University of Alberta

Cardiovascular medication utilization and adherence
in rural and urban patients

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science
in
Epidemiology

Public Health Sciences

Fall 2013
Edmonton, Alberta

ABSTRACT

Rural residents face numerous barriers to health care access that have been postulated to result in decreased utilization and adherence to evidence-based medications. The objectives of this research were to examine cardiovascular medication use and adherence for rural versus urban patients with cardiovascular disease or diabetes, which were accomplished through a systematic review of published studies and a retrospective cohort study of incident heart failure patients in Alberta. The systematic review included 51 studies and found no consistent rural-urban differences in medication usage patterns. Rural residents with heart failure were less likely to receive evidence-based medications, specifically renin angiotensin system (RAS) agents or beta blockers, but exhibited similar adherence compared to their urban counterparts. Importantly, adherence with heart failure therapy was suboptimal for rural and urban patients leading to an increased risk of mortality. This research suggests that interventions to promote optimal cardiovascular medication utilization and adherence are needed.

ACKNOWLEDGMENTS

Dr. Dean Eurich is a Population Health Investigator with Alberta Innovates Health Solution (AIHS) and the Canadian Institutes of Health Research (CIHR). Dr. Finlay McAlister is a senior health scholar with AIHS and holds the Capital Health Chair in Cardiovascular Outcomes. Ms. Daniala Weir is a Master of Science student with the School of Public Health at the University of Alberta and Ms. Lisa Tjosvold is a Research Librarian with the University of Alberta and the Institute of Health Economics. The study sponsors played no role in study design or conduct; collection, analysis, or interpretation of data; writing of the report; or the decision to submit the paper for publication.

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LIST OF ABBREVIATIONS

ACEI – Angiotensin converting enzyme inhibitor

aOR – Adjusted odds ratio

ARB – Angiotensin receptor blocker

BB – Beta blocker

CI – Confidence interval

HF – Heart failure

ICD – International Classification of Diseases

OR – Odds ratio

PDC – Proportion of days with medication coverage

RAS – Renin angiotensin system

SD – Standard deviation

UK – United Kingdom

US – United States

CHAPTER 1: INTRODUCTION

1.1. Statement of the Problem

1.1.1. Rural residence and health

Where we live is associated with health status, health behaviors, utilization and adequacy of health care services.[1,2] Our place of residence can promote health and also impacts health risks through environmental conditions, socioeconomic factors, occupational activities, ethnic composition, culture and community features.[2] These individual and community factors are broadly defined as the social determinants of health and are increasingly being discussed not only in developing countries, but also in well-established western societies where inequities and disparities are increasing. The interplay of these individual and community factors is extremely complex, and along with the health care system, have a substantial bearing on health outcomes.[3]

Rural communities and their residents have different characteristics than urban populations that may predispose them to health disparities. Rural residents in Canada and the US tend to be older, are more likely to be Caucasian, be obese and have less education and lower income than urban residents.[4-7] Some studies, but not all, have shown that rural populations have a higher prevalence of chronic conditions, such as diabetes or heart disease, and have worse health outcomes.[3-5,7,8] Although there is much heterogeneity between rural areas, particularly in Canada where there are vast geographical, cultural and ethnic

differences,[1] in general, these characteristics have been interpreted by many to suggest poorer overall health among rural communities.

In addition, rural communities often have, or are perceived to be, disadvantaged in their access to health care services. Physician shortages in rural areas are an ongoing issue, and specialists, in particular, are in short supply.[3,9,10] Not surprisingly, the ratio of specialists per population consistently declines as locations become smaller and more remote, and utilization of specialist care is less likely among those living in small or remote rural communities.[3,10,11] Moreover, specialized clinics for the management of chronic disease tend to be located in urban centers and even in a universal health care environment, access to clinics is limited for both urban and rural dwelling patients.[12] Rural patients report several barriers to accessing health care including transportation difficulties and distance to care, lack of quality health care, social isolation, financial constraints, and limited health care facilities.[13] Although new initiatives like telemedicine are trying to overcome some of these barriers, their impact is yet unknown. Furthermore, these access barriers have been postulated to result in decreased prescribing and utilization of evidence based medications for rural patients with chronic conditions such as cardiovascular disease or diabetes.

1.1.2. Cardiovascular disease burden

Cardiovascular disease is the leading cause of death globally.[14] In the US, cardiovascular disease accounted for 1 in every 3 deaths in 2008 (245 deaths per 100,000 population), and was responsible for an estimated $298 billion in direct

and indirect health care costs, the highest cost of any diagnostic group.[15] Similarly, in Canada, cardiovascular disease represents a substantial disease burden with an age- and sex-standardized rate of hospitalization and death of 1306 and 253 cases per 100,000, respectively, in 2004.[14] Diabetes is a significant risk factor for cardiovascular disease and the majority of those with diabetes will die from heart disease.[15-17] The dramatically increasing prevalence of diabetes is predicted to substantially increase the cardiovascular disease burden.[15,18]

Of the cardiovascular diseases, heart failure is a leading cause of hospitalization and is a contributing factor in 1 of every 9 deaths.[15,19-21] It is a chronic progressive condition caused by structural or functional disorders of the heart that impair the ability of the ventricle to fill with or eject blood.[22] The most common etiologies are ischemic heart disease, hypertension, dilated cardiomyopathy and valvular heart disease.[22] Patients with heart failure experience dyspnea, fatigue, exercise intolerance and fluid retention, which impair functional capacity and quality of life. Although recent studies have reported declining incidence of heart failure in Canada, the prevalence has increased, and 1-year mortality rates remain high.[21,23] Overall, the one-year mortality rate for patients with heart failure is approximately 25%, but ranges from 7% to 35% for patients diagnosed as outpatients or inpatients, respectively.[21,23]

Management of cardiovascular risk for those with diabetes and other high-risk populations includes evidence-based treatments such as antithrombotic, angiotensin converting enzyme inhibitors (ACEI), antihypertensive, and lipid lowering therapy.[24] Recent declines in the age-adjusted death rate for coronary heart disease have been attributed, in part, to these pharmacotherapies.[15,18] The optimal use of these medications represents a significant opportunity to impact morbidity and mortality due to cardiovascular disease.

In heart failure specifically, management includes treatments to control predisposing or comorbid conditions (e.g., hypertension, coronary artery disease, diabetes, valve or lipid disorders), dietary salt restriction, exercise, poly-pharmacotherapy, and in some cases, resynchronization therapy or implantable cardioverter-defibrillator.[22] There is strong evidence that medications such as ACEI, angiotensin receptor blockers (ARB), beta blockers (BB), aldosterone antagonists (e.g., spironolactone) and digoxin reduce morbidity or mortality in patients with heart failure,[22,25-28] yet despite this evidence, these medications are underutilized.[29-32]

1.1.3. Medication utilization and adherence

Underuse of treatments of known benefit is a global problem that threatens the successful management of chronic diseases.[33] Half of patients prescribed medications for chronic conditions do not take them.[33] This may be due to the failure to obtain a prescribed medication (primary non-adherence),[34,35] a failure

to take medications as agreed upon with the provider (adherence),[32,36] or to continue on medications (persistence).[30,33]

In heart failure and diabetes specifically, underutilization of evidence-based medications is not uncommon,[37-45] although utilization of evidence-based medications, such as ACEI and BB has been increasing over time.[29,31,38] Non-adherence to medications and dietary restrictions can rapidly alter patients' clinical status and is linked to poor outcomes including hospitalization and death.[22,30,37,39,40,46] Moreover, the economic impact of non-adherence on total health care costs is substantial.[33]

Studies have shown that non-adherence is highest in the first year of therapy, with patients frequently stopping treatment after a single prescription fill.[33,47,48] Indeed, approximately a quarter of prescriptions are never filled.[34,35] Interventions to enhance adherence have not shown consistent improvement in adherence or outcomes.[49,50] Although patient-related factors, such as patients' resources, knowledge, attitudes, beliefs and expectations are often the focus of adherence studies or interventions, these represent just one dimension affecting adherence behavior.[33] The broader social and economic conditions, health care system, and provider also have an impact on patients' behavior and capacity to adhere to treatment. These constitute the health care environment in which patients receive care and are key determinants of utilization and adherence with medications.

There is also increasing focus on the impact of geography on utilization and adherence to drug therapies and subsequent outcomes for patients with cardiovascular disease. Given the resources consumed by avoidable hospitalizations, attention has focused on optimizing primary care and outpatient management, particularly for patients residing in rural or remote locations. Rural-urban differences in health service utilization and outcomes have been documented for patients with heart failure[51-53] and diabetes,[6,7,45,54,55] but it is unclear if the differences in outcomes are related to decreased prescribing, utilization or adherence to evidence-based cardiovascular medications for rural patients with cardiovascular disease.

1.2. Summary

There are disparities between rural and urban communities in access and utilization of health care. Rural residents with cardiovascular or other chronic diseases face several barriers to obtaining quality health care and these barriers have been postulated to result in decreased utilization and adherence to evidence-based medications. For patients with cardiovascular disease in particular, suboptimal use of evidence-based medications has been observed and is associated with increased hospitalization and mortality. Thus, this research will examine rural-urban differences in medication utilization, adherence, and mortality among patients with cardiovascular disease.

1.3. Objectives

The objectives of this program of research were: 1) to systematically review existing studies comparing rural versus urban cardiovascular medication utilization and adherence patterns; 2) to estimate medication utilization, adherence, persistence, and subsequent mortality for rural versus urban patients with heart failure. These objectives were accomplished through two complementary studies.

1.4. Program of research

Two papers contributed to the overall study goals. The first study (Chapter 2) was a systematic review that evaluated whether cardiovascular medication utilization and adherence patterns differed for rural versus urban adults with cardiovascular disease or diabetes. The 51 included studies were abstracted, appraised, and where appropriate, their results were pooled through meta-analysis.

The second study (Chapter 3) estimated rural-urban differences in medication utilization, adherence, persistence, and subsequent 1-year mortality among incident heart failure patients greater than 65 years of age in Alberta. This retrospective cohort study was conducted using administrative data from Alberta Health that included prescription drug claims, hospitalizations, physician visits, ambulatory care visits, demographic and vital statistics data. The association between residence and the medication use and mortality outcomes were explored using multiple regression analyses.

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CHAPTER 2: SYSTEMATIC REVIEW

2.1. Introduction

Rural and urban communities have distinct characteristics in terms of demographics, social, and physical environments, and may vary in access to health care facilities and services. Rural residents tend to be older and are more likely to be obese, have less education, and lower income than urban residents.[1-4] Rural populations also have a higher prevalence of chronic conditions such as diabetes and heart disease[1,5] and worse health outcomes.[3,4] Collectively, these characteristics suggest increased health care needs for those living in rural communities.

However, rural residents report several barriers to accessing health care including transportation difficulties and distance to care, social isolation, financial constraints, limited health care facilities (hospitals and pharmacies), physician shortages, and lack of access to specialist care.[6-11] Indeed, in the US, rural areas contain 19% of the population but only 11% of the physician workforce,[7] and the ratio of specialists per population consistently declines as locations become smaller and more remote.[7,9] The lack of access to primary care physicians, specialists, or health care facilities has been postulated to result in decreased prescribing of evidence based medications. However, a previous systematic review found no clear rural-urban difference in the prevalence or intensity of prescription drug use in older adults – although that review included

a wide variety of health conditions and medications.[12] It is possible that important differences may exist for certain disease states or medication conditions. As a result, we conducted a systematic review that evaluated whether cardiovascular-related medication utilization and adherence patterns differ for rural versus urban adults with cardiovascular disease or diabetes. These two disease states were selected as they affect a large number of patients, are associated with high morbidity and mortality, often require multiple medications to manage, and outcomes are known to be different between rural and urban patients.[13]

2.2. Methods

Inclusion and exclusion criteria

Controlled clinical trials or observational studies were included if they enrolled adults with established cardiovascular disease (atrial fibrillation, hypertension, heart failure, coronary artery disease) or diabetes, and reported cardiovascular medication use or adherence patterns for patients living in rural versus urban communities. Medications of interest included acetylsalicylic acid (ASA), antithrombotic, anticoagulant, antihypertensive (including angiotensin converting enzyme inhibitors and angiotensin receptor blockers), or lipid lowering agents. The research question, inclusion and exclusion criteria, and review methods were outlined in a protocol developed a priori according to the PRISMA guidelines.[14]

Since the definition of rural and urban varied substantially between studies, we a priori defined populations described as urban, city dwelling, or metropolitan in the primary publication as urban. Conversely, rural descriptors included town, village, country dwelling, non-metropolitan or remote communities. Any definition of adherence or persistence used in primary studies was accepted. Only full text, peer reviewed articles, were included. Studies evaluating the use of medications for acute management, such as during hospitalization, were excluded, as were studies conducted in developing countries where management approaches may be substantially different. The populations of interest were those with established cardiovascular disease or diabetes, in whom several evidence-based medications are recommended for use. Two researchers (GM, DW) independently screened all studies and extracted all data using pre-defined forms and definitions, and disagreements were resolved through discussion, or by a third researcher (DTE).

Literature search strategy

A comprehensive search strategy implemented by a research librarian was done in April 2012 in the following electronic databases: MEDLINE®, Embase, International Pharmaceutical Abstracts, CINAHL, and Web of Science® and reference lists of included articles were also manually searched. Previously identified included studies were searched in Scopus to gather additional subject headings. No language, study design or date restrictions were applied. The MEDLINE® search strategy is listed in Table 2-1.

Data extraction and quality assessment

Studies were evaluated for bias, and the STROBE checklist was used to assess the quality of reporting.[15] Study authors were contacted for missing information on rural-urban comparisons, and in two cases additional data were provided.[16,17] Both unadjusted and adjusted data were abstracted or calculated where possible.[18] If more than one adjusted analysis was reported, the analysis that adjusted for the most confounders was extracted, and medication use data for patients without contraindications to treatment were preferred over populations that may have included patients who were not eligible for a specific therapy. Where possible, studies reporting multiple rural or urban populations were combined.

Data analysis methods

To summarize the effects of rural and urban location on medication utilization or adherence both unadjusted and adjusted pooled effects were calculated. As we expected heterogeneity between studies, we pooled effect estimates using a random effects model with inverse variance weighting and Review Manager 5.1 software.[19] Heterogeneity was assessed using the I^2 statistic with an I^2 statistic >50% being considered as moderate heterogeneity. There was no a priori degree of heterogeneity that precluded pooling. For studies reporting multiple outcomes within the same cohort [e.g., % receiving beta-blockers (BB) and % receiving angiotensin converting enzyme inhibitors (ACEI)], a pooled estimate of the odds of treatment were calculated using methods recommended by Borgenstein et al.[20] that accounts for the fact that patients within each outcome are not mutually

exclusive (i.e., a patient may have received both a BB and an ACEI). Since the correlation of outcomes is unknown, we used a moderate correlation of 0.5 with sensitivity analyses using 0.25, 0.75 or 1 and found there was little impact on the results (data available upon request). Subgroup analyses were further conducted to explore the robustness of our results and potential sources of heterogeneity. Studies reporting data not suitable for meta-analysis (e.g. outcomes other than OR, or with missing data) were summarized narratively. Publication bias was assessed using funnel plots and Egger's test.

