A novel superior medication-based chronic disease score (medCDS) predicted all-cause mortality in independent geriatric cohorts

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Abstract

Objective

On the basis of current treatment guidelines, we developed and validated a medication-based chronic disease score (medCDS) and tested its association with all-cause mortality of older outpatients.

Study Design and Setting

Considering the most prevalent chronic diseases in the elderly German population, we compiled a list of evidence-based medicines used to treat these disorders. Based on this list, a score (medCDS) was developed to predict mortality using data of a large longitudinal cohort of older outpatients (training sample; MultiCare Cohort Study). By assessing receiver-operating characteristics (ROC curves), the performance of medCDS was then confirmed in independent cohorts (ESTHER, KORA-Age) of community-dwelling older patients and compared with already existing medication-based scores and a score using selected anatomical-therapeutic-chemical (ATC) codes.

Results

The final medCDS score had a ROC area-under-the-curve (AUC) of 0.73 (95 %-CI 0.70-0.76). In the validation cohorts, its ROC AUCs were 0.79 (0.76-0.82, KORA-Age) and 0.74 (0.71-0.78, ESTHER), which was superior to already existing medication-based scores (RxRisk, CDS) and scores based on pharmacological ATC code subgroups (ATC3) or age and sex alone (Age&Sex).

Conclusion

A new medication-based chronic disease score (medCDS), which is based on actual treatment standards, predicts mortality of older outpatients significantly better than already existing scores.

Key words:

Medication-based chronic disease score, multimorbidity, risk assessment, mortality, elderly

What is new?

1. In a prospective cohort of older patients with multiple morbidities, a new medication-based, disease-oriented score (medCDS) was developed on the basis of current treatment guidelines for the most prevalent chronic diseases in older patients.
2. medCDS more accurately predicted mortality than established medication-based scores (e.g. RxRisk or CDS), which are still used for morbidity assessment.
3. The score was validated in two independent large longitudinal cohorts of community-dwelling older patients and performed similarly well.
4. medCDS is designed to allow easy maintenance and expansion of the score as new and effective medicines become available.
5. In its current form, it performed better than an empirical score that used a set of selected anatomical-therapeutic-chemical (ATC) codes or only age and sex.

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1. Introduction

More than half of all older outpatients suffer from multiple chronic conditions (multimorbidity) [Fortin et al. 2012]. The presence of multiple morbidities is associated with several adverse outcomes such as functional impairment, reduced quality of life, frequent hospitalization, and increased mortality, health care utilization, and cost [Vogeli et al. 2007, Huntley et al. 2012, Lehnert and König 2012]. Applying disease-specific guidelines to patients with multiple morbidities may be inadequate [Fried et al. 2011, Boyd et al. 2011] because they tend to neglect patient preferences and co-morbidities and also because their benefit in patients with multiple morbidities is rarely well established. Hence, instruments to estimate disease burden and associated risks might help identifying patients in need of care and facilitate tailoring of treatment efforts.

To characterize nature and extent of disease burden, to assess its impact on different health outcomes such as mortality, hospitalization, health care utilization, or costs, and also to control confounding by co-morbidity in epidemiological studies, it is therefore necessary to measure multimorbidity. In the last two decades, several multimorbidity scores have been developed, which are either diagnosis-related or medication-based and help predicting mortality, health care utilization, and quality of life [Schneeweiss et al. 2001, Huntley et al. 2012]. While many but not all [e.g. von Korff et al. 1992] of these scores typically also include important co-factors such as age and sex, their assessment of multimorbidity varies; some scores simply count items such as diagnoses or drugs, while others differentiate between them, taking into account that not all diagnoses or drugs are equally predictive of an outcome [Huntley et al. 2012]. Theoretically, the performance of such a score can further improve if specific patient details (e.g. drug combinations to account for disease severity) are considered, but, to our knowledge, this has not yet been studied.

Medication-based scores are attractive whenever diagnostic data are not available, inconsistent, or unreliable. In these cases, medication data reflect the currently treated chronic diseases and might have better predictive values and be more reliable, complete, and timely than diagnostic data [Erler et al. 2009]. Moreover, compared to diagnosis-based chronic disease scores (e.g. the Charlson score [Charlson et al. 1987] or its modifications [Rius et al. 2008, Quan et al. 2011]), medication-based scores are robust against under-documentation of diagnoses or up-coding. However, it has to be acknowledged that not all relevant diseases (e.g. dementia) and geriatric conditions or syndromes (e.g. immobility, frailty, or falls) are sufficiently treatable with drugs and therefore part of the disease burden of a patient may go unrecognized using a medication-based approach. Many of these scores are primarily developed and optimized for the prediction of endpoints other than mortality such as cost [Von Korff et al. 1992, Clark et al. 1995, Fishman et al. 2003] and, therefore, their performance might be worse when used for other purposes. However, also these

scores predicted mortality often well [Perkins et al. 2004, Huber et al. 2013, Huntley et al. 2012, Yurkovich et al. 2015].

Examples of medication-based multimorbidity indices that are suitable for an analysis of prescription data are the Chronic Disease Score (CDS) [von Korff et al. 1992], RxRisk [Fishman et al. 2003], their modifications and updates [e.g. Clark et al. 1995, Lamers 1999, Huber et al. 2013, Radomski et al. 2017], and others [Roblin 1998]. These scores link patterns of medication prescriptions with selected chronic diseases. However, in these scores, the selection criteria of diseases are often not transparent (expert opinion) and relevant diseases are missing. Typically, these scores were not specifically developed to predict mortality but rather aimed to estimate cost [Von Korff et al. 1992, Clark et al. 1995, Lamers 1999, Fishman et al. 2003], suggesting that they were not optimized for survival prediction. Moreover, these scores are not kept up-to-date and a number of drugs are included that are not marketed anymore (e.g. isoproterenol, guanethidine, procainamide, or disopyramide [Von Korff et al. 1992, Fishman et al. 2003]) whereas important new pharmacological treatment options with substantial impact on clinical endpoints (e.g. angiotensin II receptor antagonists) or drugs for common chronic conditions (e.g. bisphosphonates for osteoporosis) are missing.

2. Objectives

The aims of this study were to develop and validate a medication-based chronic disease score (medCDS) primarily developed for the prediction of all-cause mortality as a major and unequivocal clinical endpoint. Furthermore, the medCDS score was compared with different medication-based chronic disease scores that have been used for decades to this end and also with scores assessing influential covariates such as age and sex or numbers of drugs.

3. Methods

3.1 Study design

Considering the most prevalent chronic diseases in the older German population, we compiled a list of evidence-based medicines used to treat these disorders. In an iterative process, this list was refined to best predict the respective diseases. To keep the allocation of diseases to drugs unequivocal, we clustered disorders that are treated with the same compounds. Then a score was developed (medCDS score) to predict mortality using data of a large longitudinal cohort of older ambulatory patients (training sample; MultiCare Cohort Study; [Schäfer et al. 2009 and 2012]) and its performance was evaluated in independent cohorts (ESTHER [Löw et al. 2004, Raum et al. 2007] and KORA-Age [Holle et al. 2005]) of

older patients (supplementary Table S1). Concurrently, independent of current treatment guidelines and similar to earlier attempts [Schneeweiss et al. 2001, Perkins et al. 2004, Brilleman and Salisbury 2013], we also empirically developed a score (ATC3) based only on pharmacological subgroups of the anatomic-therapeutic-chemical (ATC) codes (3rd level) and assessed its association with mortality. Then, these scores were compared with two previously developed and widely used medication-based morbidity scores (CDS [von Korff et al. 1992] and RxRisk [Fishman et al. 2003]) and also with a score only evaluating age and sex as covariates (Age&Sex) [Schneeweiss et al. 2004] to define the net contribution of these important variables to mortality in the investigated populations. Finally, for comparison, we also evaluated the performance of the disease-based original [Charlson et al. 1987] and a recently updated Charlson score [Quan et al. 2011] in the MultiCare Cohort Study and assessed the impact of also considering age and sex in these analyses. The different steps are described in detail below.

This study was approved by the Ethics Committee of the Medical Faculty of Heidelberg University, Germany (#S-258/2011).

All steps of the drug selection and coding process were independently performed by at least two health care professionals (pharmacist or physician). If necessary, consensus was reached within a working group consisting of seven pharmacists and physicians.

3.2 Item selection of the medCDS score

The medCDS score focuses on the most common and relevant diagnoses of outpatients and the corresponding medication used in Germany. The target population are ambulatory adults aged 65 years or older. The items for the medCDS score were selected in a multilevel process:

In a first step, medical conditions (diseases) with corresponding ICD-10 codes were selected based on the presence of the following criteria: 1) The disease prevalence was ≥ 1 % within a standard statutory health insurance dataset (GEK) as described by Schäfer and co-workers [Schäfer et al. 2010] or within a national cross-sectional study representative for Germany (Bundes-Gesundheitssurvey 1997/98; [Bellach 1998]) and 2) diseases must be chronic and continuously treated with specific medication, which is taken on a regular basis.

In a second step, for each selected chronic medical condition, currently effective treatment guidelines were identified by literature search and on the pertinent website of the German Association of the Scientific Medical Societies (AWMF, https://www.awmf.org) and the suggested drug treatment was extracted. Treatment guidelines were considered if 1) they had the highest possible evidence level, 2) were up-to-date (not older than five years), and 3) valid in Germany. If no national guideline was available, another guideline was chosen,

preferably European or American. Proposed diagnoses were not included if the medical condition was typically not treated with drugs (e.g. hypotension or diverticulosis).

