Supplementary Materials

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Supplementary Table S15: Results from the index of local sensitivity to nonignorability (ISNI) method for the linear regression model for systolic blood pressure and hemoglobin A1c

Supplementary Table S16: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and in the over-aggressive treatment of chronic conditions sub-domain for the primary cohort comparing methods using multiple imputation (MI) (primary analysis) and the index of local sensitivity to nonignorability (ISNI) (sensitivity analysis)

Supplementary Figure S1: Example outline of cohort entry and timing of medication assessment for an individual enrolled in the Health and Retirement study

Supplementary Figure S2: Flow chart of individuals aged 66 years and older with and without dementia in the Health and Retirement Study from 2008-2018 included in this study

Supplementary Figure S3: Distribution of the number of potentially problematic medications identified across all criteria among persons with and without dementia in the primary matched cohort

Supplementary Figure S4: Histograms representing the distribution of systolic blood pressure and hemoglobin A1c values under the different methods, including index of local sensitivity to nonignorability (ISNI), multiple imputation, and non-missing observed data

Supplementary Methods

Cohort construction:

Supplementary Figure S1 shows the flow chart used to identify individuals included in the study. We identified persons with dementia (PWD) based on a previously validated algorithm developed by Hurd et al.[1] This algorithm was developed using data from the Aging, Demographics, and Memory Study (ADAMS), a sub-study from the 2000 and 2002 waves of the Health and Retirement Study (HRS) in which a random sample of participants aged 70 years and older underwent full neuropsychological evaluations.[2] An ordered probit model was developed using predictors such as age, sex, education, cognitive test results, and physical functioning to classify individuals in subsequent HRS waves as having dementia. We used a predicted dementia probability >0.5 with this algorithm to classify individuals as having probable dementia. This algorithm has been shown to have good accuracy in validation studies.[3]

Once an individual was classified as having dementia at a specific HRS interview wave, that individual was then classified as having dementia for all subsequent interview waves. For individuals classified as having dementia with only one interview wave available, we used this interview wave as the index date to obtain medication information in the previous year. For individuals with multiple HRS interview waves having a classification of dementia, we randomly selected one of their interview waves to use as the index interview wave for which all medication information was obtained in the year prior. We prioritized the waves in which the individual was selected for the enhanced face to face interview as this would allow us to collect information on their hemoglobin A1c, cystatin C, and systolic blood pressure if the patient had these measured.

An individual could have been in the control pool during earlier HRS interview waves (probability of dementia using the Hurd algorithm <0.5 indicating no classification of dementia)

before later having a classification of dementia during a later wave (dementia probability >0.5 indicating classification of dementia). Once the individual had a classification of dementia at an HRS interview wave, they were no longer eligible for the control pool in subsequent years. For example, an individual who was interviewed in 2008 and 2010 and not classified as having dementia would be included in the control pool for those time points but would be included in the dementia pool if they were classified as having dementia at the 2012 HRS interview wave.

After applying our inclusion and exclusion criteria, a total of 9,844 distinct individuals were ultimately eligible. From this cohort, 1,475 distinct individuals were classified as having dementia at least once during the study period based on the dementia classification algorithm. There were 9,199 individuals who were ultimately included in the control pool (individuals without classification of dementia). The sum of these numbers (1,475 + 9,199 = 10,674) is greater than 9,844 as some individuals were included first in the control cohort and later in the dementia cohort.

Classification of medication overuse

We identified individuals for the over-aggressive treatment of hypertension criterion based on an average systolic blood pressure <110 with a prescription for certain antihypertensives. We applied a series of exclusion criteria to ensure they did not have an alternative indication for an antihypertensive even with an average systolic blood pressure <110. This may occur for individuals with heart failure with reduced ejection fraction on a beta-blocker, angiotensin converting enzyme inhibitor, or spironolactone. This may also occur for individuals with atrial fibrillation on a beta blocker which is used for rate control rather than blood pressure. Therefore, we checked if individuals had certain combinations of comorbidities prior to them being flagged as receiving a potentially problematic medication in the setting of

average systolic blood pressure <110. We first excluded alpha-1 blockers such as doxazosin, prazosin, and terazosin and loop diuretics since these medications are often not used explicitly for hypertension (i.e., commonly used for benign prostatic hyperplasia, posttraumatic stress disorder, and edema in the setting of chronic kidney disease or heart failure). We then split individuals into 8 mutually exclusive groups based on the presence of 1) cardiac conditions, 2) arrhythmias, and 3) chronic kidney disease or diabetes. We used the Clinical Classifications Software (CCS) to map International Classification of Diseases (ICD)-9 and -10 codes onto categories of conditions. Cardiac conditions were defined as a diagnosis code for essentially any heart condition other than essential hypertension. This was to be as conservative as possible when flagging a medication as potentially problematic based on this criteria. This included ICD9 CCS 7.1.2 (HTN with complications), 7.2 (disease of the heart) except for 7.2.9 (cardiac dysrhythmias), CCS procedure codes 7.2, 7.3 and ICD10 CCS CIR001-CIR006, CIR008-CIR016, CIR018-CIR019 (excludes CIR007 = essential hypertension and CIR017 = cardiac dysrhythmias). Arrhythmias were generally defined as atrial fibrillation, atrial flutter, or supraventricular tachycardia using diagnosis codes ICD 9 427.0, 427.3 or ICD10 I47.1, I48*. Chronic kidney disease and diabetes were defined using diagnosis codes ICD 9 CCS 3.2 & 3.3 (diabetes), 10.1.3, 10.1.2.2 (chronic renal failure) and ICD10 CCS END 002-END006 (diabetes), GEN003 (chronic kidney disease).

Finally, we characterized potentially problematic medication use based on the presence or absence of these diagnosis codes. The 8 mutually exclusive groups are shown in Supplementary Table S1 where 1 = condition present based on diagnosis codes and 0 = absent based on diagnosis codes. The bullet points list the medications that were considered potentially inappropriate for each group.

If an individual who met the criteria for over-aggressive treatment of hypertension or diabetes was on multiple antihypertensive or antidiabetic agents, we ultimately decided to randomly flag one of the medications. For example, an individual with an average systolic blood pressure of 105 who was on metoprolol, amlodipine, and hydrochlorothiazide without any other identifiable diagnosis codes that would indicate these medications may be potentially appropriate, we would randomly select one of these medications as indicative of over-aggressive treatment of hypertension. We did this because we felt it would be unfair to identify all 3 medications as potentially problematic. Similarly, for an individual with diabetes who had a hemoglobin A1c of 7.0% and was on insulin and glipizide, we randomly flagged one of these medications as potentially problematic.

We recognize that this classification system is not perfect, and some medications identified as potentially problematic may be reasonable choices based on individual circumstances. We also did not factor in dose modifications for medications like insulin in the setting of hemoglobin A1c <7.5%. However, our aim was to identify medications often considered overused and frequently represent high-value candidates to consider for discontinuation.

Classification of medications that negatively affect cognition

Medications classified as those that negatively affect cognition included strongly anticholinergics and sedative-hypnotics. Strongly anticholinergic medications included those in Table 7 of the 2019 Beers criteria as shown in Supplementary Table S2.[4] Multiple tools have been developed for classifying medications based on anticholinergic burden, such as the Anticholinergic Cognitive Burden (ACB) scale and Anticholinergic Risk Scale (ARS).[5] We ultimately settled on the medications listed in Table 7 of the 2019 Beers criteria as this represents

common medications with strong anticholinergic properties. These included various antidepressants, antiemetics, antihistamines, antimuscarinics, antiparkinsonian agents, antipsychotics, antispasmodics, and skeletal muscle relaxants. While these medications overlap with the 2019 Beers criteria sub-domain, we ensured that each medication was only flagged once when computing the overall results for frequency and mean.

Medications classified as sedative-hypnotics are shown in Supplementary Table S3. There are comparatively fewer sedative burden scales with the most prominent being the Sedative Load Model (SLM).[6,7] This model classifies drugs into no, low, moderate, or high sedative potency based on clinical expertise. Based on the SLM and in line with a previous study of polypharmacy among older adults with and without dementia, we included medications such as benzodiazepines, nonbenzodiazepine hypnotics, selected antiepileptic drugs, selected antipsychotics, selected antihistamines, and doxepin.[8]

Classification of medications to avoid based on specific criteria

Operationalizing the 2019 American Geriatrics Society Beers criteria and Screening Tool of Older Persons' Prescriptions (STOPP) Version 2 criteria using only claims data can often be challenging. Previous attempts have been made to apply the STOPP Version 2 criteria using only electronic health record data.[9,10] While we generally followed the guidance from this multidisciplinary consensus procedure, we chose a more conservative approach. For example, we excluded criteria such as avoiding “Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias” or “Beta-blockers in diabetes mellitus with frequent hypoglycemic episodes.” These criteria could be operationalized based on the absence of prescriptions of first-line antiarrhythmics in the year prior (e.g., beta-blockers) or the presence of

diagnosis code for hypoglycemia. However, we felt that this would not be a fair representation of inappropriate medication use in the absence of additional clinical information.

Overlapping medication criteria

A few criteria involved flagging medications as potentially problematic if they were used in combination (e.g., overlapping use of benzodiazepines and opioids). For these criteria, for each medication prescription we looked at the prescription fill day and days supply to specify a date range for when the medication may be in use. We recognize that this is not perfect as individuals may fill a medication but not take it for several weeks after that. However, this is a limitation inherent in pharmacoepidemiology research using prescription fill information. For the medications in question (e.g., benzodiazepine and opioid), we flagged them as using in combination if the date ranges for the individual medications overlapped for at least 7 days. We chose a 7 day overlap period as some of these medications may only be prescribed for short courses or for as needed use (e.g., 1 time prescription for 1 pill of lorazepam prior to a flight or MRI scan).

Chronic medication criteria

We operationalized a few criteria based on chronic use which was variably defined (e.g., proton pump inhibitor use for >8 weeks, non-steroidal anti-inflammatory drug (NSAID) use for >3 months or NSAID use for >1 month with a diagnosis code of heart failure). The definitions of chronic medication use varied slightly. For example, to ascertain that an individual was on a medication for >8 weeks, we required 2 consecutive fills in the past year that were filled within 30 days of each other with at least 28 days per fill. We also included a single fill with a day supply greater than 8 weeks (i.e., >56 days).

Chronic kidney disease criteria

Several criteria involved identifying potentially problematic medications based on an individual's creatinine clearance (CrCl). For example, both the 2019 Beers and STOPP Version 2 criteria have sections on medications that should be avoided in chronic kidney disease (CKD). The 2019 Beers criteria recommends avoiding duloxetine if CrCl <30 and reducing the dose of gabapentin if CrCl <60. We included most criteria that recommending avoiding medications based on a CrCl cut-off and excluded those that recommended reducing the dose as these were challenging to operationalize.

To ascertain an individual's kidney function for these criteria, we looked at both diagnosis codes for CKD and an individual's cystatin C if available from the enhanced face to face interview. The CKD diagnosis codes are all based on estimated glomerular filtration rate (eGFR) cut-offs. Similarly, cystatin C allows for the calculation of eGFR. While CrCl and eGFR are not equivalent, for our purpose, we considered them roughly similar. We used the CKD-Epi cystatin C formula to convert the cystatin C values available to an eGFR as follows: eGFR = 133 x min(Scys/0.8, 1)-0.499 x max (Scys/0.8, 1)-1.328 x 0.996Age x 0.932 [if female] where eGFR = mL/min/1.73 m2, Scys (standardized serum cystatin C) = mg/l, min = indicates the minimum of Scys/0.8 or 1, max = indicates the maximum of Scys/0.8 or 1, and age = years.

Methods to handle missing data

For the sub-domain of over-aggressive treatment of diabetes and hypertension, many individuals did not have an available hemoglobin A1c (HbA1c) or systolic blood pressure (SBP) measured. These values were collected during the enhanced face to face interview in the Health and Retirement Study. Among the 1,441 individuals without dementia in the primary matched cohort, 1,441 (100%) had a SBP measured and 1,074 (75%) had a HbA1c measured. Among the 1,441 individuals with dementia in the primary matched cohort, 538 (37%) had a SBP measured

and 381 (26%) had a HbA1c measured. Given that the control pool of persons without dementia was larger and we prioritized individuals who had an enhanced face to face interview, we were able to identify a higher percentage of persons without dementia who had an available SBP or HbA1c measured.

Due to the amount of missingness in SBP and HbA1c, ignoring the missing measures would lead to cohort selection bias and sample size reduction, reducing the study power and skewing the results for the sub-domain of over-aggressive treatment of diabetes and hypertension. To handle the missing data, we applied the multiple imputation (MI) method to fill in the missing SBP and A1c. We also conducted a sensitivity analysis using the index of local sensitivity to nonignorability (ISNI) (see sensitivity analysis section below).

Multiple Imputation

For the primary analysis, we used multiple imputation to create 10 complete datasets. The missing SBP and HbA1c were drawn from the two conditional distributions, where

$$\text{SBP} \mid X_1, X_2, \ldots\ldots, X_{22} \sim \mathbb{N}(\mu_1, \sigma_1^2),$$

$$\text{HbA1c} \mid X_1, X_2, \ldots\ldots, X_{22} \sim \mathbb{N}(\mu_2, \sigma_2^2).$$

$X_1, X_2, \ldots\ldots, X_{22}$ are the covariates listed in Supplementary Table S15. After the imputing step, we linked the 10 imputed datasets to an individual's medications and identified the overuse medication cases across all 10 datasets. Then we produced the mean, frequency of overuse, odds ratio, and incidence rate ratio for dementia vs non-dementia groups through a pooling step where we combined the parameter estimate and standard error from each imputed dataset for the final inference. MI is highly precise and efficient. The random draw for the missing data from the conditional distribution produces unbiased estimates. The pooling step captures the missing data

uncertainty and sampling variation, rendering high coverage probability for the parameter estimation.[11] We used the SAS PROC MI procedure to conduct the multiple imputation.

Sensitivity analyses

We performed several sensitivity analyses to examine the robustness of our findings. First, we created 2 additional matched cohorts: first matched only on year of assessment and another matched on several additional factors. For the first cohort, we 1:1 matched individuals with a classification of dementia to those without a classification of dementia based only on their year of assessment. In the second cohort, we 1:1 matched individuals with and without dementia by year of assessment, age, sex, comorbidity count, race/ethnicity, education, marital status, lives alone, Medicaid eligibility, body mass index, smoking status, region of country, hospitalization or emergency department visit in the past year, outpatient visits in the past year, activities of daily living (ADL) difficulty score, and instrumental ADL (IADL) difficulty score.

Second, we used inverse probability of treatment weighting (IPTW) instead of propensity score matching to calculate the results in the primary cohort. IPTW involves comparing individuals with and without dementia in the sample weighted by the inverse probability of treatment (where in this case "treatment" indicates the presence of dementia). IPTW uses the entire cohort, and each individual is assigned a weight based on the likelihood that they have dementia.

Third, we considered alternative ways of including certain criteria that were either 1) different between individuals with and without dementia or 2) only apply to individuals with dementia since this would lead to a higher number of flagged medications in those with dementia (Supplementary Table S4). For example, STOPP Version 2 D1 which advises to stop tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities,

prostatism, or prior history of urinary retention would apply to everyone in the dementia cohort and only those with the certain medical conditions in the non-dementia cohort. Similarly, STOPP Version 2 D9 which recommends stopping antipsychotics in patients with behavioral and psychological symptoms of dementia would only apply to individuals with dementia. Including these criteria could create an unfair comparison between those with and without dementia. In our primary analysis for the overall mean number of flagged medications and percentage of individuals with at least 1 flagged medication, we excluded these criteria to avoid this unfair comparison. As a sensitivity analysis, we included these criteria when calculating the overall measure to see how our results changed. In our primary analysis for the individual domains (e.g., medications to avoid based on specific criteria such as 2019 Beers/STOPP Version 2), we included the criteria that were specific to individuals with dementia. As a sensitivity analysis, we excluded these criteria when calculating the individual domain measures.

Fourth, we repeated an analysis in which the non-dementia cohort was not preferentially selected based on the presence of an enhanced face-to-face (EFTF) interview. In 2006, HRS initiated EFTF interviews which included additional measures such as physical performance tests and blood samples. At each HRS interview wave, half of the sample is assigned an EFTF interview. This alternates every wave such that the EFTF interview is available every 4 years at the individual level. When constructing the control pool involving individuals without dementia, we decided to preferentially select individuals who had an EFTF interview. We did this so that we could maximize the number of people with an available hemoglobin A1c, systolic blood pressure, and cystatin C to ascertain information on potentially problematic medication use in the medication overuse domain. While assignment to an EFTF interview is random and alternates every other HRS interview wave, individuals who complete the EFTF interview (with blood

draw and SBP measured) may differ than those who do not (e.g., if they declined the EFTF interview when given the opportunity). Therefore, we repeated the analysis in which the control pool (individuals without dementia) was not preferentially selected based on the presence of an EFTF interview.

Fifth, we conducted an index of local sensitivity to nonignorability (ISNI) sensitivity analysis as explained below to assess the robustness of the multiple imputation procedure.

ISNI Sensitivity Analysis

a. Rationale

While MI is one of the most common and widely used missing data methods, its validity is built upon one key assumption: ignorability. That is, the missing data mechanism (MDM) follows the missing at random (MAR) assumption; the parameters for the observed data (θ) and missing data (φ) are distinct.[12] The missing data follows the MAR assumption if the probability of missingness only depends upon the observed variables.[13] When ignorability holds, we can directly draw inferences from the observed data without modeling the MDM. In our study, we assumed the missing SBP and HbA1c were MAR and implemented the MI method for the analyses. The MAR assumption is usually unverifiable. When the MDM pivots from MAR to missing not at random (MNAR), the probability of missingness is related to both observed and unobserved data, and the MI method is no longer robust as it produces biased parameter estimation.[11] Therefore, incorrectly assuming MAR can negatively impact the research results, and it is important to conduct a sensitivity analysis that compares the estimates and inference results once the missing mechanism departs from MAR to MNAR.

b. Theoretical outline

The ISNI method is a principled sensitivity index method that evaluates the reliability of the analysis under the MAR assumption. When the missingness is MNAR, the missing mechanism can no longer be ignored. That is, one must model the observed and missing data jointly to draw valid and robust parameter estimates and inferences. Nevertheless, fitting a nonignorable missing data model is both conceptually and computationally challenging. Moreover, it was not in our primary interest to model the missingness. On the other hand, the ISNI method provides a fast-implemented easy-to-use method that requires fitting no nonignorable models. Starting with the MAR model, ISNI measures the deviation of the parameter estimates when the MDM changes from MAR to MNAR. A general ISNI sensitivity method outline works like this:

1. Let G_i be the missing indicator for the outcome Y_i. G_i=1(0) if Y_i is missing (or observed). We model the missing indicator (MDM) via a selection model, where G is conditional on both observed and unobserved outcomes (Y^{obs}, Y^{mis}). The probability density function (PDF) for G |Y is denoted as $f_{\gamma}^{G|Y}(g|y)$.
2. We introduce the parameter, γ, for modeling the MDM. γ is broken down as γ_0 and γ_1, where γ_0, γ_1 reflect the effects on the probability of missingness from the fully observed Y^{obs} and potentially unobserved Y^{mis}. Therefore, the PDF is denoted as $f_{\gamma_0,\gamma_1}^{G|Y}\left(g\middle|y^{obs}, y^{mis}\right)$. Since we often model the observed outcomes with a set of covariates (Y^{obs}=$X\beta$) for the MAR model, γ_0 can also refer to the set of coefficients for the fully observed covariates for missingness.
3. For example, we model G|Y^{obs}, Y^{mis} via a logistic regression model, which is specified as follows:

$$\ln\left(\frac{P(G_i=1)}{1-P(G_i=1)}\right) = \gamma_0 X + \gamma_1 Y_i^{mis}.$$

Here γ_1 is referred to as a nonignorable parameter. When $\gamma_1 = 0$, the missing probability does not depend on the missing outcome hence the model reduces to ignorable missingness (MAR model); when $\gamma_1 \neq 0$, the missing probability depends upon the missing outcome hence the missingness is nonignorable (MNAR model).