2.3. Results

A total of 11092 citations were identified in the literature search and 51 unique studies (described in 52 publications), met the inclusion criteria (Figure 2-1).[2,21-71] Fifteen studies were cohort studies and 36 were cross sectional or repeat cross sectional studies (Table 2-2). The included studies were published over a 21-year time span (1990 to 2011) and had quality scores based on the STROBE checklist that ranged from 8.5 to 21 (median 17.5) out of a total of 22 possible items (0.5 points given for partial reporting). Two reports provided data on the same study,[39,43] and six studies included data for more than one patient cohort.[38,44,49,62,67,68] Thus, 58 patient populations (or cohorts) were included in our study. Two studies were in a language other than English and were translated using on-line resources and local expertise.[32,66] There was good agreement between reviewers on study selection (kappa 0.82, 95% confidence interval [CI] 0.75 to 0.90).

Patients were selected from a hospital setting in 12 studies, from ambulatory care practices in 17 studies, and in 22 studies, patients were selected from population-based or community-dwelling samples. Exploring rural-urban differences was the primary objective of 18 studies (35%).[2,21,22,24,25,30,31,34,38,39,44,46,49,54,64,65,67,69] Seven studies reported medication adherence (the proportion of doses taken as prescribed over a specific time period) or persistence (the length of continuous treatment),[72] and 47 reported outcomes related to medication utilization. Among the studies, there were substantial variations in how medication utilization or adherence to medications was assessed. Overall, 16 studies included patient self-report, 31 studies included data from medical records or registries, and 5 studies were conducted using administrative databases. Nineteen studies reported crude utilization or adherence outcome data only.[22,26,30-32,34,35,45,46,48,49,58,59,63,64,67,69-71]

Included studies varied in their characteristics (Table 2-2). Studies ranged in sample size from 32 to approximately one million and were conducted in a range of areas including the US (30 studies), Europe (14), Canada (5) and Australia (2). Patient populations included those with acute myocardial infarction or coronary artery disease (18 studies), hypertension (16), diabetes (8), chronic heart failure (6), atrial fibrillation (5), or mixed cardiovascular disease populations (5). The average age of study participants ranged from 42 to 80 years, and 28% to 63% were female.

Medication utilization

Forty seven (92%) studies[2,21-31,33-42,44,46-65,67-69,71] evaluated cardiovascular medication utilization with 20 (39%) studies specifically evaluating utilization of ASA or other anti-thrombotic agents, 34 (67%) evaluating antihypertensive use, and 11 (22%) evaluating the use of lipid lowering agents (Table 2-3). Substantial variation in the use of cardiovascular medications was observed between studies and between rural versus urban sub-populations within each study. Indeed, the absolute difference in the utilization of cardiovascular medications ranged from -46% to +4% in rural versus urban patients for ASA or other anti-thrombotic drugs, -37% to +25% for antihypertensive drugs, and -45% to +8% for lipid lowering agents. Of the 47 studies that evaluated cardiovascular medication use, sufficient data for pooling were available in 34 studies (39 separate cohorts as two cohorts were included in three studies[38,62,68] and three cohorts in one study[67]). In the unadjusted pooled analyses, patients in rural areas with cardiovascular disease or diabetes were less likely to receive evidence-based cardiovascular drug therapy compared to urban residents (pooled unadjusted OR 0.88, 95% CI 0.79, 0.98, p=0.02; I^2=97%) (Table 2-4). However, among the 21 studies that adjusted for potential confounders, pooled analysis indicated no statistically significant difference between rural and urban patients in the use of cardiovascular medications (pooled adjusted OR 1.02, 95% CI 0.91 to 1.13, p=0.77, I^2=97%) (Figure 2-2). In both analyses there was substantial heterogeneity between studies. Although numerous subgroup analyses by setting, drug class, disease, age, country, and publication year were undertaken,

similar results were observed and these factors only partially explained some of the variation between studies (Table 2-4, Figures 2-2 and 2-3). Moreover, when studies were categorized according to how the outcome was assessed (patient self-report, medical chart review, or administrative data), similar results were observed (Table 2-4). Additional analyses by study quality, for countries with universal health care systems, and for specific drugs, such as angiotensin converting enzyme inhibitors, also found similar findings (data not shown). Among studies reporting data not suitable for meta-analysis, the findings were also consistent in that there was no clear trend towards a reduction or increase in cardiovascular medication utilization between rural and urban patients.[2,24-28,35,44,49,54,58,60,63]

Publication bias was assessed by visually examining funnel plots and no obvious asymmetry was noted (Egger's p value=0.98).

Medication adherence or persistence

Six (12%) studies[23,32,41,66,69,70] evaluated cardiovascular medication adherence and two (4%) studies[41,45] evaluated medication persistence. Adherence was measured as the percentage of doses taken,[69] the proportion of patients with a medication possession ratio ≥0.8,[23,41] and was undefined in three studies.[32,66,70] Persistence was measured as the proportion of patients remaining on the same[41,45] or any treatment[41] at the end of the follow up. In five of these studies,[32,41,45,66,70] the drugs evaluated were antihypertensive agents, one study

evaluated heart failure medications,[69] and one assessed ASA or ACEI/ARB adherence.[23]

Cardiovascular medication adherence or persistence findings were inconsistent across studies (Table 2-3). The absolute difference in proportion adherent or persistent with medications ranged from -41% to +8% for rural versus urban patients. The odds of treatment persistence were significantly higher in rural versus urban patients in one report (adjusted OR 1.28, 95% CI 1.25, 1.32),[41] but was not statistically different in a second study (OR 0.96, 95% CI 0.55, 1.67).[45] Medication adherence data from three studies (4 cohorts) were pooled and showed no statistically significant difference between rural and urban patients (unadjusted OR 0.94, 95% CI 0.39, 2.27, p=0.89, I^2=91%).[23,32,66] In two other reports with data not suitable for meta-analysis, medication adherence was significantly higher in one study (92% versus 83% of doses taken, p=0.01),[69] and significantly lower in the other (10% versus 17% of patients 'compliant', p<0.01),[70] for rural versus urban patients, based on unadjusted data. The three studies reporting treatment adherence adjusted for confounders reported adherence to be significantly higher in rural patients (OR medication possession ratio ≥0.8: antihypertensive agents 1.2, 95% CI 1.1, 1.3;[41] ASA 1.14, 95%CI 1.10, 1.18;[23] ACEI/ARB 1.18, 95% CI 1.14, 1.23[23]) or rural men (OR adherent 4.0, 95% CI 1.1, 13.9) (Table 2-3).[66]

2.4. Discussion

Our systematic review of the literature found that rural patients were 12% less likely to receive cardiovascular medications than urban patients in unadjusted analyses; however, pooling of data adjusted for patient, practitioner or other factors revealed no differences in the proportions of rural and urban patients receiving therapy. This suggests that differences in these characteristics between rural and urban residents are largely responsible for the discrepancies in medication use observed and is consistent with previous studies showing important differences in the demographics, health behaviors, and overall health of people living in rural and urban areas.[1,3-5] In this review, many of the included reports provided little data on the demographics or comorbidities of the rural and urban patient groups, which hindered our ability to assess the similarity of these populations. As a result, it is difficult to draw conclusions from those studies that reported only unadjusted rural-urban comparisons.

When medication utilization data were pooled, substantial between-study heterogeneity was observed (I^2 =97%). Some of this variability could be explained by differences in the setting (hospital, ambulatory care practice or community-based sample), age, and disease state. While most studies adjusted for some clinical characteristics, only some controlled for socioeconomic factors that could also have impacted medication use. Indeed only fourteen studies[21,27,29,37,38,40,42,47,52,53,56,57,62,65] reported adjustment for health insurance and previous studies have shown patients with a chronic condition who lack

medication insurance are less likely to take medications or frequently skip doses due to cost.[47,62,73]

Similarly, we found no consistent relationship between rural residence and cardiovascular medication adherence or persistence rates based on unadjusted data. The adjusted analysis suggested higher adherence and persistence for rural residents, although there were few studies reporting these outcomes. Rural-urban differences in other health behaviors, such as smoking, exercise, and consumption of fruits and vegetables have been reported,[4] and considering the link between adherence and positive health outcomes,[74] further study is warranted.

Although we conducted an exhaustive search for literature and conducted our systematic review in accordance to the highest reporting standards, our review is not without limitations. Firstly, studies evaluating differences in urban versus rural settings within subgroup analyses may not have been easily identified. Second, as in any systematic review, the findings are limited by the quality of the individual studies. Potential limitations included reporting bias,[27,28,35,36,40,44,46,49,67,68] selection bias,[30,49,61] lack of generalizability,[22,31,32,34,45,46,54,61,67,69,70] limited sample size,[22,31,32,34,45,59,69] no adjustment for confounders,[22,26,30-32,35,45,49,59,70,71] and poor reporting (STROBE score below the 25th percentile).[22,26,31,32,35,39,45-47,49,54,59,66,67,70] Third, we accepted a broad range of definitions for rural and urban populations, which may have

affected study results. In 25 studies[22,26,29,31,32,35-38,40,41,45,47,48,50-55,59,60,62,68,70] no clear definition of rural and urban were provided and various definitions were used in the remaining studies. It is possible some of the heterogeneity observed in our pooled analysis is related to these differences in definitions, although subgroup analysis by studies with defined and undefined rural populations showed similar results. Fourth, between-study heterogeneity was high and not fully explained despite multiple subgroup analyses by setting, drug class, disease, age, country, publication year, and data source (self-report, administrative or medical records). Last, our review only included adults with established cardiovascular disease as medication utilization for secondary prevention was expected to be high within patients; thus, improving the power to detect differences if differences exist between rural and urban patients. Moreover, as cardiovascular medications are widely prescribed medications in the general adult population, our results would be expected to be highly generalizable.

In conclusion, we found no consistent relationship between rural versus urban residence and utilization of, or adherence with evidence-based cardiovascular medications among adults with cardiovascular disease or diabetes. There was substantial between-study variation that was only partially explained by the setting, age, and disease. Higher quality evidence is needed to determine if differences in cardiovascular medication utilization and adherence between urban and rural patients truly exist.

Table 2–1: Literature search strategy – Medline

Medline and Medline In-Process (Licensed Ovid Interface) 1950 to Apr Week 2 2012
1. diabetes mellitus/
2. Diabetes Mellitus, Type 2/
3. ((diabet* or DM) adj5 ("type 2" or "type ii" or non insulin dependent or matur* onset or late onset)).ti,ab.
4. (diabet* not (juvenile or "type 1")).ti.
5. (diabetes adj5 (complication* or education)).mp.
6. (niddm or mody or T2DM).ti,ab.
7. (diabet* not gestational).ti.
8. or/1-7
9. exp Cardiovascular Diseases/
10. exp Hyperlipidemias/
11. ((cardiovascular or coronary or heart or cardia* or cardio* or myocardi* or pericardi*) adj3 disease).ti,ab.
12. or/9-11
13. 8 or 12
14. rural population/ or suburban population/ or urban population/
15. rural health/ or suburban health/ or urban health/
16. rural health services/ or suburban health services/ or urban health services/
17. "Catchment Area (Health)"/
18. (rural* or urban or semi-rural or semi-urban or city or non-urban or farm* or agricultur* or town* or village* or metropolitan or non-metropolitan or suburb* or remote or region or residence or jurisdiction or geographic or geography or location or residence or catchment).ti,ab.
19. (community adj (dwelling or resid* or based)).ti,ab.
20. (care adj network).ti,ab.
21. or/14-20
22. exp Drug Utilization/
23. Pharmacies/ut [Utilization]
24. exp Prescriptions/
25. exp Patient Compliance/
26. or/22-25
27. (Drug or drugs or prescrib* or prescription* or medication* or medicine or pharmac* or agent* or inhibitor* or intravenous or oral).ti,ab.
28. dt.fs.
29. exp Pharmaceutical Preparations/
30. or/27-29
31. exp "Physician's practice patterns"/
32. (adherence or compliance or concordance or usage or utilisation or utilization or underutili* or consumption or nonadherence or uptake).ti,ab.
33. ut.fs.
34. or/31-33

35. 30 and 34
36. ((Drug or drugs or prescrib* or prescription* or medication* or medicine or pharmac*) adj4 use*).ti,ab.
37. or/26,35-36
38. 13 and 21 and 37
39. animals/ not humans/
40. 38 not 39
41. (exp child/ or exp adolescent/ or exp infant/) not exp adult/
42. 40 not 41

Table 2–2: Study characteristics

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
de Oliveira-Martins 2011[33]	cross-sectional	HTN	Portugal	1,042	community pharmacy (patient interview)	53.7 (SD 7.1)	59	24	19
Funkhouser 2011[42]	cohort	AMI	US	1,901	ambulatory care practice (medical chart)	<65y: 13% 65-74y: 34% >74y: 53%	41	30	20
Maio 2011[16,51]	cohort	AMI	Italy	24,367	population sample (administrative data)	70.8 (SD 13.0)	36	32	19.5
Strom 2011[65]	cross-sectional	DM	US	52,817	population sample (BRFSS)	18-34y: 6% 35-49y: 19% 50-64y: 38% >=65y: 38%	50	21	19
Yusuf 2011[71,75]	cohort	CAD	Canada, Sweden, United Arab Emirates	16,073	community (patient interview)	52.7 (SD 9.4)	NR	28	20
Ambardekar 2010[21]	cross-sectional	CAD	US	352,034	hospital (Get With the Guidelines CAD Quality Improvement Program)	rural: 67.4 urban: 66.3	rural: 43 urban: 42	6	19

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
Asghari 2010[23]	cohort	DM	Canada	170,381	population sample (administrative data)	62 (SD 14)	52	22	17.5
Baldwin 2010[24]	cross-sectional	AMI	US	21,616	hospital (medical chart)	77.3 (SE 0.07)	49	25	19.5
DiMartino 2010[37]	cohort	HF	US	2,689	Community dwelling (MCBS)	79 (SE 0.2)	56	28	19
Ellis 2010[38]	cross-sectional	HTN	US	45,024	population sample (BRFSS)	18-34y: 6% 35-49y: 20% 50-64y: 37% >=65y: 37%	rural: 52 urban: 52	37	20
Friedman 2010[41]	cohort	HTN	Canada	207,473	population sample (administrative data)	66-70y: 40% 71-75y: 28% 76-80y: 18% 81-85y: 9% 85+ y: 5%	58	14	19
Hicks 2010[46]	cross-sectional	DM with HTN	US	778	ambulatory care practice (physician survey)	rural: 58.3 (SE 1.2) urban: 56.1 (SE 0.9)*	rural: 63 urban: 63	38	14.5
Vanasse 2010[2]	cohort	AMI	Canada	44,806	population sample (administrative data)	66.5 (SD NR)	35	25	18.5

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
Wu 2010[69]	cohort	HF	US	136	ambulatory care practice (medical chart, patient interview)	rural: 60 (SD 11) urban: 62 (12)	rural: 25 urban: 39	64	20.5
Fonarow 2009[40]	repeat cross-sectional	AMI	US	996,364	hospital (NRMI)	68.1 (SD 13.7)	40	hospitals: 8	18.5
Niska 2009a[56]	cross-sectional	CVD, DM, HTN, other	US	4,964	ambulatory care practice (NAMCS, NHAMCS)	55-64y: 45% 65-80y: 55%	56	20	17
Niska 2009b[57]	cross-sectional	AF	US	1,771	ambulatory care practice (NAMCS, NHAMCS)	<65y: 25% 65-75y: 29% >75y: 46%	49	14	17
Goldman 2008[44]	cross-sectional	AMI, HF	US	2847 hospitals	hospital (Hospital Compare data)	NR	NR	hospitals: 38	20
Ma 2008[50]	cross-sectional	HTN	US	50,574	ambulatory care practice (NAMCS)	NR	NR	NR	18
Wan 2008[67]	repeat cross-sectional	DM	Australia	6,305	ambulatory care practice (CARDIAB registry)	rural: 64 urban: 60	NR	54	16
Williams 2008[68]	cross-sectional	AMI, HF	US	3,138 hospitals	hospital (Joint Commission performance indicator data)	NR	NR	hospitals: 30	17.5

