Potential Therapeutic Competition in Community-Living Older Adults in the U.S.: Use of Medications That May Adversely Affect a Coexisting Condition

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Abstract

Objective: The 75% of older adults with multiple chronic conditions are at risk of therapeutic competition (i.e. treatment for one condition may adversely affect a coexisting condition). The objective was to determine the prevalence of potential therapeutic competition in community-living older adults.

Methods: Cross-sectional descriptive study of a representative sample of 5,815 community-living adults 65 and older in the U.S, enrolled 2007–2009. The 14 most common chronic conditions treated with at least one medication were ascertained from Medicare claims. Medication classes recommended in national disease guidelines for these conditions and used by \geq 2% of participants were identified from in-person interviews conducted 2008–2010. Criteria for potential therapeutic competition included: 1), well-acknowledged adverse medication effect; 2) mention in disease guidelines; or 3) report in a systematic review or two studies published since 2000. Outcomes included prevalence of situations of potential therapeutic competition and frequency of use of the medication in individuals with and without the competing condition.

Results: Of 27 medication classes, 15 (55.5%) recommended for one study condition may adversely affect other study conditions. Among 91 possible pairs of study chronic conditions, 25 (27.5%) have at least one potential therapeutic competition. Among participants, 1,313 (22.6%) received at least one medication that may worsen a coexisting condition; 753 (13%) had multiple pairs of such competing conditions. For example, among 846 participants with hypertension and COPD, 16.2% used a nonselective beta-blocker. In only 6 of 37 cases (16.2%) of potential therapeutic competition were those with the competing condition less likely to receive the medication than those without the competing condition.

Conclusions: One fifth of older Americans receive medications that may adversely affect coexisting conditions. Determining clinical outcomes in these situations is a research and clinical priority. Effects on coexisting conditions should be considered when prescribing medications.

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Introduction

Almost three quarters of older adults have multiple chronic conditions, also referred to as multi-morbidity.[1] The health care costs, adverse health effects, and treatment burden associated with multi-morbidity have been well chronicled.[2–8] Older adults with multi-morbidity are prescribed multiple medications for their individual conditions. While benefiting one condition, it is possible that some of these medications may adversely affect a coexisting condition, a situation we refer to as therapeutic competition. Therapeutic competition is one type of disease-drug interaction in which a treatment recommended for one condition may adversely affect (i.e. compete with) another coexisting condition. A few well publicized cases of therapeutic competition, such as the effects of COX-2 inhibitors on arthritis versus heart disease or rosiglitazone on diabetes versus heart failure, have increased awareness of the potential adverse outcomes of therapeutic competition.[9–11] The extent of therapeutic competition remains unknown but may be widespread given the frequency of multimorbidity in older adults and the emphasis of disease guidelines on prescribing one or more medications for treatment of chronic conditions. There has been no systematic examination of the prevalence of this problem.

In a nationally representative sample of older adults, we determined the prevalence of the most common pairs of coexisting chronic conditions in which a medication recommended by a national specialty organization for one condition may worsen the coexisting (i.e. competing) condition. Among all individuals with the chronic condition for which the medication is recommended, we compared the frequency of use of the medication in individuals with and without the competing condition.

Methods

Study Population and Data

Participants were members of the Medicare Current Beneficiary Survey. Medicare is the federal government health insurance program for essentially all persons aged 65 and older, and some younger people with disabilities, in the United States. The Medicare Current Beneficiary Survey is a nationally representative sample of Medicare beneficiaries obtained using stratified multistage sampling from the enrollment files of Centers for Medicare and Medicaid Services (CMS), the governmental agency that runs the Medicare program. [12,13] A new cohort is added yearly; each cohort is then interviewed and followed for four years. The current study included cohort members enrolled from 2007-2009. Response rates for the baseline interview were 78.0%, 79.5%, and 77.5% for the 2007, 2008, and 2009 cohorts, respectively. For the current study, we included all cohort members who: 1) were age 65 years or older, 2) did not reside in a skilled nursing facility (medication data was not available for skilled nursing facility residents), 3) completed the in-person interview during which medications were ascertained, and 4) participated in the traditional fee-for-service Medicare. Only traditional Medicare beneficiaries were included because health claims used to ascertain chronic conditions were not available for the 25% of Medicare beneficiaries enrolled in a Health Maintenance Organization plan, referred to as Medicare Advantage. All 5,815 MCBS participants who met these inclusion criteria constituted the study population. The study was deemed exempt from review by the Yale University Human Investigation Committee because it involved existing, publicallyavailable, de-identified data.

Socio-demographic, behavioral, and functional data were obtained from the Cost and Use files based on in-person interviews that occurred yearly; the baseline interview was used for the current study.[12] Dependency in basic activities of daily living (BADLs) was defined as not performing independently one or more of transferring, walking, dressing, bathing, eating or toileting. Medication use was ascertained from 2008–2010 Cost and Use files for cohort members.[12,13] The data obtained during the inperson interviews are those included in Table 1. The Interviews were conducted by Westat Inc. under contract from CMS Further details on the interview process are available on the MCBS website.[12,13]

Ascertainment of Study Chronic Conditions

Study conditions included all nonmalignant chronic conditions experienced by at least 5% of participants for which at least one oral or inhaled prescription medication is recommended by national disease guidelines for most persons with the condition. Chronic conditions were ascertained from hospital, outpatient, and physician claims data during the first two years of MCBS enrollment. At least one hospital or two nonhospital claims at least one month apart were required for every condition. All disease claims were assigned to a single level Clinical Classification System (CCS) code based on their International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) codes.[14] When appropriate, clinically identical or similar disease codes were combined. The chronic conditions meeting study criteria included atrial fibrillation, benign prostatic hypertrophy (BPH), coronary artery disease, chronic obstructive pulmonary disease (COPD), dementia, depression, diabetes (type 2), gastrointestinal esophageal reflux and peptic ulcer disease (GERD/PUD), heart failure, hyperlipidemia, hypertension, hypothyroidism, osteoarthritis, and osteoporosis. We determined the frequency of all pairs of these chronic conditions experienced by study participants.

Ascertainment of Medications

Prescription medications were ascertained by direct observation of the medication containers of currently used medications during the year two in-home interviews which occurred between 2008– 2010. Nonprescription medications were not available in the MCBS database. We categorized medications into medication classes based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system.[15]

Identification of Condition Pairs with Potential Therapeutic Competition

Three investigators including two practicing geriatricians (MET, MG) and a PhD clinical pharmacologist and pharmacist (DSHL) reviewed the national disease guidelines for these 14 chronic conditions. Two investigators reviewed each guideline, identifying all medication classes that were recommended on a continual basis for most individuals with the condition. When there was more than one national U.S. specialty organization, we selected the most recent guideline published.[16-29] When the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system was used, all medication classes with an A (strong evidence) or B (moderate) grade were recorded.[30] When the GRADE system was not used, reviewers recorded medication classes with an evidence level of I or II. If no evidence grading was used, all medications recommended were recorded. For coronary artery disease (CAD), we identified medication recommendations for post myocardial infarction, acute coronary syndrome (ACS), and angina. Discrepancies among the medication lists generated by the three reviewers were reconciled by consensus. Medication subclasses (selective and nonselective betablockers and alpha-beta blockers and dihydropyridine and nondihydropyridine calcium channel blockers) were each considered separately when guidelines recommended for or against a medication subclass. For guidelines that did not stipulate subclass, we assumed all subclasses might be prescribed for the condition. Because it was not possible to determine for which of their coexisting conditions a guideline recommended medication was given, individuals were included in all possible potential therapeutic competition situations for which they had an indicated and competing condition and received a recommended medication for any indicated condition. For example, if an individual with diabetes received a glitazone and had both CAD and heart failure, that individual was included in potential therapeutic competition frequencies for both CAD and heart failure. The 27 prescription medication classes (including the three beta-blocker, and two calcium channel blocker, subclasses) meeting our selection criteria are listed in Table 1.

To determine which of the medication classes selected by review of the disease guidelines might constitute a possible therapeutic competition, we evaluated every combination of two coexisting conditions. For each combination of coexisting conditions, we first identified medications recommended for one of the conditions that are well acknowledged to adversely affect the coexisting condition (i.e. corticosteroids in persons with DM, osteoporosis, or GERD/PUD; warfarin in persons with GERD/PUD; tricyclic
 Table 1. Characteristics of Participants by Number of Coexisting Chronic Condition Pairs (N = 5,815).