If a pertinent treatment guideline was identified, all drugs mentioned in it were selected and, if possible, drug groups rather than single substances were chosen. Inclusion criteria for drugs were 1) chronic or regular use (excluding as needed medication), 2) drugs are systemically available (e.g. excluding topical dermatological drugs), 3) use in and by outpatients (exclusion of medication only used in a hospital setting), and 4) the medicines are used for the primary disorder of interest and not for the treatment of co-morbidities caused by it. All drugs were linked to the corresponding ATC code.

Subsequently the allocation of drugs (ATC codes) to specific diseases (ICD-10 codes) (candidate predictors) was tested using medication data of the MultiCare Cohort Study [Schäfer et al. 2009 and 2012] in order to detect potential areas of optimisation in the drug and disease coding process. Therefore, all ATC codes of patients with a specific disease but without any of the allocated ATC codes were selected to detect potentially missing ATC codes. Conversely, all ICD-10 codes of patients with ATC codes of interest but without suspected underlying ICD-10 codes were selected to detect possibly missing ICD-10 codes.

For the development and application of the score the relationship between each combination of drug and disease must be one-to-one; hence, whenever the same drug was mentioned in more than one diagnosis,

1) the relationship between drug and corresponding diagnosis was further specified by defining medical conditions predictive of the respective disease (e.g. antidepressants were linked with depression, but whenever antidepressants were given in combination with opioids, the suspected underlying condition was neuropathic pain),
2) diagnoses were combined (e.g. arterial hypertension and heart failure) to one cluster (i.e. cardiovascular diseases), if a drug (class) (e.g. angiotensin-converting enzyme inhibitors) was a current cornerstone of the guidelines of multiple diseases, or
3) the drug was excluded (e.g. if it was unspecific, second line, or off-label medication).

The final selection of medical conditions used for the development of medCDS is shown in supplementary Table S2.

Within each medical condition of the medCDS, the number of different ATC codes a patient used served as a proxy of disease severity.

3.3 Development and translation of other medication-based chronic disease scores

ATC3 score: We also tested a score counting the number of drugs [Schneeweiss et al. 2001, Brilleman and Salisbury 2013] that was based exclusively on ATC codes, age and sex. Therefore, the ATC code of each prescribed drug was truncated to the third level and the number of different codes was counted (ATC3 score) and used for score development. The final selection of ATC codes used for the development of ATC3 is shown in supplementary Table S3.

Translation and item selection of CDS and RxRisk: To compare the medCDS score with already existing medication-based chronic disease scores (CDS: [von Korff et al. 1992] and RxRisk: [Fishman 2003]), we linked drug classes of these scores with the corresponding ATC codes used in medCDS. We used the CDS for comparison because in a previous study it predicted mortality better [Schneeweiss et al. 2004] than the updated version of Clark and co-workers [1995].

CDS: First we linked all medicines mentioned in the CDS [von Korff et al. 1992] to the corresponding ATC codes (CDS; see supplementary Table S4). In a second step, we added drug classes recommended in up-to-date treatment guidelines for the mentioned chronic diseases but not mentioned in the CDS (e.g. angiotensin II receptor antagonists for heart disease or proton pump inhibitors for gastric ulcer) yielding a CDS score adapted to current treatment standards (updated CDS, see supplementary Table S5). As suggested in the original publication, this score did not consider age or sex as covariates.

RxRisk: Of all RxRisk classes, we only selected those that are relevant for adults because the medCDS was developed in a setting of older patients. We linked all drugs mentioned in RxRisk with corresponding ATC codes; in ambiguous cases (e.g. RxRisk's category antineoplastics miscellaneous) consensus was reached within the working group (see supplementary Table S6). As suggested in the original publication, this score considered age or sex as co-variates.

Age&Sex: Finally, we also developed a score exclusively based on age and sex of the participants.

3.4 Endpoint definition

Because of its clinical relevance and differences in the length of follow-up of the analysed cohorts, time to all-cause mortality was chosen as a primary endpoint for score development. In the MultiCare Cohort Study, all deaths of participants were confirmed by the treating general practitioner and/or the relatives of the patients. In ESTHER and KORA-Age, death was ascertained by reviewing the death certificates.

3.5. Study population and setting

The score was developed using data of the MultiCare Cohort Study [Schäfer et al. 2009 and 2012]. At baseline, 3,189 elderly people with multiple morbidities were enrolled between July 2008 and November 2009. The participants were recruited via general practitioners' offices. After 3.75 years and until the end of 2013, the third follow-up assessment was done. Diseases were documented by the patients' general practitioners and drug information was collected during a visit of a trained scientist or study nurse at the patient homes using a brown-bag medication review method [Schäfer et al. 2009]. Out of 3,189 patients, 26 did not report any drug intake; the remaining 3,163 patients reported taking altogether 22,973 drugs. Of these, 20,825 drugs (90.6 %) could be assigned to an ATC code. The mean number of drugs per patient was 7.3 (median 7, maximum 27). Four patients had no documented survival status and were therefore excluded, leaving 3,159 patients for analysis.

The score performance was tested in two independent cohorts (ESTHER and KORA-Age) of older community-dwelling patients in Germany. The ESTHER population consisted of a subsample of 2,703 participants of the ESTHER study (ESTHER = Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung), a large population-based cohort study conducted in the State of Saarland, Germany [Löw et al. 2004, Raum et al. 2007] that initially enrolled 9,949 outpatients aged between 50 and 74 years during a general health check-up by general practitioners between 2000 and 2002 and monitored the patients in follow-ups after 2, 5, 8, 11, and 14 years. The medCDS score was tested in the subsample that received a home visit by a trained study physician during the 8-year follow-up, which took place between July 2008 and December 2010. During this home visit, a comprehensive medication inventory was taken and information on mortality was subsequently collected until March 2013.

The Cooperative Health Research in the Region of Augsburg (KORA)-Age Study is a follow-up study of the four cross-sectional, population-based Multinational Monitoring of Trends and Determinants in Cardiovascular disease MONICA/KORA surveys (S1-S4), carried out between 1984 and 2001 in the region of Augsburg, Southern Germany [Holle et al. 2005]. Study design, sampling method, and data collection have been previously reported in detail [Peters et al. 2011]. Briefly, between November 2008 and November 2009, a self-administered questionnaire was sent to all S1-S4 participants born before 1944 (aged ≥ 65 years), in which information about drug consumption of the last seven days, prescribing status, and administration regimen were gathered including the unique package codes used in Germany (Pharmazentralnummer). The pharmaceutical products were classified according to their active ingredients following the ATC classification system. For the present analysis, only regularly consumed drugs prescribed or advised by a physician were included.

Approximately 16,000 preparations were reported. In 2011, a mortality follow-up of the KORA-Age population was conducted. Vital status was ascertained by the registration offices. Follow-up time was calculated from date of answering the questionnaire to the last date confirmed of being alive or dead, or the last date of registration in case of leaving the catchment area or unknown vital status, whichever came first (median follow-up 2.53 years). Altogether 4,127 participants of KORA-Age were included in this analysis.

3.6 Score development and statistical analysis

Multivariate Cox proportional hazard regression was applied to assess the influence of the candidate predictors in the time until death in the MultiCare Cohort Study used as the training sample. A backward stepwise selection of variables based on the Schwarz Bayesian information criterion (BIC) was applied to reduce over-fitting. The BIC penalizes the log likelihood of a model (a measure of its fit) by a factor related to the number of predictor variables in the model (a measure of its complexity) and the number of cases. A reduction of BIC indicates model improvement. To derive a simplified score, the β coefficients of the final model were transformed into integer score points by dividing through the lowest β coefficient and rounding. The medCDS score was calculated as the sum of these score points. The upper decile and the upper quintile of the score were used to define the cut-points for the corresponding risk groups (low – medium – high risk). The cumulative hazard rates for the respective risk groups were calculated using the Kaplan-Meier method.

For validation, the predictive accuracy of the medCDS score was assessed in the independent cohorts ESTHER and KORA-Age.

To assess the discrimination of the score, the receiver operating characteristics (ROC), the area under the ROC curve (AUC), its 95 % confidence interval (95 %-CI), and c-statistics were calculated. The discrimination was then compared to the other medication-based chronic disease scores (CDS, the updated CDS, RxRisk, Age&Sex, and ATC3).

The score development of the ATC-based score (ATC3) was similar and applied a Cox proportional hazard regression model with backward stepwise selection based on the BIC. The score based on age and sex (Age&Sex) was derived by applying a Cox proportional hazard regression model with age and sex as predictors and by using the rounded β coefficients as score points. The final score was derived by dividing the β coefficients through the lowest β coefficient and rounding.

For the statistical analyses and the score development SAS Version 9.3 was applied.

4. Results

After linking with drugs and clustering, twenty-eight medical conditions remained and were used for score development (supplementary Table S2). It was assumed that a patient suffers from a condition, if at least one of the corresponding drugs was taken. Altogether six out of 28 medical conditions as well as age and sex were significantly associated with mortality (Table 1) and thus included in the final medCDS. The estimated β coefficients, the hazard risk ratios, the 95 %-CI, and the derived score points are shown in Table 2. All corresponding medicines of these diagnosis groups are listed in Table 1. Aside from age, cancer and heart failure (CVD2) were associated with the highest mortality risk (3 points each) (Table 2).