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
Clark 2007[30]	cross-sectional	HF	Australia	22,060	ambulatory care practice (CASE study)	NR	NR	29	16.5
Colleran 2007[31]	cohort	CVD	US	200	ambulatory care practice (medical chart)	range rural: 50-82y urban: 52-74y	rural: 40 urban: 55	50	15
Lutfiyya 2007[49]	cross-sectional	AMI, HF	US	4,203 hospitals	hospital (Hospital Compare data)	NR	NR	hospitals: 11	13.5
Perez-Fernandez 2007[59]	cross-sectional	HTN	Spain	2,884	population sample (patient survey)	41.6 (SD 15.3)	54	45	16
Rowan 2007[63]	cross-sectional	AF	US	NR	ambulatory care practice (NAMCS)	18-59y: 11% 60-75y: 37% >75y: 52%	49	23	17
Byrne 2006[29]	cross-sectional	CAD	Ireland	1,611	ambulatory care practice (medical chart)	66 (SD 9.1)	35	NR	20
Czarnecka 2006[32]	cross-sectional	HTN	Poland	222	ambulatory care practice (patient survey)	56.9 y (SD 8.6)*	55	20	8.5

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
DeWilde 2006[36]	repeat cross-sectional	AF	UK	12,267	ambulatory care practice (DIN-LINK data)	35-64y: 16% 65-74y:25% 75-84y: 39% ≥85y: 20%	47	NR	16.5
Tuesca-Molina 2006[66]	cross-sectional	HTN	Spain	1,719	population sample (patient survey)	60-69y: 42% 70-79y: 39% 80+y: 19%	63	6	15
Bradley 2005[28]	cross-sectional	AMI	US	60,363	hospital (NRMI)	67.7 (SD 13.9)	39	hospitals: 17	20
Nguyen 2005[55]	cross-sectional	DM	US	NR	ambulatory care practice (NAMCS)	30-44y: 10% 45-59y: 30% 60-74y: 40% >74y: 21%	53	21	17
Rice 2005[62]	cross-sectional	cardiac	US	2,121	population sample (CHI survey)	18-24y: 4% 25-34y: 9% 35-44y: 16% 45-54y:32% 55-64y: 38%	48	14	18.5
		HTN	US	8,243	population sample (CHI survey)	18-24y: 5% 25-34y: 12% 35-44y: 22% 45-54y:32% 55-64y: 29%	47	14	18.5
Yiannakopoulou 2005[70]	cross-sectional	HTN	Greece	1,000	hospital (patient survey)	58.5 (SD 11.3)	45	28	13

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
Andrus 2004[22]	cohort	DM	US	187	ambulatory care practice (medical chart)	rural: 55.1 (SD 13.7) urban: 65.8 (SD 12.3)*	rural: 64 urban: 60	42	13
Baldwin 2004[25]	cross-sectional	AMI	US	135,759 (4,085 hospitals)	hospital (medical chart)	76.6 (SD 7.4)	49	25	20.5
Bradley 2004[27]	repeat cross-sectional	AMI	US	335,244	hospital (NRMI)	67.1 (SD 13.9)	38	hospitals: 18	20.5
Ko 2004[48]	cohort	CVD, DM	Canada	396,077	population sample (administrative data)	median 72 y	55	18	19.5
Pittrow 2004[60]	cross-sectional	HTN	Germany	17,485	ambulatory care practice (physician survey)	63.2 (SD 12.4)	57	NR	17
Psaltopoulou 2004[61]	cross-sectional	HTN	Greece	26,913	community (patient interview)	25-44y: 10%, 45-64y: 49%, >=65y: 41%	rural: 62 urban: 52	62	19.5
DeWilde 2003[35]	repeat cross-sectional	CAD	UK	30,448	ambulatory care practice (DIN)	35-44y: 1% 45-54y: 8% 55-64y: 21% 65-74y: 37% 75-84y: 33%	41	practices: 18	15

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
Huttin 2002[47]	cross-sectional	HTN	US	1,844	ambulatory care practice (NAMCS)	≤44y: 11% 45-54y: 17% 55-64y: 21% 65-74: 27% 75-84y: 20% >85y: 5%	56	NR	13.5
Majumdar 2001[53]	cross-sectional	AMI	US	5,138	hospital (medical chart)	67 (SD 14)*	38	18	21
Sheikh 2001[64]	cohort	AMI	US	2,285	hospital (medical chart)	rural: 78.2 semi-rural: 76.6 urban: 74.1	rural:43 semi-rural: 46 urban: 43	20	17
Obisesan 2000[58]	cross-sectional	HTN	US	6,278	population sample (NHANES III)	NR	NR	NR	16.5
Dellasega 1999[34]	cohort	cardiac	US	32	hospital (patient survey)	rural: 73.3 (SD 4.6) urban: 73.2 (SD 6.3)	rural: 33 urban: 24	47	18
Flaker 1999 (Gage 2000)[39,43]	cross-sectional	AF	US	597	hospital (medical chart)	rural: 80.7 (SD 7.6) urban: 79.6 (SD 8.3)*	rural: 58 urban:54	26	16
Majumdar 1999[52]	cross-sectional	AMI	US	622	hospital (medical chart)	66.4	37	27	20

Author, year	Study design	Population	Country	Total N†	Setting (primary data source)	Age (y), mean (SD/SE)‡	Female (%)‡	Rural (%)‡	STROBE score§
Banegas 1998[26]	cross-sectional	HTN	Spain	2,021	community (patient interview)	NR	NR	NR	12.5
Munschauer 1997[54]	cohort	AF	US	651	hospital (medical chart)	NR	NR	hospitals: 50	13
Hense 1990[45]	cohort	HTN	Germany	289	community dwelling sample (patient survey)	30-49y: 24% 50-64y: 76%	57	54	14

AF=atrial fibrillation; AMI=acute myocardial infarction; BRFSS=Behavioral Risk Factor Surveillance System: CAD=coronary artery disease; CASE=Cardiac Awareness Survey and Evaluation study; CHI=California Health Insurance; CVD=cardiovascular disease; DM=diabetes; DIN=Doctor's Independent Network database; HF=heart failure; HTN=hypertension; MCBS=Medicare Current Beneficiary Survey: MEPS=Medical Expenditure Panel Survey: NAMCS=National Ambulatory Medical Care Survey; NHAMCS=National Hospital Ambulatory Medical Care Survey: NHANES=National Health and Nutritional Examination Survey; NR=not reported; NRMI=National Registry of Myocardial Infarction; SD=standard deviation; SE=standard error; y=years
†All patients included in study; ‡When available, the age, sex and proportion rural data were reported for the subset of patients most relevant to this report's outcomes (e.g. the subset with DM or CVD) §Studies were given 1 point for complete reporting and 0.5 points for partial reporting of items listed on the STROBE checklist (total possible points = 22); *Assumed to be SD or SE: measure of variance was not reported clearly by study authors.

Table 2–3: Study results

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
Medication Adherence or Persistence								
Asghari 2010[23]	community	DM	Regular user ASA (MPR≥ 0.8)	47,829	67.7%	63.0%	1.24 (1.18, 1.29)*	1.14 (1.10, 1.18)
			Regular user ACEI/ARB (MPR≥ 0.8)	76,482	73.5%	70.5%	1.16 (1.12, 1.21)*	1.18 (1.14, 1.23)
Friedman 2010[41]	community	HTN	therapy persistence over 2 years (any HTN medication)	206,603	NR	NR	NR	1.28 (1.25, 1.32)
			drug class persistence over 2 years (same class of medication as initial therapy) over 2 years	206,603	NR	NR	NR	1.27 (1.23, 1.30)
			MPR ≥ 0.8 over 2 years	136,673	NR	NR	NR	1.22 (1.14, 1.32)
Wu 2010[69]	amb. care practice	HF	medication adherence over 3 mo (% doses taken)	136	91.6%	83.4%	p=0.011 (data NR)	NR
Czarnecka 2006[32]	amb. care practice	HTN	regular users of meds	222	25.0%	66.3%	0.17 (0.08, 0.36)*	NR
Tuesca-Molina 2006[66]	community	HTN	adherent to HTN medications: men	530	NR	NR	5.36 (1.57, 18.23)	3.98 (1.13, 13.93)
			adherent to HTN medications: women	905	NR	NR	1.01 (0.58, 1.77)	NR
Yiannakopoulou 2005[70]	hospital	HTN	compliant with HTN meds	1,000	10.0%	16.90%	p<0.01 (data NR)	NR
Hense	community	HTN	treatment persistence	204	55.0%	55.9%	0.96 (0.55, 1.67)*	NR

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
1990[45]			(identical medication at baseline and follow-up)					
Medication utilization								
de Oliveira-Martins 2011[33]	community	HTN	treated for HTN	571	NR	NR	0.51 (0.34, 0.75)	0.46 (0.30, 0.72)
Funkhouser 2011[42]	amb. care practice	AMI	prescribed BB (no contraindications)	1,901	74.7%	66.7%	1.33 (1.12, 1.72)	1.72 (1.31, 2.48)
Maio 2011 (unpublished data)[16,51]	community	AMI	initiated on BB (no contraindications)	24,367	68.4%	67.3%	1.08 (1.02, 1.15)*	rural (hill): 1.05 (0.91, 1.20), rural (mountain): 0.92 (0.80, 1.04)
Strom 2011[65]	community	DM	ASA user (weighted %)	52,817	55.7%	53.8%	p=0.15 (data NR)	1.08 (0.96, 1.21)
Yusuf 2011[71,75]	community	CAD	antiplatelet drug user	669	64.2%	64.1%	1.00 (0.69, 1.45)*	NR
			taking any HTN drug (ACE, ARB, BB, CCB, diuretic)		77.2%	78.7%	0.91 (0.60, 1.40)*	NR
			statin user		64.8%	72.8%	0.69 (0.47, 1.00)*	NR
Ambardekar 2010[21]	hospital	CAD	ASA at discharge	352,034	90.5%	95.0%	0.58 (0.45, 0.75)	0.80 (0.56, 1.16)
			ACEI/ARB at discharge		82.4%	81.3%	1.02 (0.82, 1.26)	1.25 (1.03, 1.53)
			BB at discharge		86.2%	91.3%	0.62 (0.47, 0.83)	0.96 (0.69, 1.33)
			LLD at discharge		83.4%	86.5%	0.60 (0.43, 0.84)	1.12 (0.83, 1.52)
Asghari 2010[23]	community	DM	ASA user	170,381	31.0%	27.0%	1.21 (1.18, 1.25)*	1.26 (1.22, 1.29)
			ACEI/ARB user		49.0%	44.0%	1.22 (1.20, 1.25)*	1.29 (1.26, 1.32)
Baldwin 2010[24]	hospital	AMI	ASA on discharge (no contraindications, weighted N, %)	68,343	Large: 78.0%, Small: 77.4%,	82.0%	Large: RR 0.95 (p = NS), Small: RR 0.94 (p<=0.05), Isolated: RR 0.79 (p	Large: RR 0.97 (0.93, 1.00), Small: RR 0.99 (0.94, 1.02), Isolated: RR

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
					Isolated: 64.7%		<=0.001)	0.84 (0.73, 0.93)
			ACEI at discharge (weighted N, %)	30,011	Large: 62.7%, Small: 62.6%, Isolated: 68.8%	61.2%	Large: RR 1.03 (p = NS), Small: RR 1.02 (p = NS), Isolated: RR 1.12 (p = NS)	Large: RR 1.05 (0.96, 1.13), Small: RR 1.04 (0.90, 1.17), Isolated: RR 1.16 (0.85, 1.37)
			BB on discharge (no contraindications, weighted N, %)	86,233	Large: 68.3%, Small: 59.9%, Isolated: 53.4%	69.2%	Large: RR 0.99 (p = NS), Small: RR 0.87 (p<=0.001), Isolated: RR 0.77 (p <=0.001)	Large: RR 1.01 (0.97, 1.05), Small: RR 0.92 (0.85, 0.98), Isolated: RR 0.82 (0.69, 0.94)
DiMartino 2010[37]	community	HF	ACEI/ARB user	2,689	NR	NR	NR	1.18 (0.98, 1.41)
			BB user		NR	NR	NR	1.04 (0.86, 1.27)
Ellis 2010[38]	community	HTN	HTN medication user: Caucasian race	38,268	87.9%	87.1%	1.08 (1.01, 1.15)*	1.15 (0.93, 1.42)
			HTN medication user: Black race	6,756	89.5%	88.9%	1.07 (0.91, 1.25)*	NR
Friedman 2010[41]	community	HTN	ACEI user	95,773	47.1%	46.0%	1.04 (1.02, 1.07)*	NR
			ARB user	9,452	3.5%	4.7%	0.74 (0.69, 0.79)*	NR
			BB user	21,973	12.2%	10.3%	1.21 (1.16, 1.26)*	NR
			CCB user	23,603	10.3%	11.6%	0.88 (0.84, 0.91)*	NR
			diuretic user	56,672	32.9%	26.4%	1.36 (1.33, 1.40)*	NR
Hicks 2010[46]	amb. care practice	DM, HTN	prescribe HTN medication or increase HTN dose for uncontrolled HTN	478	21.1%	33.2%	0.54 (0.35, 0.83)*	NR
Vanasse	community	AMI	ASA user	NR	NR	86.3%	NR	multiple urban and

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
2010[2]								rural groups; RR [p-value 99% CI] for urban (CA), rural (strong MIZ), (mod MIZ), (weak MIZ), (no MIZ), reference urban (CMA): 1.01 [NS], 1.03 [p<0.001], 1.03 [p<0.001], 0.98 [NS], 0.97 [NS]
			ACEI user	NR	NR	74.7%	NR	RR 1.00 [NS], 1.02 [NS], 1.05 [p<0.0001], 1.03 [NS], 1.04 [NS]
			BB user	NR	NR	81.2%	NR	RR 0.98 [NS], 1.02 [NS], 1.00 [NS], 0.95 [p<0.01], 0.97 [NS]
			statin user	NR	NR	72.1%	NR	RR 0.99 [NS], 1.02 [NS], 1.03 [NS], 1.02 [NS], 1.03 [NS]
Wu 2010[69]	amb. care practice	HF	ACEI user (at baseline)	136	80.5%	55.1%	3.36 (1.55, 7.27)*	NR
			BB user (at baseline)		89.7%	87.8%	1.21 (0.40, 3.63)*	NR
Fonarow 2009[40]	hospital	AMI	LLD at discharge	996,364	NR	NR	NR	0.88 (0.86, 0.89)
Niska 2009a[56]	amb. care practice	CVD, DM,	prescribed statin at physician visit	4,964	36.2% (95% CI	38.1% (35.2, 41.1%)	p=0.64 (data NR)	0.96 (0.70, 1.31)