4. When the missingness is nonignorable, one must model the joint likelihood for both observed data and the missing data. As aforementioned, θ denotes the parameter governing the complete observed data. Therefore, the joint log-likelihood function is specified as

$$L(\theta, \gamma_0, \gamma_1; y^{obs}, g) = \ln \int_{\Omega_{Ymis}} f_\theta^Y(y^{obs}, y^{mis}) f_{\gamma_0, \gamma_1}^{G|Y}(g|y^{obs}, y^{mis}) dy^{mis}$$

5. ISNI measures the rate of change from $\hat{\theta}(\gamma_1)$ to the MAR estimator $\hat{\theta}(\gamma_1 = 0)$. To identify the optimal value of θ , we take the derivative of the jointly log likelihood function with respect to θ , resulting in a function of θ and γ_1. ISNI in calculation is defined as the derivative $\frac{\partial \hat{\theta}(\gamma_1)}{\partial \gamma_1}$ evaluated at $\gamma_1 = 0$, which measures the rate of deviation in $\hat{\theta}(\gamma_1)$ from the standard MAR estimate $\hat{\theta}(0)$.[14] The mathematical expression for ISNI is

$$ISNI = \frac{\partial \hat{\theta}(\gamma_1)}{\partial \gamma_1} = -\nabla^2 L_{\theta,\theta}^{-1} \nabla^2 L_{\theta, \gamma_1},$$

Where $\nabla^2 L_{\theta,\theta} = \frac{\partial^2 L(\theta, \gamma_0, \gamma_1)}{\partial \theta \partial \theta^T} = \frac{\partial^2 f_\theta(y^{obs})}{\partial \theta \partial \theta^T}|_{\hat{\theta}(0), \widehat{\gamma_0}(0), \gamma_1 = 0}$ represents the Fisher's information, the inverse variance-covariance matrix of the MAR estimate $\hat{\theta}(0)$; $\nabla^2 L_{\theta,\gamma_1} = \frac{\partial^2 L(\theta, \gamma_0, \gamma_1)}{\partial \theta \partial \gamma_1}|_{\hat{\theta}(0), \widehat{\gamma_0}(0), \gamma_1 = 0}$ represents the level of nonorthogonality of θ and γ_1 and can be evaluated by the readily available MAR estimates $\hat{\theta}(0)$ and $\widehat{\gamma_0}(0)$.

When applying the ISNI method for the sensitivity analysis, we impose a plausible range of values for γ_1 which allows the ignorable model (MAR) to pivot to nonignorable model (MNAR), and examine the extent of the change in $\hat{\theta}(\gamma_1)$. For example, when $\gamma_1 = 1$, $ISNI \approx \hat{\theta}(1) - \hat{\theta}(0)$, where $\hat{\theta}(0)$ is the maximum likelihood estimator (MLE) from the MAR estimate. In general, we impose $\gamma_1 = \pm 1$ to allow the model to pivot locally in the nonignorable direction.

6. When $\gamma_1 \neq 0$, we can approximate the parameter estimate as $\hat{\theta}(\gamma_1) \approx \hat{\theta}(0) + ISNI \cdot \gamma_1$. Although ISNI measures the rate of change in parameter estimate when the model pivots from MAR to MNAR, it does not infer the level of significance for the parameter change. To gauge whether a change in the MLE estimate is significant, we define the index 'minimum degree of nonignorability', MinNI (also previously known as c index in Troxel 2004),[14] specified as

$$\text{MinNI}=\left|\frac{\sigma_Y SE}{ISNI}\right|,$$

where σ_Y is the standard deviation of the observed outcome, and SE is the standard error of $\hat{\theta}(0)$. We consider a one-SE change in the MAR estimate to be significant ($\hat{\theta}(\gamma_1) = \hat{\theta}(0) + SE_\theta$). Given the parameter approximation under nonignorable model, $\frac{ISNI}{SE_\theta} = 1$. The ratio > 1 would indicate that the estimate is highly subject to nonignorable missingness.

Recall the selection model in step 3, $\gamma_1 = 1$ indicates that one unit increase in y is associated with a 2.7-fold (e^1) increase in odds of being missing. This interpretation is valid when the outcome is categorical or count; however, when y is a continuous variable and has different scale, such as SBP reading or HbA1c, one unit increase in SBP or HbA1c has the same increase

in the odds of being missing but, SBP and HbA1c had different range values, and a slight change in y relative to its entire range can be associated with a substantial change in the probability of missingness. Therefore, instead of one-unit change in y, we consider one standard deviation (σ_Y) increase in y is associated with 2.7-fold odds increase. That is, we vary γ_1 from $-\frac{1}{\sigma_Y}$ to $\frac{1}{\sigma_Y}$, and examine the parameter estimate $\hat{\theta}(0) \pm ISNI \cdot \frac{1}{\sigma_Y}$. Furthermore, we proposed the MinNI that quantify the level of σ_Y. That is, a change of 1/MinNI standard deviation of y is associated in the increase odds of 2.7 for being missing. Therefore,

$$ISNI \cdot \frac{MinNI}{\sigma_Y} / SE_\theta = 1 \rightarrow MinNI = \left|\frac{\sigma_Y SE_\theta}{ISNI}\right|$$

MinNI is scale independent. A small MinNI means modest nonignorable missingness could lead to sensitivity; a large MinNI means only extreme level of nonignorability could it induce the sensitivity. Troxel (2004) suggested that using MinNI<1 as threshold for nonignorable sensitivity.[14]

c. Application

Assuming MAR, we fit two linear regression models for SBP and HbA1c. With the moderate amount of missing data, we conducted sensitivity analysis that two logistic regression models were adopted the missing model, specified as

$$\ln \frac{P(G_i = 1)}{1 - P(G_i = 1)} = (X_1 + X_2 + \cdots, X_{22})_i^T \gamma_0 + \gamma_1 \cdot SBP;$$

$$\ln \frac{P(G_i = 1)}{1 - P(G_i = 1)} = (X_1 + X_2 + \cdots, X_{22})_i^T \gamma_0 + \gamma_1 \cdot HbA1c.$$

We used the R package "isni" to conduct the sensitivity analysis. Columns "MAR Est." and "Std. Error" in Supplementary Table S15 represent the regression coefficient estimates and standard errors, respectively. The results suggest that age, male, smoking status, education level,

hospitalization, South region, arthritis, cancer, heart disease, hypertension, lung disease were significant predictors for SBP; male, race, living status, college and above education, >1 hospitalization, >1 ER visits, heart disease, and diabetes were significant predictors for HbA1c. Baseline SBP (intercept), activities of daily living (ADL) dependencies, instrumental activities of daily living (IADL) dependencies, and college and above level of education were all sensitive to nonignorable missingness, as the MinNI values were less than 1. Under the MAR model, controlling for all other variables, the baseline SBP (intercept) was 95.27. However, when the missingness pivots to MNAR, the baseline SBP should be adjusted upwards by 95.27 + 222.74/19.72=106.57 (19.72 is the standard deviation of SBP). Therefore, the MAR model underestimated the true intercept (based on the observable values) compared to the estimate from the nonignorable selection model. One unit increase in ADL/IADL dependency would decrease SBP by 0.26 and 0.18 using the MAR model. Under the nonignorable model, both estimates were adjusted upwards by 5.56/1.17 and 8.19/0.95. Hence, one unit increase in ADL/IADL dependency would increase SBP by 4.51 (-0.26 +5.56/1.17) and 8.43 (-0.18+8.19/0.95). Moreover, patients with college and above level of education in comparison to less than high school education should have on average a SBP that is 2.86 lower, and the nonignorable model further adjusts it downwards by 11.62. On the other hand, no MinNI value was less than one in the HbA1c selection model.

Comparing the results of MI and ISNI

We used the ISNI adjusted coefficient estimates to predict the missing SBP and HbA1c. Then we compared the ISNI predicted results to multiple imputed results. Supplementary Figure S3 demonstrates the histograms of the SBP and HbA1c under ISNI predicted, multiple imputed (10 datasets), and non-missing observed data.

The SBP and HbA1c values under the three methods overlapped. The ISNI predicted SBP tended to overestimate the true value of SBP (mean SBP was shifted to the right). However, it was still within the range of multiple imputed values. Therefore, despite the nonignorable parameters, the SBP outcomes showed similar distribution under the two methods.

As shown in Supplementary Table S16, results for the percentage of individuals with at least 1 problematic medication and mean number of problematic medications per person in the "over-aggressive treatment of chronic condition domain" were comparable between the MI and ISNI analyses. No significant differences in IRR and OR were found between the matched cohorts of persons with dementia and persons without dementia. The overall medication results were also similar between the MI and ISNI analyses. This provided evidence that the MI results were robust for the analysis.

Supplementary Table S1: Classification of potentially problematic medication use for over-aggressive treatment of hypertension (i.e., average systolic blood pressure <110 during enhanced face to face interview and on certain antihypertensives without clear alternative reason)

Mutually exclusive groups[a]	**Potentially problematic medication**
1. Heart condition = 1 + SVT = 0 + CKD = 0[b]	Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Vasodilators (excluding isosorbide-hydralazine combination) Thiazide and thiazide-like diuretics
2. Heart condition = 0 + SVT = 1 + CKD = 0	CCBs other than verapamil/diltiazem ACEi ARB Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Eplerenone Potassium sparing diuretics Vasodilators Thiazide and thiazide-like diuretics Nitrates
3. Heart condition = 0 + SVT = 0 + CKD = 1	Beta-blockers CCBs Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Eplerenone Potassium sparing diuretics Vasodilators Thiazide and thiazide-like diuretics Nitrates
4. Heart condition = 1 + SVT = 1 + CKD = 0	Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Vasodilators (excluding isosorbide-hydralazine combination) Thiazide and thiazide-like diuretics
5. Heart condition = 1 + SVT = 0 + CKD = 1	Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Vasodilators (excluding isosorbide-hydralazine combination) Thiazide and thiazide-like diuretics
6. Heart condition = 0 + SVT = 1 + CKD = 1	CCBs other than verapamil/diltiazem Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Eplerenone Potassium sparing diuretics

	Vasodilators Thiazide and thiazide-like diuretics Nitrates
7. Heart condition = 1 + SVT = 1 + CKD = 1	Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Vasodilators (excluding isosorbide-hydralazine combination) Thiazide and thiazide-like diuretics
8. Heart condition = 0 + SVT = 0 + CKD = 0	Beta-blockers CCBs ACEi ARB Aliskiren Antiadrenergic antihypertensives (excluding doxazosin, prazosin, terazosin) Eplerenone Vasodilators Potassium sparing diuretics Thiazide and thiazide-like diuretics Nitrates

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; SVT, supraventricular tachycardia

a Mutually exclusive groups were created as the medications that were considered eligible to be flagged as potentially problematic varied based on diagnosis codes. The number “1” indicates that the condition was present based on diagnosis codes, and the number “0” indicates that the condition was absent based on diagnosis codes.

b See the supplementary methods for definitions of these conditions. For example, “heart conditions” were defined as a diagnosis code for essentially any heart condition other than essential hypertension. This was to be as conservative as possible when flagging a medication as potentially problematic based on this criteria. This included ICD9 CCS 7.1.2 (HTN with complications), 7.2 (disease of the heart) except for 7.2.9 (cardiac dysrhythmias), CCS procedure codes 7.2, 7.3 and ICD10 CCS CIR001-CIR006, CIR008-CIR016, CIR018-CIR019 (excludes CIR007 = essential hypertension and CIR017 = cardiac dysrhythmias).

Supplementary Table S2: Classification of strongly anticholinergic medication use based on the 2019 Beers criteria Table 7

Medication class	**Individual medications**
Antiarrhythmics	disopyramide
Antidepressants	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine, protriptyline, and trimipramine
Antiemetics	prochlorperazine, promethazine
Antihistamines (first generation)	brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine (oral), doxylamine, hydroxyzine, meclizine, clidinium-chlordiazepoxide, dicyclomine, homatropine (excludes ophthalmic), methscopolamine, propantheline, promethazine, pyrilamine, triprolidine
Antimuscarinics (urinary incontinence)	darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium
Antiparkinsonian agents	benztropine, trihexyphenidyl
Antipsychotics	chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine, trifluoperazine
Antispasmodics	atropine, belladonna alkaloids, scopolamine (excluded ophthalmic)
Skeletal muscle relaxants	cyclobenzaprine, orphenadrine

Supplementary Table S3: Classification of sedative-hypnotic medications based on previous studies and the Sedative Load Model

Medication class	**Individual medications**
Benzodiazepines	Alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, prazepam, clobazam, clonazepam, midazolam, estazolam, flurazepam, quazepam, remimazolam, remazepam, triazolam
Nonbenzodiazepine sedative hypnotics	Zolpidem, zaleplon, eszopiclone
Selected antiepileptic drugs	Phenobarbital, gabapentin, pregabalin
Selected antipsychotics	All first generation antipsychotics, quetiapine, olanzapine, and clozapine
Selected antihistamines	Promethazine and diphenhydramine
Additional antidepressant	doxepin

Supplementary Table S4: List of criteria that were either different between individuals with and without dementia or only applied to individuals with dementia

Criteria that are different between individuals with and without dementia	
STOPP-V2 D1	Stop tricyclic antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
STOPP-V2 I1	Stop antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).
Criteria that only apply to individuals with dementia	
STOPP-V2 D8	Stop anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
STOPP-V2 D9	Stop neuroleptic antipsychotic in patients with behavioral and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
STOPP-V2 D11	Stop acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury)
STOPPFrail memantine	Memantine: Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD.
2019 Beers cholinesterase inhibitors in syncope	Acetylcholinesterase inhibitors cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia

Abbreviations: STOPP-V2, Screening Tool of Older Persons' Prescriptions Version 2; STOPPFrail, Screening Tool of Older Persons' Prescriptions in Frail adults with a limited life expectancy

Supplementary Table S5: Number of individuals with a dementia classification in the Health and Retirement Study by interview wave year and overall

Year of interview	Total number of individuals interviewed at specific wave	Number with classification of dementia in the specific wave	Percentage of individuals with classification of dementia in specific wave
2008	5,078	364	7.2%
2010	5,145	358	7.0%
2012	5,250	382	7.3%
2014	5,752	418	7.3%
2016	5,784	445	7.7%
2018	4,912	354	7.2%
Overall	9,844	1,475	15.0%

Supplementary Table S6: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and across the different domains in the primary cohort matched on age, sex, comorbidity count, and year of assessment

Medication domain	Outcome measures	Persons with dementia (N = 1,441)	Persons without dementia (N = 1,441)	OR or IRR (95% CI)
Overall	% with ≥1 flagged med	73%	67%	OR=1.34 (1.12, 1.62) (p=0.002)
	Mean number of flagged medications	2.09	1.62	IRR=1.29 (1.17, 1.42) (p<0.001)
Medication overuse				
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	17%	14%	OR=1.25 (0.98, 1.60) (p=0.07)
	Mean number of flagged medications	0.18	0.15	IRR=1.21 (0.98, 1.50) (p=0.08)
Medications inappropriate near end of life (STOPPFrail)	% with ≥1 flagged med	4%	2%	OR = 1.78 (1.10, 2.86) (p = 0.02)
	Mean number of flagged medications	0.06	0.04	IRR = 1.59 (0.96, 2.63) (p = 0.07)
Medication misuse				
Medications that negatively affect cognition	% with ≥1 flagged med	41%	30%	OR = 1.59 (1.33, 1.89) (p < 0.001)
	Mean number of flagged medications	0.61	0.42	IRR = 1.45 (1.26, 1.67) (p < 0.001)
2019 Beers criteria	% with ≥1 flagged med	60%	51%	OR = 1.45 (1.23, 1.72) (p < 0.001)
	Mean number of flagged medications	1.53	1.06	IRR = 1.44 (1.28, 1.63) (p < 0.001)
STOPP Version 2 criteria	% with ≥1 flagged med	66%	53%	OR = 1.69 (1.42, 2.00) (p < 0.001)
	Mean number of flagged medications	1.32	0.96	IRR = 1.37 (1.24, 1.51) (p < 0.001)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; STOPP, Screening Tool of Older Persons' Prescriptions; STOPPFrail, Screening Tool of Older Persons' Prescriptions in Frail adults with a limited life expectancy

Supplementary Table S7: Number and survey weighted percentage of persons with diabetes and hypertension who met criteria for over-aggressive treatment of these conditions in the primary cohort matched on age, sex, comorbidity count, and year of assessment

	Persons with dementia (n=1,441)	Persons without dementia (n=1,441)
	Number (survey weighted percentage)	
Individuals with diabetes[a]	504 (32.6%)	444 (30.2%)
Individuals with diabetes with hemoglobin A1c <7.5% and on insulin/sulfonylurea[b]	203 (39.9%)	179 (39.0%)
Individuals with hypertension[c]	1,178 (79.1%)	1,194 (81.6%)
Individuals with hypertension with an average systolic blood pressure <110 and on qualifying potentially problematic antihypertensive[d]	72 (5.8%)	47 (3.8%)

a We identified individuals with diabetes through either International Classification of Diseases (ICD)-9 or ICD-10 diagnoses codes for Type 2 diabetes (250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, E11*) or prescription for any antidiabetic drug in the year prior to the interview date.

b Among individuals with diabetes, we identified individuals with a hemoglobin A1c<7.5% who were also receiving insulin/sulfonylurea. The numbers presented were averaged over the 10 imputed datasets. The number and percentage reported here answers the question "among individuals with diabetes, how many were receiving over-aggressive treatment for their diabetes?" The denominator for this calculation is the number of individuals with diabetes which is different than what is presented in Table 3 and Figure 1 where the denominator is the whole cohort (n=1,441).

c We identified individuals with hypertension through either self-report during the enhanced face to face interview or prescription for antihypertensives in the year prior to the interview date. While certain antihypertensives can be used for multiple indications (e.g., metoprolol for atrial fibrillation rather than hypertension), our numbers align with other national survey data in an older population where the prevalence of hypertension is in the range of 80%.

d Among individuals with hypertension, we identified individuals with an average systolic blood pressure <110 who were also receiving potentially problematic antihypertensives. This was operationalized in the same way as done in Table 3 and Figure 1 (see supplementary methods; for example, an individual who was on metoprolol with SBP <110 and diagnosis code for atrial fibrillation would not be included here). The numbers presented were averaged over the 10 imputed datasets. The number and percentage reported here answers the question "among individuals with hypertension, how many were receiving over-aggressive treatment for their hypertension?" The denominator for this calculation is different than what is presented in Table 3 and Figure 1 where the denominator is the whole cohort (n=1,441).