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Ortearthis187 (49)190 (94)141 (19,0)147 (84)Diabets180 (63)10 (10,0)43 (50,0)143 (30,0)Gronary artey discas131 (20,2)21 (20,2)41 (53,0)144 (30,3)Gronary artey discas104 (17,4)10 (15,0)57,7040 (20,2)Hypotyodism102 (17,7)12 (09,0)67 (83,0)94 (25,1)Hypotyodism66 (13,0)8 (04,0)55 (72,0)65 (73,0)Benig prostati hypertopic66 (10,0)10 (10,0)65 (72,0)65 (73,0)Depression46 (10,0)24 (19,0)10 (20,0)46 (14,0)Depression140 (20,0)10 (20,0)10 (20,0)46 (14,0)Depression140 (20,0)10 (20,0)10 (20,0)46 (14,0)Depression140 (20,0)10 (20,0)10 (20,0)10 (20,0)Angletensin enceptor blocker25 (14,0)12 (12,0)12 (12,0)12 (12,0)Brabelocker25 (14,0)12 (12,0)12 (12,0)12 (13,0)Calcium channel blocker13 (12,0)14 (13,0)10 (14,0)13 (12,0)Calcium channel blocker10 (11,0)12 (12,0)12 (12,0)12 (12,0)Disposphonte10 (11,0)12 (12,0)12 (12,0)12 (12,0)Calcium channel blocker10 (11,0)12 (12,0)12 (12,0)12 (12,0)Calcium channel blocker10 (11,0)12 (12,0)12 (12,0)12 (12,0)Disposphonte10 (11,0)12 (12,0)12 (12,0)12 (12,0)Calcium channel block	Hyperlipidemia	3467 (59.6)	84 (6.6)	360 (47.2)	3023 (80.0)
Diabetes130 (26.3)18 (1.4)75 (9.8)14 37 (3.80)Coronary artery disease144 (9 (25.3)11 (0.9)45 (5.8)1415 (37.4)Gatenese phage arteful disease/peptic uler121 (20.7)2 (2.0)45 (5.8)94 (2.5)Chronic obstructive pulmonary disease1027 (17.7)12 (0.9)67 (8.8)94 (2.5)Atrial Fibrillation1027 (17.7)8 (0.6)30 (3.9)731 (19.3)Heart Fallure66 (11.5)3 (0.2)8 (5.0)55 (7.2)Ottoporosis65 (0.1)3 (0.2)49 (6.4)46 (1.4)Degression142 (7.6)5 (0.4)24 (2.6)32 (2.6)Beniga prostatic hypertrophy616 (1.6)3 (0.2)21 (2.6)32 (2.6)Dementa169 (0.6)5 (0.4)21 (2.6)32 (2.6)Dementa169 (0.6)18 (2.6)21 (2.6)23 (2.6)Betafon prostatic hypertrophy55 (4.5)18 (2.5)21 (2.5)21 (2.6)Dementa255 (4.5)18 (2.6)22 (2.9)186 (4.9)Angiotensin converting enzyme inhibitor259 (4.6)21 (2.5)21 (2.5)21 (2.5)Beta-blocker ⁴ 35 (3.6)21 (2.5)21 (2.6)186 (3.6)21 (2.9)186 (3.6)21 (2.9)Coritosteroid blocker135 (2.6)167 (1.3)10 (1.4)123 (2.7)13 (2.7)Coritosteroid blocker135 (2.6)14 (1.13)14 (1.9)129 (2.6)Coritosteroid blocker137 (2.7)13 (2.6)13 (2.7)13 (2.1)Coritosteroid blocker </td <td>Osteoarthritis</td> <td>2857 (49.1)</td> <td>120 (9.4)</td> <td>241 (31.6)</td> <td>2496 (66.0)</td>	Osteoarthritis	2857 (49.1)	120 (9.4)	241 (31.6)	2496 (66.0)
Corony array disease1469 (25)10 (0)41 (5)41 (5) (3)Gatocsphagel reflux disease/paticula121 (20)2 (20)4 (5)141 (30)Choric obstructive pulmonary disease1041 (7)10 (0)5 (7)940 (24)Mypothyoidism102 (17)10 (0)5 (7)940 (24)Atali Finilaton66 (11)3 (0)8 (10)5 (5) (7)Beingin prostatic hypertrophy66 (11)6 (0)9 (20)9 (20)Beingin prostatic hypertrophy940 (20)9 (20)9 (20)9 (20)Deression44 (26)5 (04)20 (20)9 (21)Deression44 (26)10 (20)20 (20)9 (21)Deression55 (40)3 (12)20 (20)9 (5) (3)Angiotensin converting engression hypertrophy55 (40)21 (22)9 (5) (3)Beta biocker ⁶ 215 (30)21 (12)21 (21)10 (21)Calcium channel biologe ⁴ 130 (21)12 (12)10 (21)10 (21)Calcium channel biologe ⁴ 10 (11)10 (12)10 (21)10 (21)Calcium channel biologe ⁴ 10 (11)10 (21)10 (21)10 (21)Seletavescrint re-uptrophypertrophype	Diabetes	1530 (26.3)	18 (1.4)	75 (9.8)	1437 (38.0)
Gastesphagel reflux disease/peptic value121 (20)25 (20)44 (5.8)114 (0.3)Chonic obstructive pulmonary disease104 (17.4)19 (15)55 (7.2)940 (2.4)Hypothyoldim1027 (17.7)12 (0.9)67 (8.8)948 (2.5)Atrial Finllation660 (1.5)80.0)81 (0.0)55 (7.3)Date approximation prostatic hypertrophy636 (1.0)50.0281 (0.0)55 (7.3)Benign prostatic hypertrophy619 (10.6)50.4)94 (6.4)417 (11.0)Dementa44 (5.9)50.2)17 (2.2)24 (8.6)Dementa44 (5.9)30.2)12 (2.3)25 (5.4)Anglotensi neceptor blocker55 (9.4)32 (2.5)25 (3.4)Anglotensi neceptor blocker55 (9.4)24 (1.3)24 (9.2)Patchardors ⁴ 55 (9.4)21 (2.5)26 (3.4)15 (3.2)Patchardors ⁴ 55 (9.4)21 (2.5)26 (3.4)16 (9.2)Anglotensi neceptor blocker55 (9.4)24 (9.2)16 (9.2)15 (3.2)Patchardors ⁴ 195 (9.4)12 (1.2)21 (3.2)16 (9.2)15 (1.2)Calciam channel blocker195 (9.4)12 (1.2)16 (1.4)16 (9.2)16 (1.4)Calciam channel blocker10 (2.1)10 (2.1)10 (2.1)16 (2.1)16 (2.2)Stabposhonat10 (1.2)10 (1.4)10 (1.4)16 (1.4)16 (1.4)Calciam channel blocker10 (1.6)16 (3.6)16 (3.6)16 (3.6)Stabposhonat10 (1.6)16 (1.6)16	Coronary artery disease	1469 (25.3)	11 (0.9)	43 (5.6)	1415 (37.4)
Chronic obstructive pulmonary disease104 (17.4)19 (15.5)56 (7.2)94 (0.49)Hypothyoidism102 (17.7)12 (0.4)67 (0.4)94 (0.4)94 (0.4)Arial Fibiliation66 (0.1)10 (0.4)56 (0.1)56 (0.1)56 (0.1)Beinge prostatic hypertrophy69 (0.0)24 (0.4)56 (0.4)56 (0.4)56 (0.4)Depression42 (7.6)50 (0.4)10 (0.4)10 (0.4)10 (0.4)Depression42 (7.6)50 (0.4)10 (0.4)10 (0.4)10 (0.4)Depression42 (7.6)10 (0.4)10 (0.4)10 (0.4)10 (0.4)Depression42 (7.6)10 (0.4)10 (0.4)10 (0.4)10 (0.4)Anglotensin receptor blocker55 (0.4)12 (0.4)22 (0.4)10 (0.4)10 (0.4)Anglotensin receptor blocker10 (0.5)10 (0.4)12 (0.4)10 (0.4)10 (0.4)Thaizdes10 (0.5)10 (0.4)10 (0.4)12 (0.4)10 (0.4)10 (0.4)Cotrosteronin blocker*10 (0.5)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)Biotophonate10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)Stortophonate10 (0.5)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)Stortophonate10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)10 (0.4)Stortophonate10 (0.6)10 (0.4)10 (0.4)10 (0.4)10 (0.4) <td>Gastroesophageal reflux disease/peptic ulcer disease</td> <td>1213 (20.9)</td> <td>25 (2.0)</td> <td>44 (5.8)</td> <td>1144 (30.3)</td>	Gastroesophageal reflux disease/peptic ulcer disease	1213 (20.9)	25 (2.0)	44 (5.8)	1144 (30.3)
Hypothysoidism1022 (17,7)12 (0.9)67 (8.8)948 (25.1)Atrial Finiliation76 (15.2)8 (0.6)3 (0.3)3 (0.19,3)3 (0.19,3)Heart Failure66 (0.15.0)5 (0.4)5 (7.12,0)5 (65.17.3)Osteoporsis66 (10.9)2 (1.9)9 (0.4)5 (6.14,2)Beingin prostatic hypertrophy619 (0.6)5 (0.4)2 (0.2,0)417 (1.0)Demensia442 (7.5)5 (0.4)2 (0.2,0)417 (1.0)Bementia442 (7.5)18 (2.5,0)7 (2.2,0)205 (54.4)Metications ¹ 55 (4.5,0)2 (2.2,0)25 (54.4)205 (54.4)Angiotensin converting enzyme inhibitor55 (4.0)2 (2.2,0)15 (1.3,0)Bigtotensin converting enzyme inhibitor255 (4.0)242 (1.90,0)242 (2.9,0)165 (1.3,0)Calcium channel bocker ⁶ 137 (23.6)167 (13.1)101 (14.1)121 (2.1,0)Calcium channel bocker ⁶ 137 (23.6)167 (13.1)101 (14.2)128 (2.6,0)Calcium channel bocker ⁶ 102 (13.1)102 (13.2)162 (13.2)162 (13.2)Corticosteroid102 (17.4)129 (9.0)163 (13.4)150 (13.4)Edethysoinen enzyme inhibitor67 (13.0)163 (13.4)150 (13.2)162 (13.2)Corticosteroid139 (13.4)140 (13.2)163 (13.4)150 (13.2)163 (13.2)Corticosteroid bocker ⁶ 102 (13.4)163 (13.4)150 (13.4)150 (13.4)Corticosteroid ne-upke inhibitor67 (13.0)163 (13.4)150 (13.4)	Chronic obstructive pulmonary disease	1014 (17.4)	19 (1.5)	55 (7.2)	940 (24.9)
Arial Fibrilation760 (132)8 (0.6)9 (0.9)73 (19.3)Hart Falare660 (1.5)3 (0.2)8 (0.7)5 (5 (7.3)5 (5 (7.3)Osteoporsis60 (0.0)2 (0.9)5 (7.2)5 (5 (7.4)5 (7.4)Denensiat hypertrophy412 (0.6)2 (0.9)2 (0.2)3 (1.6)3 (1.6)Dementia412 (0.6)5 (0.4)2 (0.2)3 (0.2)3 (0.6)3 (0.6)Meticators ⁶ 5 (0.6)1 (0.2)2 (0.2)3 (0.6)3 (0.6)3 (0.6)Angiotensin converting enzyme inhibitor5 (0.6)2 (0.6)2 (2 (0.3)3 (0.6)3 (0.6)Angiotensin converting enzyme inhibitor2 (0.6)2 (0.6)2 (2 (0.4)1 (0.6)3 (0.6)Angiotensin converting enzyme inhibitor2 (0.6)2 (0.6)2 (2 (0.4)1 (0.6)3 (0.6)Angiotensin converting enzyme inhibitor3 (0.6)2 (0.1)2 (2 (0.4)1 (0.6)3 (0.6)Angiotensin converting enzyme inhibitor3 (0.6)2 (0.1)2 (0.6)3 (0.6)3 (0.6)Angiotensin converting enzyme inhibitor3 (0.6)2 (0.7)3 (0.6)3 (0.6)3 (0.7)3 (0.6)Angiotensin converting enzyme inhibitor3 (0.6)3 (0.7)3 (0.6)3 (0.6)3 (0.7)3 (0.6)3 (0.6)Colconverting enzyme inhibitor3 (0.6)3 (0.7)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6)3 (0.6) <td>Hypothyroidism</td> <td>1027 (17.7)</td> <td>12 (0.9)</td> <td>67 (8.8)</td> <td>948 (25.1)</td>	Hypothyroidism	1027 (17.7)	12 (0.9)	67 (8.8)	948 (25.1)
Hear Failure666 (11.5)8 (0.2)8 (1.0)65 (7.3)65 (7.3)Octoporosis63 (0.0)5 (0.4)5 (7.2)57 (1.5.2)Benign porstatic hypertrophy44 (7.6)5 (0.4)49 (6.4)54 (1.4.0)Depression442 (7.6)5 (0.4)17 (2.2)324 (8.6)Dementia442 (7.6)10 (2.5.2)17 (2.2)324 (8.6)Metications ⁶ 55.018 (2.5.2)26 (3.7.3)26 (5.7.3)Angiotensi norvering expansion history259 (4.0.2)181 (2.5.2)26 (2.4.3)196 (5.2.3)Beta-blocker ⁶ 253 (4.0.5)269 (2.1.1)224 (2.9.4)165 (4.3.7)Poton Pump inhibitor ⁴ 1490 (5.3.1)27 (2.9.1)124 (2.9.4)163 (3.2.1)Poton Pump inhibitor ⁴ 149 (2.5.4)167 (1.3.1)194 (1.9.1)182 (2.8.6)Caticum channel blocker ⁶ 137 (2.3.6)17 (1.3.1)194 (1.9.1)182 (2.8.6)Caticum channel blocker ⁶ 137 (2.3.6)164 (1.9.1)194 (2.9.1)182 (2.8.6)Caticum channel blocker ⁶ 102 (1.7.1)197 (3.9.1)184 (2.9.1)182 (2.8.6)Caticum channel blocker ⁶ 103 (1.6.1)197 (3.9.1)184 (2.9.1)182 (2.8.6)Caticum channel blocker102 (1.7.1)197 (3.9.1)182 (2.9.6)197 (3.9.1)Selective sectorin re-uptake inhibiton160 (1.0.1)164 (3.0.1)163 (3.0.1)163 (1.1.1)Marfarin161 (1.0.1)164 (3.0.1)164 (3.0.1)164 (3.0.1)164 (3.0.1)Selective sectorin re-uptake	Atrial Fibrillation	769 (13.2)	8 (0.6)	30 (3.9)	731 (19.3)