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
		HTN, other	(weighted %)		29.7, 43.4%)			
Niska 2009b[57]	amb. care practice	AF	prescribed warfarin at physician visit (no contraindications, weighted %)	1,771	50.4% (95% CI 39.8, 61.0%)	52.6% (48.4, 56.7%)	NS (data NR)	1.02 (0.61, 1.70)
Goldman 2008[44]	hospital	AMI	mean % difference in ASA at discharge stratified by bed size: <31 beds	2573 hospitals			NR	-6.13% (95% CI -9.81, -2.43)
			31 to <65 beds				NR	-5.03% (-7.03, -3.02),
			65 to <120 beds				NR	-2.19% (-3.52, -0.86)
			120 to <240 beds				NR	-0.12% (-1.44, 1.20)
			>=240 beds				NR	-2.86% (-4.90, -0.82)
			mean % difference in BB at discharge stratified by bed size: <31 beds	2302 hospitals			NR	-6.22% (-10.85, -1.59)
			31 to <65 beds				NR	-4.76% (-7.20, -2.32)
			65 to <120 beds				NR	-2.43% (-4.01, -0.84)
			120 to <240 beds				NR	1.25% (-0.25, 2.76)
			>=240 beds				NR	-0.59% (-3.06, 1.87)

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
		HF	mean % difference in ACEI at discharge stratified by bed size: <31 beds	2297 hospitals			NR	-1.58% (-8.71, 5.55)
			31 to <65 beds				NR	-4.07% (-7.82, -0.32)
			65 to <120 beds				NR	-2.43% (-4.96, 0.001)
			120 to <240 beds				NR	-0.02% (-2.33, 2.29)
			>=240 beds				NR	3.51% (-0.28, 7.31)
Ma 2008[50]	amb. care practice	HTN	prescribed >=1 HTN medication at physician visit	1,865	47.0%	65.0%	0.48 (0.37, 0.61)*	1.89 (0.96, 3.70)
Wan 2008[67]	amb. care practice	DM	HTN medication user (2002)	3,219	34.0%	26.5%	1.43 (1.23, 1.66)*	NR
			HTN medication user (2001)	1,690	32.0%	21.1%	1.75 (1.40, 2.20)*	NR
			HTN medication user (2000)	1,396	28.8%	14.1%	2.46 (1.88, 3.21)*	NR
			LLD user (2002)	3,219	20.4%	23.9%	0.82 (0.70, 0.97)*	NR
			LLD user (2001)	1,690	24.8%	18.4%	1.46 (1.15, 1.86)*	NR
			LLD user (2000)	1,396	22.5%	14.1%	1.76 (1.34, 2.33)*	NR
Williams 2008[68]	hospital	AMI	ASA on discharge (no contraindications)	2881 hospitals	NR	NR	NR	0.88 (0.79, 1.00)
			ACEI/ARB at discharge (no contraindications)	2709 hospitals	NR	NR	NR	0.85 (0.76, 0.95)
			BB at discharge (no	2887	NR	NR	NR	0.80 (0.71, 0.90)

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
			contraindications)	hospitals				
		HF	ACEI/ARB at discharge (no contraindications)	3127 hospitals	NR	NR	NR	0.88 (0.81, 0.96)
Clark 2007[30]	amb. care practice	HF	ACEI user	2,735	54.8%	60.1% (95% CI 58, 62%)	0.81 (0.68, 0.95)*	NR
			loop diuretic user		68.0%	66.9% (65, 69%)	1.05 (0.88, 1.26)*	NR
			BB user		11.5%	11.8% (10, 13%)	0.97 (0.75, 1.25)*	NR
Colleran 2007[31]	amb. care practice	CVD	ASA/anti-platelet user	200	47.0%	93.0%	0.07 (0.03, 0.16)*	NR
			ACEI/ARB user		55.0%	77.0%	0.37 (0.20, 0.67)*	NR
			BB/CCB user		51.0%	88.0%	0.14 (0.07, 0.29)*	NR
			statin user		42.0%	87.0%	0.11 (0.05, 0.22)*	NR
Lutfiyya 2007[49]	hospital	AMI	weighted mean % per hospital receiving ASA at discharge (no contraindications)	NR	82.0%	93.9%	Mean difference: -11.9% (99% CI -4.4, -19.2%), p<0.01	NR
			weighted mean % per hospital receiving BB at discharge (no contraindications)	NR	78.4%	91.2%	-12.8% (99% CI -4.6, -20.8%), p<0.01	NR
		HF	weighted mean % per hospital receiving ACEI at discharge (no contraindications)	NR	75.5%	75.3%	0.2% (99% CI -7.0, 7.4%)	NR
Perez-Fernandez 2007[59]	community	HTN	HTN medication user	372	72.7% (95% CI 66.2, 79.2%)	71.4% (65.0, 77.8%)	1.06 (0.68, 1.67)*	NR

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
Rowan 2007[63]	amb. care practice	AF	warfarin user (weighted n, %)	40,506,313	45.9%	45.6%	p=0.94 (data NR)	NR
Byrne 2006[29]	amb. care practice	CAD	prescribed ASA (no contraindications)	1,587	82.0%	80.0%	NS (data NR)	0.95 (0.68, 1.33)
			prescribed ACEI		31.0%	23.0%	p<0.01 (data NR)	0.56 (0.44, 0.78)
			prescribed LLD		47.0%	47.0%	NS (data NR)	1.07 (0.81, 1.41)
			prescribe nitrates		46.0%	55.0%	p<0.01 (data NR)	NR
DeWilde 2006 (unpublished data)[17,36]	amb. care practice	AF	anticoagulant user	9,399	Town 48.0%; Village 50.1%	48.9%	Town: 0.96 (0.84, 1.10)*; Village: 1.05 (0.93, 1.19)*	Town: 0.96 (0.76, 1.20); Village: NR
Bradley 2005[28]	hospital	AMI	BB at discharge	60,363	NR	NR	NR	NS (data NR)
Nguyen 2005[55]	amb. care practice	DM	ASA user (no contraindications, weighted n, %)	134 940 000	3.0%	2.5%	NR	1.23 (1.15, 1.33)
Rice 2005[62]	community	CVD	taking medications to control heart disease	2,114	NR	NR	NR	0.95 (0.71, 1.28)
		HTN	HTN medication user	8,217	NR	NR	NR	1.14 (0.97, 1.33)
Andrus 2004[22]	amb. care practice	DM	ASA user	187	17.9%	39.4%	0.34 (0.17, 0.67)*	NR
Baldwin 2004[25]	hospital	AMI	ASA at discharge (no contraindications)	43634	Large: 74.4%, Small: 71.1%, Remote: 67.7%	76.4%	p<=0.001 (data NR)	Large: RR 0.99 (0.96, 1.01), Small: 0.95 (0.92, 0.98), Remote: 0.90 (0.86, 0.96)
			BB at discharge (no contraindications)	10056	Large: 49.6%, Small:	51.8%	p=0.16 (data NR)	Large: RR 0.97 (0.89, 1.05), Small: 0.93 (0.83,

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
					47.2%, Remote: 55.4%			1.05), Remote: 1.07 (0.83, 1.38)
			ACEI at discharge	12459	Large: 63.1%, Small: 56.9%, Remote: 64.0%	59.4%	p=0.021 (data NR)	Large: RR 1.06 (1.01, 1.11), Small: 0.94, (0.87, 1.02), Remote: 1.08 (0.93, 1.24)
			avoid CCB at discharge	6334	Large: 84.7%, Small: 86.2%, Remote: 89.7%	83.6%	p=0.27 (data NR)	Large: RR 1.01 (0.97, 1.05), Small: 1.03 (0.98, 1.08), Remote: 1.06 (0.99, 1.14)
Bradley 2004[27]	hospital	AMI	BB at discharge (crude rate over study period, mean (SD))	335,244	56.2% (12.8)	57.5% (12.2)	NR	NR
			BB at discharge (adjusted rate over study period, mean (SD))		59.9% (NR)	60.9% (NR)	NR	NR
Ko 2004[48]	community	CVD, DM	prescribed statin	388,845	15.9%	19.9%	0.76 (0.75, 0.78)*	NR
Pittrow 2004[60]	amb. care practice	HTN	prescribed HTN medication	17,485	NR	NR	NR	NS (data NR)
Psaltopoulou 2004[61]	community	HTN	HTN medication user	6501	NR	NR	NR	1.34 (1.15, 1.57)
DeWilde 2003[35]	amb. care practice	CAD	prescribed statin	30,448	27.0%	27.0%	p=0.79 (data NR)	NR

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
Huttin 2002[47]	amb. care practice	HTN	HTN medication user	1,884	NR	NR	NR	0.99 (0.80, 1.23)
Majumdar 2001[53]	hospital	AMI	CCB at discharge	5,138	11.8%	17.2%	0.65 (0.52, 0.80)	0.98 (0.65, 1.49)
Sheikh 2001[64]	hospital	AMI	ASA at discharge (no contraindications)	643	68.7%	81.5%	0.50 (0.34, 0.73)*	NR
			BB at discharge (no contraindications)	199	32.4%	37.0%	0.82 (0.38, 1.74)*	NR
Obisesan 2000[58]	community	HTN	Age adjusted prevalence of treatment for HTN: 40 to 59 years, Southern states	NR			NR	NR
			Black women		67.6%	63.1%		
			Black men		41.1%	32.0%		
			White men		35.6%	53.0%		
			Age adjusted prevalence of treatment for HTN: 40 to 59 years, Non-Southern states	NR			NR	NR
			White women		59.1%	74.5%		
			White men		0.2%	5.8%		
			Age adjusted prevalence of treatment for HTN: 60 to 79 years, Southern states	NR			NR	NR
			Black women		76.1%	69.6%		
			Black men		65.2%	69.0%		
			White women		66.5%	57.6%		
			White men		54.7%	61.8%		

Author, year	Setting	Population	Outcome	Total N	Rural	Urban	Rural/urban unadjusted OR (95% CI) †	Rural/urban adjusted OR (95% CI)†
			Age adjusted prevalence of treatment for HTN: 60 to 79 years, non-Southern states Black women Black men White women White men	NR	 71.0% 52.2% 58.0% 62.5%	 70.7% 55.1% 65.8% 45.5%	NR	NR
Dellasega 1999[34]	hospital	CVD	CV medication user (at 20 weeks)	32	87%	76.5%	2.00 (0.31, 12.89)	NR
Flaker 1999 (Gage 2000)[39,43]	hospital	AF	antithrombotic at discharge (all patients)	597	46.8%	57.9%	0.64 (0.45, 0.92)	0.59 (0.40, 0.83)
			antithrombotic at discharge (no contraindications)	234	54.8%	74.5%	0.41 (0.23, 0.74)	NR
Majumdar 1999[52]	hospital	AMI	LLD upon admission	622	32.1%	38.8%	0.75 (0.51, 1.09)	p=NS (data NR)
Banegas 1998[26]	community	HTN	HTN medication user (weighted)	NR	69.1% (60.1, 77.1%)	73.0% (67.5, 78.1%)	p=NS (data NR)	NR
Munschauer 1997[54]	hospital	AF	antithrombotic at discharge	651	43.0%	64.0%	NR	p<0.0001 (data NR)

amb.=ambulatory; ACEI=angiotensin converting enzyme inhibitor; AF=atrial fibrillation; AMI=acute myocardial infarction; ARB=angiotensin receptor blocker; ASA=acetylsalicylic acid; BB=beta-blocker; CA=Census Agglomerations; CAD=coronary artery disease; CCB=calcium channel blocker; CMA=Census Metropolitan Area; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes; HF=heart failure; HTN=hypertension; LLD=lipid lowering drug; MIZ=Metropolitan Influenced Zone; MPR=medication possession ratio; N=number; NR=not reported; NS=not statistically significant; OR=odds ratio; RR=relative risk; SD=standard deviation

† Data are OR (95% CI) unless specified otherwise; *Calculated using Review Manager software

Table 2–4: Meta-analysis of medication utilization and adherence outcomes

Analysis	N	Rural/urban OR of treatment (95% CI)	I^2 (%)	Subgroup difference
Cardiovascular medication utilization				
Overall - unadjusted	26	0.88 (0.79, 0.98)	97	NA
Overall - adjusted	23	1.02 (0.91, 1.13)	97	NA
Subgroup analysis – adjusted				
Setting				
Community or population-based	8	1.15 (1.06, 1.25)	71	P<0.0001
Hospital	6	0.87 (0.83, 0.92)	34	
Ambulatory care practice	9	1.02 (0.85, 1.24)	78	
Drug class				
Antithrombotic or anticoagulant	9	1.00 (0.88, 1.14)	88	P=0.62
Antihypertensive	16	1.03 (0.90, 1.17)	92	
Lipid lowering agent	4	0.94 (0.83, 1.07)	37	
Disease				
Atrial fibrillation	3	0.83 (0.59, 1.16)	67	P=0.0001
Cardiovascular disease	11	0.95 (0.88, 1.03)	67	
Hypertension	6	1.07 (0.87, 1.33)	79	
Diabetes	3	1.21 (1.12, 1.31)	76	
Age (study mean or median)				
<65 years	8	1.15 (1.04, 1.26)	80	P=0.005
≥65 years	12	0.98 (0.88, 1.08)	70	
Not reported	3	0.89 (0.77, 1.02)	64	
Country				
US	18	1.01 (0.92, 1.10)	87	P=0.67
Non-US	5	1.05 (0.88, 1.26)	88	
Publication Year				
1999-2005	7	1.06 (0.91, 1.22)	76	P=0.66
2006-2011	16	1.01 (0.88, 1.15)	98	
Data source				
Administrative data	2	1.17 (0.97, 1.41)	87	P=0.19
Medical record	14	0.97 (0.87, 1.08)	86	
Patient self-report	7	1.07 (0.93, 1.22)	72	
Study quality				P=0.67
Above median STROBE score	13	1.04 (0.92, 1.17)	87	
Median or lower STROBE score	10	1.00 (0.85, 1.16)	94	
*Primary study objective**				P=0.63
Rural-urban differences	4	0.97 (0.79, 1.20)	75	
Other objective	19	1.03 (0.91, 1.16)	98	

Analysis	N	Rural/urban OR of treatment (95% CI)	I^2 (%)	Subgroup difference
Cardiovascular medication adherence				
Overall - unadjusted	4	0.94 (0.39, 2.27)	91	NA

CI=confidence interval; N=number of cohorts pooled; NA=not applicable; OR=odds ratio; US=United States

*Studies were stratified based on their primary objective. Those whose primary goal was to examine differences between rural and urban patient groups were pooled separately from studies where data comparing rural versus urban groups was a subgroup analysis or secondary objective.