Supplementary Table S8: Baseline characteristics of community-dwelling older adults with and without dementia enrolled in the Health and Retirement Study from 2008-2018 in the cohort matched only on year of assessment

	Individuals with dementia (n = 1, 475)	**Individuals without dementia (n = 12,492)[a]**	
Characteristic	**Number (weighted %)**	**Number (weighted %)**	**SMD**
Age in years, median (IQR)	83.9 (78.3-89.3)	73.6 (69.3-79.4)	0.02
Female sex	976 (66.9%)	7815 (60.5%)	-0.13
Race/Ethnicity			0.32
Non-Hispanic White	892 (69.0%)	9322 (82.1%)	
Non-Hispanic Black	303 (14.7%)	1624 (7.6%)	
Hispanic	250 (14.1%)	1300 (8.0%)	
Other	30 (2.2%)	246 (2.3%)	
Marital status (%)			-0.42
Married or partnered	7081 (57.4%)	556 (36.7%)	
Single or widowed	5411 (42.6%)	919 (63.3%)	
Lives alone (%)	3824 (32.3%)	464 (34.9%)	0.05
Comorbidities			
Cancer	350 (23.3%)	2583 (21.1%)	0.05
Diabetes	492 (30.7%)	3500 (27.6%)	0.07
Heart disease	659 (44.5%)	4257 (34.1%)	0.21
Hypertension	1130 (74.7%)	8910 (69.1%)	0.13
Lung disease	221 (16.6%)	1601 (12.8%)	0.11
Stroke	402 (26.6%)	1380 (10.6%)	0.42
Median (IQR) number of IADL dependencies (range 0-5)	1.8 (0-3.7)	0 (0-0)	0.02
Median (IQR) number of ADL dependencies (range 0-6)	0.8 (0-3.2)	0 (0-0)	0.02
Number of medications (median, IQR)	8.0 (4.6-12.3)	7.6 (4.4-12.0)	0.0007
Polypharmacy (≥5 medications)	1010 (77.8%)	1192 (80.1%)	0.06

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; IQR, interquartile range; SMD, standardized mean difference

a A single individual without dementia could be counted multiple times if they participated in multiple interviews during their enrollment in the Health and Retirement Study.

Supplementary Table S9: Baseline characteristics of community-dwelling older adults with and without dementia enrolled in the Health and Retirement Study from 2008-2018 in the fully matched cohort[a]

	Individuals with dementia (n = 971)	**Individuals without dementia (n = 971)**	
Characteristic	**Number (weighted %)**	**Number (weighted %)**	**SMD**
Age in years, median (IQR)	82.3 (75.9-87.8)	82.2 (76.3-87.3)	-0.0005
Female sex	639 (65.2%)	639 (65.7%)	0.01
Race/Ethnicity			0.09
Non-Hispanic White	604 (70.0%)	617 (72.5%)	
Non-Hispanic Black	186 (13.8%)	169 (11.3%)	
Hispanic	159 (13.9%)	165-170 (~14.0%)[b]	
Other	22 (2.4%)	<25 (<3%)[b]	
Marital status (%)			-0.008
Married or partnered	404 (41.0%)	427 (41.4%)	
Single or widowed	567 (59.0%)	544 (58.6%)	
Lives alone (%)	320 (35.3%)	324 (38.0%)	-0.05
Comorbidities			
Cancer	233 (23.3%)	203 (21.5%)	0.04
Diabetes	331 (31.2%)	281 (26.9%)	0.10
Heart disease	411 (42.1%)	425 (43.4%)	-0.03
Hypertension	736 (72.9%)	728 (73.0%)	-0.001
Lung disease	141 (16.3%)	154 (16.0%)	0.008
Stroke	236 (24.0%)	177 (18.0%)	0.15
Median (IQR) number of IADL dependencies (range 0-5)	0.6 (0-2.0)	0.6 (0-1.8)	0.0003
Median (IQR) number of ADL dependencies (range 0-6)	0 (0-1.8)	0.05 (0-1.8)	0.001
Number of medications (median, IQR)	6.4 (3.9-9.9)	6.8 (4.1-10.6)	-0.002
Polypharmacy (≥5 medications)	731 (74.0%)	755 (75.6%)	-0.04

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; IQR, interquartile range; SMD, standardized mean difference

a In the fully matched cohort, we 1:1 matched individuals with and without dementia by year of assessment, age, sex, comorbidity count, race/ethnicity, education, marital status, lives alone, Medicaid eligibility, body mass index, smoking status, region of country, hospitalization or emergency department visit in the past year, outpatient visits in the past year, activities of daily living (ADL) difficulty score, and instrumental ADL (IADL) difficulty score.

b Results are presented in this manner due to the Centers for Medicare and Medicaid Services (CMS) cell suppression size policy which sets the minimum threshold for the display of CMS data. This was necessary as the "Other" category involved <25 individuals.

Supplementary Table S10: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and across the different domains in the cohort matched only on year of assessment

Medication domain	Outcome measures	Persons with dementia (N = 1,475)	Persons without dementia (N = 12,492)[a]	OR or IRR (95% CI)
Overall	% with ≥1 flagged med	73%	67%	OR=1.31 (1.14, 1.51) (p<0.001)
	Mean	2.08	1.66	IRR=1.25 (1.18, 1.35) (p<0.001)
Medication overuse				
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	17%	14%	OR=1.28 (1.06, 1.55) (p=0.010)
	Mean	0.18	0.15	IRR=1.22 (1.04, 1.44) (p=0.017)
Medications inappropriate near end of life	% with ≥1 flagged med	4%	2%	OR=2.89 (2.09, 4.00) (p<0.001)
	Mean	0.07	0.02	IRR=2.68 (1.91, 3.76) (p<0.001)
Medication misuse				
Medications that negatively affect cognition	% with ≥1 flagged med	40%	31%	OR = 1.53 (1.35, 1.74) (p<0.001)
	Mean	0.61	0.43	IRR = 1.41 (1.27, 1.56) (p<0.001)
2019 Beers criteria	% with ≥1 flagged med	60%	56%	OR = 1.18 (1.04, 1.34) (p = 0.01)
	Mean	1.54	1.26	IRR = 1.26 (1.15, 1.38) (p<0.001)
STOPP Version 2 criteria	% with ≥1 flagged med	66%	50%	OR = 1.89 (1.66, 2.16) (p < 0.001)
	Mean	1.31	0.88	IRR = 1.49 (1.39, 1.60) (p < 0.001)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; STOPP, Screening Tool of Older Persons Prescriptions

a A single individual without dementia could be counted multiple times if they were included in multiple interviews during their enrollment in the Health and Retirement Study.

Supplementary Table S11: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and across the different domains in the fully matched cohort[a]

Medication domain	Outcome measures	Persons with dementia (N = 971)	Persons without dementia (N = 971)	OR or IRR (95% CI)
Overall	% with ≥1 flagged med	73%	71%	OR=1.11 (0.88, 1.40) (p=0.37)
	Mean	2.09	2.04	IRR=1.02 (0.91, 1.15) (p=0.72)
Medication overuse				
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	18%	17%	OR=1.33 (0.98, 1.80) (p=0.07)
	Mean	0.18	0.14	IRR=1.282 (0.994, 1.654) (p=0.06)
Medications inappropriate near end of life	% with ≥1 flagged med	4%	3%	OR = 1.17 (0.69, 1.98) (p =0.57)
	Mean	0.06	0.05	IRR = 1.16 (0.69, 1.95) (p =0.58)
Medication misuse				
Medications that negatively affect cognition	% with ≥1 flagged med	39%	32%	OR = 1.36 (1.10, 1.68) (p =0.005)
	Mean	0.59	0.46	IRR = 1.28 (1.07, 1.52) (p =0.006)
2019 Beers criteria	% with ≥1 flagged med	59%	60%	OR = 1.01 (0.81, 1.24) (p =0.96)
	Mean	1.51	1.47	IRR = 1.04 (0.90, 1.21) (p = 0.61)
STOPP Version 2 criteria	% with ≥1 flagged med	65%	59%	OR = 1.31 (1.06, 1.62) (p =0.001)
	Mean	1.33	1.18	IRR = 1.14 (1.01, 1.28) (p =0.004)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; STOPP, Screening Tool of Older Persons Prescriptions

a In the fully matched cohort, we 1:1 matched individuals with and without dementia by year of assessment, age, sex, comorbidity count, race/ethnicity, education, marital status, lives alone, Medicaid eligibility, body mass index, smoking status, region of country, hospitalization or emergency department visit in the past year, outpatient visits in the past year, activities of daily living (ADL) difficulty score, and instrumental ADL (IADL) difficulty score.

Supplementary Table S12: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and across the different domains using propensity score matching and inverse probability of treatment weighting

		Primary cohort matched on year of assessment, age, sex, and comorbidity count			IPTW cohort		
Medication domain	**Outcome measures**	**Persons with dementia (N = 1,441)**	**Persons without dementia (N = 1,441)**	**OR or IRR (95% CI)**	**Persons with dementia (N = 1,475)**	**Persons without dementia (N = 12,492)[a]**	**OR or IRR (95% CI)**
Overall	% with ≥1 flagged med	73%	67%	OR=1.34 (1.12, 1.62) (p=0.002)	73%	67%	OR=1.33 (1.14, 1.55) (p<0.001)
	Mean	2.09	1.62	IRR=1.29 (1.17, 1.42) (p<0.001)	2.08	1.66	IRR=1.29 (1.20, 1.40) (p<0.001)
Medication overuse							
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	17%	14%	OR=1.25 (0.98, 1.60) (p=0.07)	18%	17%	OR=1.28 (1.05, 1.56) (p=0.013)
	Mean	0.18	0.15	IRR=1.21 (0.98, 1.50) (p=0.08)	0.18	0.15	IRR=1.23 (1.04, 1.46) (p=0.012)
Medications inappropriate near end of life	% with ≥1 flagged med	4%	2%	OR = 1.78 (1.10, 2.86) (p = 0.02)	7%	4%	OR=1.88 (1.30, 2.73) (p=0.001)
	Mean	0.06	0.04	IRR = 1.59 (0.96, 2.63) (p = 0.07)	0.04	0.02	IRR=1.88 (1.30, 2.73) (p<0.001)
Medication misuse							
Medications that negatively	% with ≥1 flagged med	41%	30%	OR = 1.59 (1.33, 1.89) (p < 0.001)	40%	30%	OR=1.60 (1.39-1.83) (p<0.001)

affect cognition	Mean	0.61	0.42	IRR = 1.45 (1.26, 1.67) (p < 0.001)	0.61	0.40	IRR=1.51 (1.36, 1.68) (p<0.001)
2019 Beers criteria	% with ≥1 flagged med	60%	51%	OR = 1.45 (1.23, 1.72) (p < 0.001)	60%	52%	OR=1.40 (1.22, 1.61) (p<0.001)
	Mean	1.53	1.06	IRR = 1.44 (1.28, 1.63) (p < 0.001)	1.51	1.06	IRR=1.43 (1.30, 1.58) (p<0.001)
STOPP Version 2 criteria	% with ≥1 flagged med	66%	53%	OR = 1.69 (1.42, 2.00) (p < 0.001)	66%	52%	OR=1.76 (1.53, 2.03) (p<0.001)
	Mean	1.32	0.96	IRR = 1.37 (1.24, 1.51) (p < 0.001)	1.31	0.92	IRR=1.88 (1.30, 2.73) (p=0.001)

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; IRR, incidence rate ratio; OR, odds ratio; STOPP, Screening Tool of Older Persons' Prescriptions

a For the control pool (i.e., persons without dementia) in the inverse probability of treatment weighting analysis, the number of persons without dementia included was greater than the number of unique individuals without dementia because a person could contribute information from multiple waves in this analysis. For example, a person with an HRS interview in 2008, 2010, and 2012 who did not have a classification of dementia during any of these waves would be included 3 times in this analysis. We accounted for intra-individual correlation and repeated measures in calculating the odds ratio, incidence rate ratio, and p-value using a generalized estimating equation (GEE) model.

Supplementary Table S13: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and across the different domains in the primary matched cohort including and excluding criteria that are specific to individuals with dementia[a]

		All criteria			Excluding criteria specific to persons with dementia		
Medication domain	**Outcome measures**	**Persons with dementia (N = 1,441)**	**Persons without dementia (N = 1,441)**	**OR or IRR (95% CI)**	**Persons with dementia (N = 1,441)**	**Persons without dementia (N = 1,441)**	**OR or IRR (95% CI)**
Overall[a]	% with ≥1 flagged med	77%	67%	OR=1.58 (1.31, 1.90) (p<0.001)	73%	67%	OR=1.34 (1.12, 1.62) (p=0.002)
	Mean	2.20	1.63	IRR=1.35 (1.22, 1.48) (p<0.001)	2.09	1.62	IRR=1.29 (1.17, 1.42) (p<0.001)
Medication overuse							
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	17%	14%	OR=1.25 (0.98, 1.60) (p=0.07)	17%	14%	OR=1.25 (0.98, 1.60) (p=0.07)
	Mean	0.18	0.15	IRR=1.21 (0.98, 1.50) (p=0.08)	0.18	0.15	IRR=1.21 (0.98, 1.50) (p=0.08)
Medications inappropriate near end of life[a]	% with ≥1 flagged med	4%	2%	OR = 1.78 (1.10, 2.86) (p = 0.02)	4%	2%	OR = 1.73 (1.07, 2.78) (p = 0.025)
	Mean	0.06	0.04	IRR = 1.59 (0.96, 2.63) (p = 0.07)	0.06	0.04	IRR =1.52 (0.92, 2.51) (p = 0.105)
Medication misuse							
Medications that negatively affect cognition	% with ≥1 flagged med	41%	30%	OR = 1.59 (1.33, 1.89) (p < 0.001)	41%	30%	OR=1.59 (p<0.001)
	Mean	0.61	0.42	IRR = 1.45 (1.26, 1.67)	0.61	0.42	IRR=1.45 (p<0.001)

				(p < 0.001)			
2019 Beers criteria[b]	% with ≥1 flagged med	60%	51%	OR = 1.45 (1.23, 1.72) (p < 0.001)	58%	51%	OR = 1.37 (1.16, 1.62) (p<0.001)
	Mean	1.53	1.06	IRR = 1.44 (1.28, 1.63) (p < 0.001)	1.48	1.06	IRR = 1.40 (1.23, 1.58) (p<0.001)
STOPP Version 2 criteria[b]	% with ≥1 flagged med	66%	53%	OR = 1.69 (1.42, 2.00) (p < 0.001)	53%	52%	OR = 1.02 (0.86, 1.20) (p = 0.82)
	Mean	1.32	0.96	IRR = 1.37 (1.24, 1.51) (p < 0.001)	0.98	0.94	IRR = 1.04 (0.94, 1.15) (p = 0.49)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; STOPP, Screening Tool of Older Persons' Prescriptions

a There were some criteria in the subdomains of "Medications inappropriate near end of life," "2019 Beers criteria," and "STOPP Version 2 criteria" which were specific to individuals with dementia or differed between those with and without dementia (see supplementary methods and Supplementary Table S4 for additional details). The boxes shaded in yellow represent the sensitivity analysis which excluded criteria that were specific to individuals with dementia. The boxes shaded in green represent the primary analysis in Table 3 and Figure 1. For the overall results in the primary analysis (results displayed in Table 3 and Figure 1, green shaded boxes in this supplementary table), we excluded the criteria specific to individuals with dementia in order to make a fairer comparison between those with and without dementia when calculating the overall measure. In a sensitivity analysis, we included all criteria in calculating the overall results (yellow shaded boxes in this supplementary table). In the primary analysis for the individual sub-domains (results displayed in Table 3 and Figure 1, green shaded boxes in this supplementary table), we did not exclude these criteria. In a sensitivity analysis, we excluded these criteria in calculating the results for these sub-domains (yellow shaded boxes in this supplementary table). Since a single medication could be identified as potentially problematic in multiple different ways, the overall results of this sensitivity analysis are similar to the primary analysis.

Supplementary Table S14: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and in the medication overuse domain in the primary matched cohort and a separate matched cohort in which the non-dementia controls were not preferentially selected based on presence of enhanced face to face interview

		EFTF matched cohort (primary analysis from Table 3 and Figure 1)			**Matched cohort where persons without dementia were not specifically selected based on the presence of EFTF interview (sensitivity analysis)**		
Medication domain	**Outcome measures**	**Persons with dementia (N = 1,441)**	**Persons without dementia (N = 1,441)**	**OR or IRR (95% CI)**	**Persons with dementia (N =1,470)**	**Persons without dementia (N =1,470)**	**OR or IRR (95% CI)**
Overall	% with ≥1 flagged med	73%	67%	OR=1.34 (1.12, 1.62) (p=0.002)	73%	69%	OR=1.21 (1.00, 1.46) (p=0.049)
	Mean	2.09	1.62	IRR=1.29 (1.17, 1.42) (p<0.001)	2.08	1.73	IRR=1.20 (1.09-1.33) (p<0.001)
Medication overuse							
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	17%	14%	OR=1.25 (0.98, 1.60) (p=0.07)	17%	16%	OR=1.11 (0.85-1.45) (p=0.43)
	Mean	0.18	0.15	IRR=1.21 (0.98, 1.50) (p=0.08)	0.18	0.16	IRR=1.09 (0.86-1.38) (p=0.48)

Abbreviations: CI, confidence interval; EFTF, enhanced face to face; IRR, incidence rate ratio; OR, odds ratio

Supplementary Table S15: Results from the index of local sensitivity to nonignorability (ISNI) method for the linear regression models for systolic blood pressure and hemoglobin A1c

	Systolic blood pressure model					**Hemoglobin A1c model**				
Variable	MAR est.	Std. error	P-value	ISNI	MinNI	MAR est.	Std. error	P-value	ISNI	MinNI
(Intercept)	95.27	8.87	< 2e-16	222.74	0.78	7.53	0.43	< 2e-16	0.38	1.03
Age	0.28	0.03	< 2e-16	0.23	2.33	0.00	0.00	0.51	0.00	1.68
Male sex	1.41	0.38	0.00	-0.93	8.06	0.04	0.02	0.01	0.00	4.50
Race										
Other	.									
Non-Hispanic White	13.32	8.62	0.12	-23.90	7.10	-1.84	0.42	0.00	-0.07	5.19
Non-Hispanic Black	15.24	8.63	0.08	-24.70	6.88	-1.56	0.42	0.00	-0.06	6.30
Hispanic	13.74	8.65	0.11	-29.72	5.73	-1.70	0.42	0.00	-0.06	5.96
ADL	-0.26	0.21	0.21	5.56	0.73	-0.01	0.01	0.27	0.00	2.63
IADL	-0.18	0.27	0.52	8.19	0.66	0.01	0.01	0.27	0.01	1.40
Lives alone	-0.03	0.53	0.95	1.83	5.75	0.05	0.02	0.04	0.00	5.24
Current smoker	1.65	0.65	0.01	-3.27	3.89	0.01	0.03	0.77	-0.01	3.13
Married or partnered	0.84	0.53	0.11	3.03	3.43	-0.01	0.02	0.57	0.01	3.67
Education										
< high school	.									
High School or GED	-1.26	0.47	0.01	-8.38	1.10	-0.04	0.02	0.07	0.00	3.60
College and above	-2.86	0.47	0.00	-11.62	0.80	-0.08	0.02	0.00	0.01	1.35
Hospitalization										
0	.									
1	-1.43	0.71	0.04	-1.02	13.73	-0.05	0.03	0.08	-0.01	3.99
>1	-2.32	1.18	0.05	15.97	1.45	-0.12	0.05	0.01	0.01	5.31
ER Visit										
0	.									
1	0.35	0.82	0.67	2.27	7.12	0.01	0.04	0.80	0.01	2.59