Oteoporsis636 (0.9)5 (0.4)5 (7.2)76 (15.2)Benign postatic hypertrophy619 (0.6)24 (1.9)49 (6.4)40 (1.4)Depression42 (2.7)5 (0.4)20 (2.6)47 (1.0)Dementia44 (5.9)3 (0.2)72 (2.6)24 (6.6) Metactors 55 (7.4)318 (2.5)25 (3.4)055 (5.4.4)Angiotensi receptor blocker55 (9.4.9)21 (2.5.2)26 (3.3.2)196 (6.2.3)Betablocker235 (3.5.1)24 (1.9.1)24 (2.9.4)160 (4.9.2)Patablocker116 (3.6.4)24 (1.9.1)21 (2.9.2)161 (3.7.1)Proton Pump inhibitor ⁴ 109 (2.5.3)101 (1.4.2)123 (2.7.1)Calcium channel blocker ⁶ 103 (3.6.1)14 (1.3.1)101 (1.4.2)123 (2.7.1)Catorium channel blocker ⁶ 102 (2.1.1)102 (2.1.1)102 (2.1.1)102 (2.1.1)Catorium channel blocker ⁶ 102 (3.1.1)101 (1.4.1)123 (3.2.1)102 (3.2.1)Catorium channel blocker ⁶ 102 (3.1.1)102 (3.1.1)102 (3.2.1)102 (3.2.1)Stephosphonate102 (1.1.1)102 (3.1.1)102 (3.1.1)102 (3.1.1)102 (3.1.1)Stephosphonate101 (1.9.1)101 (1.9.1)102 (3.1.1)102 (3.1.1)102 (3.1.1)Stephosphonate102 (1.1.1)102 (1.1.1)102 (3.1.1)102 (3.1.1)102 (3.1.1)Stephosphonate101 (1.9.1)101 (1.9.1)102 (1.9.1)102 (3.1.1)102 (3.1.1)Stephosphonate103 (1.0.1)101 (1.9.1)102	Heart Failure	666 (11.5)	3 (0.2)	8 (1.0)	655 (17.3)
Benign prostatic hypertrophy619 (10.6)24 (1.9)49 (6.4)54 (14.4)Depression442 (7.6)5 (0.4)20 (2.6)417 (1.0)Dementia34 (45)3 (0.2)10 (2.6)324 (8.6) Medications⁶ 555 (44.7)318 (25.0)285 (37.4)205 (54.4)Angiotensin converting enzyme inhibitor angiotensin receptor blocker2559 (44.0)212 (2.2)224 (29.4)1976 (52.3)Beta-blocker ⁶ 2353 (0.5)669 (21.1)242 (29.0)1651 (43.7)186 (49.2)Proton Pump inhibitor ⁴ 149 (25.6)167 (13.1)10 (14.4)1213 (2.1)Calcium channel blocker ⁶ 103 (18.6)93 (7.3)94 (12.8)1892 (23.6)Cotricosteroid102 (17.4)129.6)168 (14.2)82 (20.7)Bisphophonte102 (17.4)129.6)18 (14.2)56 (14.7)Keformin re-uptake inhibitor616 (1.6)91 (7.8)96 (12.8)56 (14.7)Keformin re-uptake inhibitor610 (1.6)81 (6.4)56 (1.6)56 (14.7)Keformin re-uptake inhibitor610 (1.6)81 (6.4)31 (3.2)12 (1.6)Keformin re-uptake inhibitor610 (1.6)81 (6.1)31 (3.1)32 (3.1)32 (3.1)Keformin re-uptake inhibitor610 (1.6)81 (6.1)31 (3.1)32 (3.1)32 (3.1)Keformin re-uptake inhibitor610 (1.6)81 (6.1)31 (3.1)32 (3.1)32 (3.1)Keformin re-uptake inhibitor610 (1.6)81 (1.6)31 (1.6)31 (1.6)Keformin re-uptake i	Osteoporosis	636 (10.9)	5 (0.4)	55 (7.2)	576 (15.2)
Depression442 (7.6)5 (0.4)0 (2.6,0)417 (1.0)Dementia944 (5.9,0)3 (0.2,0)17 (2.2,0)24 (8.6)Metations ⁶ 18 (2.5,0)28 (3.7,0)28 (5.5,64,0)28 (3.7,0)28 (3.7,0)28 (3.7,0)Angiotensin converting enzyme inhibitor255 (4.0,0)29 (2.1,0)24 (2.9,0)24 (2.9,0)160 (4.9,0)Betabcker ⁶ 29 (3.6,0)29 (2.1,0)24 (2.9,0)24 (2.9,0)160 (2.9,0)160 (2.9,0)Poton Pump inhibitor ⁴ 190 (5.6,0)67 (1.3,0)10 (1.4,1)10 (2.9,0)10 (2.9,0)10 (2.9,0)Colticosteroid102 (7.2,0)102 (7.2,0)102 (7.2,0)102 (7.2,0)102 (7.2,0)102 (7.2,0)102 (7.2,0)Colticosteroid102 (7.1,0)21 (7.2,0)10 (7.2,0)102 (7.2,0)102 (7.2,0)102 (7.2,0)102 (7.2,0)Biphosphonat102 (7.1,0)102 (7.2,0)102 (Benign prostatic hypertrophy	619 (10.6)	24 (1.9)	49 (6.4)	546 (14.4)
Dementia344 (5.9)3 (0.2)17 (2.2)324 (8.6)Medications ^b Statin2658 (45.7)318 (25.0)285 (37.4)205 (54.4)Anglotensin converting enzyme inhibitor on angiotensin receptor blocker2559 (44.0)212 (25.2)262 (3.3)1860 (49.2)Beta-blocker ⁶ 2353 (0.5)269 (21.1)224 (29.4)1860 (49.2)1861 (43.7)Thiazides116 (36.4)242 (19.0)223 (29.2)1651 (3.3.7)Proton Pump inhibitor ^d 1390 (25.6)167 (13.1)110 (14.4)1213 (32.1)Calciur channel blocker ⁶ 1375 (23.6)144 (11.3)149 (19.5)1822 (28.6)Corticosteroid1031 (18.6)93 (73.3)98 (12.8)892 (28.6)Bisphosphonate702 (12.1)129 (78.3)98 (12.8)55 (14.7)Gettive serotonin re-uptake inhibitor67 (11.6)64 (5.0)67 (13.9)55 (14.7)Metformin610 (10.5)81 (64.4)81 (63.6)81 (28.0)55 (14.7)Metformin610 (10.5)81 (64.3)81 (63.6)81 (63.6)81 (63.6)81 (63.6)Metformin610 (10.5)81 (64.3)81 (63.6)81 (63.6)81 (63.6)81 (63.6)81 (63.6)Metformin610 (10.5)81 (64.7)81 (63.6) </td <td>Depression</td> <td>442 (7.6)</td> <td>5 (0.4)</td> <td>20 (2.6)</td> <td>417 (11.0)</td>	Depression	442 (7.6)	5 (0.4)	20 (2.6)	417 (11.0)
Medications ⁶ Stain 688 (A7.0 818 (20.0 285 (37.4) 2055 (64.4) Angiotensin converting enzyme historer 559 (40.4) 212 (22.2) 224 (29.4) 180 (49.2) Beta-blocker ⁶ 233 (03.0 269 (21.1) 224 (29.4) 180 (49.2) Thizides 116 (36.4) 242 (19.0) 232 (29.2) 165 (14.3) Proton Pump inhibitor ⁴ 130 (25.6) 144 (13.3) 190 (14.4) 121 (23.1) Calcium channel blocker ⁶ 130 (30.6) 197 (30.1) 190 (14.2) 192 (28.6) Carcitox channel blocker ⁶ 102 (17.4) 122 (96.1) 190 (12.2) 192 (28.6) Carcitox channel blocker ⁶ 102 (17.4) 122 (96.1) 192 (12.2) 192 (28.6) Carcitox channel blocker ⁶ 102 (17.4) 122 (96.1) 192 (12.2) 192 (12.6) Carcitox channel blocker ⁶ 102 (17.4) 122 (96.1) 192 (12.6) 192 (12.6) Carcitox channel blocker 102 (17.4) 123 (13.6) 192 (13.6) 192 (13.6) Sate Start channel blocker 102 (13.6) 102 (13.6)	Dementia	344 (5.9)	3 (0.2)	17 (2.2)	324 (8.6)
Statin2658 (45.7)318 (25.0)285 (37.4)2055 (54.4)Angiotensin converting enzyme inhibitor or angiotensin receptor blocker2559 (44.0)321 (25.2)262 (34.3)1976 (52.3)Beta-blocker'2353 (40.5)269 (21.1)242 (29.4)1860 (49.2)Beta-blocker'2116 (36.4)242 (19.0)223 (29.2)1651 (43.7)Proton Pump inhibitor ⁴ 1490 (25.6)167 (13.1)110 (14.4)1213 (32.1)Calcium channel blocker'1375 (23.6)144 (11.3)149 (19.5)1082 (28.6)Carticosteroid1081 (18.6)93 (7.3)98 (12.8)892 (23.6)Corticosteroid1012 (17.4)122(9.6)108 (14.2)782 (20.7)Bisphosphonate702 (12.1)91 (7.8)98 (12.8)505 (13.4)Selective serotonin re-uptake inhibitor676 (1.6)64 (5.0)56 (7.3)55 (14.7)Metformin610 (10.5)81 (6.4)30 (3.9)53 (41.1)Beta agonist506 (0.6)81 (6.3)30 (3.9)53 (41.1)Clopidogref506 (0.6)86 (5.3)31 (3.6)492 (13.0)Alpha-drenergic blocker412 (7.1)47 (3.7)31 (3.6)492 (13.0)Sulforylurea142 (1.1)15 (2.0)14 (1.8)27 (7.3)Insulin14 (54)25 (2.0)14 (1.8)27 (7.3)Gitazone25 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)13 (5.6)Guitazone25 (3.9)27 (3.1)15	Medications ^b				
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker2559 (44.0)321 (25.2)262 (34.3)1976 (52.3)Beta-blocker2353 (40.5)669 (21.1)224 (29.4)1860 (49.2)Beta-blocker2116 (36.4)242 (19.0)223 (29.2)1651 (43.7)Proton Pump inhibitor ^{d1} 1490 (25.6)167 (13.1)110 (14.4)1213 (32.1)Calcium channel blocker ^e 1375 (23.6)144 (11.3)149 (19.5)1082 (28.6)Levothyroxine1083 (18.6)93 (7.3)98 (12.8)892 (23.6)Corticosteroid1012 (17.4)122(9.6)108 (14.2)782 (20.7)Bisphosphonate702 (12.1)99 (7.8)98 (12.8)505 (13.4)Selective serotonin re-uptake inhibitor676 (11.6)64 (5.0)56 (7.3)556 (14.7)Metfornin610 (10.3)81 (6.4)45 (5.9)475 (12.6)Warfari610 (10.5)64 (3.6)30 (3.9)534 (14.1)Beta agonist560 (9.6)35 (2.7)33 (4.3)492 (13.0)Clopidogrel560 (9.6)55 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker48 (8.4)76 (6.0)30 (3.9)342 (9.1)Insulin14 (2.1)47 (3.7)23 (3.0)342 (9.1)Insulin134 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone25 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.	Statin	2658 (45.7)	318 (25.0)	285 (37.4)	2055 (54.4)
Beta-blocker ^c 2353 (40.5) 269 (21.1) 224 (29.4) 1860 (49.2) Thiazides 2116 (36.4) 242 (19.0) 223 (29.2) 1651 (43.7) Proton Pump inhibitor ^d 1490 (25.6) 167 (13.1) 110 (14.4) 1213 (32.1) Calcium channel blocker ^e 1375 (23.6) 144 (11.3) 149 (19.5) 1082 (28.6) Levothyroxine 1083 (18.6) 93 (7.3) 98 (12.8) 892 (23.6) Corticosteroid 1012 (17.4) 122(9.6) 108 (14.2) 782 (20.7) Bisphosphonate 702 (12.1) 91 (7.8) 98 (12.8) 505 (13.4) Selective serotonin re-uptake inhibitor 67 (11.6) 64 (5.0) 56 (7.3) 556 (14.7) Metformin 610 (10.3) 81 (6.4) 45 (5.9) 475 (12.6) Wafarin 610 (10.5) 86 (8.3) 31 (3.3) 492 (13.0) Ippla-adrenergic blocker 560 (9.6) 35 (2.7) 33 (4.3) 492 (13.0) Ippla-darlenergic blocker 86 (8.4) 76 (6.0) 49 (6.4) 31 (9.6) Ippla-darlenergic blocker <	Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	2559 (44.0)	321 (25.2)	262 (34.3)	1976 (52.3)