Figure 2–1: Flow chart of systematic search

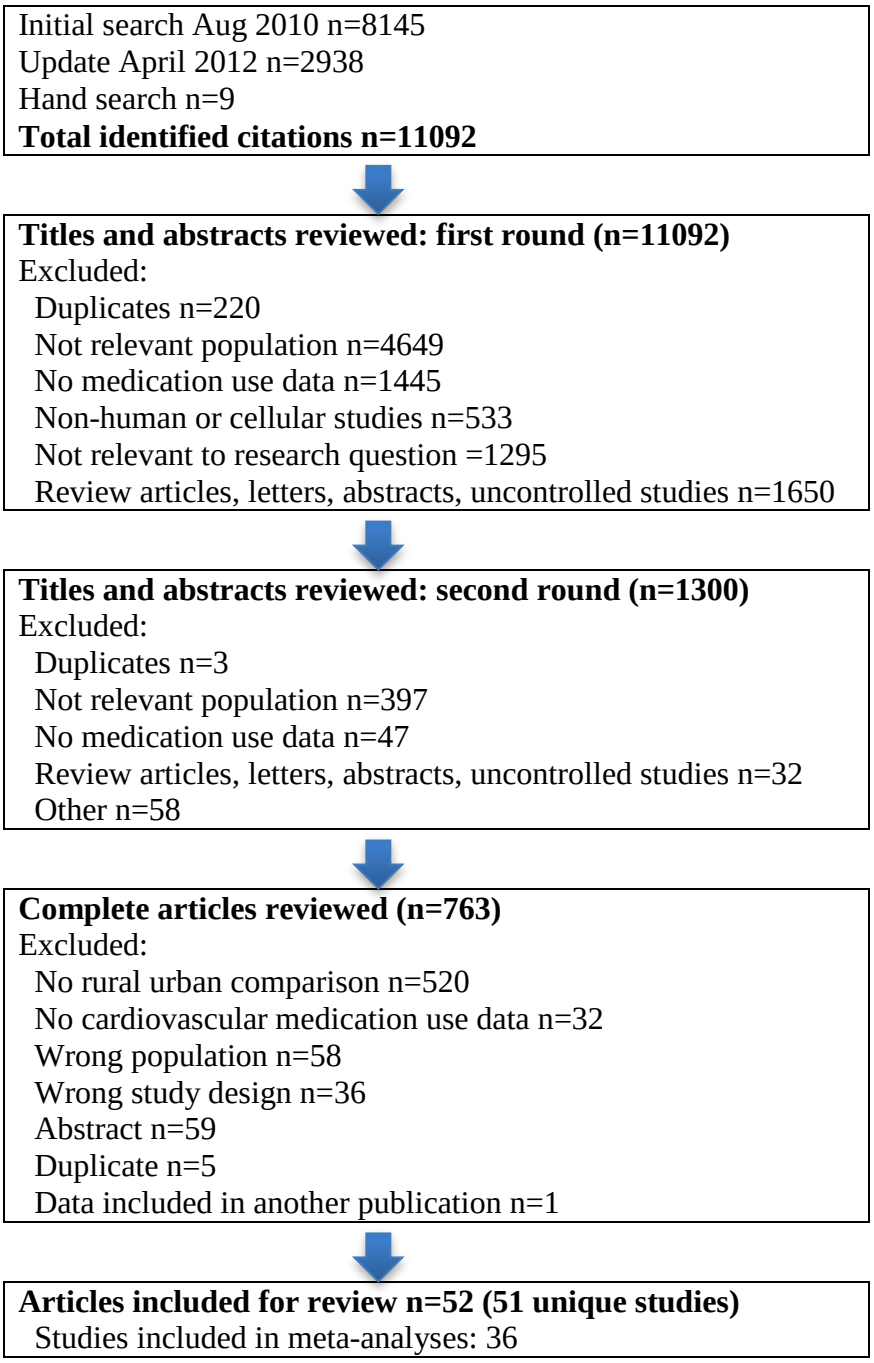


Figure 2–2: Use of evidence-based cardiovascular drugs by rural versus urban patients, stratified by study setting (adjusted analysis)

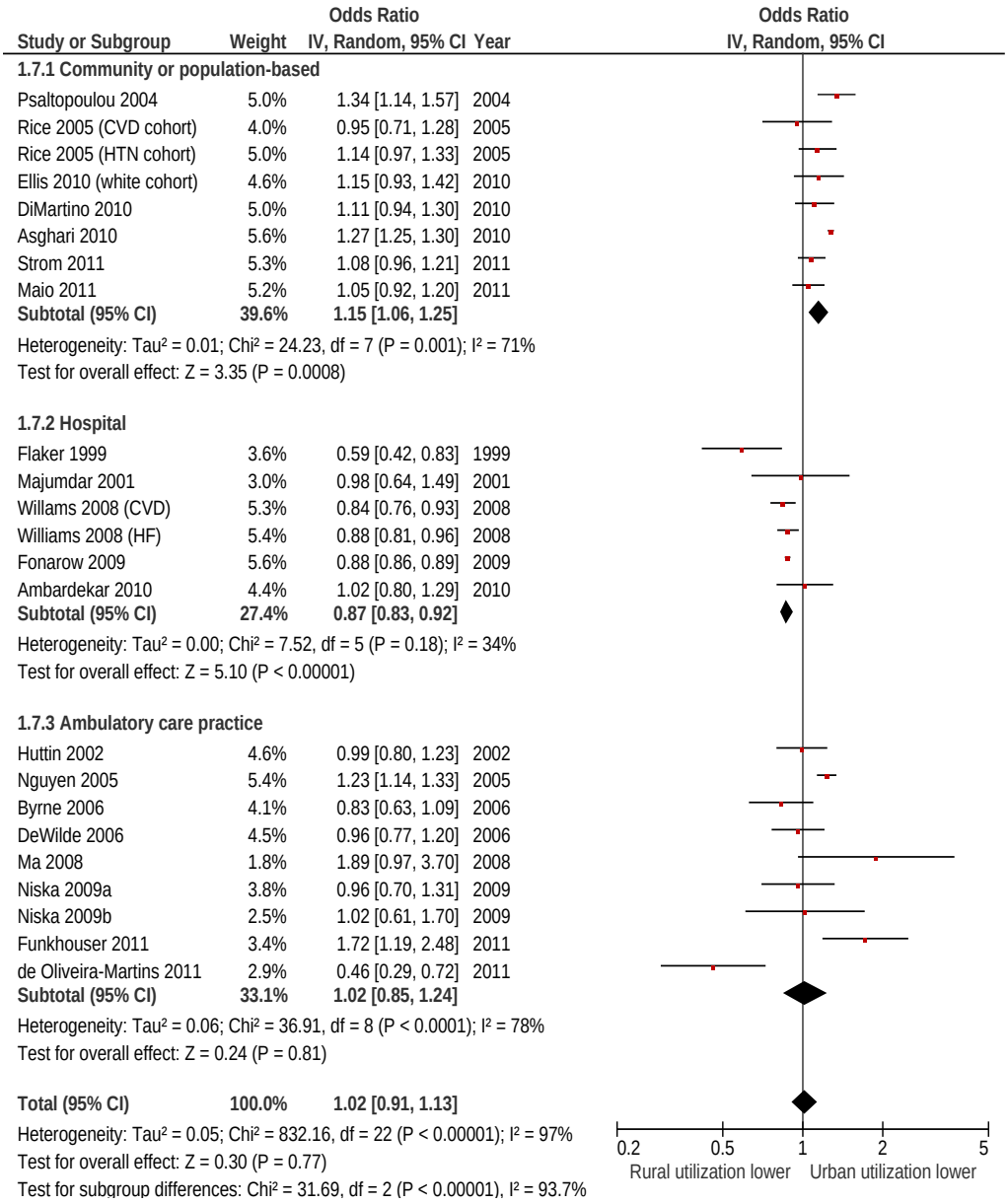
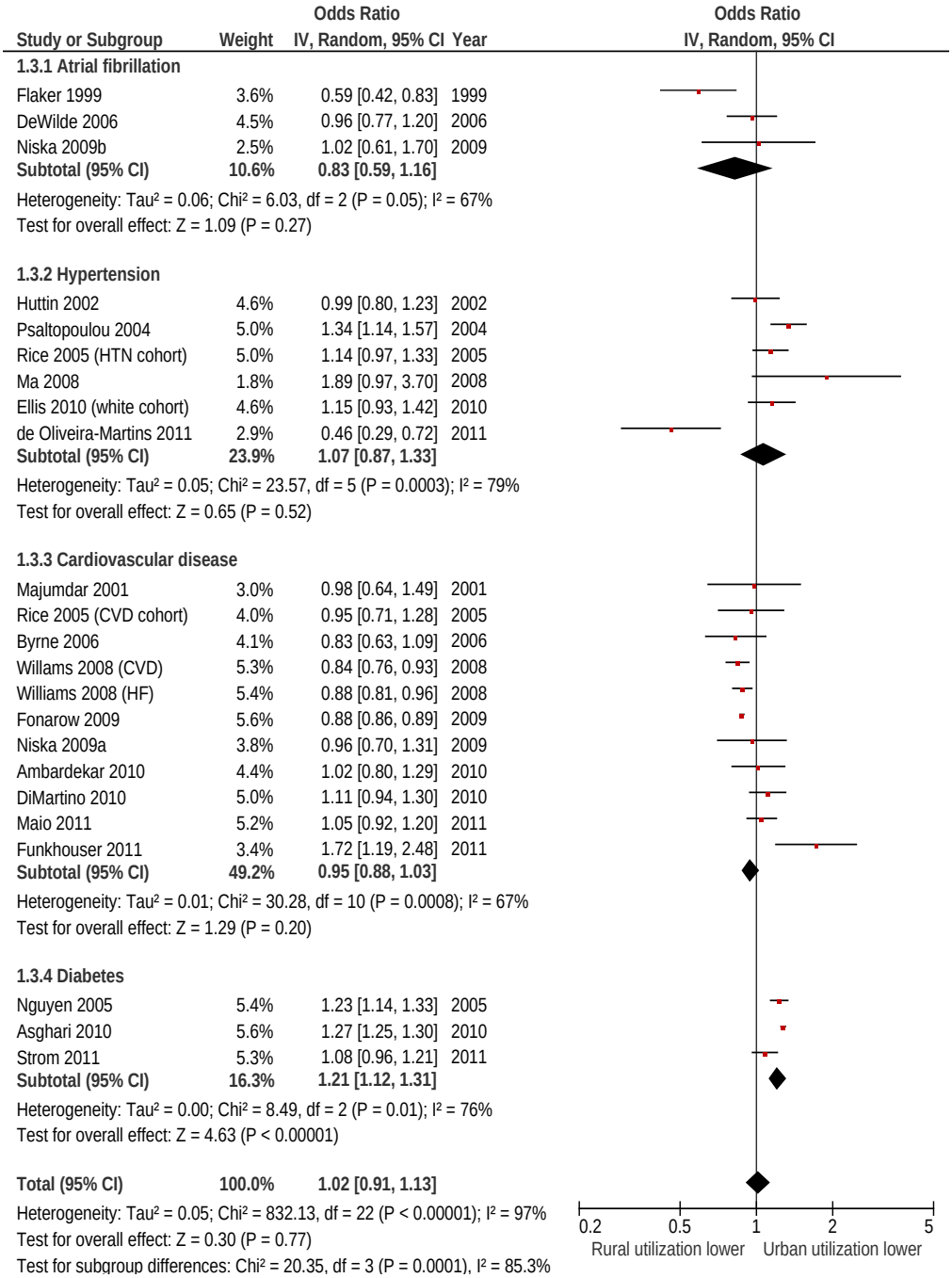


Figure 2–3: Use of evidence-based cardiovascular drugs by rural versus urban patients, stratified by disease (adjusted analysis)



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CHAPTER 3: COHORT STUDY

3.1. Introduction

Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), hydralazine with long-acting nitrates, beta blockers (BB), and spironolactone have all been shown to decrease morbidity and mortality in patients with heart failure (HF) in both randomized controlled trials and population based studies.[1-5] Despite this evidence, these medications are often underutilized due to a failure to initiate, persist with, or adhere to therapy.[6-9]

In patients with HF, non-adherence to medications can rapidly alter the clinical status of patients and is associated with poor outcomes.[1,6,10] Although patient-related factors, such as resources, knowledge, attitudes, and expectations, are often the focus of adherence studies or interventions, these represent just one dimension affecting adherence behavior. There is increasing focus on the impact of geography on utilization and adherence to drug therapies and subsequent outcomes. Previous studies have observed rural-urban variations in HF outcomes[11] that may, at least partially, be related to barriers such as social isolation, financial constraints, lower education, limited health care facilities, distance to care, physician shortages, and lack of access to specialist care.[12,13] While it has been speculated that these barriers would cause harm through primary under-use of evidence-based medications (i.e. rural patients never getting, or never filling, a prescription), it is possible that these barriers may also

negatively impact patient adherence to therapies, although data to support this premise is lacking.[14]

Previous studies have shown that lower adherence to evidenced based medications among HF patients is associated with increased risk of hospitalization and death.[15,16] However, we are not aware of any studies that have evaluated potential adherence differences according to rural-urban residence. Thus, this study was undertaken to determine if, among newly diagnosed HF patients, the utilization, adherence, and persistence with HF-specific medications differs between those living in rural and urban areas, and whether these medication use patterns could explain 1-year mortality differences.

3.2. Methods

Setting

A population-based cohort of patients with incident HF was assembled using de-identified administrative databases from Alberta Health. Alberta Health manages a single-payer government-funded health care system that provides universal access to hospital, emergency department and physician services for all 3.7 million residents within the province of Alberta, Canada. Using unique de-identified lifetime health numbers, patient data from 5 demographic, vital statistic and health care utilization databases were linked as described previously.[17] Briefly, the Canadian Institute for Health Information Discharge Abstract Database supplied data on hospital admission dates, most responsible

diagnosis and up to 24 secondary diagnoses. The Alberta Blue Cross Medication Database provided outpatient prescription drug utilization data for all Alberta residents 65 years of age or older. The Alberta Health Care Insurance Plan Registry file provided demographic and vital statistics data, and the Ambulatory Care and Practitioner Claims Databases were used to obtain information on emergency department visits and office based physician visits. The Health Ethics Research Board at the University of Alberta approved this study (Pro00033827).

Study cohort

We identified all subjects >65 years of age discharged from hospital between April 1, 1999 and December 31, 2008 with the most responsible diagnosis of HF (International Classification of Diseases (ICD) 9 or 10 code of 428.x or I50.x).[18-20] To ensure subjects had newly diagnosed HF, we excluded those with a HF-related hospitalization (ICD9/10 HF claim code in any diagnosis field) within five years prior to the index. As we were primarily interested in the utilization and adherence with medications after diagnosis, to ensure subjects had sufficient opportunity to initiate therapies we excluded all patients who died within 90 days of hospital discharge. In addition, those with an index hospitalization length of stay >365 days, missing postal code data, and patients with no claims in any of the databases during the follow up period were also excluded. All patients were followed until death or 365 days after discharge from their index HF hospitalization. As per previous methodology employed by Statistics Canada and others,[11,21] rural and urban residence was determined using the second character

of the forward sortation area of each patient's home address obtained from the registry file.

Outcomes

The co-primary outcomes were the proportion of patients utilizing and adherent to HF-related medications. Utilization of HF-related medications was defined as at least 1 dispensation 7 days before and up to 1 year of discharge. Seven days prior to discharge was used to capture new prescriptions that may have been filled during the hospital stay or while patients were transitioning to out of hospital care. Adherence was defined as proportion of days with medication coverage (PDC) ≥0.8 for the medications of interest (ACEI, ARB, BB, digoxin and spironolactone). By convention, the PDC was calculated as the sum of days with medication available divided by the total days of follow up for patients with a minimum of two dispensations for that drug class.[22,23] The primary analysis assumed medication was available on the dispensation date and for the estimated number of days supplied, based on the quantity dispensed and usual dosing frequency. An 80% adherence level has been associated with a reduced risk of death in HF[10] and is the threshold commonly used in studies of cardiovascular medication adherence.[24] Secondarily we evaluated medication persistence at 1 year. Persistence was defined as the availability of the medication of interest for at least one day during each subsequent 30-day window after the first dispensation, until death or censoring for all patients with at least one dispensation of a study medication. In addition, we evaluated whether adherence to HF-related medications within the first 6 months of discharge was associated

with mortality in the subsequent 6 months. All outcomes were estimated for each drug class separately and for the renin angiotensin system (RAS) agents combined (i.e., ACEI or ARB).

Statistical analysis

Differences in baseline characteristics between urban and rural residents were compared using Chi^2, Student t, or Mann-Whitney U tests, as appropriate. Multivariable logistic regression was used to evaluate the association between rural-urban residence on the proportion treated, adherent, and persistent to each drug class. For all-cause mortality, multivariable logistic regression was used to assess the impact of optimal adherence, defined as a BB or RAS agent available 80% of days in the first 6 months after discharge, on mortality for the subsequent 6 months, after adjustment for all other covariates. In addition, we included the interaction between rural-urban residence and adherence to determine any potential rural-urban differences by adherence on 1-year mortality.