>1	0.03	1.41	0.98	-5.68	4.90	0.14	0.06	0.02	0.00	548.42
Outpatient visit										
0	.									
1	1.23	0.93	0.19	12.75	1.44	-0.04	0.04	0.28	0.00	30.46
>1	0.54	0.36	0.13	0.65	10.82	0.01	0.02	0.65	-0.01	1.24
Region										
Northeast or Other	.									
Midwest	-0.68	0.57	0.23	-3.50	3.23	0.01	0.03	0.57	-0.01	1.63
South	-1.08	0.53	0.04	-1.48	7.02	-0.05	0.02	0.04	-0.01	2.35
West	-0.03	0.60	0.96	-4.12	2.87	0.01	0.03	0.82	-0.02	1.34
Dementia status	-1.30	0.94	0.17	-7.21	2.58	-0.07	0.04	0.11	0.01	3.20
Comorbidities										
Arthritis	-1.29	0.40	0.00	-7.90	1.01	-0.02	0.02	0.33	0.00	4.27
Cancer	-0.88	0.42	0.04	0.05	179.71	-0.01	0.02	0.58	0.00	6.37
Diabetes	0.52	0.39	0.18	-0.48	16.10	1.10	0.02	< 2e-16	0.01	2.27
Heart	-2.12	0.37	0.00	-0.55	13.41	0.06	0.02	0.00	0.00	233.08
Hypertension	7.18	0.39	< 2e-16	2.88	2.65	0.02	0.02	0.26	0.00	3.36
Lung disease	-2.41	0.52	0.00	-3.56	2.90	0.00	0.02	0.90	0.00	7.79
Stroke	0.19	0.54	0.73	-1.42	7.58	-0.04	0.02	0.06	0.00	5.57

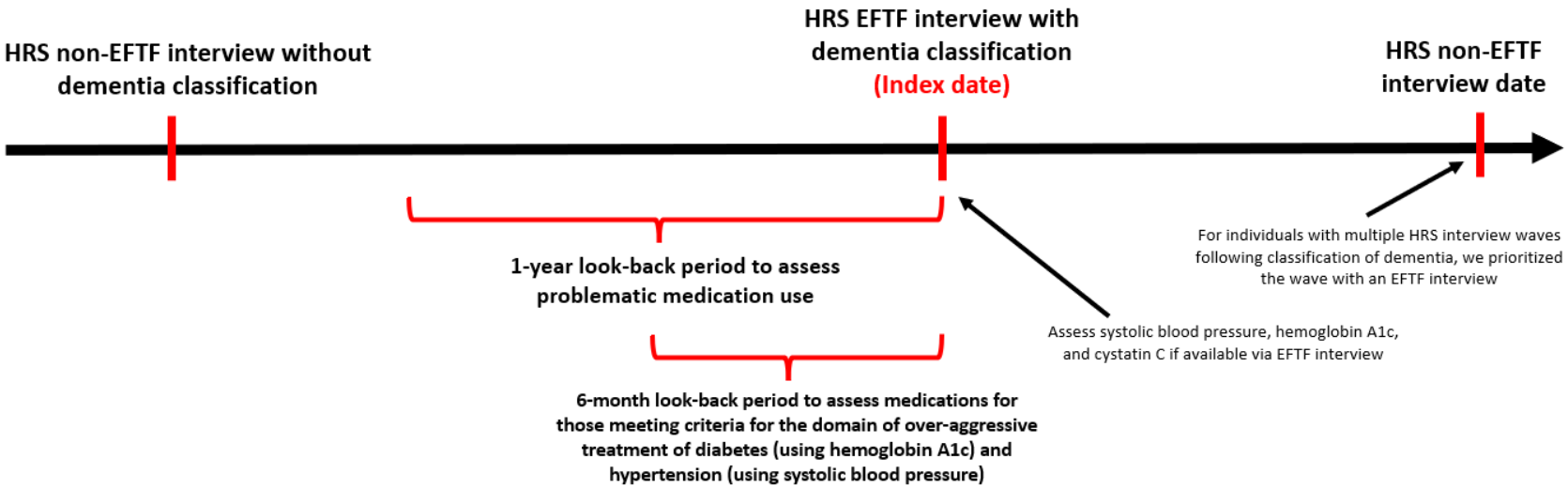
Abbreviations: ADL, activities of daily living; Est, estimate; GED, General Educational Development; IADL, instrumental activities of daily living; ISNI, index of local sensitivity to nonignorability; MAR, missing at random; MinNI, minimum degree of nonignorability; Std. error, standard error

Supplementary Table S16: Frequency and mean number of potentially problematic medications among community-dwelling older adults with and without dementia overall and in the over-aggressive treatment of chronic conditions sub-domain for the primary cohort comparing methods using multiple imputation (MI) (primary analysis) and the index of local sensitivity to nonignorability (ISNI) (sensitivity analysis)

		Multiple Imputation (primary results)			**ISNI method (sensitivity analysis)**		
Medication domain	**Outcome measures**	**Persons with dementia (n=1,441)**	**Persons without dementia (n=1,441)**	**OR or IRR (95% CI)**	**Persons with dementia (n=1,441)**	**Persons without dementia (n=1,441)**	**OR or IRR (95% CI)**
Overall	% with ≥1 flagged med	73%	67%	OR=1.34 (1.12, 1.62) (p=0.002)	73%	67%	OR=1.29 (1.08, 1.55) (p<0.001)
	Mean	2.09	1.62	IRR=1.29 (1.17, 1.42) (p<0.001)	2.08	1.62	IRR=1.28 (1.16, 1.41) (p<0.001)
Medication overuse							
Over-aggressive treatment of chronic conditions	% with ≥1 flagged med	17%	14%	OR=1.25 (0.98, 1.60) (p=0.07)	16%	15%	OR=1.10 (0.88, 1.38) (p=0.42)
	Mean	0.18	0.15	IRR=1.21 (0.98, 1.50) (p=0.08)	0.16	0.15	IRR=1.06 (0.87, 1.29) (p=0.56)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ISNI, index of local sensitivity to nonignorability; OR, odds ratio

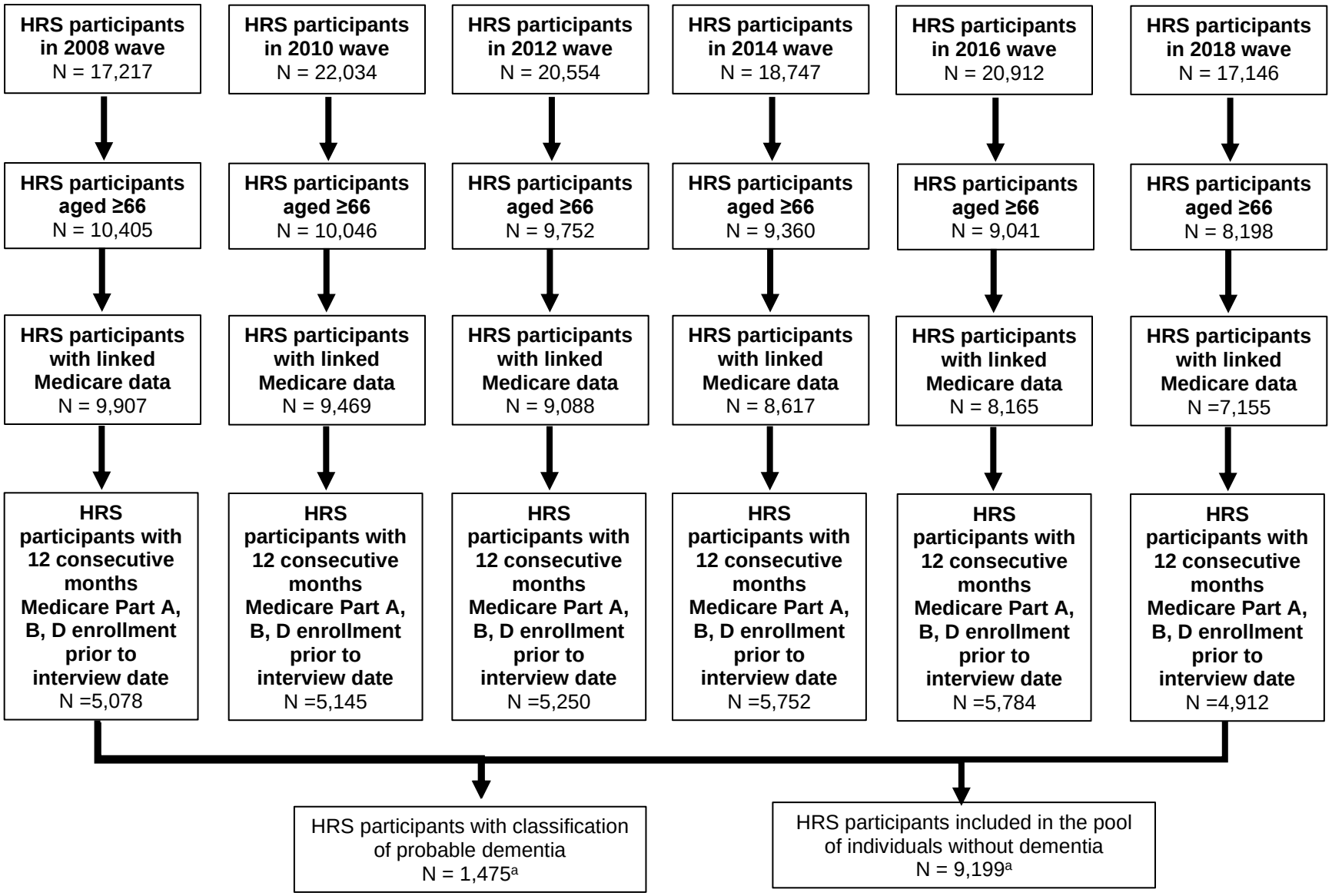
Supplementary Figure S1: Example outline of cohort entry and timing of medication assessment for an individual enrolled in the Health and Retirement study[a]



Abbreviations: EFTF, enhanced face-to-face; HRS, Health and Retirement Study

a This figure represents an example participant in the Health and Retirement Study who was followed for multiple interview waves. During their first interview wave, the participant did not have a dementia classification. During their second interview wave 2 years later, the participant had a dementia classification and participated in the enhanced face-to-face interview. During their third interview wave 2 years later, the participant had an additional non-enhanced face to face interview. Since we prioritized waves in which the individual participated in the enhanced face to face interview, we would select the second interview wave as the index date (first date when the individual was classified as having dementia and had enhanced face to face interview performed). Medication use was then assessed in the 1-year period prior to this index date. For over-aggressive treatment of diabetes/hypertension, we used a 6-month look-back period.

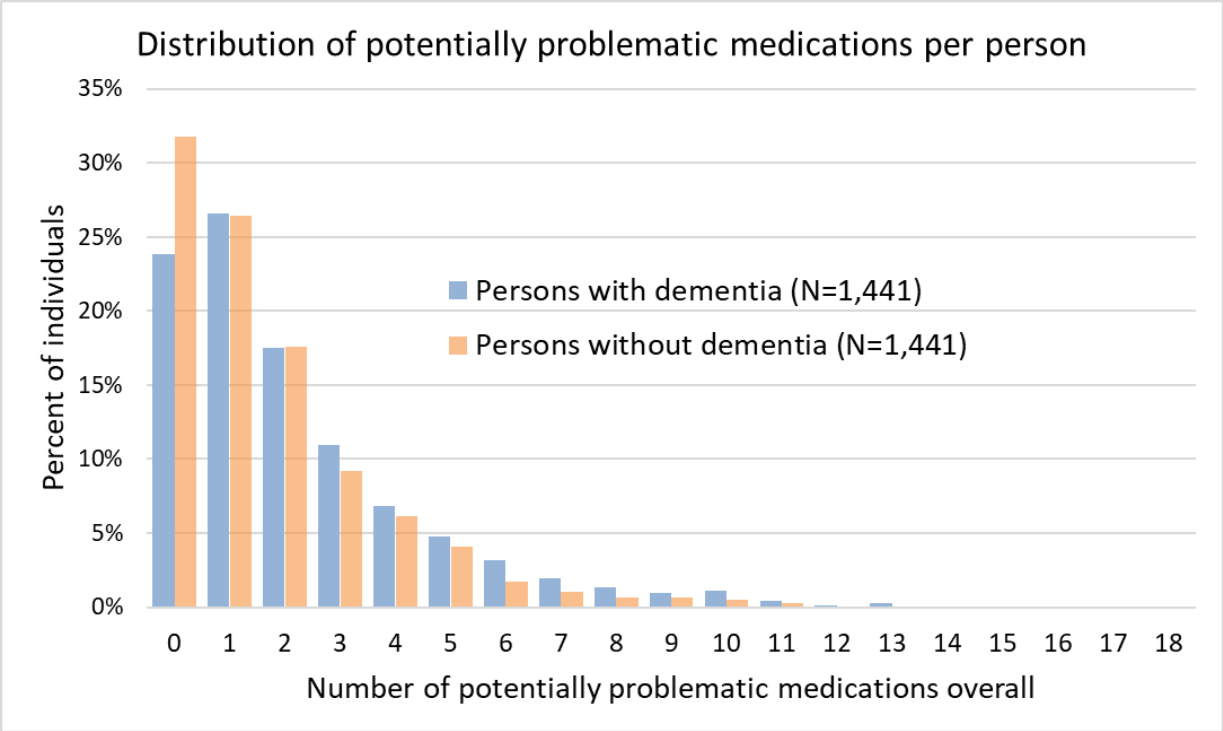
Supplementary Figure S2: Flow chart of individuals aged 66 years and older with and without dementia in the Health and Retirement Study from 2008-2018 included in this study



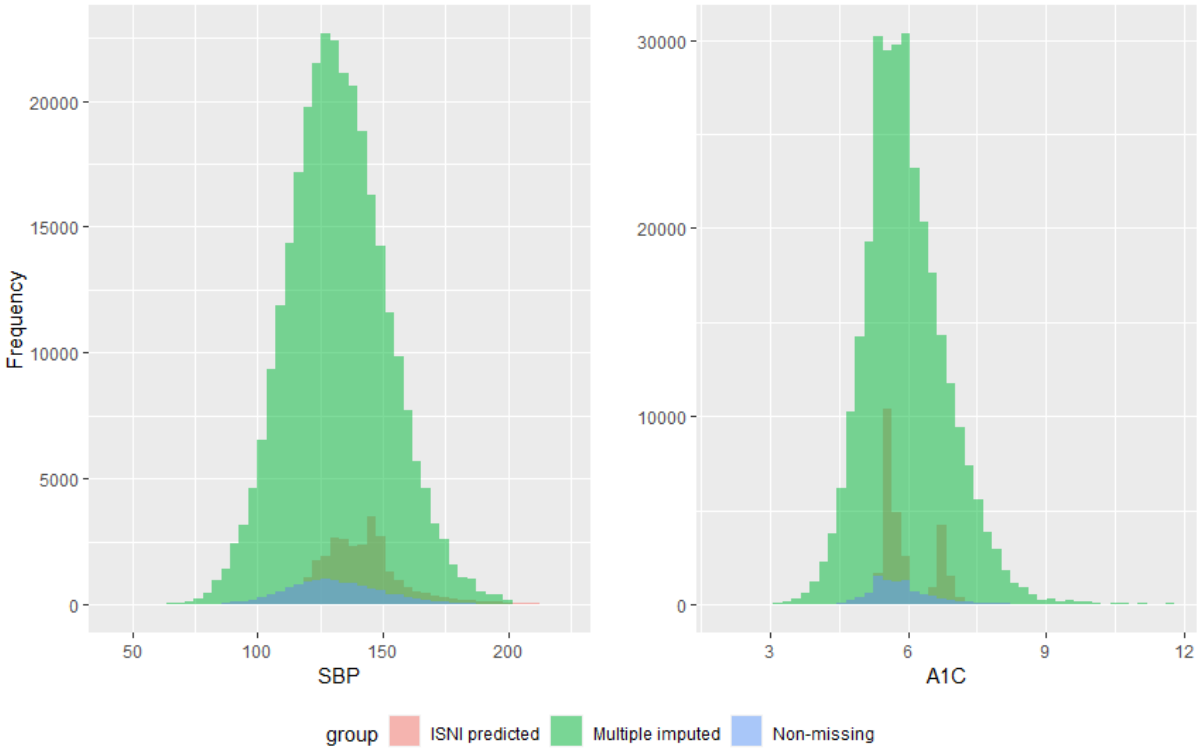
Abbreviations: HRS, Health and Retirement Study

a In the figure, many individuals participated in multiple HRS interview waves. Therefore, the sum total of people in at least one wave is much greater than the sum of participants in each individual wave. After applying our inclusion and exclusion criteria, a total of 9,844 distinct individuals were ultimately eligible. From this cohort, 1,475 distinct individuals were classified as having dementia during the study period based on the dementia classification algorithm. There were 9,199 individuals who were included in the control pool. The sum of these numbers (1,475 + 9,199 = 10,674) is greater than 9,844 as some individuals were included in the control pool during earlier waves (no classification of dementia) before eventually having a classification of dementia during a later wave. For example, an individual who was interviewed in 2008 and 2010 and not classified as having dementia would be included in the control pool for those time points but could later be included in the dementia pool if they were classified as having dementia at the 2012 HRS interview wave.