Thiazides2116 (36.4)242 (19.0)223 (29.2)1651 (43.7)Proton Pump inhibitord1490 (25.6)167 (13.1)110 (14.4)1213 (32.1)Calcium channel blocker ⁶ 1375 (23.6)144 (11.3)149 (19.5)1082 (28.6)Levothyroxine1083 (18.6)93 (7.3)98 (12.8)892 (23.6)Corticosteroid1012 (17.4)122(9.6)108 (14.2)782 (20.7)Bisphosphonate702 (12.1)99 (7.8)98 (12.8)505 (13.4)Selective serotonin re-uptake inhibitor67 (11.6)64 (5.0)56 (7.3)556 (14.7)Metformin61 (10.3)81 (64.0)56 (7.3)534 (14.1)Beta agonist61 (0.15)68 (5.3)31 (3.9)534 (14.1)Clopidogrel50 (9.6)55 (27.7)31 (3.3)492 (13.0)Alpha-adrenergic blocker48 (8.4)76 (6.0)49 (6.4)31 (9.6)Sulfonylurea142 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin14 (5.4)52 (20.1)15 (20.1)183 (14.8)Gltazone25 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor16 (3.4)15 (12.2)16 (3.4)14 (3.8)Chiresterase Inhibitor16 (3.4)15 (12.8)14 (3.6)14 (3.6)Tricyclic Antidepressant174 (3.0)13 (10.2)13 (3.2)13 (3.7)	Beta-blocker ^c	2353 (40.5)	269 (21.1)	224 (29.4)	1860 (49.2)
Proton Pump inhibitor ^d 1490 (25.6) 167 (13.1) 110 (14.4) 1213 (32.1) Calcium channel blocker ^e 1375 (23.6) 144 (11.3) 149 (19.5) 1082 (28.6) Levothyroxine 1083 (18.6) 93 (7.3) 98 (12.8) 892 (23.6) Corticosteroid 1012 (17.4) 122(9.6) 108 (14.2) 782 (20.7) Bisphosphonate 702 (12.1) 99 (7.8) 98 (12.8) 505 (13.4) Selective serotonin re-uptake inhibitor 676 (11.6) 64 (50.0) 56 (7.3) 556 (14.7) Metformin 601 (10.3) 81 (64.4) 45 (5.9) 475 (12.6) Warfarin 610 (10.5) 46 (3.6) 30 (3.9) 534 (14.1) Beta agonist 586 (10.1) 68 (53.7) 33 (4.3) 492 (13.0) Alpha-adrenergic blocker 468 (84.0) 76 (6.0) 49 (6.4) 361 (9.6) Sulfonylurea 142 (7.1) 47 (3.7) 23 (3.0) 342 (9.1) Insulin 314 (5.4) 25 (2.0) 14 (1.8) 275 (7.3) Glitazone 22 (3.9) 22 (3.9) <td>Thiazides</td> <td>2116 (36.4)</td> <td>242 (19.0)</td> <td>223 (29.2)</td> <td>1651 (43.7)</td>	Thiazides	2116 (36.4)	242 (19.0)	223 (29.2)	1651 (43.7)
Calcium channel blocker ^e 1375 (23.6) 144 (11.3) 149 (19.5) 1082 (28.6) Levothyroxine 1083 (18.6) 93 (7.3) 98 (12.8) 892 (23.6) Corticosteroid 1012 (17.4) 122(9.6) 108 (14.2) 782 (20.7) Bisphosphonate 702 (12.1) 99 (7.8) 98 (12.8) 505 (13.4) Selective serotonin re-uptake inhibitor 676 (1.6) 64 (5.0) 56 (7.3) 556 (14.7) Metformin 601 (10.3) 81 (6.4) 45 (5.9) 475 (12.6) Warfarin 610 (10.5) 46 (3.6) 30 (3.9) 534 (14.1) Beta agonist 560 (9.6) 35 (2.7) 31 (4.3) 492 (13.0) Clopidogrel 560 (9.6) 35 (2.7) 31 (4.3) 422 (9.1) Sulfonylurea 486 (8.4) 76 (6.0) 49 (6.4) 361 (9.6) Sulfonylurea 141 (5.4) 25 (2.0) 14 (1.8) 275 (7.3) Sulfonylurea 216 (3.9) 27 (2.1) 14 (1.8) 275 (7.3) Glitazone 25 (3.9) 27 (2.1) 15 (2.0) 183 (14.8) Cox-2 inhibitor 26 (4.4) 21 (1.9)	Proton Pump inhibitor ^d	1490 (25.6)	167 (13.1)	110 (14.4)	1213 (32.1)
Levothyroxine1083 (18.6)93 (7.3)98 (12.8)892 (23.6)Corticosteroid1012 (17.4)122(9.6)108 (14.2)782 (20.7)Bisphosphonate702 (12.1)99 (7.8)98 (12.8)505 (13.4)Selective serotonin re-uptake inhibitor676 (11.6)64 (5.0)56 (7.3)556 (14.7)Metformin601 (10.3)81 (6.4)45 (5.9)475 (12.6)Warfarin601 (10.5)46 (3.6)30 (3.9)534 (14.1)Beta agonist560 (9.6)35 (2.7)33 (4.3)492 (13.0)Clopidogrel560 (9.6)35 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea112 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)13 (5.6)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tryctic Antidepressant174 (3.0)13 (1.0)22 (2.9)19 (3.7)	Calcium channel blocker ^e	1375 (23.6)	144 (11.3)	149 (19.5)	1082 (28.6)
Corticosteroid1012 (17.4)122(9.6)108 (14.2)782 (20.7)Bisphosphonate702 (12.1)99 (7.8)98 (12.8)505 (13.4)Selective serotonin re-uptake inhibitor676 (11.6)64 (5.0)56 (7.3)556 (14.7)Metformin601 (10.3)81 (6.4)45 (5.9)475 (12.6)Warfarin610 (10.5)46 (3.6)30 (3.9)534 (14.1)Beta agonist586 (10.1)68 (5.3)43 (5.6)475 (12.6)Clopidogrel560 (9.6)35 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea112 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tryctic Antidepressant174 (3.0)13 (1.0)21 (2.9)139 (3.7)	Levothyroxine	1083 (18.6)	93 (7.3)	98 (12.8)	892 (23.6)
Bisphosphonate 702 (12.1) 99 (7.8) 98 (12.8) 505 (13.4) Selective serotonin re-uptake inhibitor 676 (11.6) 64 (5.0) 56 (7.3) 556 (14.7) Metformin 601 (10.3) 81 (6.4) 45 (5.9) 475 (12.6) Warfarin 610 (10.5) 46 (3.6) 30 (3.9) 534 (14.1) Beta agonist 586 (10.1) 68 (5.3) 43 (5.6) 475 (12.6) Clopidogrel 560 (9.6) 35 (2.7) 33 (4.3) 492 (13.0) Alpha-adrenergic blocker 486 (8.4) 76 (6.0) 49 (6.4) 361 (9.6) Sulfonylurea 112 (7.1) 47 (3.7) 23 (3.0) 342 (9.1) Insulin 314 (5.4) 25 (2.0) 14 (1.8) 275 (7.3) Glitazone 225 (3.9) 27 (2.1) 15 (2.0) 183 (14.8) Cox-2 inhibitor 196 (3.4) 15 (1.2) 36 (4.7) 145 (3.8) Cholinesterase Inhibitor 256 (4.4) 23 (1.8) 20 (2.6) 213 (5.6) Cholinestersati 174 (3.0) 13 (1.0) 22 (2.9) <t< td=""><td>Corticosteroid</td><td>1012 (17.4)</td><td>122(9.6)</td><td>108 (14.2)</td><td>782 (20.7)</td></t<>	Corticosteroid	1012 (17.4)	122(9.6)	108 (14.2)	782 (20.7)
Selective serotonin re-uptake inhibitor 676 (11.6) 64 (5.0) 56 (7.3) 556 (14.7) Metformin 601 (10.3) 81 (6.4) 45 (5.9) 475 (12.6) Warfarin 610 (10.5) 46 (3.6) 30 (3.9) 534 (14.1) Beta agonist 586 (10.1) 68 (5.3) 43 (5.6) 475 (12.6) Clopidogrel 560 (9.6) 55 (2.7) 33 (4.3) 492 (13.0) Alpha-adrenergic blocker 486 (8.4) 76 (6.0) 49 (6.4) 361 (9.6) Sulfonylurea 412 (7.1) 47 (3.7) 23 (3.0) 342 (9.1) Insulin 314 (5.4) 25 (2.0) 14 (1.8) 275 (7.3) Glitazone 225 (3.9) 27 (2.1) 15 (2.0) 183 (14.8) Cox-2 inhibitor 196 (3.4) 15 (1.2) 36 (4.7) 145 (3.8) Cholinesterase Inhibitor 256 (4.4) 23 (1.8) 20 (2.6) 213 (5.6) Tricyclic Antidepressant 174 (3.0) 13 (1.0) 20 (2.6) 213 (5.6)	Bisphosphonate	702 (12.1)	99 (7.8)	98 (12.8)	505 (13.4)
Metformin601 (10.3)81 (6.4)45 (5.9)475 (12.6)Warfarin610 (10.5)46 (3.6)30 (3.9)534 (14.1)Beta agonist586 (10.1)68 (5.3)43 (5.6)475 (12.6)Clopidogrel560 (9.6)35 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea412 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tricyclic Antidepressant174 (3.0)13 (1.0)2 (2.9)39 (3.7)	Selective serotonin re-uptake inhibitor	676 (11.6)	64 (5.0)	56 (7.3)	556 (14.7)
Warfarin610 (10.5)46 (3.6)30 (3.9)534 (14.1)Beta agonist586 (10.1)68 (5.3)43 (5.6)475 (12.6)Clopidogrel560 (9.6)35 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea412 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tricyclic Antidepressant174 (3.0)13 (1.0)2 (2.9)139 (3.7)	Metformin	601 (10.3)	81 (6.4)	45 (5.9)	475 (12.6)
Beta agonist586 (10.1)68 (5.3)43 (5.6)475 (12.6)Clopidogrel560 (9.6)35 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea412 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Trycylic Antidepressant174 (3.0)13 (1.0)2 (2.9)139 (3.7)	Warfarin	610 (10.5)	46 (3.6)	30 (3.9)	534 (14.1)
Clopidogrel560 (9.6)35 (2.7)33 (4.3)492 (13.0)Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea412 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tricyclic Antidepressant174 (3.0)13 (1.0)2 (2.9)139 (3.7)	Beta agonist	586 (10.1)	68 (5.3)	43 (5.6)	475 (12.6)
Alpha-adrenergic blocker486 (8.4)76 (6.0)49 (6.4)361 (9.6)Sulfonylurea412 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tricyclic Antidepressant174 (3.0)13 (1.0)22 (2.9)139 (3.7)	Clopidogrel	560 (9.6)	35 (2.7)	33 (4.3)	492 (13.0)
Sulfonylurea412 (7.1)47 (3.7)23 (3.0)342 (9.1)Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tricyclic Antidepressant174 (3.0)13 (1.0)22 (2.9)139 (3.7)	Alpha-adrenergic blocker	486 (8.4)	76 (6.0)	49 (6.4)	361 (9.6)
Insulin314 (5.4)25 (2.0)14 (1.8)275 (7.3)Glitazone225 (3.9)27 (2.1)15 (2.0)183 (14.8)Cox-2 inhibitor196 (3.4)15 (1.2)36 (4.7)145 (3.8)Cholinesterase Inhibitor256 (4.4)23 (1.8)20 (2.6)213 (5.6)Tricyclic Antidepressant174 (3.0)13 (1.0)22 (2.9)139 (3.7)	Sulfonylurea	412 (7.1)	47 (3.7)	23 (3.0)	342 (9.1)
Glitazone 225 (3.9) 27 (2.1) 15 (2.0) 183 (14.8) Cox-2 inhibitor 196 (3.4) 15 (1.2) 36 (4.7) 145 (3.8) Cholinesterase Inhibitor 256 (4.4) 23 (1.8) 20 (2.6) 213 (5.6) Tricyclic Antidepressant 174 (3.0) 13 (1.0) 22 (2.9) 139 (3.7)	Insulin	314 (5.4)	25 (2.0)	14 (1.8)	275 (7.3)
Cox-2 inhibitor 196 (3.4) 15 (1.2) 36 (4.7) 145 (3.8) Cholinesterase Inhibitor 256 (4.4) 23 (1.8) 20 (2.6) 213 (5.6) Tricyclic Antidepressant 174 (3.0) 13 (1.0) 22 (2.9) 139 (3.7)	Glitazone	225 (3.9)	27 (2.1)	15 (2.0)	183 (14.8)
Cholinesterase Inhibitor 256 (4.4) 23 (1.8) 20 (2.6) 213 (5.6) Tricyclic Antidepressant 174 (3.0) 13 (1.0) 22 (2.9) 139 (3.7)	Cox-2 inhibitor	196 (3.4)	15 (1.2)	36 (4.7)	145 (3.8)
Tricyclic Antidepressant 174 (3.0) 13 (1.0) 22 (2.9) 139 (3.7)	Cholinesterase Inhibitor	256 (4.4)	23 (1.8)	20 (2.6)	213 (5.6)
	Tricyclic Antidepressant	174 (3.0)	13 (1.0)	22 (2.9)	139 (3.7)