The maximum attainable sum of the score points of the final medCDS score was 16, the maximum observed in the training cohort was 14 points, and the corresponding ROC AUC was 0.73 (95 %-CI 0.70-0.76) (Table 3). The clustering of the patients into the three risk groups (low, medium, and high) is shown in supplementary Table S7. The consideration of the number of drugs within a disease group as a proxy for disease severity rather reduced than increased the performance of the medCDS (ROC AUC 0.70; 95 %-CI 0.67-0.74; Figure 1).

The risk groups were defined using the upper quintile and the upper decile of the score; this led to the cut-points ≤ 5 points (low risk), 6 points (medium risk) and ≥ 7 points (high risk). The corresponding Kaplan-Meier curves are presented in Figure 2. The Log rank test shows a highly significant difference between the risk groups in the MultiCare Cohort Study ($p < 0.001$; Figure 2).

In the validation cohort KORA-Age, the ROC AUC of the medCDS was 0.79 (95 %-CI 0.76-0.82; Figure 3). The difference between the risk groups regarding survival is highly significant ($p < 0.001$, Log Rank test; Figure 4).The ROC curves of the validation in the ESTHER cohort are shown in Figure 5, their ROC AUC values are reported in Table 3, the corresponding Kaplan-Meier curves show a highly significant difference ($p < 0.001$, Log Rank test; Figure 6).

The performance of the medCDS was superior to the already existing medication-based scores RxRisk and CDS. Updating of the CDS with drugs missing according to current treatment guidelines did not improve its performance (Table 3). The performance of the medCDS was better than the simple score based on pharmacological subgroups of the ATC code (ATC3) ($p = 0.022$) (Table 3). In all analyses, the score merely considering age and sex (Age&Sex) performed worse than medCDS and ATC3.

The c-statistics of the original Charlson score in the MultiCare Cohort Study was 0.6190 and, considering also age and sex, 0.6911; the respective values for the updated Charlson score were 0.6142 and 0.6884 thus predicting mortality significantly less well than medCDS.

5. Discussion

The newly developed medCDS score, which is based on current treatment guidelines, more reliably predicts mortality than the already established medication-based chronic disease scores CDS and RxRisk, which are still used for morbidity assessment [O'Shea et al. 2013, Desai et al. 2014]. Its validity was confirmed in two independent cohorts of ambulatory older persons and medCDS was even superior to the CDS when the CDS was up-dated to reflect current evidence-based treatment guidelines.

The performance of the simple score that included ATC codes (ATC3) was almost as good as the performance of the more complex medCDS. Similar observations were made by several groups that demonstrated that simple counts of medications may perform better than more complex measures in predicting health care costs and utilization as endpoint [Schneeweiss et al. 2001, Perkins et al. 2004, Brilleman and Salisbury 2013].

We established and validated the medCDS score in three large cohorts with rather exhaustive information on current drug therapy because in these studies drug histories were either taken at a home visit using a technique similar to the brown-bag review procedure (MultiCare, ESTHER) or information was collected in a questionnaire survey asking for unique package code information of all drugs (KORA-Age) [Quinzler et al. 2007]. medCDS was therefore developed and optimized in a setting with rather comprehensive and unequivocal drug information and its predictive power will thus be best if the amount and depth of information is comparable to the information considered during score development.

Another important prerequisite defining the predictability of medication-based scores is that the drugs are used consistently in the respective population and that they are allocated to only one risk group. A number of drugs are approved for different conditions (e.g. angiotensin-converting enzyme inhibitors) and the endpoint of interest (e.g. mortality) can vary between indications (e.g. heart failure and hypertension), which can limit the performance of scores using this information. In addition, drugs can also be used outside the labeled indications, incorrectly dosed, or may not be taken at all. Therefore, these scores will never be perfect and always require updating when new indications with relevant impact on the endpoint of interest emerge. In theory, ambiguities arising when drugs are approved for indications with differing risk profiles can be resolved by considering also medical conditions in the score. Several scores have successfully combined information on diseases and medication in the past, which helped avoid undercoding and often improved the predictive power [e.g. Bang et al. 2013, Mehta et al. 2016]. Whether medCDS will also improve if it is combined with medical conditions will have to be assessed.

Not all initially selected chronic medical conditions significantly predicted mortality; not surprisingly, the mortality risk was highest in patients with medications for the treatment of

cancer and heart failure whose association with high mortality rates is well established [Groenveld et al. 2008; Siegel et al. 2015]. The risk was also increased in patients using medications for ulcer, psychiatric diseases, asthma/COPD, and arrhythmia, confirming the results of epidemiological studies showing an increased mortality risk for GERD patients in the general population as well as for patients suffering from COPD, arrhythmia, or psychiatric diseases such as depression [Becher and El-Serag 2008, Mannino and Kiriz 2006, Ouyang et al. 2015, Park et al. 2013]. However, other diseases that are clearly associated with increased mortality such as Parkinson's disease [Xu et al. 2014] were not predictive and thus not selected in the final score. This may be due to fact that the prevalence of patients with Parkinson's disease was very low in the MultiCare Cohort Study (2.1 % of all patients), which was used for score development. Also, drugs used in the treatment of cardiovascular and cerebrovascular disease such as platelet aggregation inhibitors or anticoagulants (prevalence in MultiCare: 52.3 %) or lipid lowering drugs (42.4 %) were not indicators of mortality in our assessment albeit their high prevalence in the MultCare Cohort. The reasons for the poor prediction of mortality by these medicines are unknown but numerous factors may have influenced such a result. (1) Accurate prediction of mortality risk by a medication-based score depends on the effectiveness of the respective treatment in preventing disease-related death. Hence, the better the treatment works, the more difficult it becomes to detect a mortality difference to patients having other diseases or even no disease. (2) Mortality also depends on the available therapeutic alternatives and their effectiveness if drug treatment fails, which means that for coronary heart disease patients on aspirin and lipid lowering drugs effective alternatives (e.g. cardiac interventions in acute coronary syndromes) are available in emergency situations. Finally, (3) even in advanced stages of coronary heart disease [Head et al. 2014], 5-year mortality rates are manifold lower than in heart failure patients [Mosterd et al. 2001], making it difficult to detect corresponding signals in relatively small cohorts and short follow-up periods.

5.1 Limitations and strengths of the medCDS score

The medCDS score was developed to predict all-cause mortality and was based on the MultiCare Cohort, which had a follow-up period of 3.75 years. Its validation was performed in two independent cohorts of ambulatory patients with a comparable length of follow-up. While the score performed at least equally well in the confirmatory analyses, these assessments cannot prove that medCDS will also be able to predict longer term mortality. Moreover, other important endpoints such as quality of life, or health care services utilization (e.g. hospitalization), which also have an important impact on the health care system, have not yet been studied. It is thus open whether the medCDS will predict other endpoints as well and whether the score will require adaptation of the medical conditions and weights. However,

previous experiences with medication based scores clearly indicate that not all scores predict all endpoints similarly well, suggesting that the medCDS score may also require adaptation [Perkins et al. 2004, von Korff et al. 1992, Huntley et al. 2012]. Similarly unknown is whether the performances of ATC3 and medCDS scores will differ more from each other when other endpoints are considered.

We included common chronic diseases of outpatients that are treated with drugs. However, other diseases and drugs may also be associated with mortality; pertinent examples are i) conditions that are not treated with drugs in ambulatory care (e.g. obesity, renal dysfunction), ii) acute events (e.g. stroke), iii) treatments that are only applied in hospitals and may have long-lasting effects (e.g. parenteral antineoplastic agents), or iv) rare diseases with significant mortality that are too rare to meet the inclusion criterion of 1 % prevalence (e.g. pancreatic cancer). This may become more relevant if larger cohorts with more diverse populations such as general health insurance data will be evaluated.

For the allocation of drugs to diseases, we primarily used the German summary of product characteristics (drug label) and guidelines approved in Germany because all evaluated cohorts were established in Germany. It is well known that guidelines can differ across different countries and continents (e.g. with respect to specific treatment goals [Nayor and Vasan 2016]) but the sole allocation of drugs to diseases is likely less sensitive to such differences and transferability of the results appears thus not limited.

Moreover, medication underuse, which is common in ambulatory care, is associated with poorer outcomes [Beer et al. 2001], and was also frequent in one of the included cohorts (ESTHER, [Meid et al. 2016]). Because the medCDS is medication-based and independent of diagnostic criteria and coding, it will fail to detect patients not treated with indicated drugs, which may lead to misclassification and reduce the prediction of the score. In addition, medication-based scores will neither be suitable to detect medication misuse (e.g. inappropriately dosed drugs), which can result in both toxicity and nonresponse. However, because the accuracy of diagnosis codes has also been frequently questioned, medication data are nevertheless considered reliable alternatives [Erler et al. 2009, Levy et al. 2003]. However, as shown in this analysis, medCDS can serve as a tool to compare morbidity-related burden of disease between different populations and settings (e.g. primary care and public health).

There are also several strengths of the introduced medCDS score. To be as comprehensive as possible, all common chronic diseases of outpatients that are treated with drugs were considered when developing the score. However, to simplify score application, we included only medical treatments in the final medCDS score with a significant impact on the primary outcome. The medCDS focuses on mortality, which is a major clinical endpoint. In an

ambulatory setting the medCDS score is superior to already existing medication-based scores such as CDS and RxRisk even when they are updated to match current treatment standards of the diseases considered therein. Moreover, its high external validity shows its robustness and immediate applicability to other ambulatory cohorts.