Supplementary Figure S3: Distribution of the number of potentially problematic medications identified across all criteria among persons with and without dementia in the primary matched cohort



Supplementary Figure S4: Histograms representing the distribution of systolic blood pressure and hemoglobin A1c values under the different methods, including index of local sensitivity to nonignorability (ISNI), multiple imputation, and non-missing observed data



Abbreviations: A1c, hemoglobin A1c; ISNI, index of local sensitivity to nonignorability; SBP, systolic blood pressure

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Supplementary Appendix: Details on the characterization of different criteria included in this study

Domain	Criteria
Medication overuse	Over-aggressive treatment of diabetes
Medication overuse	Over-aggressive treatment of hypertension
Strongly anticholinergic	Selected antiarrhythmics (disopyramide)
Strongly anticholinergic	Selected antidepressants
Strongly anticholinergic	Selected antiemetics
Strongly anticholinergic	First generation antihistamines
Strongly anticholinergic	Urinary antimuscarinics
Strongly anticholinergic	Antiparkinson anticholinergics (e.g., benztropine/trihexyphenidyl)
Strongly anticholinergic	Selected antipsychotics
Strongly anticholinergic	Antispasmodics
Strongly anticholinergic	Selected skeletal muscle relaxants
Sedative-hypnotics	Benzodiazepines
Sedative-hypnotics	Z-drugs
Sedative-hypnotics	Selected antiepileptic drugs
Sedative-hypnotics	Selected antipsychotics
Sedative-hypnotics	Selected antihistamines
Sedative-hypnotics	Additional antidepressant
STOPPFrail	Lipid-lowering therapies (statins, ezetimibe, sequestrants, fibrates, niacin)
STOPPFrail	Memantine in moderate to severe dementia
STOPPFrail	Theophylline and aminophylline
STOPPFrail	Anti-resorptive/bone anabolic drugs for osteoporosis
STOPPFrail	NSAIDs for >2 months
STOPPFrail	Drugs for overactive bladder (muscarinic antagonists and mirabegron)
Beers (2019 version)	First generation antihistamines
Beers (2019 version)	Antiparkinsonian agents
Beers (2019 version)	Antispasmodics
Beers (2019 version)	Dipyridamole
Beers (2019 version)	Nitrofurantoin
Beers (2019 version)	Peripheral alpha-1 blockers for hypertension
Beers (2019 version)	Central alpha-agonists for hypertension (excluding clonidine)
Beers (2019 version)	Disopyramide
Beers (2019 version)	Nifedipine, immediate release
Beers (2019 version)	Selected antidepressants
Beers (2019 version)	Antipsychotics except in schizophrenia/bipolar
Beers (2019 version)	Barbiturates
Beers (2019 version)	Benzodiazepines
Beers (2019 version)	Meprobamate
Beers (2019 version)	Z-drugs
Beers (2019 version)	Ergoloid mesylates
Beers (2019 version)	Androgens without hypogonadism
Beers (2019 version)	Desiccated thyroid
Beers (2019 version)	Estrogens (oral/topical patch)
Beers (2019 version)	Growth hormone
Beers (2019 version)	Megestrol
Beers (2019 version)	Long-acting sulfonylureas
Beers (2019 version)	Metoclopramide except for gastroparesis
Beers (2019 version)	PPI for >8 weeks unless high-risk patient
Beers (2019 version)	Meperidine
Beers (2019 version)	Non-COX-selective NSAIDs, chronic use (>90 days)
Beers (2019 version)	Indomethacin, ketorolac
Beers (2019 version)	Skeletal muscle relaxants

Beers (2019 version)	Desmopressin
Beers (2019 version)	Cilostazol in heart failure
Beers (2019 version)	NSAIDs (all) in heart failure
Beers (2019 version)	Thiazolidinediones in heart failure
Beers (2019 version)	Cholinesterase inhibitors in syncope
Beers (2019 version)	Peripheral alpha-1 blockers in syncope
Beers (2019 version)	Tertiary TCAs in syncope
Beers (2019 version)	Selected antipsychotics in syncope
Beers (2019 version)	Selected antiemetics in Parkinson disease
Beers (2019 version)	Selected antipsychotics in Parkinson disease
Beers (2019 version)	Non-COX-selective NSAIDs with GI ulcers
Beers (2019 version)	NSAIDS (all) in CKD Stage 4 or higher
Beers (2019 version)	Estrogen in women with urinary incontinence
Beers (2019 version)	Peripheral alpha-1 blockers in women with urinary incontinence
Beers (2019 version)	Strongly anticholinergic drugs with LUTS/BPH
Beers (2019 version)	Opioid and benzodiazepine in combination
Beers (2019 version)	Opioid and gabapentin/pregabalin in combination
Beers (2019 version)	Strongly anticholinergic and strongly anticholinergic in combination
Beers (2019 version)	Three or more CNS-active drugs
Beers (2019 version)	TMP-SMX with reduced kidney function
Beers (2019 version)	Amiloride with reduced kidney function
Beers (2019 version)	Apixaban with reduced kidney function
Beers (2019 version)	Dabigatran with reduced kidney function
Beers (2019 version)	Dofetilide with reduced kidney function
Beers (2019 version)	Edoxaban with reduced kidney function
Beers (2019 version)	Fondaparinux with reduced kidney function
Beers (2019 version)	Rivaroxaban with reduced kidney function
Beers (2019 version)	Spironolactone with reduced kidney function
Beers (2019 version)	Triamterene with reduced kidney function
Beers (2019 version)	Duloxetine with reduced kidney function
Beers (2019 version)	Tramadol with reduced kidney function
Beers (2019 version)	Probenecid with reduced kidney function
STOPP Version 2	Verapamil/diltiazam with heart failure
STOPP Version 2	Beta-blocker and verapmil/diltiazem in combination
STOPP Version 2	Beta-blocker with bradycardia/heart block
STOPP Version 2	Centrally-acting antihypertensives
STOPP Version 2	PDE-5 inhibitors in heart failure
STOPP Version 2	Antiplatelet/anticoagulant with significant bleeding risk
STOPP Version 2	Ticlopidine
STOPP Version 2	NSAID and anticoagulant in combination
STOPP Version 2	TCAs in dementia, glaucoma, BPH/urinary retention, cardiac issues
STOPP Version 2	Anticholinergic antipsychotics with BPH/urinary retention
STOPP Version 2	Selected antipsychotics in Parkinson disease
STOPP Version 2	Strongly anticholinergics in dementia
STOPP Version 2	Antipsychotics in BPSD
STOPP Version 2	Cholinesterase inhibitors in bradycardia/syncope/heart block
STOPP Version 2	Levodopa or dopamine agonists for benign essential tremor
STOPP Version 2	First generation antihistamines
STOPP Version 2	Digoxin at doses > 125 ug/day with reduced kidney function
STOPP Version 2	Direct thrombin inhibitors with reduced kidney function
STOPP Version 2	Factor Xa inhibitors with reduced kidney function
STOPP Version 2	NSAIDs with reduced kidney function
STOPP Version 2	Colchicine with reduced kidney function

STOPP Version 2	Metformin with reduced kidney function
STOPP Version 2	Selected antiemetics with Parkinson disease (metoclopramide/prochlorperazine)
STOPP Version 2	PPI for >8 weeks unless high-risk patient
STOPP Version 2	Theophylline as monotherapy in COPD
STOPP Version 2	Antimuscarinic bronchodilators with specific comorbidities (inhaled anticholinergics)
STOPP Version 2	COX-2 selective NSAIDs with CV disease
STOPP Version 2	Oral bisphosphonate with GI issues
STOPP Version 2	Bladder antimuscarinics with dementia, narrow angle glaucoma, BPH
STOPP Version 2	Long-acting sulfonylureas
STOPP Version 2	Thiazolidinediones in heart failure
STOPP Version 2	Estrogens with breast cancer/VTE
STOPP Version 2	Androgens without hypogonadism
STOPP Version 2	Benzodiazepines
STOPP Version 2	Z-drugs
STOPP Version 2	Strongly anticholinergic and strongly anticholinergic in combination (same as Beers)

Medication Overuse

METADATA ID	METADATA Description	METADATA	A Diagnosis code	B Diagnosis code	C Medication code *Aspirin*	RISK	NOTES	Limitations/Issues
Aspirin	Aspirin for primary prevention of ASCVD in participant aged 70 years and older	ICD9 ICD10 Medication variable	Omitted as very few people are getting aspirin through prescription					Most of the people are receiving dipyridamole/aspirin combination which is unlikely to represent a primary prevention population

METADATA ID	METADATA Description	METADATA	A Medication code *Iron*	B Diagnosis code *Iron deficiency anemia*	RISK	CODE	NOTES	Limitations/Issues
Iron supplementation	Prescription for iron in the absence of diagnosis code for iron deficiency anemia	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people are getting iron through prescription					

METADATA ID	METADATA Description	METADATA	A Laboratory value *A1c*	B Medication code *Insulin*	C Medication code *Sulfonylurea*	D Diagnosis code *Type 2 diabetes*	RISK	CODE	NOTES	Limitations/Issues
Over-aggressive treatment of diabetes	Prescription for insulin or sulfonylureas with A1c < 7.5% in patient with diabetes	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable Laboratory value	A1c < 7.5%	insulin	sulfonylurea	250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92 E11*	A & (B | C within 180 days of A1c)	A & (Prescription for B | C within 180 days prior to A1c blood draw) & D	1. Only include diagnosis codes for Type 2 diabetes (do not want to include patients with Type 1 diabetes) 2. Only includes medications with highest hypoglycemia risk 3. Assess medication prescription 180 days before	Presumes doctor knows a recent A1c although they will not have the HRS blood draw result. Cannot differentiate decreasing insulin dose in response to A1c < 7.5.

METADATA ID	METADATA Description	METADATA	A Diagnosis codes	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Over-aggressive treatment of hypertension	Prescription for antihypertensive medication with average SBP < 110 mm Hg during enhanced face to face interview	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	See supplementary methods section for details				1. Time window of prescription within 180 days of BP measurement 2. Applies only to those with average SBP < 110 based on 3 measurements during face-to-face interview	Defining over-treatment based on blood pressure readings on a single day, which may not be reflective of blood pressures over longer time period

Medications inappropriate near the end of life (only applied to those with limited life expectancy)

Rules represent the STOPPFrail criteria applied to participants with limited life expectancy, which was operationalized as 50% mortality rate at 1 year based on the Gagne mortality index. This corresponds to a comorbidity score >9 (https://pubmed.ncbi.nlm.nih.gov/21208778/). Applying the STOPPFrail criteria to EHR data was partially adapted from "Use and Deprescribing of Potentially Inappropriate Medications in Frail Nursing Home Residents" (https://link.springer.com/article/10.1007%2Fs40266-020-00805-7).

METADATA ID	METADATA Description	METADATA	A Medication code Antihyperlipidemics	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Lipid-lowering therapies	Lipid-lowering therapies, including statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antihyperlipidemics		A	A	1. Antihyperlipidemics variable includes all statins (with statin combinations), ezetimibe, bile acid sequestrants, fibrates, niacin	Bile acid sequestrants are sometimes used off-label for chronic diarrhea

METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Antihypertensive therapies	Antihypertensive therapies (carefully reduce or discontinue these drugs in patients with systolic blood pressure (SBP) persistently <130 mmHg.)	Omitted due to difficulty in defining SBP persistently < 110 and addressed in other category using SBP < 110						

METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Anti-anginal therapy in absence of symptoms	Anti-anginal therapy (specifically, nitrates, nicorandil, ranolazine). Aim to carefully reduce and discontinue these drugs in patients who he've had no reported anginal symptoms in the previous 12 months AND who have no proven or objective evidence of coronary artery disease	Omitted due to difficulty in operationalizing definition						

METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Antiplatelets for primary ASCVD prevention	Antiplatelets for primary cardiovascular prevention	Omitted as very few participants were receiving prescribed aspirin						

METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Aspirin for atrial fibrillation	Aspirin for stroke prevention in atrial fibrillation	Omitted as very few participants were receiving prescribed aspirin						

METADATA ID	METADATA Description	METADATA	A Medication code Antipsychotics	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Antipsychotics in patients with dementia	Neuroleptic antipsychotics in patients with dementia: Aim to reduce dose and discontinue these drugs in patients taking them for longer than 12 weeks if there are no current clinical fixtures of behavioural and psychiatric symptoms of dementia (BPSD).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing dose reductions					

METADATA ID	METADATA Description	METADATA	A Medication code Memantine	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Memantine in moderate to severe dementia	Memantine: Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	memantine		A	A	1. Not able to operationalize "unless memantine has clearly improved BPSD." Memantine may be appropriate to continue in PWD in last year of life in ways that we are not able to capture	

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis	C Medication code	D Medication code	E Medication code	RISK	CODE	NOTES	Limitations/Issues
			PPI high dose	*Barrett's esophagus, GI ulcer, esophagitis, GI hemorrhage*	*Anticoagulant (e.g., warfarin, factor Xa inhibitor, direct thrombin inhibitors)*	*Any NSAID*	*Corticosteroids*				
Proton pump inhibitors for extended duration	Proton pump inhibitors: Reduce dose of proton pump inhibitors when used at full therapeutic dose ≥8 weeks, unless persistent dyspeptic symptoms at lower maintenance dose	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing								

METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	RISK	CODE	NOTES	Limitations/Issues
H2 antagonists for extended duration	H2 antagonist: Reduce dose of H2 antagonist when used at full therapeutic dose ≥8 weeks, unless persistent dyspeptic symptoms at lower maintenance dose	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					

METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	RISK	CODE	NOTES	Limitations/Issues
Theophylline and aminophylline	Theophylline and aminophylline (narrow therapeutic index, doubtful therapeutic benefit and require monitoring of serum levels)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	theophylline	aminophylline	A | B	A | B		

METADATA ID	METADATA Description	METADATA	A Medication code *Leukotriene antagonist*	B Diagnosis code *COPD*	C Diagnosis code *Asthma*	Diagnosis code *Allergic rhinitis*	RISK	CODE	NOTES	Limitations/Issues
Leukotriene antagonists in setting of COPD	Leukotriene antagonists (montelukast, zafirlukast) in setting of COPD. Only indicated in asthma.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing							

METADATA ID	METADATA Description	METADATA	A Medication code Calcium	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Calcium supplements	Calcium supplements: Unlikely to be of any benefit in short-term unless proven, symptomatic hypocalcemia	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people receive prescriptions for calcium supplements					

METADATA ID	METADATA Description	METADATA	A Medication code Vitamin D	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Vitamin D	Vitamin D (ergocalciferol and colecalciferol): Lack of clear evidence to support the use of vitamin D to prevent falls and fractures, cardiovascular events or cancers.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people receive prescriptions for vitamin D					

METADATA ID	METADATA Description	METADATA	A Medication code *Osteoporosis drugs*	B Diagnosis code *Osteoporosis*	C Diagnosis code *Secondary malignant neoplasm of bone*	RISK	CODE	NOTES	Limitations/Issues
Anti-resorptive/bone anabolic drugs for osteoporosis	Anti-resorptive/bone anabolic drugs for osteoporosis (bisphosphonates, strontium, teriparatide, denosumab)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	osteoporosis	13.4 / 733.0* MU3013 / M80*, M81*	198.5 C79.51	A &&	A && & IC	1. We attempt to exclude those participants who are receiving biophosphonates (e.g., zoledronic acid) for bony metastases using ICD diagnosis code of secondary malignant neoplasm of bone	

METADATA ID	METADATA Description	METADATA	A Medication code NSAID	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Long-term oral NSAID (>2 months)	Long-term oral NSAID use: Increased risk of side effects (e.g. peptic ulcer disease, bleeding, worsening heart failure) when taken regularly for ≥2 months.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaid		A && duration > 2 months	A && duration > 2 months	1. Includes all NSAIDs. 2. Using this definition will include people who are on NSAID + PPIs	

METADATA ID	METADATA Description	METADATA	A Medication code *Corticosteroids*	B Diagnosis code *Certain rheumatologic conditions (e.g., PMR, RA, GPA)*	C Diagnosis code *Adrenal insufficiency*	RISK	CODE	NOTES	Limitations/Issues
Long-term corticosteroids (>2 months)	Long-term oral corticosteroids: Increased risk of major side effects when taken regularly for ≥2 months. Consider careful dose reduction and discontinuation.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing and challenging to determine appropriateness of steroids at end of life (e.g., steroids for end-stage COPD)						

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Drugs for BPH in catheterized male patients	Drugs for benign prostatic hyperplasia (5-alpha reductase inhibitors and alpha-blockers) in catheterised male patients: No benefit with long-term bladder catheterisation	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on catheried patients					

METADATA ID	METADATA Description	METADATA	A Medication code *Overactive bladder medications*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Drugs for overactive bladder	Drugs for overactive bladder (muscarinic antagonists and mirabegron): No benefit in patients with persistent, irreversible urinary incontinence unless clear history of painful detrusor hyperactivity	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	urinary_all				1. Exclude "clear history of painful detrusor hyperactivity" 2. "Urinary_all" medication classification includes urinary antimuscarinics and mirabegron	

METADATA ID	METADATA Description	METADATA	A Medication code *Diabetes medications (insulin and sulfonylureas)*	B Laboratory value	C Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
				A1c < 7.5%	*Type 2 diabetes*				
Anti-diabetic drugs	Anti-diabetic drugs (avoid A1c targets <7.5% associated with net harm in this population)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as covered under medication overuse category						

METADATA ID	METADATA Description	METADATA	A Medication code *Multivitamin*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Multivitamins	Multivitamin combination supplements: Discontinue when prescribed for prophylaxis rather than treatment of hypovitaminosis	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to limited number of people getting these prescribed					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Folic acid	Folic acid: Discontinue when treatment course is completed. The usual treatment duration is 1–4 months unless malabsorption, malnutrition or concomitant methotrexate use	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people getting these prescribed					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Nutritional supplements	Nutritional supplements: Discontinue when prescribed for prophylaxis rather than treatment of malnutrition.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as these are not prescribed					

Strongly anticholinergic medications

High-risk anticholinergic medications from the 2019 American Geriatrics Society Beers criteria Table 7

METADATA ID	METADATA Description	METADATA	A Medication code *disopyramide*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antiarrhythmics	Disopyramide	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	disopyramide		A	A		
ID	**Description**		**Medication code** *Anticholinergic antidepressants*	**Diagnosis code**				
Antidepressants	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine, protriptyline, and trimipramine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antidepressants_AC		A	A		
METADATA ID	METADATA Description	METADATA	A Medication code *Antiemetics*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antiemetics	prochlorperazine, promethazine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antiemetics		A	A		
METADATA ID	METADATA Description	METADATA	A Medication code *First generation antihistamine*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antihistamines (first generation)	brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine (oral), doxylamine, hydroxyzine, meclizine, clidinium-chlordiazepoxide, dicyclomine, homatropine (excludes ophthalmic), methscopolamine, propantheline, promethazine, pyrilamine, triprolidine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	first_gen_antihistamine		A	A		
METADATA ID	METADATA Description	METADATA	A Medication code *Antimuscarinics*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antimuscarinics (urinary incontinence)	darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Antimuscarinics		A	A		
METADATA ID	METADATA Description	METADATA	A Medication code *Antiparkinsonian agents*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antiparkinsonian agents	benztropine, trihexyphenidyl	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	ac_park		A	A		
METADATA ID	METADATA Description	METADATA	A Medication code *Antipsychotics*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antipsychotics	chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine, trifluoperazine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antipsychotics_beers		A	A	1. All these medications also included in highly sedating list	
METADATA ID	METADATA Description	METADATA	A Medication code *Antispasmodics*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antispasmodics	atropine, belladonna alkaloids, scopolamine (excluded ophthalmic)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antispasmodics		A	A		
METADATA ID	METADATA Description	METADATA	A Medication code *Skeletal muscle relaxants*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Skeletal muscle relaxants	cyclobenzaprine, orphenadrine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	muscle		A	A		

Sedative hypnotics

Medication list modified from sedative load model and Growdon et al. (2020)

METADATA ID	METADATA Description	METADATA	A Medication code / Diagnosis code	B	RISK	CODE	NOTES	Limitations/Issues
			Benzodiazepines					
Benzodiazepines	Alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, prazepam, clobazam, clonazepam, midazolam, estazolam, flurazepam, quazepam, remimazolam, remazepam, triazolam	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	benzo		A	A		
			Non-benzo sedative hypnotics					
Nonbenzodiazepine sedative hypnotics	Zolpidem, zaleplon, eszopiclone	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	z_drug		A	A		
			antiepileptic					
Selected antiepileptic drugs	Phenobarbital, gabapentin, pregabalin	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antiepileptic		A	A		
			Sedating antipsychotics					
Selected antipsychotics	All first generation antipsychotics, quetiapine, olanzapine, and clozapine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antipsychotics_sedating		A	A		
			Promethazine & diphenhydramine					
Antihistamine	Promethazine and diphenhydramine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antihistamine_sedative_load		A	A		
			Doxepin					
Additional antidepressant	Doxepin	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	doxepin		A	A	1. Includes low-dose doxepin for insomnia	

STOPP Version 2 Criteria

Definitions modified from: Ribe et al. 2021 (https://bmjopen.bmj.com/content/11/7/e046756) & Huibers et al. 2019 (https://pubmed.ncbi.nlm.nih.gov/30914175/)

METADATA ID	METADATA Description	METADATA	A Medication code *Digoxin*	B Diagnosis code *diastolic heart failure*	C Diagnosis code *atrial fibrillation*	RISK	CODE	NOTES	Limitations/Issues
B1. Digoxin for heart failure with normal systolic funcction	Stop digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on systolic ventricular function						

METADATA ID	METADATA Description	METADATA	A Medication code *Verapamil or diltiazem*	B Diagnosis code *Heart failure*	RISK	CODE	NOTES	Limitations/Issues
B2. Verapamil or diltiazem + NYHA Class III or IV heart failure	Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	verapamil_diltiazem	428*, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 I50*, I11.0, I13.0, I13.2	A	A &B	1. "NYHA Class III or IV heart failure" excluded from definition. 2. No well-established criteria for assessing heart failure from diagnosis codes. The ICD codes included here reflect a consensus from several different sources.	