Covariates included in the multivariable models included age, sex, median neighborhood income quartile, comorbidities (myocardial infarction, angina, diabetes, cerebrovascular disease, hypertension, valvular disease, arrhythmias, chronic pulmonary disease, peripheral vascular disease, neoplasm, dementia, peptic ulcer or renal disease based on the index hospital admission and any admissions in the year prior), year of index hospitalization (i.e. year of diagnosis), number of hospitalizations, physician or emergency department visits in the year prior to index event, physician specialty (general practitioner, internal

medicine or cardiologist), and medications dispensed in the 90 days prior to index hospitalization (BB, RAS, digoxin, statin, spironolactone, loop diuretic, amiodarone, warfarin).[19] First order interactions between rural-urban status and age and sex were tested for all outcomes and no clinically important interactions were identified. The median neighborhood income was estimated using postal codes and neighborhood-level census data.[17] All analyses were done using STATA version 12.1 (StataCorp LP, College Station, TX). Model goodness of fit was tested using the Hosmer-Lemeshow test and none were significant. Diagnostic plots of adherence as a continuous outcome showed some evidence of skew; however analyses using the log transformation of adherence showed the same results and are otherwise not presented.

To evaluate the robustness of our study results, we undertook several ancillary analyses. First, we adjusted the PDC for: (a) hospitalization (total days in hospital during follow up were added to the days with drug coverage); (b) overlapping days supply (dispensation date of overlapping dispensations were moved forward to the end of supply date of the previous dispensation); and (c) medication discontinuation (follow-up was truncated at the date of the last dispensation for those who discontinued therapy - defined as a 30 day gap with no medication available, and no further dispensations). Second, analyses using alternate thresholds to define adherence (PDC $\geq$0.7 or $\geq$0.9) were conducted as some studies[15,16] have linked both higher and lower adherence cut points to HF-related outcomes. Third, we included all patients who were alive for at least 30

days (our primary analysis was restricted to 90 days) after the index hospitalization. Last, we evaluated 'new users' of our medications of interest by restricting analyses to those who had no dispensations for HF-related medications in the 90 days prior to the index hospitalization (i.e. not current users prior to diagnosis).

3.3. Results

Of 23,767 potentially eligible patients, we identified 10,430 patients with an incident HF hospitalization between April 1, 1999 and December 31, 2008 that met the cohort inclusion criteria. The reasons for exclusion were: prior HF-related hospitalization (n=8014); age <66 years (2934), death during index hospitalization (1417) or within 90 days of discharge (928), no health care claims during follow up (40), length of stay >365 days (3), and missing postal code (1).

The mean age was 80.2 years (standard deviation (SD) 7.7), 4909 (47%) were male, and 2580 (25%) were rural residents (Table 3-1). At baseline, rural residents were younger, more likely to be female, had fewer comorbidities, lower neighborhood income, had fewer outpatient physician visits (especially with specialists) but more hospitalizations and emergency department visits in the year prior to HF diagnosis than urban patients. In the 90 days prior to the index hospitalization, 45% of rural patients filled a prescription for a RAS agent, 27% used a BB, 13% used digoxin, and 5% used spironolactone compared to

49%, 33%, 12%, 5%, of urban patients, respectively. The use of other HF-related medications was similar in rural and urban patients.

Among the cohort who survived at least 90 days after the index hospitalization, the average follow-up was 343 days (SD 61) days, and 1197 (15.2%) urban and 359 (13.9%) rural residents died (adjusted odds ratio [aOR] 0.95, 95% confidence interval [CI] 0.82, 1.09). During follow-up, rural patients had a higher number of repeat hospitalizations (mean 1.5 (SD 1.9) versus 1.1 (SD 1.5), $p<0.001$) with 23% of rural patients hospitalized once, and 37% hospitalized two or more times, compared to 25% and 29% of urban patients. The total days in hospital during follow up (rural mean 17.1 (SD 30.6) days; urban 17.4 (SD 32.9), $p=0.6$) and time to first hospitalization (rural 113 (SD 100) days; urban 117 (SD 101), $p=0.26$) were similar.

Medication treatment

In the year following the index hospitalization, 8072 (77%) filled at least one prescription for a RAS agent [6863 (66%) for an ACEI and 2258 (22%) for an ARB] (Table 3-2) with 3497 (43%) of RAS users considered new users (i.e. no dispensations for that drug class within 90 days prior to the index hospitalization). A total of 5368 (51%) patients received a BB (2525 (47%) were new users); most (4582, 44%) were prescribed bisoprolol, carvedilol, or metroprolol. Overall, 8104 (78%) HF patients filled at least one prescription for a RAS agent or hydralazine/long-acting nitrate and 4706 (45%) filled prescriptions for a RAS agent and a BB concurrently. While most patients (8362,

80%) filled at least one prescription for a loop diuretic, other HF-related medications were used in less than one third of this cohort (Table 3-2). The majority of patients filled their first prescription within 90 days of discharge (ACEI 92%, ARB 79%, BB 87%, digoxin 87%, spironolactone 79%).

Rural patients were less likely to fill prescriptions for RAS agents (74% versus 79%, aOR 0.78, 95% CI 0.69, 0.89), BB (44% versus 54%, aOR 0.83, 95%CI 0.73, 0.93), or RAS agent and BB (37% versus 48%, aOR 0.78, 95%CI 0.70, 0.88) in the first year after discharge than urban residents, but had similar rates of use of loop diuretics (80% versus 80%), digoxin (29% versus 30%) or spironolactone (27% versus 25%) (Table 3-2; Figure 3-1).

Medication adherence

The proportion of patients who were adherent (PDC ≥0.8) was lowest for spironolactone (rural 56%, urban 50%, aOR 1.18 (95%CI 0.95, 1.45) and highest for RAS agents (rural 66%, urban 70%, aOR 0.88, 95%CI 0.78, 1.00, p=0.049) (Table 3-3). Rural patients were slightly less likely to be adherent to RAS agents than urban patients, although the differences were small. For BB, digoxin and spironolactone, no significant rural-urban differences in adherence were observed in adjusted analyses Table 3-3).

Medication persistence

Persistence declined after discharge with the greatest reduction in persistence occurring in the first 3 months after initiating treatment (Figure 3-2). Of those

alive, approximately 15% to 30% of patients were not on treatment at 3 months following their initial dispensation: half of these patients had only a single dispensation of medication (Table 3-4). By 1 year, or until death or censoring, persistence was highest for RAS agents (76%), lowest for spironolactone (57%), and similar (~70%) for BB or digoxin. The proportion of patients who were persistent at 1 year or until death or censoring ranged from 60% to 74% for rural residents, and 57% to 77% in urban residents. The differences between rural and urban patients were not significantly different except for ARB at 3 months (77% versus 80%, aOR 0.75, 95%CI 0.57, 0.98) and RAS agents at 12 months (74% versus 77%, aOR 0.86, 95%CI 0.75, 0.98) in the adjusted analyses; however, the clinically importance of these differences is questionable.

Mortality

Of the 7911 patients who survived 180 days after discharge, 158 (8.5%) of rural and 538 (8.9%) of urban residents died by 1 year (OR 0.95, 95%CI 0.79, 1.14) (Table 3-5). Patients who demonstrated optimal adherence (had a BB, ACEI or ARB available for at least 80% of days) within the first 6 months had a lower risk of death at 1-year than those who were sub-optimally adherent (aOR 0.78, 95%CI 0.65, 0.94). We did not detect any significant differences in 1-year mortality for rural versus urban patients who were adherent (aOR 1.09, 95%CI 0.86, 1.38) nor who were non-adherent (aOR 0.95, 95%CI 0.66, 1.35) (p=0.50 for interaction).

Sensitivity analyses

Analyses accounting for time in hospital, early discontinuation, overlapping supply, alternate adherence definitions (≥ 0.7 or ≥ 0.9), or including all patients who survived at least 30 days after discharge were generally consistent with our primary analysis (Tables 3-6 and 3-7). In the analyses restricted to 'new users', rural patients were significantly less likely to receive RAS agents or BB than urban patients (Table 3-8). The association between adherence and mortality using the alternate adherence definitions was similar to our main analysis (Table 3-9).

3.4. Discussion

We found that clinically important differences exist between rural and urban HF patients in the use of evidence based therapies, with rural patients being less likely to receive RAS agents and BB, however, few differences in adherence were noted between rural and urban patients in the year following their index HF hospitalization. Importantly, lower adherence to RAS agents or BB within the first 6 months of hospital discharge was associated with an increased risk of mortality in both rural and urban patients.

Among those initiated on therapy, approximately 25% of patients had stopped RAS agents or BB at the end of follow up (median 318 days from first dispensation to end of follow-up). Moreover, less than 69% of patients on RAS agents and 53% of those on BB had medication available for at least 80% of days. In general, the adherence and persistence values we observed were similar

to other HF studies.[6,8,25] We have extended this literature to show that rural patients may not be substantially different compared to urban patients in this regard. Overall, a substantial proportion of patients demonstrate sub-optimal adherence or stop therapy irrespective of geography. More importantly, good adherence was associated with a lower mortality risk and despite the differences we observed between the rural and urban patients in comorbidities, baseline health care service utilization, and socioeconomic status; we found no significant differences in 1-year mortality between adherent rural and urban patients after adjustment. In an earlier study, we had demonstrated no significant mortality differences between rural and urban HF patients, although urban patients were more likely to have office-based physician visits after discharge and exhibited 30% lower rates of hospitalization and emergency department visits after discharge compared to rural patients.[11]

Despite our population based sample and large rural subgroup, several limitations must be acknowledged. First, our study is based on administrative data and lacks detailed clinical information, such as ejection fraction or symptom status, and other data that may be used to identify patients with contraindications or intolerance to medications. Although the diagnostic codes we used to identify the incident HF cohort are used frequently[11,25] and validated in our province,[18-20] one study found that the diagnostic accuracy of hospital abstract data was lower for rural than urban hospitals in a different Canadian province.[26] Thus, differences in diagnostic accuracy could potentially explain some of the

observed rural-urban differences in medication utilization if a greater proportion of rural patients were misclassified as having HF. However, differential diagnostic accuracy is unlikely to bias measures of adherence or persistence, as these analyses are all conducted in treated patients. Secondly, estimates of adherence based on prescription refill data are indirect measures that may overestimate actual consumption, and cannot provide information on the prevalence of primary non-adherence (failure to fill a prescription).[23] That being said, we used accepted methods for measuring adherence from population-based administrative data.[22,23,27] Further, we selected a cohort that survived at least 90 days after discharge to minimize bias by ensuring patients had an adequate opportunity to fill prescriptions, and that adherence was not biased upward by patients with a short follow up time. We also calculated persistence until death or censoring to account for differences in the length of follow. In addition we conducted several sensitivity analyses to confirm our findings were robust. However, we do not know if patients were truly non-adherent or non-persistent, or if the medications were stopped due to clinical or tolerance issues. Thirdly, unmeasured confounding may be present despite adjustment for variables known to predict outcomes in HF which may also have lead to difficult to identify channeling or confounding by indication biases. Adherence is affected by numerous interacting elements that include socioeconomic, condition, therapy, patient, and health-system related factors,[28] and many of these factors are not available or may be incompletely measured in administrative data. Finally, our results may not be generalizable to the overall HF population as our cohort was

limited to those >65 years of age diagnosed in hospital. Patients diagnosed in hospital have a substantially poorer prognosis than those diagnosed in the emergency department or outpatient clinics.[29] However, hospitalized patients are more homogeneous at baseline and the administrative data case definition performs best for hospital data.

Conclusions

Rural residents were less likely to receive RAS agents or BB following discharge from hospital with a first diagnosis of HF. Rural patients exhibited similar adherence and persistence compared to urban patients for most evidence based HF therapies. Irrespective of geographic locale, adherence and persistence to proven efficacious HF therapies are suboptimal for both rural and urban patients leading to increased risk of mortality. Future interventions should aim to improve utilization of evidence-based therapies for HF particularly among rural residents, but regardless of geography, more intensive follow up may be warranted to ensure therapies are being adhered to and are not discontinued inappropriately by patients.

Table 3–1: Baseline characteristics

Characteristic	Rural		Urban		p value
	n	%	n	%	
total N=10,430	2580	24.7%	7850	75.3%	
age, years, mean (SD)	79.8 (7.9)		80.3 (7.3)		0.005
male	1281	49.7%	3628	46.2%	0.002
discharge year					0.007
1999	243	9.4%	599	7.6%	
2000	244	9.5%	811	10.3%	
2001	301	11.7%	800	10.2%	
2002	279	10.8%	769	9.8%	
2003	251	9.7%	816	10.4%	
2004	261	10.1%	817	10.4%	
2005	286	11.1%	890	11.3%	
2006	267	10.3%	793	10.1%	
2007	224	8.7%	753	9.6%	
2008	224	8.7%	802	10.2%	
median neighborhood household income					<0.001
< $50,149	1077	41.7%	2998	38.2%	
$50,150 to $69,434	912	35.3%	1841	23.5%	
$69,435 to $89,005	326	12.6%	1528	19.5%	
>= $89,006	84	3.3%	1188	15.1%	
missing	181	7.0%	295	3.8%	
Drug treatment 90 days prior to index hospitalization					
RAS agents	1169	45.3%	3826	48.7%	0.002
ACEI	923	35.8%	2881	36.7%	0.4
ARB	321	12.4%	1204	15.3%	<0.001
BB	707	27.4%	2595	33.1%	<0.001
amiodarone	57	2.2%	200	2.5%	0.34
digoxin	326	12.6%	976	12.4%	0.79
hydralazine	10	0.4%	45	0.6%	0.26
long acting nitrates	269	10.4%	1011	12.9%	0.001
loop diuretic	941	36.5%	2916	37.1%	0.54
spironolactone	140	5.4%	373	4.8%	0.17
statin	466	18.1%	1687	21.5%	<0.001
warfarin	415	16.1%	1558	19.8%	<0.001
number dispensations (any	10.8 (12.4)		11.0 (13.0)		0.35

Characteristic	Rural		Urban		p value
	n	%	n	%	
drug), mean (SD)					
number of drugs, mean (SD)	5.8 (4.1)		6.1 (4.1)		<0.001
Health care services in previous year					
general practitioner visit	2541	98.5%	7686	97.9%	0.065
internal medicine visit	1130	43.8%	5618	71.6%	<0.001
cardiologist visit	412	16.0%	2899	36.9%	<0.001
number of physician visits, mean (SD)	19.3 (14.2)		22.2 (17.4)		<0.001
number of hospitalizations, mean (SD)	0.7 (1.2)		0.6 (1.0)		<0.001
number of emergency department visits, mean (SD)	3.2 (3.9)		2.3 (2.4)		<0.001
Comorbidities					
Charlson comorbidity score, mean (SD)	2.3 (1.5)		2.6 (1.6)		<0.001
ischemic heart disease	840	32.6%	3614	46.0%	<0.001
myocardial infarction	388	15.0%	1710	21.8%	<0.001
angina	158	6.1%	571	7.3%	0.047
diabetes	755	29.3%	2399	30.6%	0.21
cerebrovascular disease	142	5.5%	552	7.0%	0.007
hypertension	1070	41.5%	4352	55.4%	<0.001
valvular disease	267	10.3%	1558	19.8%	<0.001
cardiac arrhythmias	782	30.3%	3214	40.9%	<0.001
atrial fibrillation	512	19.8%	2131	27.1%	<0.001
other arrhythmias	354	13.7%	1493	19.0%	<0.001
chronic pulmonary disease	719	27.9%	2246	28.6%	0.47
peripheral vascular disease	74	2.9%	345	4.4%	0.001
neoplasm	141	5.5%	371	4.7%	0.13
dementia	122	4.7%	555	7.1%	<0.001
peptic ulcer disease	16	0.6%	73	0.9%	0.14
renal disease	225	8.7%	1075	13.7%	<0.001