6. Conclusion

In conclusion, based on current treatment guidelines for the most prevalent chronic diseases in older outpatients, we developed a medication-based chronic disease score (medCDS) that predicts mortality of ambulatory patients better than already existing scores (CDS, RxRisk) and confirmed its validity in two independent large longitudinal cohorts of older patients (KORA-Age, ESTHER). While in its current form the medCDS well predicted the mortality risk of independent populations, further research is now needed to adapt the medCDS to other relevant outcomes, e.g. (avoidable) hospitalization, health care services utilization, quality of life, or limitations in activities of daily living. Moreover, also this score will require periodic updating as science progresses.

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Table 1: Medical conditions / disease groups and the corresponding drugs included in the final medCDS score

Disease	ATC name	ATC code	Not considered in the medCDS score, if drug is combined with:
Chronic gastritis, gastroesophageal reflux disease	H_2-receptor antagonists	A02BA	Non-steroidal antiinflammatory / antirheumatic drugs (M01A or M01B), because this may rather indicate prophylactic treatment and not the treatment of actual ulcer symptoms.
	Proton pump inhibitors	A02BC	
	Combinations for eradication of Helicobacter pylori	A02BD	
Cardiac arrhythmias	Vitamin K antagonists	B01AA	
	Dabigatran	B01AE07	
	Direct factor Xa inhibitors	B01AF	
	Digitalis glycosides	C01AA	
	Propafenone	C01BC03	
	Flecainide	C01BC04	
	Amiodarone	C01BD01	
	Dronedarone	C01BD07	
	Sotalol	C07AA07	
Asthma, chronic obstructive pulmonary disease (COPD)	Selective beta-2-adrenoreceptor agonists, inhalants	R03AC	
	Adrenergics in combination with corticosteroids or other drugs, excl anticholinergics, inhalants	R03AK	
	Glucocorticoids, inhalants	R03BA	
	Anticholinergics, inhalants	R03BB	
	Antiallergic agents, excl. corticosteroids, inhalants	R03BC	
	Selective beta-2-adrenoreceptor agonists	R03CC	
	Xanthines	R03DA	
	Leukotriene receptor antagonists	R03DC	
	Omalizumab	R03DX05	
	Roflumilast	R03DX07	
Cancer (colorectal, mamma, and	Capecitabine	L01BC06	
	Tegafur, combinations	L01BC53	

prostate carcinoma) including antiemetic therapy	Mistletoe	L01CH01	
		L01CP01	
		L01CP50	
	Lapatinib	L01XE07	
	Everolimus	L01XE10	
	Progestogens	L02AB	
	Gonadotropin releasing hormone analogues	L02AE	
	Anti-estrogens	L02BA	
	Anti-androgens	L02BB	
	Aromatase inhibitors	L02BG	
	Abiraterone	L02BX03	
	Alizapride	A03FA05	
	Serotonin (5HT3) antagonists	A04AA	
	Aprepitant, fosaprepitant	A04AD12	
Cardiovascular disease category 2 ('heart failure') CVD2	Ivabradine	C01EB17	
	Sulfonamides, plain	C03CA	
	Aldosterone antagonists	C03DA	
	Furosemide and triamterene	C03EB21	
	Aldosterone antagonists and low-ceiling diuretics	C03EC	
	Aldosterone antagonists and high-ceiling diuretics	C03ED	
Psychiatric diseases including depression, schizophrenia, and anxiety disorders	Non-selective monoamine reuptake inhibitors	N06AA	Opioids (N02A) because combination may rather indicate neuropathic pain[†]; Selective serotonin (5HT1) agonists (N02CC), ergot alkaloids (N02CA01, N02CA02, N02CA51, N02CA52); because combination may rather indicate migraine (only relevant for amitriptyline; N06AA09).
	Selective serotonin reuptake inhibitors (SSRI)	N06AB	Memantine (N06DX01), rivastigmine (N06DA03), donepezil (N06DA02), or galantamine (N06DA04) because combination may rather indicate dementia.
	Monoamine oxidase A inhibitor: moclobemide	N06AG02	
	Monoamine oxidase inhibitor, non-selective: tranylcypromine	N06AF04	

	Serotonin-norepinephrine reuptake inhibitor: venlafaxine	N06AX16	Opioids (N02A), because this may rather indicate neuropathic pain. Selective serotonin (5HT1) agonists (N02CC), ergot alkaloids (N02CA01, N02CA02, N02CA51, N02CA52); because combination may rather indicate migraine.
	Serotonin-norepinephrine reuptake inhibitor: duloxetine	N06AX21	Opioids (N02A), because this may rather indicate neuropathic pain.
	Norepinephrine reuptake inhibitor: reboxetine	N06AX18	
	Noradrenergic and specific serotonergic antidepressant: mianserin	N06AX03	
	Noradrenergic and specific serotonergic antidepressant: mirtazapine	N06AX11	
	Selective noradrenaline and dopamine reuptake inhibitor: bupropion	N06AX12	
	Melatonin receptor agonist: agomelatine	N06AX22	
	Trazodone	N06AX05	
	Hypericum perforatum	N06AP01	
		N06AP51	
		N05CP03	
	Benzodiazepine derivatives (anxiolytics)	N05BA	
	Antipsychotics	N05A	Memantine (N06DX01), rivastigmine (N06DA03), donepezil (N06DA02), or galantamine (N06DA04) because this may rather indicate dementia[‡].

[†]Only relevant for desipramine (N06AA01), imipramine (N06AA02), clomipramine (N06AA04), amitriptyline (N06AA09), nortriptyline (N06AA10), maprotiline (N06AA21), doxepin (N06AA12), venlafaxine (N06AX16), and duloxetine (N06AX21).

[‡]Only relevant for: citalopram (N06AB04), risperidone (N05AX08), olanzapine (N05AH03), haloperidol (N05AD01), melperone (N05AD03), quetiapine (N05AH04), pipamperone (N05AD05), and aripiprazole (N05AX12).

Table 2: Cox regression model of the final medCDS as established in the MultiCare Cohort Study.

Parameter		**β coefficients**	**p**	**HR**	**95 %-CI**	**Score points**
Sex	Female	0		1		0
	Male	0.41666	0.0006	1.517	1.198-1.921	1
Age (ys)	< 75	0		1		0
	75 - < 85	0.75689	< 0.0001	2.132	1.662-2.734	2
	≥ 85	1.66119	< 0.0001	5.266	3.133-8.849	5
Cancer (colorectal, breast, and prostate carcinoma) including antiemetic therapy	No	0		1		0
	Yes	1.15605	< 0.0001	3.177	1.879-5.374	3
Cardiac arrhythmias	No	0		1		0
	Yes	0.46329	0.0005	1.589	1.223-2.065	1
Asthma/COPD	No	0		1		0
	Yes	0.39064	0.0078	1.478	1.108-1.971	1
Chronic gastritis, gastroesophageal reflux disease	No	0		1		0
	Yes	0.49017	0.0005	1.633	1.239-2.151	1
Cardiovascular disease category 2 (CVD2) ('heart failure')	No	0		1		0
	Yes	0.92391	< 0.0001	2.519	1.960-3.238	3
Psychiatric diseases including depression, schizophrenia, and anxiety disorders	No	0		1		0
	Yes	0.36834	0.0131	1.445	1.080-1.934	1

CI: confidence interval, COPD: chronic obstructive pulmonary disease, HR: hazard ratio.

Table 3: Comparative assessment of the performance of different scores expressed as ROC AUC (95 %-CI; Harrell's C-statistic)

Cohort	medCDS	ATC3	CDS	Updated CDS	RxRisk	Age&Sex
Score development						
MultiCare	0.730 (0.699-0.761; 0.729)	0.706 (0.674-0.739; 0.710)	0.657 (0.623-0.691; 0.653)	0.653 (0.618-0.687; 0.651)	0.681 (0.649-0.713; 0.681)	0.637 (0.604-0.670; 0.637)
Score validation						
KORA-Age	0.788 (0.759-0.817; 0.783)	0.777 (0.747-0.807; 0771)	0.641 (0.603-0.679; 0.636)	0.624 (0.585-0.662; 0.619)	0.702 (0.669-0.736; 0.697)	0.732 (0.698-0.766; 0.725)
ESTHER	0.743 (0.708-0.778; 0.731)	0.724 (0.687-0.761; 0.715)	0.657 (0.619-0.696; 0.655)	0.642 (0.601-0.682; 0.637)	0.700 (0.664-0.737; 0.695)	0.658 (0.618-0.697; 0.653)

AUC: area under the curve, CI: confidence interval, ROC: receiver-operating characteristics

Legends to the figures:

Figure 1:

Results obtained in the training sample using the MultiCare Cohort Study: ROC curves of the medCDS, an ATC-based score (ATC3), a score only considering age and sex (Age&Sex), and two already existing medication-based chronic disease scores (RxRisk, CDS).

Figure 2:

Performance of the training sample MultiCare Cohort Study: Kaplan-Meier curves of the different risk groups.

Figure 3

Results obtained in the validation cohort KORA-Age: ROC curves of the medCDS, an ATC-based score (ATC3), a score only considering age and sex (Age&Sex), and two already existing medication-based chronic disease scores (RxRisk, CDS).

Figure 4:

Performance of the validation cohort KORA-Age: Kaplan-Meier curves of the different risk groups.

Figure 5:

Results obtained in the validation cohort ESTHER: ROC curves of the medCDS, an ATC-based score (ATC3), a score only considering age and sex (Age&Sex), and two already existing medication-based chronic disease scores (RxRisk, CDS).

Figure 6:

Performance of the validation cohort ESTHER: Kaplan-Meier curves of the different risk groups.