Table 1. Cont.

	No. of Pairs of Coexisting Chronic Conditions ^a			
	Total	0 Condition Pairs(N = 1273)	1–2 Condition Pairs (N = 763)	3+ Condition Pairs(N = 3779)
5-a-reductase inhibitor	244 (4.2)	47 (3.7)	16 (2.1)	181 (4.8)
Serotonin–norepinephrine reuptake inhibitor	155 (2.7)	10 (0.8)	14 (1.8)	131 (3.5)
Selective estrogen-receptor modulator	93 (1.6)	13 (1.0)	13 (1.7)	67 (1.8)

^aThe number of pairs of the 14 most common coexisting chronic conditions experienced by the MCBS cohort for which there is at least one prescription medication recommended by the national specialty organization for most individuals with the conditions. Those with zero condition pairs had only one of the 14 chronic conditions.

^bPrescription medications given a GRADE A or B or equivalent level of recommendations by the national specialty organization guideline for one or more of the 14 chronic conditions. All medications recommended by a guideline are included if evidence grading not included in the guideline. Prescription medications used by at least 2% of study participants are included. For example, fibrates, nicotinic acid, and bile sequestrants are mentioned in guidelines for hyperlipidemia but the prevalence of use was low. Nonprescription medications (e.g. aspirin, nonsteroidal anti-inflammatory drugs, H₂ receptor antagonists) were not available.

^cAmong the 2353 beta-blocker users, 1807 used a selective beta-blocker, 267 used a nonselective beta-blocker, and 279 used an alpha/beta-blocker.

^dProton pump inhibitors are likely underestimated because does not include over the counter.

^eAmong the 1375 calcium channel blocker users, 1142 used a dihydropyridine calcium channel blocker and 233 used a nondihydropyridine (primarily diltiazem; verapamil was used by <2% of the study population)

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antidepressants in persons with CAD). For all other study medications, we considered a potential therapeutic competition to be present if: 1) adverse effects on a coexisting condition were mentioned in any of the national disease guidelines reviewed; [16–29] or 2) evidence of adverse effects on the coexisting condition was reported in a systematic review or at least two studies published since 2000. [9–11;31–63] To identify the most common situations of potential therapeutic competition, we limited this search to medications reported by at least 2% of participants.

Statistical Analysis

Frequencies and percentages were calculated to describe the characteristics of the sample and the prevalence of chronic conditions and medication classes. Cross-sectional statistical weights, developed by Westat Inc. for MCBS, were used to estimate the number of persons in the U.S. population with potential therapeutic competition as represented by cohort members.[12,13,64] SAS version 9.3 software (SAS Institute Inc. 2011. SAS/STAT 9.3 User's Guide. Cary, NC) was used to compute risk differences and 95% confidence intervals between individuals with and without the competing conditions.

Results

Thirty four percent of the 5,815 participants were age 80 years and over; 56.4% were women (Table 1). Hypertension (68.4%), hyperlipidemia (59.6%), and osteoarthritis (49.1%) were the most common chronic conditions. The most frequently reported prescription medications included angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) (44.0%) and statins (45.7%); 40.5% used beta-blockers. Among betablocker users, 76.8% received selective beta-blockers (Table 1). The prevalence of use of the 27 medication classes did not change from 2008 through 2010 except for an increase in statin use (42.4% in 2008; 46.5% in 2009; and 48.5% in 2010) and a decrease in bisphosphonate use (12.6% in 2008;13.8% in 2009; and 9.9% in 2010).

Among participants, 4542 (78.1%) suffered from at least one pair of coexisting study chronic conditions; 65.0% of participants had 3 or more pairs and 31.4% had at least 10 pairs of the study conditions. Increasing numbers of chronic condition pairs were associated with older age, greater dependencies in basic ADLs, and higher frequency of hospitalizations in the past year (Table 1).

Prevalence of Potential Therapeutic Competition

Based on the criteria described in the Methods, 15 of the 27 medication classes (55.5%) recommended for one of the study conditions may adversely affect other study conditions. Among the 91 possible pairs of the study chronic conditions, 25 (27.5%) have at least one potential therapeutic competition. The prevalence of these chronic condition pairs and the frequency of use of medications that may adversely affect one or the other of the conditions are shown in Table 2. For example, among the 846 participants with coexisting hypertension and COPD, representing over 3.5 million older Americans, 16.2% used a nonselective betablocker or alpha/beta-blocker that might exacerbate their COPD while 39.6% received a beta agonist that could worsen their hypertension (Table 2). Among the estimated 1.2 million older adults with diabetes and heart failure, 27.3% received an alpha/ beta-blocker that may cause orthostasis or syncope in those predisposed because of coexisting diabetic autonomic neuropathy; 10.3% used a glitazone that could exacerbate their heart failure.

Among the 5,815 participants, 1,313 (22.6%) received at least one medication for a condition that may worsen a coexisting condition and therefore had at least one of the potential therapeutic competitions listed in Table 2. Of these individuals, 286 (4.9%) had two, while 468 (8.1%) had three or more pairs of coexisting conditions in which a medication received for one of their conditions may adversely affect the other condition.

Medication Use in Participants with and without a Competing Condition

For each of the medications recommended by national disease guidelines for the 14 conditions, we determined whether the frequency of use differed by whether participants had a competing condition (Table 3). For only 6 of the 37 condition pairs (16.2%), were participants with the competing condition less likely (i.e. 95% CI for risk difference excluded 1) to receive the potentially offending medication than participants without the competing condition. For example, among individuals with atrial fibrillation, 5.8% of individuals with concomitant COPD used a nonselective beta-blocker versus 10.7% of those without COPD (risk difference **Table 2.** Prevalence of Potential Therapeutic Competition in Common Co-existing ChronicConditions among Community-living Persons in the U.S. Aged 65 and Older (N = 5815).

