisfied with appointment lengths Constrained by time: physician/nurse practitioners	Number of patients seen per day: 75-185 Sub-optimal physician-patient ratio Constrained by time: physician, AYUSH practitioners
Task-shifting	Follow-up by NPHWs reinforces counselling Patients receive counselling from physician/nurse practitioners, nurses, pharmacists, social workers NPHWs renewing and modifying medications was supported by physician/nurse practitioners, pharmacists Access to patient medical history, lab/test results, clinical experience needed to manage medications	Patients receive counselling from physicians, medical residents/students, nurses NPHWs prescribing, renewing and modifying medications were only supported by physicians. Nurses are not capacitated to do the same Extensive clinical experience needed to manage medications
Family support	Involve family members in patient care: physician/nurse practitioners, pharmacists Family involvement: reminding to take medications, picking up medications, taking patients to appointments, asking questions about care, and motivating patients to take medications	Involve family members in patient care: physicians, AYUSH physicians, pharmacists Family involvement: reminding to take medications, taking patients to appointments, asking questions about care

Table 3

Strategies for study rigor

Criterion	Strategies
Credibility	-Included multiple subcases -Established trusting investigator-participant relationships -Maintained master code book -Used several research team members to code the data and have regularly discussions about analysis decisions -Debriefed -Sought substantiation of findings with participants
Dependability	-Adhered to the research protocol -Documented choices made about methodologies used -Maintained organized paper and electronic databases -Composed detailed summary reports for each stakeholder group
Conformability	-Sampled participants from a variety of stakeholder groups -Transcribed the interviews verbatim
Transferability	-Reported in-depth descriptions of findings

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