Figure 1

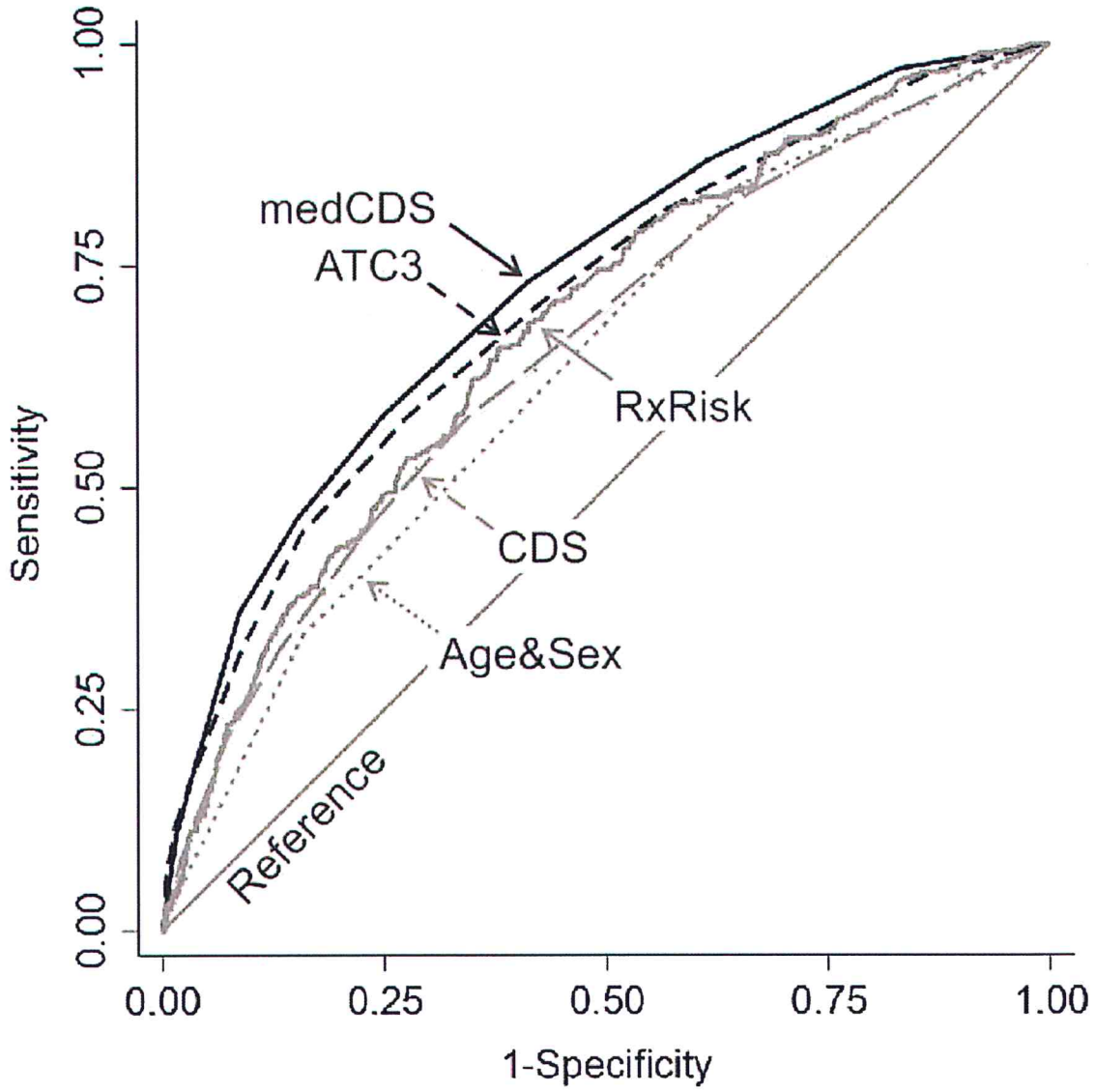


Figure 2

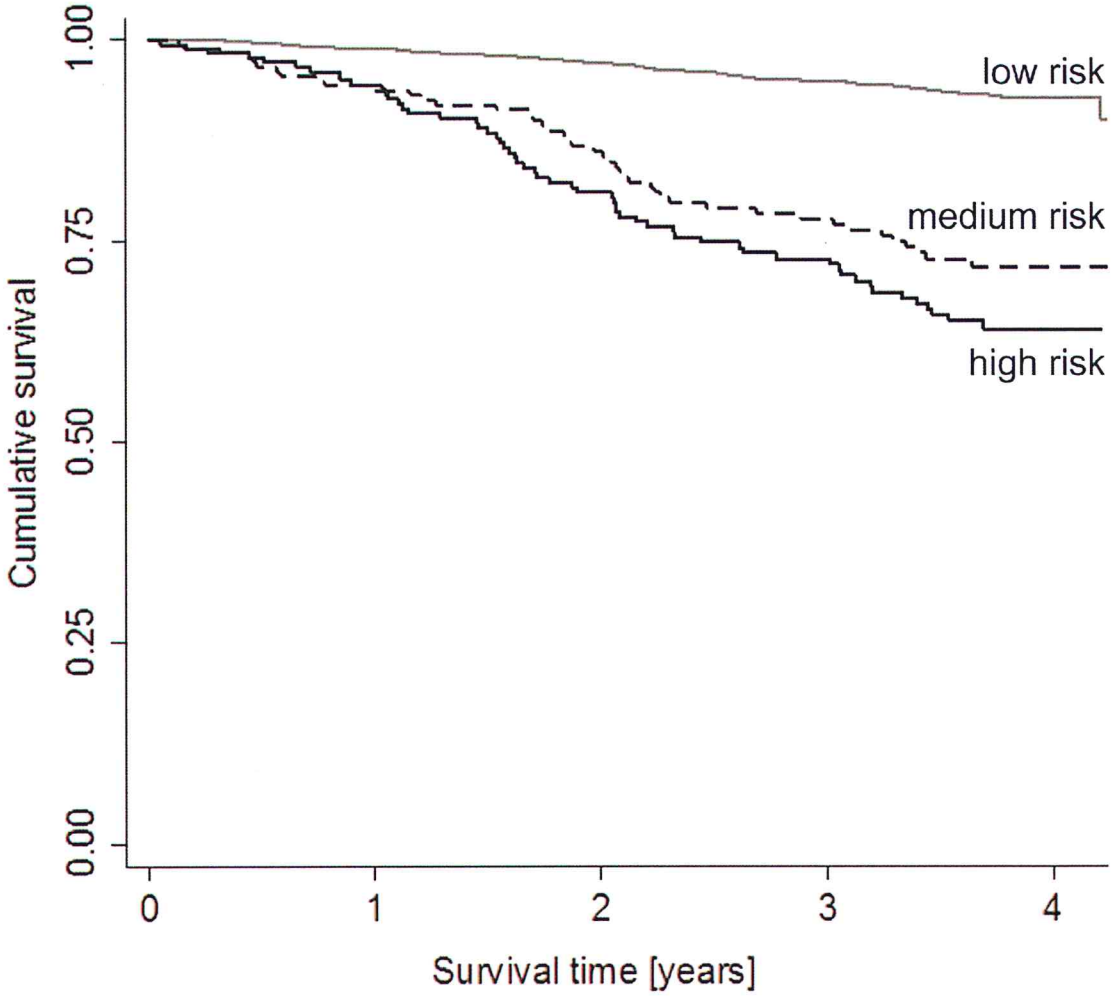


Figure 3

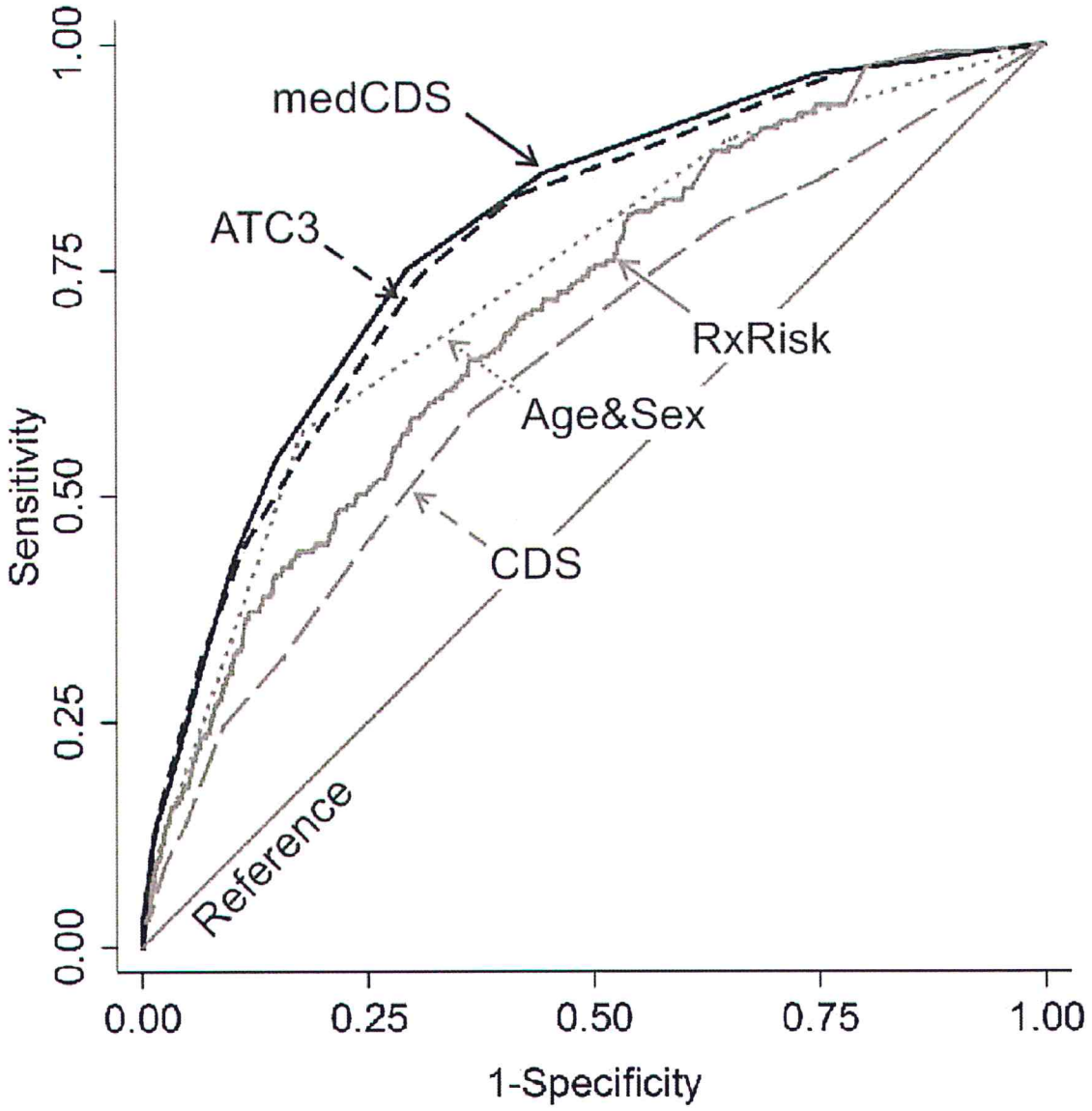