METADATA ID	METADATA Description	METADATA	A Medication code *tw*	B Medication code *verapamil/diltiazem*	RISK	CODE	NOTES	Limitations/Issues
B3. Beta-blocker + verapamil/diltiazem	Beta-blocker in combination with verapamil or diltiazem (risk of heart block).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	beta_blocker	verapamil_diltiazem	A & B	A & B (overlapping prescription)	1. Impossible to know from prescription drug data whether the patient was taking both simultaneously versus patient being told by physician to take one instead of the other	

METADATA ID	METADATA Description	METADATA	A Medication code *beta-blocker*	B Diagnosis code *Bradycardia*	C Diagnosis code *Heart block*	D Measurement *Heart rate*	RISK	CODE	NOTES	Limitations/Issues
B4. Beta-blocker with bradycardia or heart block	Beta blocker with bradycardia (< 50/min), type II heart block, or complete heart block (risk of complete heart block, asystole)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Measurement Medication variable	beta_blocker	427.8 I49.5, R00.1	426.0, 426.10, 426.12, 426.13, 426.6, 426.9, 746.86 I44.1, I44.2, I44.3, I45.5, I45.9, Q24.6	HR < 50	A	A & (B | C | D within 6 months of beta-blocker prescription)	1. Diagnosis code for bradycardia/heart block or HR measurement < 50 within 6 months of beta-blocker prescription 2. Heart rate measurement comes from HRS face-to-face interview	

METADATA ID	METADATA Description	METADATA	A Medication code *Amiodarone*	B Diagnosis code *SVT*	C Medication code *Beta blocker, digoxin, verapamil, diltiazem*	RISK	CODE	NOTES	Limitations/Issues
B5. Amiodarone as first-line antiarrhythmic for SVT	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing first-line therapy						

METADATA ID	METADATA Description	METADATA	A Medication code *Loop diuretics*	B Diagnosis code *Hypertension*	C Medication code *Other antihypertensives (CCBs, thiazides, ACEi/ARB, potassium-sparing)*	D Diagnosis code *Chronic kidney disease*	E Diagnosis code *Heart failure*	RISK	CODE	NOTES	Limitations/Issues
B6. Loop diuretic as first-line treatment for hypertension	Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing first-line therapy								

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
B7. Loop diuretic for dependent ankle edema	Loop diuretic for dependent ankle edema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
B8. Thiazide diuretics with electrolyte abnormalities	Stop thiazide diuretic with current significant hypokalaemia (i.e. serum K+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on lab values					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
B9. Loop diuretic and urinary incontinence	Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
B10. Centrally-acting antihypertensives	Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	cns_alpha_agonists		A	A	1. 'Not possible to code 'unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives'.	

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
B11. ACEi/ARB in hyperkalemia	Stop ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalemia.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on lab values					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
B12. Aldosterone antagonists and ACEi/ARB without monitoring	Stop aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l) – serum K should be monitored regularly, i.e. at least every 6 months).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on lab values and frequency of monitoring for hyperkalemia					

METADATA ID	METADATA Description	METADATA	A Medication code *PDE-5 inhibitors*	B Diagnosis code *Heart failure*	C Medication code *Nitrates (excluding PRN nitrates)*	RISK	CODE	NOTES	Limitations/Issues
B13. PDE-5 inhibitors in heart failure	Stop phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterized by hypotension i.e. systolic BP < 90 mmHg, or concurrent	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10		428*, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13. 404.91. 404.93 I50*, I11.0, I13.0, I13.2		A	A & [B | C]	1. Excludes PRN nitrates like sublingual nitroglycerin	1. Not possible to encode severe heart failure

	~~[illegible] or 30 mg/day, or concurrent~~ nitrate therapy for angina (risk of cardiovascular collapse)	Medication variable	pde			nitrates					
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
C1. Long-term aspirin > 160 mg/day	Stop long-term aspirin at doses greater than 160mg per day	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people receiving prescribed aspirin								
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
C2. Aspirin and PUD	Stop aspirin with a past history of peptic ulcer disease without concomitant PPI	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people receiving prescribed aspirin								
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	C Diagnosis code	D Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
			Antiplatelet agents, vitamin K antagonists, direct thrombin inhibitors, factor Xa inhibitors	*Bleeding diathesis*	*Recent GI bleeding*	*Cerebral hemorrhage*					
C3. Antiplatelets or anticcoagulants with concurrent significant bleeding risk	Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antiplatelets, anticoagulant	286.0, 286.1, 286.4, 287.31 D66, D67, D68.0, D69.3	578.0, 578.1, 578.9 K92.0, K92.1, K92.2	430*, 431*, 432* I60*, I61*, I62*	A	A & [B | C | D within 1 year]	1. "Uncontrolled severe hypertension" not coded. 2. Diagnosis code present within 1 year of prescription.		
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
C4. Aspirin and clopidogrel as secondary stroke prevention	Stop aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people receiving prescribed aspirin								
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
C5. Aspirin & anticoagulant	Stop aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people receiving prescribed aspirin								
METADATA ID	METADATA Description	METADATA	A Medication code	B Medication code	C Diagnosis code	D Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
			Antiplatelets	*Anticoagulant*	*Coronary implant (CABG or PCI)*	*Acute coronary syndrome*					
C6. Antiplatelets & anticoagulant	Stop antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (no added benefit from dual therapy)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing from claims data								
METADATA ID	METADATA Description	METADATA	A Medication code *Ticlopidine*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
C7. Ticlopidine	Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side-effects).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Ticlopidine		A	A					
METADATA ID	METADATA Description	METADATA	A Medication code *Anticoagulants*	B Diagnosis code *Deep venous thrombosis*	B Diagnosis code *Pulmonary embolus*	B Diagnosis code *Atrial fibrillation*	B Diagnosis code *Mechanical heart value*	RISK	CODE	NOTES	Limitations/Issues
C8. Anticoagulant for first DVT without continuing provoking risk factors for > 6 months	Stop vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing from claims data								
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
C9. Anticoagulant for first PE without continuing provoking risk factors for > 12 months	Stop vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing from claims data								
METADATA ID	METADATA Description	METADATA	A Medication code *Anticoagulants*	B Medication code *NSAID*	RISK	CODE	NOTES	Limitations/Issues			
C10. NSAID and anticoagulant in combination	Stop NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	anticoagulant	nsaid	A	A & B	1. nsaid medication variable includes all NSAIDs but excludes topicals				
METADATA ID	METADATA Description	METADATA	A Medication code *Antiplatelets*	B Medication code *NSAID*	B Medication code *PPI*	RISK	CODE	NOTES	Limitations/Issues		
C11. NSAID and antiplatelet agents without PPI prophylaxis	Stop NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antiplatelets, aspirin	nsaid	ppi	A & B	A & B & IC		Many people are likely getting PPIs over the counter		
METADATA ID	METADATA Description	METADATA	A Medication code *TCAs*	B Diagnosis code *Narrow angle glaucoma*	C Diagnosis code *Cardiac conduction abnormalities*	D Diagnosis code *BPH/urinary retention*	RISK	CODE	NOTES	Limitations/Issues	
D1. TCAs & specific conditions	Stop tricyclic antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	tca	365.2 H40.2	426 I44*, I45*	600*, 788.2* N40, R33	A	A & (B | C | D)			
METADATA ID	METADATA Description	METADATA	A Medication code *TCAs*	B Diagnosis code *Depression*	A Medication code *Other antidepressants (SSRIs, SNRIs, mirtazapine, etc)*	RISK	CODE	NOTES	Limitations/Issues		
D2. TCAs as first-line antidepressants	Stop Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in defining first-line therapy								
METADATA ID	METADATA Description	METADATA	A Medication code *Anticholinergic antipsychotics*	B Diagnosis code *BPH/urinary retention*	RISK	CODE	NOTES	Limitations/Issues			
D3. Anticholinergic neuroleptics with history of BPH/urinary retention	Stop neuroleptics with moderate-marked anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antipsychotics_ac_d3	600*, 788.2* N40, R33	A	A & B					
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues			
D4. SSRIs with hyponatremia	Stop selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatremia (risk of exacerbating or precipitating hyponatremia).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on sodium values								
METADATA	METADATA	METADATA	A	B	RISK	CODE	NOTES	Limitations/Issues			

ID	Description		Medication code *Benzodiazepines*	Diagnosis code				
D5. Benzodiazepines for >4 weeks	Stop benzodiazepines for ≥ 4 weeks (no indication for longer treatment; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	STOPP K1 is a broader category so this is excluded					

METADATA ID	METADATA Description	METADATA	A **Medication code** *Antipsychotics (except quetiapine, clozapine, and pimavanserin)*	B **Diagnosis code** *Parkinson disease and Lewy body disease*	RISK	CODE	NOTES	Limitations/Issues
D6. Antipsychotics in parkinsonism/LBD	Stop antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antipsychotics_beers_park	332, 333.0, 331.6, 331.82 G20, G21, G22, G23, G31.83, G31.85	A	A & B		

METADATA ID	METADATA Description	METADATA	A **Medication code** *Anticholinergic medications to treat EPS (e.g., benztropine)*	B **Diagnosis code** *Antipsychotics*	RISK	CODE	NOTES	Limitations/Issues
D7. Anticholinergics to treat EPS	Stop anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in determining reason for use of medications to treat EPS (and shows up in anticholinergic domain)					

METADATA ID	METADATA Description	METADATA	A **Medication code** *Anticholinergic medications from Beer's Table 7*	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
D8. Anticholinergics in dementia/delirium	Stop anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	anticholinergics_table_7		A	A	1. This criterion applies to all patients in the dementia cohort. "Anticholinergics/antimuscarinics" overlaps with anticholinergic medications from Beer's Table 7	

METADATA ID	METADATA Description	METADATA	A **Medication code** *Antipsychotics*	B **Diagnosis code** *Schizophrenia*	C **Diagnosis code** *Bipolar disorder*	RISK	CODE	NOTES	Limitations/Issues
D9. Antipsychotics in BPSD	Stop neuroleptic antipsychotic in patients with behavioral and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Antipsychotics_all	ICD9 295 (Shizophrenic disorders), 297 (delusional disorders), 298 (other nonorganic psychoses), 301.2 (Shizoid personality disorder), OR CCS 5.10 (Schizophrenia and other psychotic disorders) ICD 10 F20-F29 (Schizophrenia, schizotypal, and delusional disorders) OR CCS MBD001 (Schizophrenia spectrum and other psychotic disorders)	ICD9 296 (Episodic mood disorders) OR CCS 5.8.1 (Bipolar disorders) ICD10 F30 (manic episode), F31 (bipolar affective disorder) OR CCS MBD003 (Bipolar and related disorders)	A	A & (!B | !C)	1. We exclude patients with diagnosis code for schizophrenic disorders/psychosis or bipolar disorder. 2. Medication definition includes all antipsychotics (1st and 2nd generation)	1. Excluded "unless symptoms are severe and other non-pharmacological treatments have failed"

METADATA ID	METADATA Description	METADATA	A **Medication code**	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
D10. Neuroleptics as hypnotics	Stop neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing (and overlap with D9 given that entire cohort is patients with dementia)					

METADATA ID	METADATA Description	METADATA	A **Medication code** *Cholinesterase inhibitors*	B **Diagnosis code** *Syncope*	C **Diagnosis code** *Bradycardia*	D **Diagnosis code** *Heart block*	E **Vital sign** *Heart rate*	F **Medication** *Beta-blocker, digoxin, diltiazem, verapamil*	RISK	CODE	NOTES	Limitations/Issues
D11. ChEIs with bradycardia/heart block	Stop acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	chei	780.2 R55	427.8 I49.5, R00.1	426.0, 426.10, 426.12, 426.13, 426.6, 426.9, 746.86 I44.1, I44.2, I44.3, I45.5, I45.9, Q24.6	<60 beats/min	beta_blocker, digoxin, verapamil_diltiazem	A	A & [B within 1 year | C within 1 year | D within 1 year | E within 1 year| F (overlapping prescription with A)]		

METADATA ID	METADATA Description	METADATA	A **Medication code**	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
D12. Phenothiazines	Stop phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this is covered in other criterion and due to difficulty in operationalizing first-line therapy					

METADATA ID	METADATA Description	METADATA	A **Medication code** *Levodopa & dopamine agonists*	B **Diagnosis code** *Benign essential tremor*	C **Diagnosis code** *Parkinson disease and Lewy body disease*	RISK	CODE	NOTES	Limitations/Issues
D13. Levodopa or dopamine agonists for benign essential tremor	Stop levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	parkinson	781.0, 333.1 G25.0	332, 333.0, 331.6, 331.82 G20, G21, G22, G23, G31.83, G31.85	A	A & B & !C	1. Parkinson medication variables includes levodopa and dopamine agonists 2. Exclude diagnosis of Parkinson disease, secondary Parkinsonism, Lewy body dementia, etc	

METADATA ID	METADATA Description	METADATA	A **Medication code** *First generation antihistamines*	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
D14. First-generation antihistamines	Stop first-generation antihistamines (safer, less toxic antihistamines now widely available).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	first_gen_antihistamine		A	A		

METADATA ID	METADATA Description	METADATA	A **Medication code** *digoxin*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
E1. Digoxin at doses greater than 125 ug/day	Stop digoxin at a long-term dose greater than 125ug/day if eGFR < 30 ml/min/1.73m2 (risk of digoxin toxicity if plasma levels not measured).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	digoxin	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A at TDD greater than 125 ug/day	(A at TDD greater than 125 ug/day) & [B | C]		

METADATA ID	METADATA Description	METADATA	A **Medication code** *Direct thrombin inhibitors*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
E2. Direct thrombin inhibitors if eGFR < 30	Stop direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m2 (risk of bleeding)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	thrombin	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A	A & (B | C)		

METADATA	METADATA	METADATA	A	B	C	RISK	CODE	NOTES	Limitations/Issues

ID	Description		Medication code *Factor Xa inhibitors*	Diagnosis code *CKD Stage 5 or higher*	Laboratory value *Cystatin C*				
E3. Factor Xa inhibitors if eGFR < 15	Stop factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m2 (risk of bleeding)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	factor_Xa	585.5, 585.6 N18.5, N18.6	Calculated eGFR < 15	A	A & (B | C)		
METADATA ID	METADATA Description	METADATA	A Medication code *NSAIDs (all)*	B Diagnosis code *CKD Stage 3 or higher*	C Laboratory value *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
E4. NSAIDs if eGFR < 50	Stop NSAID's if eGFR < 50 ml/min/1.73m2 (risk of deterioration in renal function).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaid	585.3, 585.4, 585.5, 585.6 N18.3, N18.4, N18.5, N18.6	Calculated eGFR < 50	A	A & (B | C)	1. Using a definition of CKD Stage 3 or higher although technically CKD Stage 3 starts at eGFR 60	
METADATA ID	METADATA Description	METADATA	A Medication code *colchicine*	B Diagnosis code *CKD Stage 5 or higher*	C Laboratory value *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
E5. Colchicine if eGFR < 10	Stop colchicine if eGFR < 10 ml/min/1.73m2 (risk of colchicine toxicity)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	colchicine	585.5, 585.6 N18.5, N18.6	Calculated eGFR < 10	A	A & (B | C)		
METADATA ID	METADATA Description	METADATA	A Medication code *metformin*	B Diagnosis code *CKD Stage 4 or higher*	C Laboratory value *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
E6. Metformin if eGFR < 30	Stop metformin if eGFR < 30 ml/min/1.73m2 (risk of lactic acidosis).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	metformin	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A	A & (B | C)		
METADATA ID	METADATA Description	METADATA	A Medication code *Metoclopramide or prochlorperazine*	C Diagnosis code *Parkinson disease and Lewy body disease*	RISK	CODE	NOTES	Limitations/Issues	
F1. Prochlorperazine or metoclopramide with Parkinsonism	Stop prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	metoclopramide	332, 333.0, 331.6, 331.82 G20, G21, G22, G23, G31.83, G31.85	A	A & B	1. Metoclopramide medication code includes metoclopramide and prochlorperazine		
METADATA ID	METADATA Description	METADATA	A Medication code *High dose PPI*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
F2. PPIs at full dose	Stop PPI for uncomplicated peptic ulcer disease or erosive peptic esophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	ppi		A (>8 weeks or 60 days)	A (>8 weeks or 60 days)			
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
F3. Drugs likely to cause constipation	Stop drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing						
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
F4. High-dose iron	Stop oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate> 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate> 1800 mg/day; no evidence of enhanced iron absorption above these doses).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to rarity of people receiving prescription iron						
METADATA ID	METADATA Description	METADATA	A Medication code *Theophylline*	B Medication code *Inhaled corticosteroids, antimuscarinic, beta-adrenergics*	RISK	CODE	NOTES	Limitations/Issues	
G1. Theophylline as monotherapy in COPD	Stop theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing						
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
G2. Systemic corticosteroids for COPD	Stop systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing (definition of moderate/severe COPD, excluding alternative reasons for steroids)						
METADATA ID	METADATA Description	METADATA	A Medication code *Anti-muscarinic bronchodilators*	B Diagnosis code *Narrow angle glaucoma*	C Diagnosis code *BPH/urinary retention*	RISK	CODE	NOTES	Limitations/Issues
G3. Antimuscarinic bronchodilators with specific comorbidities	Stop anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	inhaled_anticholinergic	356.2 H40.2	600*, 788.2* N40, R33	A	A & (B | C)		
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
G4. Benzo and acute/crhonic respiratory failure	Stop benzodiazepines with acute or chronic respiratory failure i.e. pO2 < 8.0 kPa ± pCO2 > 6.5 kPa (risk of exacerbation of respiratory failure).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on respiratory failure						
METADATA ID	METADATA Description	METADATA	A Medication code *NSAID (non-COX-2 inhibitors)*	B Diagnosis code *History of PUD, GI bleeding*	C Medication code *PPI*	D Medication code *H2 antagonist*	RISK	CODE	NOTES	Limitations/Issues
H1. NSAIDs with GI issues unless PPI/H2 antagonist	Stop non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaid_3	530.2*, 531*, 532*, 533*, 534*, 578* K22.1, K25, K26, K27, K28, K92.0, K92.1, K92.2	ppi	h2a	A	A & B & !(C | D)	
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
H2. NSAID and severe hypertension/heart failure	Stop NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to lack of information on severe hypertension/heart failure						
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
H3. NSAIDs for OA where Tylenol has not been tried	Stop Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing (many people receive Tylenol OTC)						
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	
H4. Corticosteroids for RA	Stop long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing						
METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues	