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; N=number; RAS=renin angiotensin system agent; SD=standard deviation

Table 3–2: Evidence-based medication utilization during follow up

Outcome / Drug class	Rural		Urban		Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
	n	%	n	%				
Patients receiving drug therapy (total N=10,430)								
RAS agent	1903	73.8%	6169	78.6%	0.77 (0.69, 0.85)	<0.001	0.78 (0.69, 0.89)	<0.001
ACEI	1627	63.1%	5236	66.7%	0.85 (0.78, 0.94)	0.001	0.84 (0.75, 0.93)	0.001
ARB	494	19.1%	1764	22.5%	0.82 (0.73, 0.91)	<0.001	0.93 (0.82, 1.05)	0.24
RAS agent or hydralazine+ long acting nitrate	1907	73.9%	6197	78.9%	0.76 (0.68, 0.84)	<0.001	0.78 (0.69, 0.88)	<0.001
BB	1124	43.6%	4244	54.1%	0.66 (0.60, 0.72)	<0.001	0.83 (0.73, 0.93)	0.001
BB and RAS agent	953	36.9%	3753	47.8%	0.64 (0.58, 0.70)	<0.001	0.78 (0.70, 0.88)	<0.001
BB and RAS agent or hydralazine+ long acting nitrate	954	37.0%	3775	48.1%	0.63 (0.58, 0.69)	<0.001	0.78 (0.69, 0.87)	<0.001
digoxin	758	29.4%	2323	29.6%	0.99 (0.90, 1.09)	0.84	0.98 (0.87, 1.11)	0.76
spironolactone	688	26.7%	1979	25.2%	1.08 (0.98, 1.19)	0.14	1.10 (0.98, 1.23)	0.12
hydralazine	19	0.7%	170	2.2%	0.34 (0.21, 0.54)	<0.001	0.49 (0.30, 0.81)	0.006
long acting nitrate	778	30.2%	3199	40.8%	0.63 (0.57, 0.69)	<0.001	0.74 (0.66, 0.82)	<0.001
loop diuretic	2058	79.8%	6304	80.3%	0.97 (0.87, 1.08)	0.55	0.92 (0.81, 1.05)	0.2
amiodarone	117	4.5%	470	6.0%	0.75 (0.61, 0.92)	0.006	0.95 (0.73, 1.23)	0.68
warfarin	739	28.6%	2822	35.9%	0.72 (0.65, 0.79)	<0.001	0.89 (0.78, 1.02)	0.1
statin	710	27.5%	2608	33.2%	0.76 (0.69, 0.84)	<0.001	0.93 (0.80, 1.08)	0.34

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; N=number; OR=odds ratio; RAS=renin angiotensin system

†Model included age; sex; rural-urban residence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior

Table 3–3: Adherence to evidence-based medications

Adherent (PDC≥0.8)	Rural		Urban		Total N	Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
Drug class	**n**	**%**	**n**	**%**					
RAS agent	1161	65.6%	4059	69.8%	7587	0.82 (0.74, 0.92)	0.001	0.88 (0.78, 1.00)	0.049
ACEI	959	64.6%	3307	69.0%	6274	0.82 (0.72, 0.93)	0.001	0.88 (0.77, 1.00)	0.059
ARB	242	55.8%	946	60.1%	2009	0.84 (0.68, 1.04)	0.11	0.86 (0.68, 1.10)	0.24
BB	510	50.0%	2103	54.2%	4902	0.85 (0.74, 0.97)	0.019	0.88 (0.75, 1.03)	0.11
digoxin	476	70.0%	1491	70.7%	2790	0.97 (0.80, 1.17)	0.74	0.98 (0.79, 1.21)	0.86
spironolactone	329	56.0%	833	49.6%	2267	1.29 (1.07, 1.56)	0.008	1.18 (0.95, 1.45)	0.13

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; OR=odds ratio; PDC=proportion of days covered; RAS=renin angiotensin system

†Model included age; sex; rural-urban residence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior

Table 3–4: Persistence with evidence-based medications until death or censored

	Rural*		Urban*		Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
	n	%	n	%				
RAS agent (N=8071)								
3 months	1579	83.0%	5294	85.8%	0.81 (0.70, 0.93)	0.003	0.86 (0.74, 1.01)	0.064
6 months	1484	78.0%	4940	80.1%	0.88 (0.78, 1.00)	0.052	0.93 (0.81, 1.07)	0.32
12 months	1398	73.5%	4739	76.8%	0.84 (0.74, 0.94)	0.003	0.86 (0.75, 0.98)	0.021
ACEI (N=6860)								
3 months	1305	80.3%	4271	81.6%	0.92 (0.80, 1.06)	0.23	0.97 (0.83, 1.13)	0.69
6 months	1195	73.5%	3920	74.9%	0.93 (0.82, 1.05)	0.26	0.98 (0.85, 1.13)	0.78
12 months	1118	68.8%	3738	71.4%	0.88 (0.78, 0.99)	0.039	0.90 (0.79, 1.03)	0.11
ARB (N=2256)								
3 months	378	76.5%	1404	79.7%	0.83 (0.65, 1.05)	0.13	0.75 (0.57, 0.98)	0.034
6 months	352	71.3%	1287	73.0%	0.91 (0.73, 1.14)	0.43	0.82 (0.64, 1.05)	0.11
12 months	339	68.6%	1220	69.2%	0.97 (0.78, 1.21)	0.79	0.89 (0.70, 1.13)	0.33
BB (N=5367)								
3 months	878	78.1%	3371	79.4%	0.92 (0.79, 1.08)	0.33	0.95 (0.79, 1.13)	0.55
6 months	808	71.9%	3136	73.9%	0.90 (0.78, 1.05)	0.17	0.91 (0.77, 1.07)	0.23
12 months	789	70.2%	3026	71.3%	0.95 (0.82, 1.09)	0.46	0.97 (0.83, 1.14)	0.75
Digoxin (N=3080)								
3 months	614	81.0%	1889	81.4%	0.98 (0.79, 1.21)	0.83	0.97 (0.77, 1.23)	0.82
6 months	560	73.9%	1765	76.0%	0.89 (0.74, 1.08)	0.24	0.85 (0.69, 1.05)	0.14
12 months	532	70.2%	1645	70.8%	0.97 (0.81, 1.16)	0.73	0.94 (0.77, 1.15)	0.53

	Rural*		Urban*		Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
	n	%	n	%				
Spironolactone (N=2665)								
3 months	482	70.1%	1381	69.9%	1.01 (0.84, 1.22)	0.92	1.08 (0.88, 1.33)	0.46
6 months	430	62.5%	1212	61.3%	1.05 (0.88, 1.26)	0.58	1.04 (0.86, 1.27)	0.67
12 months	409	59.5%	1121	56.7%	1.12 (0.94, 1.34)	0.21	1.12 (0.92, 1.36)	0.27

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; N=number; OR=odds ratio; RAS=renin angiotensin system

*Includes all patients who survived at least 180 days after discharge and with at least one dispensation of study drug during follow up. Persistence defined as possession of drug for at least 1 day during each 1 month time point after the first dispensation.

†Model included age; sex; rural-urban residence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior

Table 3–5: One-year mortality for patients surviving at least 180 days after index hospitalization

Analysis	**Rural (n=1861)**	**Urban (n=6050)**
Death at 1 year, n (%)	158 (8.5%)	538 (8.9%)
Adjusted probability of death at 1 year, (95% CI)*†		
Adherent	8.8% (7.2, 10.4)	8.2% (7.4, 9.0)
Non-adherent	10.0% (7.3, 12.6)	10.5% (8.9, 12.1)
Adherent versus non-adherent*	**OR (95% CI)**	**P value**
Adjusted for rural-urban	0.69 (0.58, 0.82)	<0.001
Adjusted (main effects model†)	0.78 (0.65, 0.94)	0.008
Rural adherent versus urban adherent*		
Adjusted (interaction model‡)	1.09 (0.86, 1.38)	0.48
Rural non-adherent versus urban non-adherent*		
Adjusted (interaction model‡)	0.95 (0.66, 1.35)	0.76

CI=confidence interval; N=number; OR=odds ratio

†Main effects model included age; sex; rural-urban residence; adherence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior.
‡Interaction model included all covariates in main model plus rural*adherence interaction term
*Adherence defined as PDC≥0.8 for BB, ACEI or ARB in first 180 days after index hospitalization

Table 3–6: Medication adherence sensitivity analyses for patients who survived at least 90 days after discharge

Drug	Analysis*	Rural		Urban		Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
		n	%	n	%				
RAS agent									
N=7587	Adherence 0.8 (hospital)	1273	71.9%	4390	75.5%	0.83 (0.74, 0.94)	0.002	0.90 (0.79, 1.03)	0.12
	Adherence 0.8 (discontinue drug)	1333	75.3%	4582	78.8%	0.82 (0.72, 0.93)	0.002	0.89 (0.77, 1.02)	0.087
	Adherence 0.8 (overlapping supply)	1259	71.1%	4326	74.4%	0.85 (0.75, 0.95)	0.006	0.91 (0.80, 1.04)	0.15
	Adherence 0.7	1299	73.4%	4455	76.6%	0.84 (0.74, 0.95)	0.005	0.90 (0.79, 1.03)	0.14
	Adherence 0.9	911	51.4%	3333	57.3%	0.79 (0.71, 0.88)	<0.001	0.85 (0.76, 0.96)	0.009
ACEI									
N=6274	Adherence 0.8 (hospital)	1048	70.6%	3579	74.7%	0.81 (0.71, 0.93)	0.002	0.89 (0.77, 1.02)	0.098
	Adherence 0.8 (discontinue drug)	1157	78.0%	3900	81.4%	0.81 (0.70, 0.93)	0.003	0.88 (0.75, 1.04)	0.13
	Adherence 0.8 (overlapping supply)	1033	69.6%	3500	73.1%	0.84 (0.74, 0.96)	0.009	0.91 (0.79, 1.05)	0.21
	Adherence 0.7	1072	72.2%	3617	75.5%	0.84 (0.74, 0.96)	0.011	0.92 (0.79, 1.06)	0.24
	Adherence 0.9	749	50.5%	2730	57.0%	0.77 (0.68, 0.86)	<0.001	0.84 (0.74, 0.96)	0.009
ARB									
N=2009	Adherence 0.8 (hospital)	264	60.8%	1027	65.2%	0.83 (0.67, 1.03)	0.092	0.87 (0.68, 1.11)	0.25
	Adherence 0.8 (discontinue drug)	277	63.8%	1084	68.8%	0.80 (0.64, 1.00)	0.049	0.84 (0.66, 1.08)	0.18
	Adherence 0.8	252	58.1%	1015	64.4%	0.76 (0.62, 0.95)	0.015	0.77 (0.61, 0.99)	0.038

Drug	Analysis*	Rural		Urban		Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
		n	%	n	%				
	(overlapping supply)								
	Adherence 0.7	260	59.9%	1058	67.2%	0.73 (0.59, 0.91)	0.005	0.73 (0.57, 0.94)	0.014
	Adherence 0.9	196	45.2%	743	47.2%	0.92 (0.74, 1.14)	0.46	0.90 (0.71, 1.14)	0.38
BB									
N=4902	Adherence 0.8 (hospital)	555	54.5%	2288	58.9%	0.83 (0.73, 0.96)	0.01	0.86 (0.73, 1.00)	0.061
	Adherence 0.8 (discontinue drug)	587	57.6%	2359	60.8%	0.88 (0.76, 1.01)	0.068	0.92 (0.78, 1.08)	0.31
	Adherence 0.8 (overlapping supply)	540	53.0%	2254	58.1%	0.81 (0.71, 0.94)	0.004	0.86 (0.73, 1.00)	0.054
	Adherence 0.7	593	58.2%	2380	61.3%	0.88 (0.76, 1.01)	0.072	0.93 (0.79, 1.09)	0.35
	Adherence 0.9	389	38.2%	1667	42.9%	0.82 (0.71, 0.95)	0.006	0.85 (0.73, 1.00)	0.049
Digoxin									
N=2790	Adherence 0.8 (hospital)	531	78.1%	1650	78.2%	0.99 (0.81, 1.22)	0.95	0.99 (0.78, 1.25)	0.93
	Adherence 0.8 (discontinue drug)	566	83.2%	1764	83.6%	0.97 (0.77, 1.23)	0.82	0.95 (0.73, 1.23)	0.67
	Adherence 0.8 (overlapping supply)	504	74.1%	1597	75.7%	0.92 (0.75, 1.12)	0.41	0.92 (0.73, 1.15)	0.44
	Adherence 0.7	534	78.5%	1655	78.4%	1.01 (0.81, 1.24)	0.96	1.00 (0.79, 1.27)	1.00
	Adherence 0.9	366	53.8%	1150	54.5%	0.97 (0.82, 1.16)	0.76	1.02 (0.84, 1.24)	0.83
Spironolactone									
N=2267	Adherence 0.8 (hospital)	373	63.4%	924	55.0%	1.42 (1.17, 1.72)	<0.001	1.31 (1.05, 1.62)	0.015
	Adherence 0.8 (discontinue drug)	437	74.3%	1088	64.8%	1.57 (1.27, 1.94)	<0.001	1.31 (1.04, 1.65)	0.023

Drug	Analysis*	Rural		Urban		Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI)†	p value
		n	%	n	%				
	Adherence 0.8 (overlapping supply)	360	61.2%	927	55.2%	1.28 (1.06, 1.55)	0.011	1.15 0.93, 1.42)	0.20
	Adherence 0.7	369	62.8%	945	56.3%	1.31 (1.08, 1.59)	0.006	1.18 (0.95, 1.46)	0.13
	Adherence 0.9	256	43.5%	648	38.6%	1.23 (1.01, 1.48)	0.035	1.16 (0.93, 1.43)	0.18

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; N=number; OR=odds ratio; PDC=proportion of days covered; RAS=renin angiotensin system

*Sensitivity analyses were conducted adjusting adherence for time in hospital during follow-up, overlapping days supply and truncating follow up for patients who discontinued treatment, with adherence defined as PDC≥0.8. Other analyses defined adherence as PDC ≥0.7 or ≥0.9.

†Model included age; sex; rural-urban residence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior.

Table 3–7: Medication adherence among patients who survived at least 30 days after discharge

Drug	Rural		Urban		Total N	Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI) †	p value
	n	%	n	%					
RAS agent	1189	65.7%	4139	69.8%	7737	0.83 (0.74, 0.93)	0.001	0.88 (0.78, 1.00)	0.050
ACEI	984	64.9%	3379	69.1%	6405	0.83 (0.73, 0.93)	0.002	0.88 (0.77, 1.01)	0.069
ARB	244	55.6%	952	60.0%	2025	0.83 (0.67, 1.03)	0.094	0.86 (0.68, 1.10)	0.23
BB	521	50.3%	2136	54.2%	4975	0.86 (0.75, 0.98)	0.026	0.89 (0.76, 1.04)	0.14
Digoxin	485	69.9%	1529	70.9%	2851	0.95 (0.79, 1.15)	0.62	0.95 (0.77, 1.17)	0.63
Spironolactone	337	56.3%	853	49.9%	2309	1.29 (1.07, 1.56)	0.007	1.18 (0.96, 1.46)	0.11

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; N=number; OR=odds ratio; RAS=renin angiotensin system

†Model included age; sex; rural-urban residence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior.