Figure 4

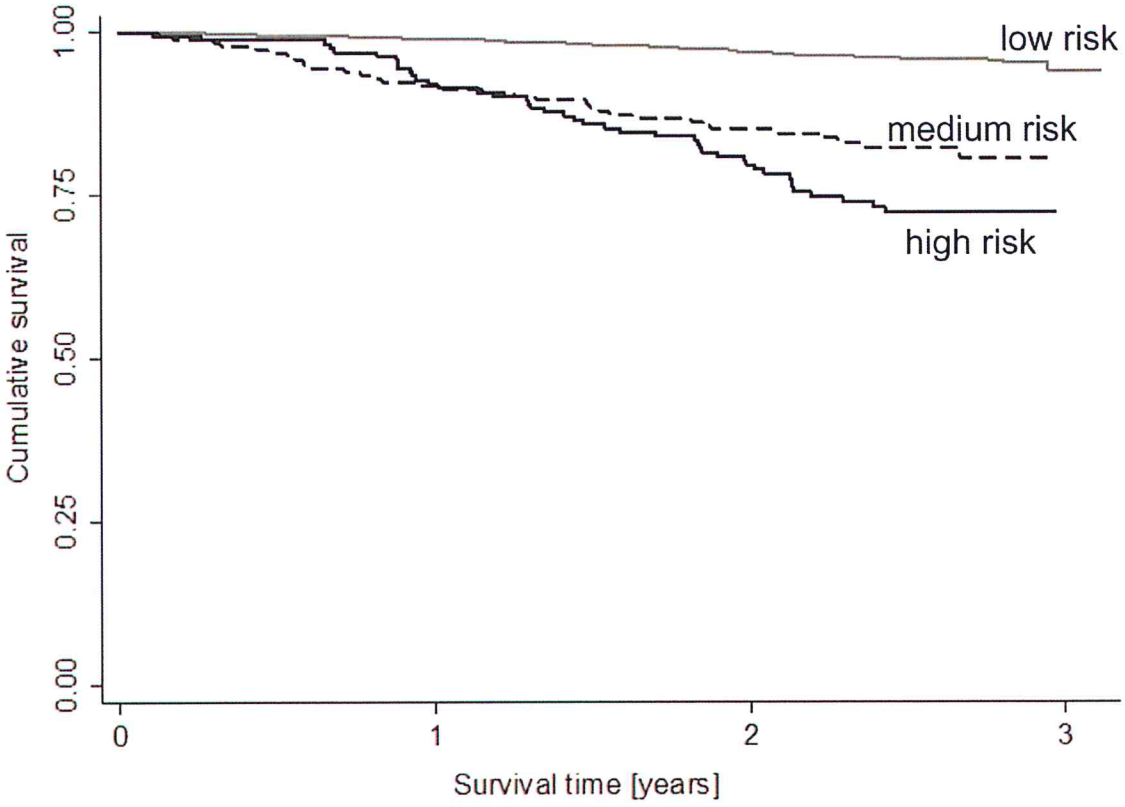


Figure 5

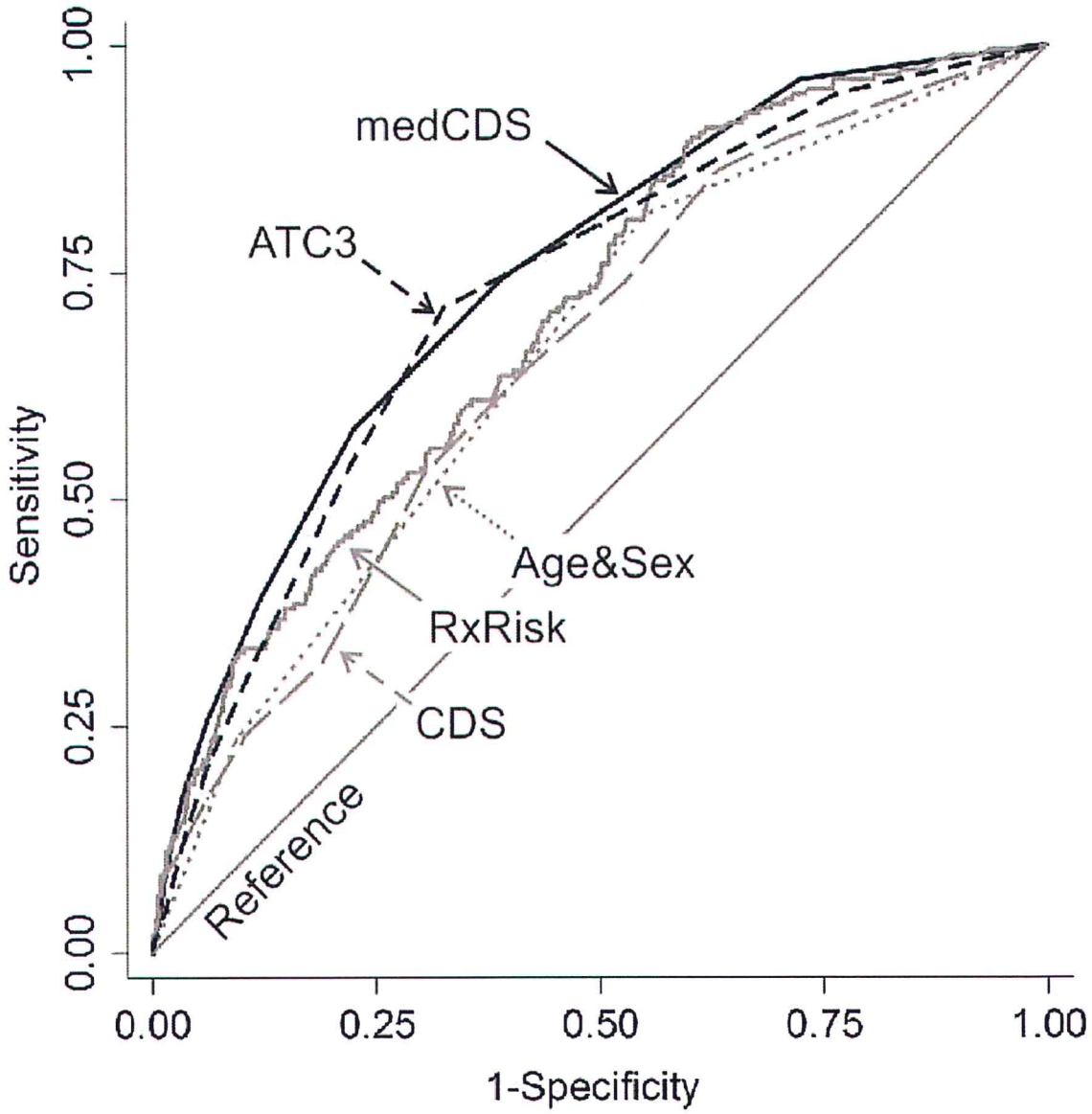
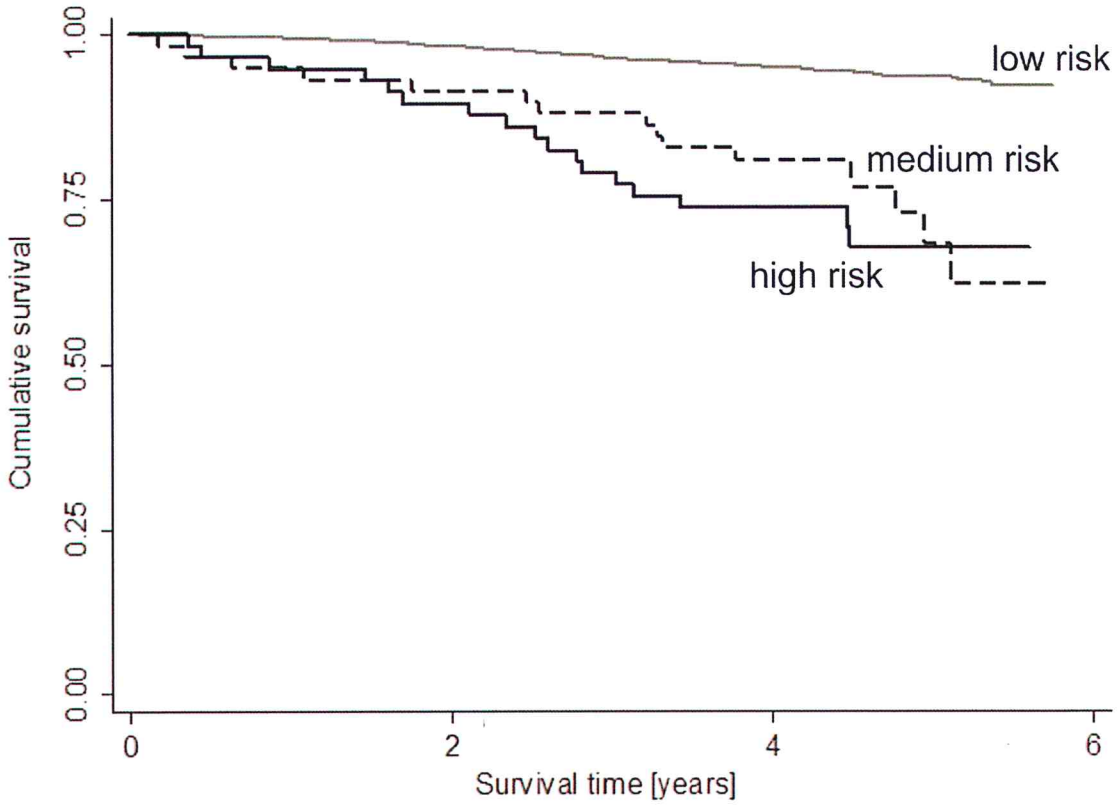