H5. Corticosteroids for OA	Stop corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing (OA is very common; when looking at overlap between OA and corticosteroid, the use of corticosteroid is likely for another condition)						
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *NSAID*	**B Medication code** *colchicine*	**C Diagnosis code** *Gout*	**RISK**	**CODE**	**NOTES**	Limitations/Issues
H6. Long-term NSAID or colchicine for gout	Stop long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing (even with diagnosis code for gout, NSAID could be for different indication; hard to tell if there is a contraindication to allopurinol)						
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *COX-2 inhibitors*	**B Diagnosis code** *ASCVD*	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
H7. COX-2 selective NSAIDs with concurrent CV disease	Stop COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	cox2	410*, 411*, 412, 413*, 414*, V45.82, V45.81, 36.0, 36.1 I20*, I21*, I22*, I24*, I25*, Z95.5, Z95.1	A	A & B			
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *NSAID*	**B Medication code** *Corticosteroids*	**C Medication code** *PPI*	**RISK**	**CODE**	**NOTES**	Limitations/Issues
H8. NSAID and corticosteroids without PPI prophylaxis	Stop NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaid	steroids	ppi	A	A & B & IC		Many people may be getting PPIs over the counter
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *Oral bisphosphonate*	**B Diagnosis** *Barrett's esophagus, GI ulcer, esophagitis, GI hemorrhage*	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
H9. Oral bisphosphonates with GI issues	Stop oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, esophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	oral_bisphosphonate	530.1 (esophagitis), 530.2 (ulcer of esophagus), 530.85 (Barrett's esophagus), 531 (gastric ulcer), 532 (duodenal ulcer), 533 (peptic ulcer site unspecified), 534 (gastrojejunal ulcer), 535 (gastritis and duodenitis), 537 (other disorders of stomach and duodenum), 578 (gastrointestinal hemorrhage), 251.5 (abnormality of secretion of gastrin) K20 (esophagitis), K21.0 (GERD with esophagitis), K22.1 (ulcer of esophagus), K22.7 (Barrett's esophagus), K25 (gastric ulcer), K26 (duodenal ulcer), K27 (peptic ulcer), K28 (gastrojejunal ulcer), K29 (gastritis and duodenitis), K31 (other diseases of stomach and duodenum), K92 (other diseases of digestive system - includes GI hemorrhage), E16.4 (increased secretion of gastrin)	A	A & B within 1 year			
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *Bladder antimuscarinic drugs*	**B Diagnosis code** *Narrow angle glaucoma*	**C Diagnosis code** *BPH/urinary retention*	**RISK**	**CODE**	**NOTES**	Limitations/Issues
I1. Bladder antimuscinarics with certain conditions	Stop antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antimuscarinics	365.2 H40.2	600*, 788.2* N40, R33	A	A		
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *Alpha-1 blockers*	**B Diagnosis code** *Orthostatic hypotension*	**C Diagnosis code** *Syncope*	**RISK**	**CODE**	**NOTES**	Limitations/Issues
I2. Selective alpha-1 blockers in orthostatic hypotension/syncope	Stop selective alpha-1 blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing						
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *Long-acting sulfonylureas (chlorpropamide, glimepiride, glyburide, glipizide ER)*	**B Diagnosis code**	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
J1. Long-acting sulfonylureas	Stop sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	sulfonylurea_LA		A	A	1. Same as Beers criteria		
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *TZD*	**B Diagnosis code** *Heart failure*	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
J2. TZDs in heart failure	Stop thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	tzd	428*, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 I50*, I11.0, I13.0, I13.2	A	A & B	1. Same as Beers criteria		
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code**	**B Diagnosis code**	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
J3. Beta-blockers with frequent hypoglycemic episodes	Stop beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycemic symptoms).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing "frequent hypoglycemic episodes"						
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *Estrogens*	**B Diagnosis code** *Breast cancer*	**C Diagnosis code** *VTE*	**RISK**	**CODE**	**NOTES**	Limitations/Issues
J4. Estrogens with history of breast cancer or VTE	Stop estrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	estrogens	174, 233.0 C50, D05	452, 453, 415.1 I80*, I81*, I82*, I26*	A	A & (B | C)		
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code**	**B Diagnosis code**	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
J5. Oral estrogens without progesterone	Stop oral estrogens without progesterone in patients with intact uterus (risk of endometrial cancer).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to unreliability in assessing whether participant has intact uterus based on ICD diagnosis code for hysterectomy alone						
METADATA ID	**METADATA Description**	**METADATA**	**A Medication code** *Androgens*	**B Diagnosis code** *Hypogonadism*	**RISK**	**CODE**	**NOTES**	Limitations/Issues	
		ICD9 / CCS for ICD9		257.1, 257.2, 758.7					

J6. Androgens in absence of specific indication	Stop androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).	ICD10 / CCS for ICD10		E29.1, E89.5, Q98.0, Q98.1, Q98.2, Q98.4	A	A & IB	1. Same as Beers criteria	
		Medication variable	androgens					
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *Benzodiazepines*	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
K1. Benzodiazepines	Stop benzodiazepines (sedative, may cause reduced sensorium, impair balance).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	benzo		A	A	1. Same as sedative-hypnotics benzo variable	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
K2. Antipsychotics	Stop neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this category is covered in D9 (dementia with BPSD symptoms)					
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
K3. Vasodilator drugs	Stop vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *eszopiclone, zaleplon, zolpidem*	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
K4. Hypnotic Z-drugs	Stop hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	z_drug		A	A	1. Same as Beers criteria variable	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
L1. Opioids	Stop use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing first-line therapy					
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
L2. Opioids without laxative	Stop use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing as many people receives laxatives OTC					
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *Anticholinergics*	B **Diagnosis code**	RISK	CODE	NOTES	Limitations/Issues
M. Concomitant use of two or more drugs with anticholinergic properties	Stop concomitant use of two or more drugs with antimuscarinic/anticholinergic properties	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	anticholinergics_table_7		A & A	A & A (overlapping prescriptions for 2 drugs with anticholinergic properties)		

2019 Beers criteria

Criteria taken from American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

METADATA ID	METADATA Description	METADATA	A Medication code *1st generation antihistamines*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
First generation antihistamines	Brompheniramine, Carbinoxamine, Chlorpheniramine, Clemastine, Cyproheptadine, Dexbrompheniramine, Deschlorpheniramine, Dimenhydrinate, Diphenhydramine (oral), Doxylamine, Hydroxyzine, Meclizine, Promethazine, Pyrilamine, Triprolidine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	first_gen_antihistamine_beers		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Antiparkinson Anticholinergics*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antiparkinsonian agents	Benztropine and trihexyphenidyl	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	ac_park		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Antispasmodics*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antispasmodics	Atropine (excludes ophthalmic), Belladonna alkaloids, Clidinium-chlordiazepoxide, Dicyclomine Homatropine (excludes opthalmic), Hyoscyamine, Methscopolamine, Propantheline, Scopolamine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antispasmodics_beers		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Dipyridamole*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Dipyridamole, oral short-acting	Dipyridamole, oral short acting (does not apply to the extended-release combination with aspirin)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Dipyridamole		A	A	1. Excludes aspirin-dipyridamole combination	

METADATA ID	METADATA Description	METADATA	A Medication code *Nitrofurantoin*	B Diagnosis code *CKD Stage 4 or higher*	C Laboratory value *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Nitrofurantoin	Nitrofurantoin has potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use. Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nitrofurantoin	585.4, 585.5, 585.6 N18.4. N18.5. N18.6	Calculated eGFR < 30	A	(A & (B | C)) | (A & days supply >= 30)	1. Criterion will apply to two different scenarios (first, in those who are on nitrofurantoin and have eGFR < 30; second, in those who are on long-term suppression defined as number of pills > 30 over a 3 month period)	

METADATA ID	METADATA Description	METADATA	A Medication code *Alpha 1 blocker*	B Diagnosis code *BPH/LUTS*	B Diagnosis code *PTSD*	RISK	CODE	NOTES	Limitations/Issues
Peripheral alpha-1 blockers for treatment of hypertension	Doxazosin, prazosin, terazosin	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	alpha_1_beers	CCS 10.2.1 (hyperplasia of prostate) and CCS 10.1.8 (genitourinary symptoms and ill-defined conditions) CCS GEN012 (hyperplasia of prostate) and CCS GEN008 (urinary incontinence)	ICD9 309* (adjustment reaction - includes PTSD and others) CCS MBD007 (trauma- and stress-related disorders) or ICD10 F43 (reaction to severe stress, and adjustment disorders)	A	A & (B | C)	1. Alpha-1 blockers are indicated for other conditions (e.g., BPH/LUTS) which we try to exclude	

METADATA ID	METADATA Description	METADATA	A Medication code *CNS alpha agonists (guanabenz, guanfacine, methyldopa, reserpine > 0.1 mg/day)*	RISK	CODE	NOTES	Limitations/Issues
Central alpha-agonists	Avoid clonidine for first-line treatment of hypertension. Avoid other CNS alpha-agonists (guanabenz, guanfacine, methyldopa, reserpine > 0.1 mg/day)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	cns_alpha_agonists	A	A	1. "Avoid clonidine for first-line treatment" was not taken into account due to difficulty in operationalizing	

METADATA ID	METADATA Description	METADATA	A Medication code *disopyramide*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Disopyramide	Avoid disopyramide (may induce heart failure; strongly anticholinergic)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	disopyramide		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Dronaderone	Avoid dronaderone in individuals with permanent atrial fibrillation or severe/recently decompensated heart failure	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to rarity of use and not included in Medi-Span classification					

METADATA ID	METADATA Description	METADATA	A Medication code *Digoxin*	B Diagnosis code *SVT (AF/AFL)*	RISK	CODE	NOTES	Limitations/Issues
Digoxin for first-line treatment of AF or heart failure	Avoid this rate control agent as first line therapy for atrial fibrillation. Avoid as first-line therapy for heart failure. If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/day	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					

METADATA ID	METADATA Description	METADATA	A Medication code *nifedipine, immediate release*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Nifedipine, immediate release	Avoid nifedipine, immediate release (potential for hypotension; risk of precipitating myocardial ischemia)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nifedipine		A	A	1. Medication definition excludes ER formulations	

METADATA ID	METADATA Description	METADATA	A Medication code *amiodarone*	B Diagnosis code *Heart failure*	RISK	CODE	NOTES	Limitations/Issues
Amiodarone	Avoid as first-line therapy for AF unless patient has HF or substantial LVH	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					

METADATA ID	METADATA Description	METADATA	A Medication code *Antidepressants*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antidepressants	Avoid amitriptyline, amoxapine, clomipramine, desipramine, doxepin > 6 mg/day, imipramine, nortriptyline, paroxetine, protriptyline, trimipramine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antidepressants_AC		A	A	Same variable as the strongly anticholinergic antidepressants	

METADATA ID	METADATA Description	METADATA	A Medication code *Antipsychotics (1st and 2nd gen)*	B Diagnosis code *Schizophrenia*	C Diagnosis code *Bipolar disorder*	D Medication code *Antiemetics (Prochlorperazine or Promethazine)*	RISK	CODE	NOTES	Limitations/Issues
Antipsychotics, first (conventional) and second (atypical) generation	Avoid, except in schizophrenia or bipolar disorder, or for short-term use as antiemetic during chemotherapy	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antipsychotics_1st_gen, antipsychotics_2nd_gen	ICD9 295 (Schizophrenic disorders), 297 (delusional disorders), 298 (other nonorganic psychoses), 301.2 (Schizoid personality disorder), OR CCS 5.10 (Schizophrenia and other psychotic disorders) ICD 10 F20-F29 (Schizophrenia, schizotypal, and delusional disorders) OR CCS MBD001 (Schizophrenia spectrum and other psychotic disorders)	ICD9 296 (Episodic mood disorders) OR CCS 5.8.1 (Bipolar disorders) ICD10 F30 (manic episode), F31 (bipolar affective disorder) OR CCS MBD003 (Bipolar and related disorders)	antiemetics	A	A & (B | IC | (ID & days supply < 30))		1. Very difficult to operationalize "short-term use as antiemetic during chemotherapy". We exclude prescriptions <30 days for prochlorperazine/promethazine.

METADATA ID	METADATA Description	METADATA	A Medication code *Barbiturates*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Barbiturates	Avoid Amobarbital, Butabarbital, Butalbital, Mephobarbital, Pentobarbital, Phenobarbital, Secobarbital	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	barbiturates		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Benzodiazepines*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Benzodiazepines	Avoid Alprazolam, Estazolam, Lorazepam, Oxazepam, Temazepam, Triazolam, Chlordiazepoxide (alone or in combination with amitriptyline or clidinium), Clonazepam, Clorazepate, Diazepam, Flurazepam	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	benzo		A	A	Same variable as the sedative-hypnotics variable	

METADATA ID	METADATA Description	METADATA	A Medication code *Meprobamate*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Meprobamate	Avoid meprobamate (high rate of physical dependence; sedating)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	meprobamate		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *eszopiclone, zaleplon, zolpidem*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (Z-drugs)	Avoid eszopiclone, zaleplon, zolpidem	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	z_drug		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Ergoloid mesylate or isoxsuprine*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Ergoloid mesylates, isoxsuprine	Avoid ergoloid mesylates (dehydrogenated ergot alkaloids) and isoxsuprine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	ergoloid_isoxsuprine		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Testosterone*	B Diagnosis code *Hypogonadism*	RISK	CODE	NOTES	Limitations/Issues
Androgens	Avoid methyltestosterone or testosterone unless indicated for confirmed hypogonadism with clinical symptoms	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	androgens	ICD 9 257.1, 257.2, 758.7 ICD 10 E29.1, E89.5, Q98.0, Q98.1, Q98.2, Q98.4	A	A & IB	1. Not able to operationalize "with clinical symptoms"	

METADATA	METADATA	METADATA	A	B	RISK	CODE	NOTES	Limitations/Issues

ID	Description		Medication code *Desiccated thyroid (eark, beef)*	Diagnosis code				
Desiccated thyroid	Avoid desiccated thyroid (concerns about cardiac effects, safer alternatives available)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	desiccated_thyroid		A	A	1. Defined based on Thyroid (Pork), Thyroid (Beef), and Thyroid Strong tablets	

METADATA ID	METADATA Description	METADATA	A Medication code *Estrogens*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Estrogens with or without progestins	Avoid systemic estrogen (oral and topical patch)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	estrogens		A	A	1. Estrogen medication variable definition excludes vaginal cream/tablets	

METADATA ID	METADATA Description	METADATA	A Medication code *Growth hormone*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Growth hormone	Avoid except for patients rigorously diagnosed with GH deficiency due to an established etiology	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	growth_hormone	253.2 (panhypopit), 253.3 (pituitary dwarfism), 253.4 (other anterior pituitary disorders), 253.7 (iatrogenic pituitary disorders), 253.8 (other disorders), 253.9 (unspecified disorder) E23* (hypofunction and other disorders of the pituitary eland)	A	A & IB		1. Not able to confirm that diagnosis of GH deficiency was well established

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Insulin, sliding scale		ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as not able to determine if participant is receiving sliding scale insulin					

METADATA ID	METADATA Description	METADATA	A Medication code *megestrol*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Megestrol	Avoid megestrol	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	megestrol		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Long-acting sulfonylurea*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Long-acting sulfonylureas	Chlorpropamide, glimepiride, glyburide	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	sulfonylurea_LA		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Metoclopramide*	B Diagnosis code *Gastroparesis*	RISK	CODE	NOTES	Limitations/Issues
Metoclopramide	Avoid unless for gastroparesis with duration of use not to exceed 12 weeks except in rare cases	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	metoclopramide_beers	536.3 K31.84	A	A & IB		1. Only factor in metoclopramide use in absence of gastroparesis diagnosis. Do not factor in "duration of use not to exceed 12 weeks" due to difficulty in determining this.

METADATA ID	METADATA Description	METADATA	A Medication code *Mineral oil*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Mineral oil, oral	Avoid oral mineral oil	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing					

METADATA ID	METADATA Description	METADATA	METADATA	A Medication code *PPI*	B Diagnosis *Barrett's esophagus, GI ulcer, esophagitis, GI hemorrhage*	C Medication code *Anticoagulant (e.g., warfarin, factor Xa inhibitor, direct thrombin inhibitors)*	D Medication code *Any NSAID*	E Medication code *Corticosteroids*	RISK	CODE	NOTES	Limitations/Issues
PPI	Avoid scheduled PPI use for >8 weeks unless for high-risk patients	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	ppi	530.1 (esophagitis), 530.2 (ulcer of esophagus), 530.85 (Barrett's esophagus), 531 (gastric ulcer), 532 (duodenal ulcer), 533 (peptic ulcer site unspecified), 534 (gastrojejunal ulcer), 535 (gastritis and duodenitis), 537 (other disorders of stomach and duodenum), 578 (gastrointestinal hemorrhage), 251.5 (abnormality of secretion of gastrin) K20 (esophagitis), K21.0 (GERD with esophagitis), K22.1 (ulcer of esophagus), K22.7 (Barrett's esophagus), K25 (gastric ulcer), K26 (duodenal ulcer), K27 (peptic ulcer), K28 (gastrojejunal ulcer), K29 (gastritis and duodenitis), K31 (other diseases of stomach and duodenum), K92 (other diseases of digestive system - includes GI hemorrhage), E16.4 (increased secretion of gastrin)	anticoagulant	nsaid	steroids	A & Continuous duration > 8 weeks (60 days)	A & Duration > 8 weeks & (IB | IC (overlapping prescription) | ID (overlapping prescription) | IE (overlapping prescription))	1. Definition attempts to capture those on long-term PPI without an indication. We exclude a number of conditions such as esophagitis, GI ulcers, Barrett's esophagus, concomitant use of anticoagulation/NSAID. We do not exclude diagnosis codes for uncomplicated gastroesophageal reflux disease. 3. This definition of PPI excludes PPI/NSAID combinations, PPI/aspirin combinations, and H pylori treatment combinations.	Might not capture all people who have legitimate reason for long-term PPI Use

METADATA ID	METADATA Description	METADATA	A Medication code *Meperidine*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Meperidine	Avoid	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	meperidine		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *NSAIDs (excluding COX2 inhibitors)*	C Medication code *PPI or misoprostol*	RISK	CODE	NOTES	Limitations/Issues
Non-COX-selective NSAIDs	Avoid chronic use of aspirin >325 mg/day, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Ibuprofen, Ketoprofen, Meclofenamate, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaids_2	ppi_misoprostol	A	(A & duration > 3 months) & IB	1. Chronic use operationalized as prescription > 3 months	"Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton-pump inhibitor or misoprostol)" - Not able to factor in whether other alternatives have been tried and many people buy PPIs OTC

METADATA ID	METADATA Description	METADATA	A Medication code *Indomethacin and ketorolac*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Indomethacin, ketorolac	Avoid	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	indomethacin_ketorolac		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Muscle relaxants*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Skeletal muscle relaxants	Avoid carisoprodol, Chlorzoxazone, Cyclobenzaprine, Metaxalone, Methocarbamol, Orphenadrine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	muscle_2		A	A		

METADATA ID	METADATA Description	METADATA	A Medication code *Desmopressin*	B Diagnosis code *Polyuria-fracturia*	RISK	CODE	NOTES	Limitations/Issues
Desmopressin	Avoid for treatment of nocturia or nocturnal polyuria	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	desmopressin	788.4 (frequency of urination and polyuria) R35 (polyuria)	A	A & B		

METADATA ID	METADATA Description	METADATA	A Medication code *Cilostazol*	B Diagnosis code *Heart failure*	RISK	CODE	NOTES	Limitations/Issues
Cilostazol in heart failure	Avoid cilostazol in heart failure	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	cilostazol	428*, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 I50*, I11.0, I13.0, I13.2	A	A & B		

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Nondihydropyridine CCBs in HFrEF	Avoid nondihydropyridine CCBs (diltiazem, verapamil) in HFrEF	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in establishing diagnosis of HFrEF in claims data					

METADATA ID	METADATA Description	METADATA	A Medication code *NSAIDs - all*	B Diagnosis code *Heart failure*	RISK	CODE	NOTES	Limitations/Issues
NSAIDs and COX-2 inhibitors in HFrEF	NSAIDs and COX-2 inhibitors: use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaid	428*, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 I50*, I11.0, I13.0, I13.2	A for greater than 30 days	A for greater than 30 days (coded as days_supply > =30) & B	1. Not able to asses symptomatic vs. asymptomatic heart failure. Instead, we require a >30 day prescription for NSAID to not penalize short-term prescriptions for NSAIDs which may be warranted.	

METADATA ID	METADATA Description	METADATA	A Medication code *Thiazolidinediones*	B Diagnosis code *Heart failure*	RISK	CODE	NOTES	Limitations/Issues
TZDs in HFrEF	Thiazolidinediones (pioglitazone, rosiglitazone): use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	tzd	428*, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 I50*, I11.0, I13.0, I13.2	A	A & B	1. Not able to asses symptomatic vs. asymptomatic heart failure.	