Table 3–8: Medication utilization and adherence for 'new users'*

Outcome / Drug class	Rural		Urban		Total N	Rural vs. urban unadjusted OR (95% CI)	p value	Rural vs. urban adjusted OR (95% CI) †	p value
	n	%	n	%					
Patients receiving drug therapy									
RAS agent	819	58.0%	2678	66.6%	5435	0.70 (0.61, 0.79)	<0.001	0.72 (0.62, 0.83)	<0.001
ACEI	805	48.6%	2709	54.5%	6626	0.79 (0.71, 0.88)	<0.001	0.76 (0.67, 0.87)	<0.001
ARB	235	10.4%	818	12.3%	8905	0.83 (0.71, 0.96)	0.016	0.91 (0.77, 1.08)	0.29
BB	517	27.6%	2008	38.2%	7128	0.62 (0.55, 0.69)	<0.001	0.78 (0.68, 0.90)	<0.001
Digoxin	491	21.8%	1553	22.6%	9128	0.95 (0.85, 1.07)	0.42	0.98 (0.86, 1.12)	0.81
Spironolactone	585	24.0%	1713	22.9%	9917	1.06 (0.95, 1.18)	0.28	1.10 (0.98, 1.25)	0.11
Adherent (PDC ≥0.8)									
RAS agent	460	62.3%	1642	66.3%	3217	0.84 (0.71, 1.00)	0.044	0.90 (0.74, 1.09)	0.28
ACEI	433	61.6%	1582	65.6%	3116	0.84 (0.71, 1.00)	0.053	0.94 (0.77, 1.14)	0.53
ARB	105	52.8%	405	57.2%	907	0.84 (0.61, 1.15)	0.27	0.91 (0.64, 1.30)	0.60
BB	197	44.4%	892	49.5%	2246	0.81 (0.66, 1.00)	0.053	0.87 (0.68, 1.10)	0.23
Digoxin	305	70.4%	989	70.8%	1830	0.98 (0.78, 1.25)	0.89	1.01 (0.77, 1.33)	0.93
Spironolactone	279	56.1%	720	49.6%	1949	1.30 (1.06, 1.60)	0.012	1.21 (0.96, 1.51)	0.11

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BB=beta blocker; CI=confidence interval; N=number; OR=odds ratio; PDC=proportion of days covered; RAS=renin angiotensin system

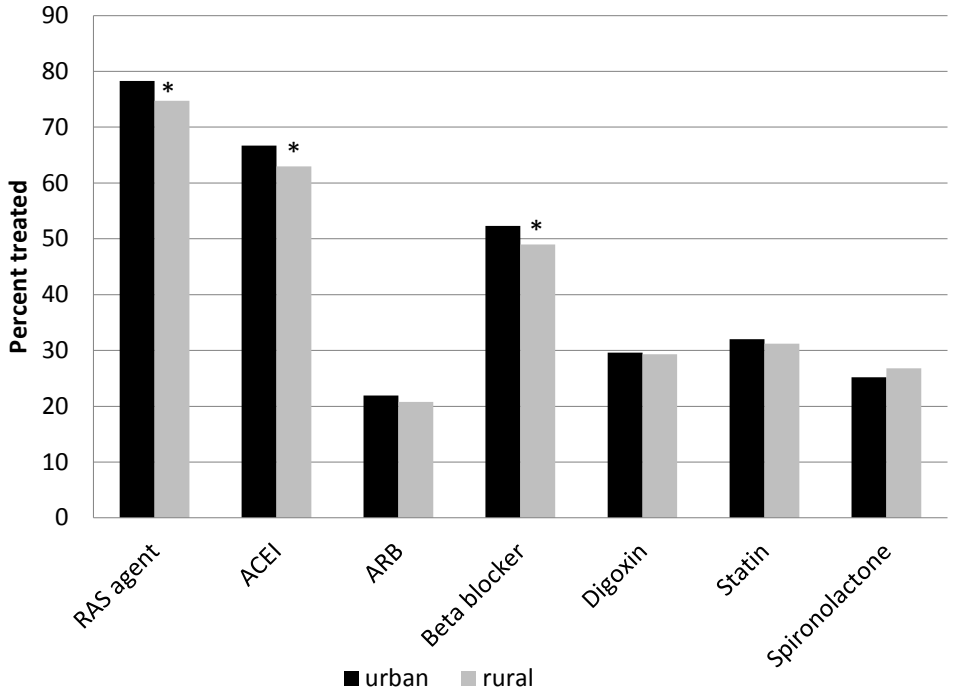
*New users had no dispensations for that drug class in the 90 days prior to the index hospitalization and survived at least 90 days after index hospitalization.

†Model included age; sex; rural-urban residence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior.

Table 3–9: Sensitivity analyses for one-year mortality in patients surviving at least 180 days after index hospitalization

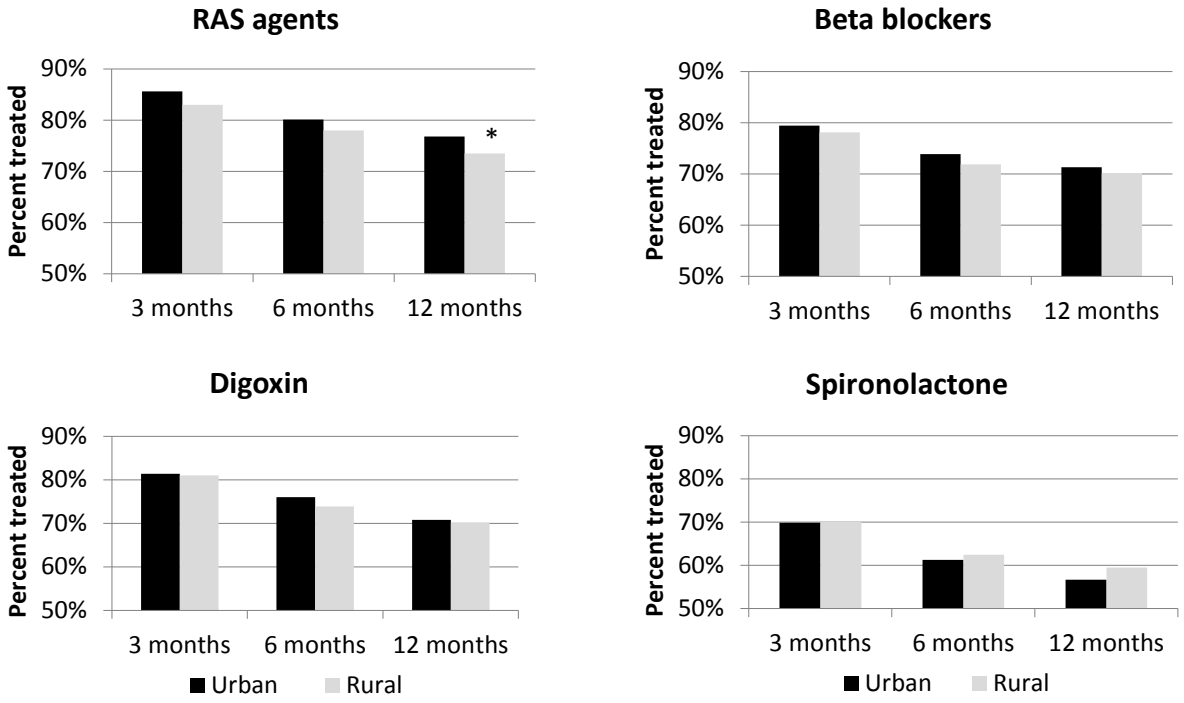
Analysis	**Rural (n=1861)**	**Urban (n=6050)**
Adherent versus non-adherent (main effect model†***)**	**Rural vs. urban adjusted OR (95% CI)**	**P value**
Adherence defined as PDC ≥0.7	0.76 (0.63, 0.93)	0.007
Adherence defined as PDC ≥0.9	0.81 (0.69, 0.96)	0.016
Rural adherent versus urban adherent (interaction model‡*)		
Adherence defined as PDC ≥0.7	1.06 (0.84, 1.33)	0.64
Adherence defined as PDC ≥0.9	1.09 (0.84, 1.40)	0.53
Rural non-adherent versus urban non-adherent (interaction model‡*)		
Adherence defined as PDC ≥0.7	1.01 (0.68, 1.49)	0.98
Adherence defined as PDC ≥0.9	0.99 (0.73, 1.35)	0.95
CI=confidence interval; N=number; OR=odds ratio; PDC=proportion of days covered		
†Main effect model included age; sex; rural-urban residence; adherence; discharge year; income; comorbidities; hospitalizations, emergency department and physician visits in 1-year prior; drug use in 90-days prior. ‡Interaction model included all covariates in main model plus rural*adherence interaction term *Adherence defined as PDC≥0.7 or PDC≥0.9 for BB, ACEI or ARB in first 180 days after index hospitalization		

Figure 3–1: Adjusted prevalence of treatment during follow up



ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; RAS=renin angiotensin system
* p<0.01

Figure 3–2: Persistence with evidence-based medication during follow-up



RAS=renin angiotensin system
*p<0.05

3.5. References

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CHAPTER 4: SUMMARY

4.1. Summary of research

Rural residents face several barriers to obtaining quality health care including limited health care facilities, physician shortages, lack of access to specialist care, transportation difficulties and distance to care, financial constraints and social isolation. These barriers have been postulated to result in decreased utilization and adherence to evidence-based medications in rural residents with chronic disease.

To address this research question we examined cardiovascular medication use and adherence for rural versus urban patients. This objective was accomplished through a systematic review of published studies (Chapter 2) and a retrospective cohort study among incident heart failure patients in Alberta (Chapter 3).

Despite some literature suggesting that differences in rural-urban medication utilization and adherence exist, our comprehensive systematic review suggested that indeed rural patients were approximately 10% less likely to receive cardiovascular medications compared to their urban counterparts but were equally likely to adhere to those medications based on unadjusted analyses. However, after accounting for differences in patient characteristics in the studies, our systematic review did not observe any clinically important or statistically significant differences between rural and urban patients; suggesting that these

differences in characteristics are a key driver of urban-rural differences with respect to medication utilization. Importantly, our results also showed that there is considerable variation in rural-urban patterns of medication utilization and adherence that was only partially explained by setting, age and disease studied. However, most studies included in the review were of moderate quality and many did not account for key demographic or socioeconomic factors between rural and urban patients. Thus, although our study was rigorously conducted, it is clear that better quality evidence is required to further explore whether differences truly exist between rural and urban patients, particularly in the Canadian context.

Therefore, to provide this higher quality evidence, our second aim evaluated medication utilization, adherence, persistence and subsequent outcomes between rural and urban patients with heart failure in Alberta. Unlike our systematic review, in our cohort of heart failure patients we observed several differences in medication use patterns between rural and urban patients. Clinically significant differences were present for important evidence-based drug classes, with rural patients less likely to receive RAS agents or BB; however utilization and adherence were similar between groups for other heart failure-related medications. Importantly, lower adherence was associated with an increased risk of mortality in both rural and urban patients.

Regardless of geographic residence, the overall utilization and adherence to evidence-based heart failure medications was suboptimal. Over the first year after the diagnosis of heart failure, three quarters of patients received an RAS agent and only half were treated with a BB. Although not all patients will be eligible to receive these therapies due to clinical or tolerance factors, a higher utilization would have been expected. Even among those treated, approximately 69% and 53% had a RAS agent or BB available for 80% of days, respectively. These findings are not uncommon, as other studies have also shown suboptimal medication utilization and adherence in patients with heart failure.[1-7]

As our results indicated, suboptimal use of heart failure-related medications has important clinical implications. Randomized trials have shown that RAS agents, BB and aldosterone antagonists are associated with a 17% to 34% relative mortality reduction in patients with heart failure and reduced ejection fraction.[8-11] It is therefore conceivable that optimization of treatment adherence provides another opportunity to prevent mortality and hospitalization.[12] Indeed, our data showed a 22% reduction in mortality for patients who were optimally adherent to RAS agents or BB. Although some studies have shown increased medication utilization or adherence over time,[2,4,6,13] there is further work to be done to ensure all heart failure patients have access to evidence-based medications.

In our cohort study, rural-urban differences in cardiovascular medication utilization persisted after adjustment for differences in patient characteristics,

whereas the systematic review found no consistent rural-urban association with medication utilization after taking patient, provider and other potential confounders into consideration. These results may appear to be inconsistent however several possible differences may explain these findings. The cohort study was conducted in an acutely ill population in a highly organized health care system with universal health coverage including drug benefits, whereas the systematic review included a broad spectrum of patient populations, in countries with diverse health care systems, or in single isolated regions. Further, many previous studies did a relatively poor job of controlling potential confounding factors. Given the significant between-study heterogeneity observed in the systematic review, which was only partially explained by age, setting and disease, it is plausible that the rural-urban relationship with medication usage truly varies, and thus the findings of the cohort study reflect this variable association.

4.2. Implications for future policy

There is potential to improve outcomes in heart failure by enhancing medication utilization and adherence to therapies of known benefit. One US study estimated over 60,000 deaths per year could be prevented by optimal implementation of evidenced based treatments for heart failure.[10] In addition, poor persistence or adherence results in wasted drug expenditures for payers when medication is taken in insufficient quantity or duration to produce any health benefits for patients. Although heart failure medication regimens are complex and are a

challenge for patients to manage, the health and economic benefits of developing effective methods to improve utilization and adherence are substantial.

Another policy implication from our research is that adherence, an important mediator of health outcomes, may be overlooked when evaluating health care services. Ideally, the impact on adherence should be assessed when developing or evaluating health policy, particularly for policies such as patient cost sharing that may be directly linked to utilization and adherence.[14-16] For rural residents, policy impacts on adherence may be more profound, considering the ongoing challenges with rural access to health care and potential for reduced financial capacity.[17-22] Finally, including utilization, persistence and adherence measures in program evaluations may help policy makers gain a better insight into program success or failure.

4.3. Implications for future research

This program of research identified rural-urban differences in cardiovascular medication utilization, and overall, the use of evidence-based medications is suboptimal in many patients with cardiovascular disease, particularly patients with heart failure. These findings build on previous studies that showed rural-urban variations in patterns of care in heart failure.[23] Future research should explore medication utilization patterns in rural communities of different sizes and degrees of remoteness as health care access and utilization varies between rural communities, with the largest discrepancies among the most rural areas.[19,22,24,25] Inequalities between rural areas may be masked in studies using

gross indicators of rural-urban. Information on medication usage patterns across the rural-urban continuum is required to appropriately target interventions to the areas of greatest need.

A prospective study of incident heart failure patients would provide an opportunity to gather clinical and prescribing information not available in administrative databases that could be used to confirm the suboptimal medication usage observed. Although there are some data on the prevalence of contraindications to heart failure medications,[10,26] information on rates of medication intolerance or discontinuation due to clinical status, and primary non-adherence (i.e. failure of patient to initiate prescribed therapy), is lacking in patients with heart failure. These data are necessary to determine the proportion of patients who are eligible for specific medications and those who have appropriately stopped treatment. In addition, prescribing information could be used to differentiate between failure to prescribe and primary medication non-adherence among patients not receiving treatment. Using clinical information to supplement data from administrative databases could provide more accurate estimates of utilization and adherence patterns and to identify determinants of suboptimal use.

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