Competing Chronic Conditions ^a	No. Participants (%)	Population Estimates ^b	Competing Medication (%) ^c
Hypertension and osteoarthritis	2309 (39.7)	9,719,789	COX-2 inhibitor (5.3%)
Hypertension and diabetes	1384 (23.8)	6,086,828	Alpha/beta-blocker (11.4%)
Hypertension and Chronic obstructive pulmonary disease	846 (14.6)	3,812,031	Nonselective beta-blocker or alpha/beta- blocker (16.2%) Beta-agonists (39.6%) Corticosteroids (43.0%)
Diabetes and coronary artery disease ^d	601 (10.3)	2,538,530	Alpha/beta-blocker (19.1%) ^e Sulfonylurea (23.3%) Glitazone (12.3%)
Coronary artery disease and Chronic obstructive pulmonary disease	433 (7.5)	1,706,201	Nonselective beta-blocker or alpha/beta- blocker (22.2%) Beta-agonists (37.0%)
Coronary artery disease and GERD/PUD	469 (8.1)	1,907,220	Clopidogrel (27.1%)
Hypertension and depression	370 (6.4)	1,695,472	Serotonin–norepinephrine reuptake inhibitor (15.4%)
Heart failure and osteoarthritis	421 (7.2)	1,568,261	COX-2 inhibitor (2.4%)
Chronic obstructive pulmonary disease and GERD/PUD	364 (6.3)	1,523,022	Corticosteroid (46.7%)
Diabetes and Chronic obstructive pulmonary disease	353 (6.1)	1,518,139	Corticosteroid (43.1%)
Diabetes and heart failure	300 (5.2)	1,182,354	Alpha/beta-blocker (27.3%) Glitazone (10.3%)
Heart failure and Chronic obstructive pulmonary disease	307 (5.3)	1,186,652	Nonselective beta-blocker or alpha/beta- blocker (29.6%)
Diabetes and atrial fibrillation	236 (4.1)	940,460	Alpha/beta-blocker (13.1%)
Diabetes and Benign prostatic hypertrophy	202 (3.5)	876,471	Alpha-adrenoreceptor antagonist (45.5%)
Chronic obstructive pulmonary disease and atrial fibrillation	225 (3.9)	875,313	Nonselective beta-blocker or alpha/beta- blocker (22.2%) Beta agonists (38.2%)
Osteoporosis and GERD/PUD	220 (3.8)	865,530	Proton pump inhibitor (64.1%) ^f Bisphosphonate (40.9%)
Atrial fibrillation and GERD/PUD	217 (3.7)	829,600	Warfarin (53.9%) Clopidogrel (12.0%)
Coronary artery disease and depression	150 (2.6)	658,174	Tricyclic antidepressant (6.0%)
Diabetes and depression	142 (2.4)	645,978	Tricyclic antidepressant (6.3%)
Osteoporosis and Coronary artery disease	155 (2.7)	587,090	COX-2 inhibitor (3.2%)
Chronic obstructive pulmonary disease and osteoporosis	149 (2.6)	568,684	Corticosteroid (40.9%)
Diabetes and osteoporosis	127 (2.2)	517,475	Glitazone (12.6%)
Atrial fibrillation and osteoporosis	102 (1.8)	366,324	Bisphosphonate (40.2%)
Atrial fibrillation and depression	79 (1.4)	331,667	Tricyclic antidepressant (2.5%)
Atrial Fibrillation and dementia	79 (1.4)	279,358	Cholinesterase inhibitor (36.7%)

Abbreviations: GERD/PUD, gastroesophageal reflux disease or peptic ulcer disease.

^aThe most common pairs of coexisting chronic conditions listed in **Table 1** for which there is at least one medication (listed in **Table 1**) recommended by the national specialty organization guidelines that may worsen the other condition in the pair (see Methods for how these competing medications were identified). Of the guideline recommended medications, only prescription medications used by at least 2% of the study sample are included.

^bEstimated number of persons in U.S. with the competing chronic conditions.

^cPercent of participants with the coexisting conditions who use the potentially competing medication, that is, a medication recommended for one chronic condition that may worsen the coexisting chronic condition. See Methods for selection criteria for competing medications.

^dCoronary artery disease includes history of myocardial infarction, acute coronary syndrome, or angina.

^eManifestations of diabetic autonomic neuropathy, such as orthostasis, may be worsened by alpha/beta-blockers.

^fProton pump inhibitors use is likely underestimated because nonprescription use of proton pump inhibitors not included in the dataset.

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-4.9; 95% CI -8.9, -0.9). For 67.6% of condition pairs (25/37), there was no difference in the frequency of use of a recommended medication between individuals who had, and those who did not have, the competing condition (Table 3). For five combinations of conditions (13.5%), participants who had a competing condition were more likely to receive the potentially harmful medication than participants without the competing condition (Table 3). For instance, 17.3% of individuals with coexisting atrial fibrillation and COPD received an alpha/beta-blocker that may exacerbate their

COPD versus 9.4% of individuals with a rial fibrillation but no COPD (risk difference 8.0; 95% CI 2.4,13.5).

Discussion

In this nationally representative sample of older adults in the U.S., over 20% took at least one medication that could adversely affect another of their chronic conditions. Because MCBS is a nationally representative sample, study estimates reflect the prevalence of potential therapeutic competition in the older U.S. population. The frequency of potential therapeutic competition is

Table 3. Frequency of Use of a Recommended Medication for a Chronic Condition According to Presence of Competing Conditions among Community-living Persons in the U.S. Aged 65 and Older (N = 5815).

		Use of Recommended Medication when:			
Indicated Condition ^a	Competing Condition	Competing condition present ^b	Competing condition absent ^c	Risk Difference (95% Confidence interval)	
		n/N (%)			
		Alpha/Beta-blocker ^d [31.3	2]		
Hypertension	Diabetes	158/1384 (11.4)	163/2592 (6.3)	5.1 (3.2, 7.1)	
Hypertension	COPD	98/846 (11.6)	223/3130 (7.1)	4.5 (2.1, 6.8)	
Coronary artery disease	Diabetes	115/601 (19.1)	97/868 (11.2)	8.0 (4.2, 11.7)	
Coronary artery disease	COPD	78/433 (18.0)	134/1036 (12.9)	5.1 (0.9, 9.2)	
Heart Failure	Diabetes	82/300 (27.3)	81/366 (22.1)	5.2 (-1.4, 11.8)	
Heart Failure	COPD	82/307 (26.7)	81/359 (22.6)	4.1 (-2.4, 10.7)	
Atrial fibrillation	Diabetes	31/236 (13.1)	59/533 (11.1)	2.1 (-3.0, 7.1)	
Atrial fibrillation	COPD	39/225 (17.3)	51/544 (9.4)	8.0 (2.4, 13.5)	
		Nonselective Beta-blocker	^d [33.34]		
Hypertension	COPD	41/846 (4.9)	207/3130 (6.6)	-1.8 (-3.5, -0.1)	
Coronary artery disease	COPD	19/433 (4.4)	68/1036 (6.6)	-2.2 (-4.6, 0.3)	
Atrial Fibrillation	COPD	13/225 (5.8)	58/544 (10.7)	-4.9 (-8.9, -0.9)	
		Beta-agonist ^d [35–37]			
COPD	Hypertension	335/846 (39.6)	72/168 (42.9)	-3.3 (-11.4, 4.9)	
COPD	CAD	160/433 (37.0)	247/581 (42.5)	-5.6 (-11.6, 0.5)	
COPD	Atrial Fibrillation	86/225 (38.2)	321/789 (40.7)	-2.5 (-9.7, 4.8)	
		Corticosteroid			
COPD	Hypertension	364/846 (43.0)	83/168 (49.0)	-64(-146,19)	
COPD	Diabetes	152/353 (43.1)	295/661 (44.6)	-16(-80, 48)	
COPD	GERD/PUD	170/364 (46.7)	277/650 (42.6)	41 (-23, 105)	
COPD	Osteoporosis	61/149 (40.9)	386/865 (44.6)	-37(-123, 49)	
	osteoporosis	Cox-2 inhibitor ^d [9.44–46]	500,005 (110)	5 (
Osteoarthritis	Hypertension	123/2309 (5.3)	34/548 (6 2)	-09(-3113)	
Osteoarthritis	CAD	37/875 (4.2)	120/1982 (6.0)	-18(-35, -01)	
Osteoarthritis	Heart failure	10/421 (2.4)	147/2436 (6.0)	-37(-54, -19)	
	incure fundre	Sulfonvlurea ^d [51,52]	117/2100 (0.0)	5.7 (5.1, 1.5)	
Diabetes	Coronary artery disease	140/601 (23.3)	214/929 (23.0)	0.3 (-4.1, 4.6)	
		Glitazone ^d [10,47–50]			
Diabetes	Coronary artery disease	74/601 (12.3)	118/929 (12.7)	-0.4 (-3.8, 3.0)	
Diabetes	Heart failure	31/300 (10.3)	161/1230 (13.1)	-2.8 (-6.7, 1.2)	
Diabetes	Osteoporosis	16/127 (12.6)	176/1403 (12.5)	0.1 (-6.0, 6.1)	
		Clopidogrel ^d [42,43]			
Atrial fibrillation	GERD/PUD	26/217 (12.0)	66/552 (12.0)	0.0 (-5.1, 5.1)	
Coronary artery disease	GERD/PUD	127/469 (27.1)	261/1000 (26.1)	1.0 (-3.9, 5.8)	
, ,		Warfarin	. ,		
Atrial fibrillation	GERD/PUD	117/217 (53.9)	322/552 (58.3)	-4.4 (-12.2, 3.4)	
		Serotonin norepinephrine	reuptake inhibitor ^d [56,57]		
Depression	Hypertension	57/370 (15.4)	13/72 (18.1)	-2.7 (-12.3, 7.0)	
		Tricyclic antidepressant ^d			
Depression	Atrial fibrillation	2/79 (2.5)	28/363 (7.7)	-5.2 (-9.6, -0.8)	
Depression	Coronary artery disease	9/150 (6.0)	21/292 (7.2)	-1.2 (-6.0, 3.6)	
Depression	Diabetes	9/142 (63)	21/300 (7.0)	-0.7(-56,43)	
	Diabetes	ענט) אדר זי	21/300 (7.0)	(J.) (J.)	

Table 3. Cont.