Figure 6



Appendices (submitted as supplementary online-only material)

Table S1: Characteristics of the evaluated populations.

Parameter		**MultiCare (N = 3159)**	**KORA-Age (N = 4127)**	**ESTHER (N = 2703)**
Sex, N	Female	1879	2112	1430
	Male	1280	2015	1273
Age, ys	< 75	1816	2676	2157
	75 - < 85	1290	1275	546
	≥ 85	53	176	0
Deaths in observation period, N		283	237	187
Mean duration of follow-up, ys		3.30	2.47	4.41
Cancer (colorectal, breast, and prostate carcinoma) including antiemetic therapy	No	3085	4080	2666
	Yes	74	47	37
Cardiac arrhythmias	No	2574	3807	2424
	Yes	585	320	279
Asthma/COPD	No	2719	3928	2447
	Yes	440	199	256
Chronic gastritis, gastroesophageal reflux disease	No	2683	3686	2285
	Yes	476	441	418
Cardiovascular disease category 2 (CVD2) ('heart failure')	No	2553	3677	2429
	Yes	606	450	274
Psychiatric diseases including depression, schizophrenia, and anxiety disorders	No	2656	3777	2376
	Yes	503	350	327

Table S2: Chronic medical conditions considered for the development of the medCDS score.

Initially selected chronic medical conditions	**Final chronic medical conditions after linking with drugs and building of clusters used for development of the medCDS (N = 28)**	**Comments**
Arterial hypertension/ High blood pressure	Cardiovascular disease category 1 ('hypertension') CVD1	Contains "basic" cardiovascular drugs mainly used for hypertension but may be used for other cardiovascular diseases as well e.g. ACE inhibitors.
Heart failure	Cardiovascular disease category 2 ('heart failure') CVD2	Contains drugs not listed in CVD1 and that are mainly used for heart failure e.g. aldosterone antagonists
Cerebral ischemia and stroke	Cardiovascular disease category 3 ('coronary heart disease, stroke') CVD3	Contains drugs not listed in CVD1 and that are mainly used for coronary heart disease or stroke e.g. trapidil
Coronary heart disease		
Peripheral arterial disease	Cardiovascular disease category 4 ('peripheral arterial disease') CVD4	Contains drugs not listed in CVD1 and that are mainly used for peripheral arterial diseases e.g. cilostazol
Hyperlipidemia	Hyperlipidemia	
Diabetes mellitus	Diabetes mellitus	
Thyroid dysfunction	Hyperthyroidism	
	Hypothyroidism, iodine deficiency	
Cancer	Cancer (colorectal, breast, and prostate carcinoma) including antiemetic therapy	Only (chronic) cancer diagnoses with a prevalence of >1% were included
Cardiac arrhythmias	Cardiac arrhythmias	
Gout	Gout	
Benign prostatic hyperplasia	Benign prostatic hyperplasia	
Asthma, COPD, and emphysema	Asthma, COPD	
Depression		Included in new cluster "Psychiatric diseases"
Osteoporosis	Osteoporosis	
Chronic gastritis, gastroesophageal reflux disease	Chronic gastritis, gastroesophageal reflux disease	
Neuropathies	Neuropathies	
Insomnia/Sleep disturbances	Insomnia / sleep disturbances	
Dementia	Dementia	
Rheumatoid arthritis	Rheumatoid arthritis	
Migraine and chronic headache	Migraine	Chronic headache is included in the new cluster "pain"
Mental disorders		Mental disorders treated with neuroleptics are included in the new cluster "psychiatric diseases"
Parkinson's disease	Parkinson's disease	
Epilepsy	Epilepsy	
Multiple sclerosis		Deleted, because multiple sclerosis was not documented in the cohort used for score development (MultiCare Cohort Study)
Urinary incontinence	Urinary incontinence	
Chronic back pain		Chronic back pain is included in the new cluster "pain"

Osteoarthritis	Osteoarthritis	
	Pain	
	Psychiatric diseases including depression, schizophrenia, and anxiety disorders	
Liver disease	Primary biliary cirrhosis	
Kidney disease	Renal failure	

Table S3: Final model of an ATC score based on the first three digits of relevant ATC groups (ATC3)

Parameter		**β coeffi-cients**	**p**	**HR**	**95 %-CI**	**Score points**
Sex	Female	0		1		0
	Male	0.45159	0.0002	1.571	1.236-1.996	1
Age (ys)	< 75	0		1		0
	75 - < 85	0.77745	< 0.0001	2.176	1.693-2.796	3
	≥ 85	1.80164	< 0.0001	6.060	3.608-10.177	6
ATC*	A02 (drugs for acid related disorders)	0.36879	0.0044	1.446	1.122-1.864	1
	A04 (antiemetics and antinauseants)	2.36744	< 0.0001	10.670	4.315-26.386	8
	A16 (other alimentary tract and metabolism products)	2.53638	0.0139	12.634	1.673-95.406	8
	B01 (antithrombotic agents)	0.30946	0.0173	1.363	1.056-1.758	1
	B03 (antianemic preparations)	0.58418	0.0154	1.794	1.118-2.878	2
	C03 (diuretics)	0.72930	< 0.0001	2.074	1.627-2.643	2
	H02 (corticosteroids for systemic use)	0.69192	0.0009	1.998	1.330-3.000	2
	L01 (antineoplastic agents)	1.95301	0.0001	7.050	2.600-19.116	6

CI: confidence interval, HR: hazard ratio.

* The reference is "no drugs" in the respective ATC-group with 0 points.

Table S4: Chronic disease score (CDS) introduced by von Korff et al.[1] Medication classes of this score were linked with the corresponding ATC codes

Chronic disease	Medication class(es) according to[1]	ATC code	ATC name	Scoring rules
Heart disease	Anticoagulants, hemostatics	B01A	Antithrombotic agents	One class = 3; two classes = 4; three classes = 5
		B02B	Vitamin K and other hemostatics	
	Cardiac agents, ACE inhibitors	C01	Cardiac therapy	
		C09A	ACE inhibitors, plain	
		C09B	ACE inhibitors, combinations	
	Diuretic loop	C03C	High-ceiling diuretics	
Respiratory illness	Isoproterenol (=Isoprenaline)	R03AB02	Isoprenaline	One class = 2; two or more classes = 3
		R03AB52*	Isoprenaline, combinations	
		R03AK02	Isoprenaline and other drugs for obstructive airway diseases	
		R03CB01	Isoprenaline	
		R03CB51	Isoprenaline, combinations	
	Beta-adrenergic, misc.	R03A (excl. R03AB02, R03AB52, R03AK02 = isoprenaline)	Adrenergics, inhalants	
		R03C (excl.R03CB01, R03CB51= isoprenaline)	Adrenergics for systemic use	
		R03DB[§]	Xanthines and adrenergics	
	Xanthine products	R03DA	Xanthines	
		R03DB [§]	Xanthines and adrenergics	
	Respiratory products including bronchodilators and mucolytics but excluding cromolyn	R03BA	Glucocorticoids	
		R03AK06 - R03AK11[§]	Misc. adrenergics and glucocorticoids	
		R03BB	Anticholinergics	
		R03DC	Leukotriene receptor antagonists	
		R03DX	Other systemic drugs for obstructive airway diseases	
		R05CA	Expectorants	
		R05CB	Mucolytics	
	Epinephrine	R03AA01	Epinephrine	
		R03AK01	Epinephrine and other drugs for obstructive airway diseases	
Asthma, rheumatism	Glucocorticoids	H02AB	Glucocorticoids	Score = 3
Rheumatoid arthritis	Gold salts	M01CB	Gold preparations	Score = 3
Cancer	Antineoplastics	L01	Antineoplastic agents	Score = 3
Parkinson's disease	L-Dopa	N04BA01	Levodopa	Score = 3
		N04BA02	Levodopa and decarboxylase inhibitor	