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Dronaderone in HFrEF	Dronaderone: use with caution in patients with heart failure who are asymptomatic; avoid in patients with symptomatic heart failure	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as not readily available in the United States					

METADATA ID	METADATA Description	METADATA	A Medication code *Cholinesterase inhibitors*	B Diagnosis code *Syncope*	C Diagnosis code *Bradycardia*	D Diagnosis code *Heart block*	E Vital sign *Heart rate*	RISK	CODE	NOTES	Limitations/Issues
		ICD9 / CCS for ICD9 ICD10 / CCS for ICD10		780.2 R55	427.8 I49.5, R00.1	426.0, 426.10, 426.12, 426.13, 426.6. 426.9. 746.86 I44.1, I44.2, I44.3, I45.5, I45.9, Q24.6					

AChEIs in syncope	AChEI cause bradycardia and should be avoided in older adults whose syncope may be due to bradycardia	Medication variable	chei				Pulse < 50 (any measured heart rate less than 50 during face to face interview)	A	A & [B | C | D | E]	

METADATA ID	METADATA Description	METADATA	A Medication code *Non-selective alpha-1 blockers*	B Diagnosis code *Syncope*	C Diagnosis code *Orthostatic hypotension*	RISK	CODE	NOTES	Limitations/Issues
Non-selective peripheral alpha-1 blockers in syncope	Nonselective peripheral alpha-1 blockers cause orthostatic blood pressure changes and should be avoided in older adults whose syncope may be due to orthostatic hypotension.	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	alpha_1_beers	780.2 R55	458 I95.1	A	A & [B | C]		

METADATA ID	METADATA Description	METADATA	A Medication code *Tertiary tricyclic antidepressants*	B Diagnosis code *Syncope*	C Diagnosis code *Bradycardia*	D Diagnosis code *Heart block*	E Diagnosis code *Orthostatic hypotension*	RISK	CODE	NOTES	Limitations/Issues
Tertiary TCAs in syncope	Tertiary TCAs increase the risk of orthostatic hypotension or bradycardia	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	tca_tertiary	780.2 R55	427.8 I49.5, R00.1	426.0, 426.10, 426.12, 426.13, 426.6, 426.9, 746.86 I44.1, I44.2, I44.3, I45.5, I45.9, Q24.6	458 I95.1	A	A & [B | C | D | E]		

METADATA ID	METADATA Description	METADATA	A Medication code *Selected antipsychotics*	B Diagnosis code *Syncope*	C Diagnosis code *Bradycardia*	D Diagnosis code *Heart block*	E Diagnosis code *Orthostatic hypotension*	RISK	CODE	NOTES	Limitations/Issues
Antipsychotics in syncope	Chlorpromazine, thioridazine, and olanzapine increase the risk of orthostatic hypotension or bradycardia	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antipsychotics_beers_3	780.2 R55	427.8 I49.5, R00.1	426.0, 426.10, 426.12, 426.13, 426.6, 426.9, 746.86 I44.1, I44.2, I44.3, I45.5, I45.9, Q24.6	458 I95.1	A	A & [B | C | D | E]		

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	C Diagnosis code	D Diagnosis code	E Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Medications in setting of delirium	Anticholinergics, antipsychotics, steroids, H2 antagonists, benzos, meperidine	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing in fair manner from claims data.								

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	C Diagnosis code	D Diagnosis code	E Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Certain medications with history of falls or fractures	Antiepileptics, antipsychotics, benzos, antidepressants, opioids	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in operationalizing in fair manner from claims data. Beers criteria does not say to avoid in general but has certain caveats such as "avoid unless safer alternatives are not available" or "avoid except for pain management in the setting of severe acute pain."								
Antiemetics (metoclopramide, prochlorperazine, promethazine) in Parkinson disease	Avoid anti-emetics with anti-dopaminergic properties due to potential to worsen parkinsonian symptoms	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	*Antiemetics (metoclopramide, prochlorperazine, promethazine)* antiemetics_beers	*Parkinson disease, Parkinson plus syndromes, Lewy Body dementia* 332, 333.0, 331.6, 331.82 G20, G21, G22, G23, G31.83, G31.85	A	A & B					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Antipsychotics (except quetiapine, clozapine, and pimavanserin) in Parkinson disease	Avoid dopamine-receptor antagonists due to potential to worsen parkinsonian symptoms	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	*Antipsychotics (except quetiapine, clozapine, and pimavanserin)* antipsychotics_beers_park	*Parkinson disease, Parkinson plus syndromes, Lewy Body dementia* 332, 333.0, 331.6, 331.82 G20, G21, G22, G23, G31.83, G31.85	A	A & B		

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Aspirin > 325 mg/day with history of gastric or duodenal ulcers	Aspirin > 325 mg/day may exacerbate existing ulcers or cause new/additional ulcers	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to rarity of prescription for aspirin					

METADATA ID	METADATA Description	METADATA	A Medication code *NSAID (excludes COX-2 inhibitors and NSAID/PPI combo)*	B Diagnosis *GI ulcer*	C Medication code *PPI or misoprostol*	RISK	CODE	NOTES	Limitations/Issues
Non-COX-2-selective NSAIDs with history of gastric or duodenal ulcers	Avoid non-COX-2-selective NSAIDs with history of gastric/duodenal ulcer unless other alternatives are not effective and patient can take gastroprotective agent (ie, proton-pump inhibitor or misoprostol)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	nsaid_3	530.2 (ulcer of esophagus). K22.1 (ulcer of esophagus), K25 (gastric ulcer), K26 (duodenal ulcer), K27 (peptic ulcer), K28 (gastrojejunal ulcer)	ppi_misoprostol	A	A & B but exclude if [B & C present]		Many people likely get PPI OTC

METADATA ID	METADATA Description	METADATA	A Medication code *NSAIDs (includes combinations; excludes topicals, ophthalmics)*	B Diagnosis code *CKD Stage 4 or higher*	B Laboratory value *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
NSAIDs in CKD stage 4 or higher (creatinine clearance < 30)	Avoid NSAIDs (all) in CKD stage 4 or higher	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable Laboratory value	nsaid	585.4, 585.5, 585.6 N18.4, N18.5	eGFR < 30 based on Cystatin C conversion when collected during HRS blood draw	A	A & [B | C]		

METADATA ID	METADATA Description	METADATA	A Medication code *Estrogen (oral and transdermal, excluding intravaginal)*	B Diagnosis code *Urinary incontinence*	RISK	CODE	NOTES	Limitations/Issues
Estrogen in urinary incontinence in women	Avoid estrogen oral and transdermal (excludes intravaginal estrogen) in women with urinary incontinence (all types)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	estrogens	788.3 N39.3, N39.4, R32	A & female	A & female & B	1. Estrogens medication variable definition excludes intravaginal estrogen	

METADATA ID	METADATA Description	METADATA	A Medication code *Peripheral alpha-1 blockers (doxazosin, prazosin, terazosin)*	B Diagnosis code *Urinary incontinence*	RISK	CODE	NOTES	Limitations/Issues
Peripheral alpha-1 blockers in women with urinary incontinence	Avoid peripheral alpha-1 blockers (doxazosin, prazosin, and terazosin) in women with urinary incontinence (all types)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	alpha_1_beers	788.3 N39.3, N39.4, R32	A & female	A & female & B		

METADATA ID	METADATA Description	METADATA	A Medication code *Anticholinergics from Table 7 except for antimuscarinics*	B Diagnosis code *BPH*	C Diagnosis code *LUTS*	RISK	CODE	NOTES	Limitations/Issues
Strongly anticholinergic drugs with LUTS/BPH	Strongly anticholinergic drugs (from Table 7) in LUTS/BPH, except antimuscarinics for urinary incontinence	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	anticholinergics_table_7_no_antimuscarinics	CCS 10.2.1 (hyperplasia of prostate) CCSR GEN012 (hyperplasia of prostate)	306.50, 306.59, 596.51, 596.52, 596.59, 596.9, 599.60, 599.69, 600.01, 600.21, 600.91, 600.11, 601.0, 601.1, 601.4, 601.8, 601.9, 788.20, 788.21, 788.41, 788.43, 788.64, 788.65, 788.3, 788.91, 788.61. 788.6. 788.63 CCSR GEN008 (urinary incontinence)	A & male	A & male & [B | C]		

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Aspirin for primary prevention of CVD and CRC	Use with caution in adults >= 70 years for primary prevention of CVD and CRC	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as very few people were receiving aspirin prescribed					

METADATA ID	METADATA Description	METADATA	A Medication code *dabigatran and rivaroxaban*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Dabigatran and rivaroxaban	Use dabigatran and rivaroxaban with caution for treatment of VTE or AF in adults >= 75 years	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this is a "use with caution criterion"					

METADATA ID	METADATA Description	METADATA	A Medication code *aripiprazol*	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Prasugrel	Use with caution in adults >= 75 years	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this is a "use with caution criterion"					

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues
Certain medications due to exacerbating/causing SIADH/hyponatremia	Use with caution antipsychotics, carbamazepine, diuretics, mirtazapine, oxcarbazepine, SNRIs, SSRIs, TCAs, tramadol	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this is a "use with caution criterion"					

METADATA ID	METADATA Description	METADATA	A Medication code *Dextromethorphan-quinidine*	B Diagnosis code *Pseudobulbar effect*	RISK	CODE	NOTES	Limitations/Issues
Dextromethorphan/quinidine	Use with caution due to limited efficacy (does not apply to treatment of PBA)	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this is a "use with caution criterion"					

METADATA ID	METADATA Description	METADATA	A Medication code *Trimethoprim-sulfamethoxazole*	B Medication code *ACEI*	C Medication code *ARB*	D Diagnosis code *CKD*	RISK	CODE	NOTES	Limitations/Issues
TMP-SMX	Use TMP-SMX with caution in patients on ACEI or ARB and decreased creatinine clearance	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted as this is a "use with caution criterion"							

METADATA ID	METADATA Description	METADATA	A Medication code	B Diagnosis code	RISK	CODE	NOTES	Limitations/Issues

			ACEI, ARB, aliskiren, or potassium-sparing diuretic	*CKD Stage 3a or higher*					
RAS inhibitors combined	RAS inhibitor (ACE, ARB, aliskiren) or potassium-sparing diuretics (amiloride, triamterene) and another RAS inhibitor in	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable				Omitted due to difficulty in determining inappropriateness			
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *opioids*	B **Medication code** *benzodiazepines*	RISK	CODE	NOTES	Limitations/Issues	
Opioid and benzodiazepines	Increased risk of overdose with opioids and benzodiazepines	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	opioids	benzo	A & B	A & B	1. Requires overlapping prescriptions for opioids and benzodiazepines		
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *opioids*	B **Medication code** *gabapentin/pregabalin*	RISK	CODE	NOTES	Limitations/Issues	
Opioids and gabapentin/pregabalin	Increased risk of severe sedation-related adverse events with opioids and gabapentin/pregabalin	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	opioids	gabapentinoids	A & B	A & B	1. Requires overlapping prescriptions for opioids and gabapentin/pregabalin	Not able to factor in some exceptions, such as transitioning from opioid therapy to gabapentin or pregabalin, or when using gabapentinoids to reduce opioid dose, although caution should be used in all circumstances	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *Anticholinergic from Table 7*	B **Diagnosis code** *Anticholinergic from Table 7*	RISK	CODE	NOTES	Limitations/Issues	
Anticholinergic and anticholinergic	Increased risk of cognitive decline	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	anticholinergics_table_7	anticholinergics_table_7	A & B	A & B	1. Requires overlapping prescription for medications in Table 7 of Beer's list		
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Medication code**	C **Medication code**	RISK	CODE	NOTES	Limitations/Issues
Combination of three or more CNS-active drugs	Antidepressants (TCAs, SSRIs, and SNRIs), antipsychotics, antiepileptics, benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs"), and opioids	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	antidepressants, tca, antiepileptic, antipsychotics_1st_gen, antipsychotics_2nd_gen, benzo, z_drug, opioids	antidepressants, tca, antiepileptic, antipsychotics_1st_gen, antipsychotics_2nd_gen, benzo, z_drug, opioids	antidepressants, tca, antiepileptic, antipsychotics_1st_gen, antipsychotics_2nd_gen, benzo, z_drug, opioids	A & B & C	A & B & C (overlapping prescriptions)		
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *NSAID (includes all NSAIDs)*	B **Medication code** *Corticosteroids (excludes ophthalmic and topical)*	RISK	CODE	NOTES	Limitations/Issues	
Corticosteroids and NSAIDs (oral or parenteral)	Avoid due to increased risk of peptic ulcer disease or GI bleeding	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *lithium*	B **Medication code** *ACEI*	RISK	CODE	NOTES	Limitations/Issues	
Lithium & ACEIs	Avoid due to increased risk of lithium toxicity	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *lithium*	B **Medication code** *loop diuretics*	RISK	CODE	NOTES	Limitations/Issues	
Lithium and loop diuretics	Avoid due to increased risk of lithium toxicity	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *Peripheral alpha-1 blockers (doxazosin, prazosin, terazosin)*	B **Medication code** *Loop diuretics*	RISK	CODE	NOTES	Limitations/Issues	
Peripheral alpha-1 blockers and loop diuretics	Avoid peripheral alpha-1 blockers and loop diuretics in older women	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *phenytoin*	B **Medication code** *TMP-SMX*	RISK	CODE	NOTES	Limitations/Issues	
Phenytoin and TMP-SMX	Increased risk of phenytoin toxicity with TMP-SMX	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *Theophylline*	B **Medication code** *cimetidine*	RISK	CODE	NOTES	Limitations/Issues	
Theophylline and cimetidine	Increased risk of theophylline toxicity	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *Theophylline*	B **Medication code** *ciprofloxacin*	RISK	CODE	NOTES	Limitations/Issues	
Theophylline and ciprofloxacin	Increased risk of theophylline toxicity	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *warfarin*	B **Medication code** *amiodarone*	RISK	CODE	NOTES	Limitations/Issues	
Warfarin and amiodarone	Increased risk of bleeding	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *warfarin*	B **Medication code** *ciprofloxacin*	RISK	CODE	NOTES	Limitations/Issues	
Warfarin and ciprofloxacin	Increased risk of bleeding	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *warfarin*	B **Medication code** *Macrolides (except azithromycin)*	RISK	CODE	NOTES	Limitations/Issues	
Warfarin and macrolides (excluding azithromycin)	Increased risk of bleeding	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *warfarin*	B **Medication code** *TMP-SMX*	RISK	CODE	NOTES	Limitations/Issues	
Warfarin and TMP-SMX	Increased risk of bleeding	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *warfarin*	B **Medication code** *NSAIDs (includes all NSAIDs)*	RISK	CODE	NOTES	Limitations/Issues	
Warfarin and NSAIDs	Increased risk of bleeding	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in determining inappropriateness				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *ciprofloxacin*	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Ciprofloxacin with reduced kidney function	Dose reduction when CrCl < 30 ml/min	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in defining dose reduction				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *TMP-SMX*	B **Diagnosis code** *CKD Stage 5 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
TMP-SMX with reduced kidney function	Dose reduction if CrCl 15-29 mL/min, avoid if CrCl < 15 mL/min	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	tmp_smx	585.5, 585.6 N18.5, N18.6	Calculated eGFR < 15	A	A & [B | C]	1. We only focus on CrCl < 15/min (not factoring in dose reduction for CrCl 15-29)	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *amiloride*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Amiloride with reduced kidney function	Avoid with CrCl < 30	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	amiloride	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A	A & [B | C]		
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *apixaban*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Apixaban with reduced kidney function	Avoid with CrCl < 25	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	apixaban	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 25	A	A & [B | C]	1. We apply CrCl <25 as CKD Stage 4 or higher	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *dabigatran*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Dabigatran with reduced kidney function	Avoid with CrCl < 30	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	dabigatran	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A	A & [B | C]		
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *dofetilide*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Dofetilide with reduced kidney function	Reduce dose if CrCl 20-59 mL/min; avoid if CrCl < 20	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	dofetilide	585.4, 585.5, 585.6 N18.4. N18.5. N18.6	Calculated eGFR < 20	A	A & [B | C]	1. We only focus on CrCl < 20 (not factoring in dose reduction)	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *edoxaban*	B **Diagnosis code** *CKD Stage 5 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Edoxaban with reduced kidney function	Reduce dose if CrCl 20-59; avoid if CrCl < 15 or > 95 mL/min	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	edoxaban	585.5, 585.6 N18.5, N18.6	Calculated eGFR < 15 or > 95	A	A & [B | C]		
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Enoxaparin with reduced kidney function	Reduce dose if CrCl < 30	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable			Omitted due to difficulty in defining dose reduction				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *fondaparinux*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Fondaparinux with reduced kidney function	Avoid if CrCl < 30	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	fondaparinux	585.4, 585.5, 585.6 N18.4. N18.5. N18.6	Calculated eGFR < 30	A	A & [B | C]		

METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *rivaroxaban*	B **Diagnosis code** *VTE (AF/AFL)*	C **Diagnosis code** *VTE*	D **Laboratory value** *Cystatin C*	E **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Rivaroxaban with reduced kidney function	Nonvalvular atrial fibrillation: reduce dose if CrCl 15-50 mL/min; avoid if CrCl <15 mL/min; Venous thromboembolism treatment and for	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	427.0, 427.3 I47.1, I48*	452. 453*. 415.1* I80*. I81*. I82*. I26*	Calculated eGFR < 15		Calculated eGFR < 30	A	A & [(B | D) | (C | E)]	Ignoring dose reduction criteria	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *spironolactone*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues		
Spironolactone with reduced kidney function	Avoid if CrCl < 30	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	spironolactone	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A	A & [B | C]				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *triamterene*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues		
Triamterene with reduced kidney function	Avoid if CrCl < 30	IC09 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	triamterene	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30	A	A & [B | C]				
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value**	RISK	CODE	NOTES	Limitations/Issues		

			duloxetine	*CKD Stage 4 or higher*	*Cystatin C*				
Duloxetine with reduced kidney function	Avoid if CrCl < 30	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	duloxetine	585.4, 585.5, 585.6 N18.4. N18.5. N18.6	Calculated eGFR < 30		A	A & [B | C]	
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Gabapentin with reduced kidney function	Reduce dose if CrCl < 60	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in defining dose reduction						
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Levetiracetam with reduced kidney function	Reduce dose if CrCl < 80	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in defining dose reduction						
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Pregabalin with reduced kidney function	Reduce dose if CrCl < 60	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in defining dose reduction						
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *tramadol ER*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Tramadol with reduced kidney function	Reduce immediate-release dose if CrCl < 30; avoid extended release if CrCl < 30	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	tramadol_ER	585.4, 585.5, 585.6 N18.4. N18.5. N18.6	Calculated eGFR < 30		A	A & [B | C]	Omitting dose reduction criteria
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
H2 antagonists with reduced kidney function	Reduce dose of cimetidine, famotidine, nizatidine, or ranitidine when CrCl < 50	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in defining dose reduction						
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code**	B **Diagnosis code**	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Colchicine with reduced kidney function	Reduce dose if CrCl < 30	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	Omitted due to difficulty in defining dose reduction						
METADATA **ID**	METADATA **Description**	METADATA	A **Medication code** *probenecid*	B **Diagnosis code** *CKD Stage 4 or higher*	C **Laboratory value** *Cystatin C*	RISK	CODE	NOTES	Limitations/Issues
Probenecid with reduced kidney function	Avoid if CrCl < 30	ICD9 / CCS for ICD9 ICD10 / CCS for ICD10 Medication variable	probenecid	585.4, 585.5, 585.6 N18.4, N18.5, N18.6	Calculated eGFR < 30		A	A & [B | C]	