Indicated Condition ^a		Use of Recommended Medication when:			
	Competing Condition	Competing condition present ^b	Competing condition absent ^c	Risk Difference (95% Confidence interval)	
		n/N (%)			
		Cholinesterase inhibitor ^d [59–61]			
Dementia	Atrial fibrillation	29/79 (36.7)	141/265 (53.2)	-16.5 (-28.7, -4.3)	
		Alpha-adrenergic antagon	ist ^d [26,62,63]		
Benign prostatic hypertrophy	Diabetes	92/202 (45.5)	156/417 (37.4)	8.1 (-0.2, 16.4)	
		Proton pump inhibitor ^d [5	3-55]		
GERD/PUD Osteoporos	Osteoporosis	141/220 (64.1)	598/993 (60.2)	3.9 (-3.2, 10.9)	
		Bisphosphonate ^d [38–41]			
Osteoporosis	GERD/PUD	90/220 (40.9)	208/416 (50.0)	-9.1 (-17.2, -1.0)	
Osteoporosis	Atrial fibrillation	41/102 (40.2)	257/534 (48.1)	-7.9 (-18.4, 2.5)	

Abbreviations: COPD, chronic obstructive pulmonary disease; GERD/PUD, gastroesophageal reflux disease or peptic ulcer disease;

^aThe first chronic condition listed for a pair is the condition for which the medication is recommended by the national specialty organization guideline; the second chronic condition in a pair is the coexisting condition that may be worsened with the medication (i.e. competing condition).

^bThe numerator is the number of participants with the indicated condition who received the recommended medication. The denominator is the number of participants who had the indicated condition who also had the competing condition.

^cThe numerator is the number of participants with the indicated condition who received the recommended medication. The denominator is the number of participants who had the indicated condition but did not have the competing condition.

^dNumbers in brackets are the reference of the studies supporting the possible adverse effect of the medication class on the competing condition. doi:10.1371/journal.pone.0089447.t003

likely related to the high prevalence of multi-morbidity in older adults combined with the focus of disease guidelines on medication benefits for individual conditions.

A few medications such as non-selective beta blockers, Cox 2 inhibitors, and bisphosphonates were used less frequently in those with, than without, a competing condition suggesting that clinicians did consider adverse effects on coexisting conditions in their clinical decision-making. In many cases, however, the medications were used at least as often in those who had the competing condition than in those who did not. The aim of this study was to identify situations of potential therapeutic competition and estimate the frequency of such situations in older adults. It remains to be determined how frequently adverse clinical outcomes occur in these situations.

Recent studies in other developed countries report similar rates of use of study medication classes as in the U.S.[65,66] Renin angiotensin system medications, for example, were used by 44%, 26%, and 32% of community-living older adults in the U.S., Sweden, and Finland respectively. The comparable percentages were 40%, 33%, and 53% for beta-blockers, and 24%, 17%, and 23% for calcium channel blockers. These comparisons suggest that potential therapeutic competition may be a common concern across developed countries with growing populations of older adults with multiple chronic conditions.

Because Medicare HMO (Medicare Advantage) patients are healthier than their age-matched traditional Medicare beneficiaries, their exclusion may have resulted in overestimating the prevalence of potential therapeutic competition. Although there is no gold standard for determining what medications communityliving older adults actually take, the direct observation of the medications in the home has been shown to be more accurate and reliable than other methods such as medication interview, medication lists, or "brown bag" in the clinic.[67] For medications used for multiple conditions, we could not be sure for which condition a medication was prescribed although we do know that participants had the study condition and received the medication. Because the data were unavailable, we were unable to assess the prevalence of potential therapeutic competition for NSAIDS, aspirin, and other nonprescription medications. For conditions in which medication recommendations depend on type, severity, or stage (e.g. heart failure), we lacked the data to determine if individuals met criteria for this type or stage.

The prevalence of individual chronic conditions and combination of conditions vary depending on criteria for diagnosis and method of ascertainment.[2] The limitations of Medicare claims data for ascertaining chronic conditions have been well-chronicled with conditions that provide more lucrative reimbursement and require more frequent medical attention being more thoroughly reported.[6,68,69] We used two years of inpatient and outpatient claims to ascertain chronic conditions, thus increasing the likelihood of ascertainment. The prevalence for all of the conditions except dementia and depression were similar to those reported on the Center for Medicare and Medicaid's ' Chronic Conditions Dashboard.[70] The underestimate of dementia and depression in claims data has been reported in previous studies.[71] The underreporting of some conditions suggests that we may have underestimated the frequency of some pairs of competing conditions. However, as we matched medications to chronic conditions, the likelihood is high that the condition was present when there were claims.

The medications were ascertained from 2008–2010; patterns of use may have changed for some medications since then although we detected few changes over the three study years. Other than subclasses of beta-blockers and calcium channel blockers, we combined all medications within a class; effects may vary within a class. Furthermore, the effects of medications vary by route. The effect of oral glucocorticoids on osteoporosis or PUD, for instance, is different than the effect of inhaled glucocorticoids.

Some of the therapeutic competitions included in this study, such as warfarin in individuals with atrial fibrillation and PUD or

glitazones in individuals with diabetes and heart failure, are well established. Determining from the available evidence whether the other medications qualified for possible therapeutic competition was challenging. There is no standard for determining harm of medications that parallels attempts to ascertain benefits. Any approach, therefore, will have limitations. An inherent problem is that adverse effects are not as carefully assessed as benefits. Clinical trials focus on evaluating benefit of medications on the indicated disease in relatively homogenous populations of younger populations with fewer chronic conditions than clinical populations of older adults. RCTs thus likely underestimate the frequency of adverse effects in clinical populations. On the other hand, observational studies, while providing evidence from actual clinical practice, are prone to bias. We attempted to be systematic and limited the current report to medications with at least two studies showing an adverse effect on the competing conditions. For some medications, the evidence remains conflicting across studies. For many of the medications that met criteria for inclusion, there were also reports that did not suggest harm. The same is true for well accepted evidence of benefits for many medications. We included medications if the preponderance of evidence supports potential therapeutic competition, such as nonselective β -Blockers with COPD. However, we did not include situations which are more uncertain such as β-Blockers with depression, nondihydropyridine CCBs in heart failure, or statins with dementia. [72] Unfortunately, because adverse consequences of medications have not been consistently measured, it currently is not possible to assess the strength of the evidence for harm in the way benefits are assessed.

The list of potentially competing conditions reported in this study is not exhaustive. To focus on the most common clinical situations, we investigated only medications used by at least 2% of participants and chronic conditions with a prevalence of at least 5%. To introduce the concept of therapeutic competition, we limited the study to pairs of coexisting conditions. Patients with MCC, however, have combinations of three, four, and more chronic conditions. Eventually, the effect of treatments for various combinations of conditions will need to be explored.

While we studied one potential mechanism of adverse medication effect in older adults with multi-morbidity, medications can adversely affect individuals through several other mechanisms. For example, many medications contribute to geriatric syndromes such as falls and delirium. Chronic kidney disease can exacerbate the adverse consequences of several medications. Treatment for one condition may mask the adverse effects of treatment of another condition such as β -blockers masking the hypoglycemic effects of anti-diabetic agents. Furthermore, medications themselves cause adverse effects such as dizziness, fatigue, and anorexia in older adults.[73]

The implications of our findings are several. We quantified the magnitude of these tradeoff decisions that face clinicians, although we cannot comment on the appropriateness of these decisions. It is likely that many of the individuals experienced net benefit from the medications despite the presence of a competing condition. The presence of competing conditions does not imply contraindication of the medication but rather the need for clinicians to weigh the effects of medications on each of a patient's conditions,

References

- Anderson G (2010) Chronic care: Making the case for ongoing care. Princeton, NJ: Robert Woods Johnson Foundation. Available: http://www.rwjf.org/files/ research/50968chronic.care.chartbook.pdf. Accessed 2013 Oct 28.
- Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, et al. (2011) Aging with multimorbidity: A systematic review of the literature. Ageing Res Rev 10: 430–439.

not just the condition for which it is recommended. Unfortunately, such evidence is lacking currently for many medications and chronic conditions. Studies of medication effects should include equally rigorous ascertainment of harms as well as benefits, not just on the disease of interest but on commonly co-existing conditions.

Evaluating the benefits and harms of cross-disease treatment regimens in individuals with common combinations of chronic conditions should be a focus of comparative effectiveness research as should identification of effective treatments that circumvent therapeutic competition. The current approach of adding a medication, such as adding a PPI to clopidogrel or corticosteroids to reduce the risk of gastrointestinal bleeding in those with PUD, may unintentionally substitute one therapeutic competition for another while adding to polypharmacy.

Currently, few guidelines developed by national specialty organizations address the harms and benefits of recommended medications in individuals with competing conditions or consider co-occurring conditions when making treatment recommendations. Recent reports suggest how guidelines could be adapted and presented in formats more useful for decision-making for patients with multi-morbidity.[74,75] At the least, guideline developers should consider how commonly coexisting conditions should influence medication recommendations.[74,75] Eventually, guideline developers and clinicians hopefully will be able to recommend medications based on evidence of absolute benefit versus harm for cross-disease universal health outcomes that are of greatest priority to individual patients such as survival, symptom burden, and function.[76]

Given the large number of potential therapeutic competitions, an evidence-based rating system that weighs the net benefit or harm of medications in persons with the coexisting conditions would help aggregate and prioritize the large amount of information for use in decision-making. The approach used to develop the Beers Criteria might serve as a model for evaluating and translating the evidence into clinically useful guidelines.[77] These evidence-based guidelines could also inform development of quality indicators of appropriate prescribing for patients with multiple chronic conditions.[78] Electronic health records, which currently check for only interactions among medications, should also include a check for interactions between medications and coexisting competing conditions.

One fifth of older adults are prescribed a medication that may adversely affect a coexisting condition. Determining the likelihood of net benefit or harm in these situations is a research and clinical priority. In addition to considering the effect of medications on coexisting conditions, heightened awareness of therapeutic competition should trigger systematic attention to identifying strategies for avoiding poor clinical outcomes in individuals with competing chronic conditions.

Author Contributions

Conceived and designed the experiments: MT SJL. Performed the experiments: SJL GM PC MT. Analyzed the data: GM PC. Wrote the paper: MT GM DSHL SJL PC MG.

- Wolff JL, Starfield B, Anderson G (2002) Prevalence, expenditures, and complications of multiple chronic diseases in elderly. Arch Intern Med 162: 2269–2276.
- Marengoni A, Rizzuto D, Wang H-X, Winblad B, Fratiglioni L (2009) Patterns of chronic multimorbidity in the elderly population. J Am Geriatr Soc 57: 225– 230.

- Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, et al. (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380: 37–43.
- Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, et al. (2004) Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes 2: 51.
- Boyd CM, Darer J, Boult C, Fried LP, Boult L, et al. (2005) Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 294: 716–724.
- Tinetti ME, Bogardus ST Jr., Agostini JV (2004) Potential pitfalls of diseasespecific guidelines for patients with multiple diseases. N Engl J Med 35: 2870– 2874.
- Graham DJ (2006) COX-2 Inhibitors, Other NSAIDs, and cardiovascular risk: The seduction of common sense. JAMA 296: 1653–1656.
- Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 356: 2457–2471.
- Winklmayer WC, Setoguchi S, Levin R, Solomon DH (2008) Comparisons of cardiovascular outcomes in elderly patients with diabetes who initiated Rosiglitazone vs Pioglitazone therapy. Arch Intern Med 168: 2368–2375.
- Medicare Current Beneficiary Survey (MCBS) (2012) Baltimore, M.D.: Centers for Medicare & Medicaid Services. Available: http://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/index.html. Accessed 2013 Oct 28.
- Medicare Current Beneficiary Survey (MCBS) (2012) Available: http://www. resdac.org/cms-data/file-family/Medicare-Current-Beneficiary-Survey-MCBS. Accessed 2013 Oct 28.
- Healthcare Cost and Utilization Project (HCUP) (2012) Clinical Classification System. Rockville, M.D.: Agency for Healthcare Research and Quality. Available: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed 2013 Oct 28.
- World Health Organization (2012) The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). Norway: Norwegian Institute of Public Health. Available: http://www.who.int/classifications/ atcddd/en. Accessed 2013 Oct 28.
- 16. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2002) Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106: 3143–3421.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 289: 2560–2572.
- American College of Rheumatology Subcommittee on Osteoarthritis Guidelines (2011) Recommendations for the medical management of osteoarthritis of the hip and knee. Atlanta, G.A.: American College of Rheumatology. Available: http://www.rheumatology.org/practice/clinical/guidelines/oa-mgmt.asp. Accessed 2013 Oct 28.
- Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, et al. (2011) AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 124: 2458–2473.
- Garber JR, Cobin RH, Ghaib H, Hennessey JV, Klein I, et al. (2012) Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid 22: 1200–1235.
- 21. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, et al. (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32: 193–203.
- 22. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, et al. (2011) 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 123: 104–123.
- National Osteoporosis Foundation (2010) Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation.
- American Thoracic Society/European Respiratory Society Task Force (2004) Standards for the diagnosis and management of patients with COPD. Version 1.2. New York: American Thoracic Society [updated 2005 September 8]. Available: http://www.thoracic.org/go/copd. Accessed 2013 Oct 28.
- Kenneth R. DeVault KR, Castell DO (2005) Diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 100: 190–200.
- McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, et al. (2010) American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH). Available: http://www.auanet.org/common/pdf/ education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf. Accessed 2013 Oct 28.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, et al. (2009) 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: A report of the American

College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 53: e1–90.

- Work Group on Major Depressive Disorder (2011) Practice guideline for the treatment of patients with major depressive disorder. Third Edition. Arlington, V.A.: American Psychiatric Publishing. Available: http://psychiatryonline.org/ content.aspx?bookid = 28§ionid = 1667485. Accessed 2013 Oct 28.
- 29. Work Group on Alzheimer's Disease and Other Dementias (2011) Practice guidelines for the treatment of patients with Alzheimer's disease and other dementias. Second Edition. Arlington, V.A.: American Psychiatric Publishing. Available: http://psychiatryonline.org/content.aspx?bookid = 28§ionid = 1679489. Accessed 2013 Oct 28.
- GRADE Working Group. (2010) Grading the quality of evidence and the strength of recommendations. The GRADE working Group. Available: http:// www.gradeworkinggroup.org/intro.htm. Accessed 2013 Oct 28.
- Galatius S, Gustafsson F, Atar D, Hildebrandt PR (2004) Tolerability of β-Blocker Initiation and Titration with Bisoprolol and Carvedilol in Congestive Heart Failure – A Randomized Comparison. Cardiology 102: 160–165.
- Düngen HD, Apostolovic S, Inkrot S, Tahirovic E, Topper A, et al. (2011) Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. Eur J Heart Fail 13: 670–680.
- Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, et al. (2011) Heart failure and chronic obstructive pulmonary disease: the quandary of Betablockers and Beta-agonists. J Am Coll Cardiol 57: 2127–2138.
- 34. Brooks TW, Creekmore FM, Young DC, Asche CV, Oberg B, et al. (2007) Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking beta-blockers. Pharmacotherapy 27: 684–690.
- Hodgkinson JA. Taylor CJ. Hobbs FD (2011) Predictors of incident atrial fibrillation and influence of medications: a retrospective case-control study. Brit J Gen Practice 61: e353–361.
- Au DH, Curtis JR, Every NR, McDonell MB, Fihn SD (2002) Association between inhaled beta-agonists and the risk of unstable angina and myocardial infarction. Chest 121: 846–851.
- Au DH, Lemaitre RN, Curtis JR, Smith NL, Psaty BM (2000) The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists. Am J Respir Crit Care Med 161: 827–830.
- Yoon KL, Jeevanantham V, Singh S (2009) Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. Drug Safety 32: 219–228.
- de Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, et al. (1996) Esophagitis associated with the use of alendronate. N Engl J Med 335: 1016– 1021.
- Ettinger B, Pressman A, Schein J, Chan J, Silver P, et al. (1998) Alendronate use among 812 women: prevalence of gastrointestinal complaints, noncompliance with patient instructions, and discontinuation. J Manag Care Pharm 4: 488–492.
- Penning-van Beest FJ, Goettsch WG, Erkens JA, Herings RM (2006) Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. Clin Ther 28: 236–242.
- Hsu PI, Lai KH, Liu CP (2011) Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. Gastroenterol 140: 791–798.
- Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, et al. (2006) Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. BMJ 333: 726.
- 44. Ray WA, Varas-Lorenzo C, Chung CP, Castellsague J, Murray KT, et al. (2009) Garcia-Rodriguez LA. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. Circ Cardiovasc Qual Outcomes 2: 155–163.
- Solomon DH, Schneeweiss S, Levin R, Avorn J (2004) Relationship Between COX-2 Specific Inhibitors and Hypertension. Hypertension 44: 140–145.
- 46. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, et al. (2005) The Effects of Cyclooxygenase-2 Inhibitors and Nonsteroidal Anti-inflammatory Therapy on 24-Hour Blood Pressure in Patients With Hypertension, Osteoarthritis, and Type 2 Diabetes Mellitus. Arch Intern Med 165: 161–168.
- Wang C-H, Weisel RD, Liu PP, Fedak PWM, Verma S (2003) Glitazones and Heart Failure: Critical Appraisal for the Clinician. Circulation 107: 1350–1354.
- Bennett WL, Odelola OA, Wilson LM, Bolen S, Selvaraj S, et al. (2012) Evaluation of guideline recommendations on oral medications for type 2 diabetes mellitus: a systematic review. Ann Intern Med 156: 27–36.
- Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, et al. (2008) PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 299: 1561–1573.
- Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M (2010) Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. Diabetes Obes Metab. 12: 716–721.
- Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, et al. (2012) Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab 14: 803–809.
- Eurich DT, McAlister FA, Blackburn DF, Majumdar SR, Tsuyuki RT, et al. (2007) Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. BMJ 335: 497.

- 53. Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, et al. (2010) Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. Arch Intern Med 170: 765–771.
- Lau YT, Ahmed NN (2012) Fracture risk and bone mineral density reduction associated with proton pump inhibitors. Pharmacotherapy 32: 67–79.
- Yang YX, Lewis JD, Epstein S, Metz DC (2006) Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 296: 2947–2953.
- Johnson EM, Whyte E, Mulsant BH, Pollock BG, Weber E, et al. (2006) Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. Am J Geriatr Psychiatry 14: 796–802.
- Degner D, Grohmann R, Kropp S, Ruther E, Bender S, et al. (2004) Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry 37 Suppl 1:S39–45.
- Cohen HW, Gibson G, Alderman MH (2000) Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. Am J Med 108: 2–8.
- Hernandez RK, Farwell W, Cantor MD, Lawler EV (2009) Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the veterans affairs new England healthcare system. J Am Geriatr Soc 57: 1997–2003.
- Park-Wyllie LY, Mamdani MM, Li P, Gill SS, Laupacis A, et al. (2009) Cholinesterase inhibitors and hospitalization for bradycardia: a populationbased study. PLoS Medicine 6: e1000157.
- Gill SS, Anderson GM, Fischer HD, Bell CM, Normand SL, et al. (2009) Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. Arch Intern Med 169: 867–873.
- 62. Chrischilles E, Rubenstein L, Chao J, Kreder KJ, Gilden D, et al (2001) Initiation of nonselective alphal-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: a retrospective cohort study. Clinical Therapeutics 23: 727–743.
- 63. Kirby R, Roehrborn C, Boyle P, Bartsch G, Jardin A, et al. (2003) Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology 61: 119.
- Lo A, Chu A, Apodaca R (2002) Redesign of the Medicare Current Beneficiary survey sample. Proceedings of the Survey Research Section of the American Statistical Association. 2139–44.
- Johnell K, Fastbom J (2012) Comparison of Prescription Drug Use between Community-Dwelling and Institutionalized Elderly in Sweden. Drugs Aging 29: 751–758.

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- Jyrkkä J, Vartiainen L, Hartikainen S, Sulkava R, Enlund H (2006) Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+Study. Eur J Clin Pharmacol 62: 151–158.
- Yang JC, Tomilinson F, Naglie G (2001) Medication lists for elderly patients: Clinic-derived versus in-home inspection and interview. J Gen Intern Med 16: 112–115.
- Klabunde CN, Harlan LC, Warren JL (2006) Data sources for measuring comorbidity. A comparison of hospital records and Medicare claims data for cancer patients. Med Care 44: 921–928.
- Lentine KL, Schnitzler MA, Abbott KC, Bramesfeld K, Buchanan PM, et al. (2009) Sensitivity of billing claims for cardiovascular disease events among kidney transplant recipients. Clin J Am Soc Nephrol 4: 1213–1221.
- (2013) Chronic Conditions Data Warehouse. Chronic Conditions Dashboard. Available: http://www.ccwdata.org/web/guest/interactive-data/chronicconditions-dashboard. Accessed 2013 Oct 28.
- Noyes K, Liu H, Lyness JM, Friedman B (2011) Medicare beneficiaries with depression: Comparing diagnoses in claims data with the results of screening. Psychiatric Services 62: 1159–1166.
- Padala KP, Padala PR, McNeilly DP, Geske JA, Sullivan DH, et al. (2012) The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's Dementia: A prospective withdrawal and rechallenge study. Am J Geriatr Pharmacother. 10(5):298–302.
- Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, et al. (2003) Incidence and Preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting. JAMA 289: 1107–1116.
- 74. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity (2012) Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. J Am Geriatr Soc 60: e1–e25.
- Guthrie B, Payne K, Alderson P, McMurdo MET, Mercer SW (2012) Adapting clinical guidelines to take account of multimorbidity BMJ 345: e6341.
- Tinetti ME, McAvay G, Chang SS, Newman AB, Fitzpatrick AL, et al. (2011) Contribution of multiple chronic diseases to universal health outcomes in older adults. J Am Geriatr Soc. 59: 1686–1691.
- The American Geriatrics Society 2012 Beers Criteria Update Expert Panel (2012) American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 60: 616–631.
- National Quality Forum (2014) Multiple chronic conditions (MCC) measurement framework. Available: http://www.qualityforum.org/Projects/Multiple_ Chronic_Conditions_Measurement_Framework.aspx. Accessed 2013 Oct 28.