		N04BA03	Levodopa, decarboxylase inhibitor and COMT inhibitor	
		N04BA10*	Levodopa and carbidopa	
		N04BA11*	Levodopa and benserazide	
Hypertension	(1) Antihypertensives (except ACE inhibitors) or calcium channel blockers	C02	Antihypertensives	If class (1) = 2; if class (2) and not (1) = 1
		C08	Calcium channel blockers	
		C09BB§	ACE inhibitors and calcium channel blockers†	
		C09DB	Angiotensin II antagonists and calcium channel blockers†	
	(2) Beta blockers, Diuretics	C07	Beta blocking agents	
		C03 (excl. C03C high ceiling diuretics)	Diuretics	
		C09DA	Angiotensin II antagonists and diuretics†	
		C09BA§	ACE inhibitors and diuretics†	
Diabetes	Insulin	A10A	Insulins and analogues	Score = 2
	Oral hypoglycemics	A10B	Blood glucose lowering drugs, excl. insulins	
Epilepsy	Anticonvulsants	N03A	Antiepileptics	Score = 2
Asthma, rhinitis	Cromolyn	R03BC01	Cromoglicic acid	Score = 2
		R01AC51	Cromoglicic acid, combinations	
		R01AC01	Cromoglicic acid	
Acne	(1) Antiacne tretinoin	D10AD01	Tretinoin	Either class with > 2 prescriptions filled = 1
		D10AD51	Tretinoin, combinations	
	(2) Topical macrolides	D10AF02	Erythromycin	
		D10AF52	Erythromycin, combinations	
Ulcers	Cimetidine	A02BA01	Cimetidine	Score = 1
		A02BA51	Cimetidine, combinations	
Glaucoma	Ophthalmic miotics	S01EB	Parasympathomimetics	Score = 1
Gout, hyperuricemia	Uric acid agents	M04AA	Preparations inhibiting uric acid production	Score = 1
		M04AB	Preparations increasing uric acid excretion	
High cholesterol	Antilipemics	C10	Lipid modifying agents	Score = 1
Migraines	Ergot derivatives	N02CA	Ergot alkaloids	Score = 1
		C06AA*	Ergotamine derivatives	
Tuberculosis	Antitubercular agents	J04A	Drugs for the treatment of tuberculosis	Score = 1

*ATC according to: Deutsches Institut für Medizinische Dokumentation und Information. Anatomisch-therapeutisch-chemische-Klassifikation mit Tagesdosen. Amtliche Fassung des ATC-Index mit DDD-Angaben für Deutschland im Jahr 2014. Available at: http://www.dimdi.de.

§ ATC contains drugs of two different medication classes relevant for the CDS. Therefore these ATCs possibly have to be counted twice when calculating the score.

† Drug combinations, drugs relevant for the respective medication class are underlined.

[1] Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin

Epidemiol. 1992;45:197-203.

Table S5: Updated version of the chronic disease score (CDS) introduced by von Korff et al.[1] Medication classes of this score were linked with corresponding ATC codes. In addition, medication classes recommended in current treatment guidelines for the respective chronic diseases but not mentioned in the CDS (e.g. angiotensin II antagonists for heart disease or proton pump inhibitors for ulcer) were added.

Chronic disease	Medication class(es) according to[1]	ATC code	ATC name	Scoring rules
Heart disease	Anticoagulants, hemostatics	B01AA	Vitamin K antagonists	One class = 3; two classes = 4; three classes = 5
		B01AB	Heparin group	
		B01AC	Platelet aggregation inhibitors excl. heparin	
		B01AE07	dabigatran etexilate	
		B01AF	Direct factor Xa inhibitors	
		B02AA	Amino acids	
		B02BA	Vitamin K	
	Cardiac agents, ACE inhibitors	C01	Cardiac therapy	
		C09A	ACE inhibitors, plain	
		C09B	ACE inhibitors, combinations	
		C09C	Angiotensin II antagonists, plain	
		C09D	Angiotensin II antagonists, combinations	
	Diuretic loop	C03C	High-ceiling diuretics	
Respiratory illness	Isoproterenol (= isoprenaline)	R03AB02	Isoprenaline	One class = 2; two or more classes = 3
		R03AB52*	Isoprenaline, combinations	
		R03AK02	Isoprenaline and other drugs for obstructive airway diseases	
		R03CB01	Isoprenaline	
		R03CB51	Isoprenaline, combinations	
	Beta-adrenergic, misc.	R03A (excl. R03AB02, R03AB52, R03AK02 = isoprenaline)	Adrenergics, inhalants	
		R03C (excl. R03CB01, R03CB51 = isoprenaline)	Adrenergics for systemic use	
		R03DB[§]	Xanthines and adrenergics	
	Xanthine products	R03DA	Xanthines	
		R03DB[§]	Xanthines and adrenergics	
	Respiratory products including bronchodilators and mucolytics but excluding cromolyn	R03BA	Glucocorticoids	
		R03AK06 - R03AK11[§]	Misc. adrenergics and glucocorticoids	
		R03BB	Anticholinergics	
		R03DC	Leukotriene receptor antagonists	
		R03DX	Other systemic drugs for obstructive airway diseases	
		R05CA	Expectorants	

		R05CB	Mucolytics	
	Epinephrine	R03AA01	Epinephrine	
		R03AK01	Epinephrine and other drugs for obstructive airway diseases	
Asthma, rheumatism	Glucocorticoids	H02AB	Glucocorticoids	Score = 3
Rheumatoid arthritis	Gold salts	M01CB	Gold preparations	Score = 3
		M01CC01	Penicillamine	
		M01CX01*	Methotrexate	
		M01CX02*	Sulfasalazine	
		L04AA13	Leflunomide	
		L04AA24	Abatacept	
		L04AB	Tumor necrosis factor alpha inhibitors	
		L04AC03	Anakinra	
		L04AC07	Tocilizumab	
Cancer	Antineoplastics	L01	Antineoplastic agents	Score = 3
Parkinson's disease	Dopaminergic agents	N04B	Dopaminergic agents	Score = 3
Hypertension	(1) Antihypertensives (except ACE inhibitors) or calcium channel blockers or Renin inhibitors	C02	Antihypertensives	If class (1) = 2; If class (2) and not (1) = 1
		C08	Calcium channel blockers	
		C09BB[§]	ACE inhibitors and calcium channel blockers[†]	
		C09DB[§]	Angiotensin II antagonists and calcium channel blockers[†]	
		C09XA	Renin inhibitors	
	(2) Beta blockers, diuretics	C07	Beta blocking agents	
		C03 (excl. C03C high ceiling diuretics)	Diuretics	
		C09DA[§]	Angiotensin II antagonists and diuretics	
		C09BA[§]	ACE inhibitors and diuretics	
Diabetes	Insulin	A10A	Insulins and analogues	Score = 2
	Oral hypoglycemics	A10B	Blood glucose lowering drugs, excl. insulins	
Epilepsy	Anticonvulsants	N03A	Antiepileptics	Score = 2
Asthma, rhinitis	Cromolyn	R03BC01	Cromoglicic acid	Score = 2
		R01AC51	Cromoglicic acid, combinations	
		R01AC01	Cromoglicic acid	
Acne	(1) Antiacne tretinoin	D10AD01	Tretinoin	Either class with > 2 prescriptions filled = 1
		D10AD51	Tretinoin, combinations	
	(2) Topical macrolides	D10AF02	Erythromycin	
		D10AF52	Erythromycin, combinations	
Ulcers	H2-receptor antagonists or proton pump inhibitors	A02BA	H2-receptor antagonists	Score = 1
		A02BC	Proton pump inhibitors	
Glaucoma	Ophthalmic miotics	S01EB	Parasympathomimetics	Score= 1

Gout, hyper-uricemia	Uric acid agents	M04AA	Preparations inhibiting uric acid production	Score= 1
		M04AB	Preparations increasing uric acid excretion	
High cholesterol	Antilipemics	C10	Lipid modifying agents	Score= 1
Migraine	Ergot derivatives, triptane	N02CA	Ergot alkaloids	Score= 1
		C06AA	Ergotamine derivatives	
		N02CC	Selective serotonin (5HT1) agonists	
Tuberculosis	Antitubercular agents	J04A	Drugs for the treatment of tuberculosis	Score= 1
*ATC according to: Deutsches Institut für Medizinische Dokumentation und Information. Anatomisch-therapeutisch-chemische-Klassifikation mit Tagesdosen. Amtliche Fassung des ATC-Index mit DDD-Angaben für Deutschland im Jahr 2014. Available at: http://www.dimdi.de.				

[§] ATC contains drugs of two different medication classes relevant for the CDS. Therefore these ATCs possibly have to be counted twice when calculating the score.

[†] Drugs relevant for the respective medication class are underlined.

[1] Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol. 1992;45:197-203.

Table S6: Overview over RxRisk classes[1] relevant for adults and the corresponding drugs that were linked with ATC codes. In equivocal cases (e.g. antineoplastics miscellaneous) consensus was reached within the working group.

RxRisk Class	Representative drug class(es) according to[1]	ATC code	ATC name
Anxiety and tension, adult	Salicylate combinations[2]	-	-
	Barbiturates	N05CA	Barbiturates, plain
		N05CB	Barbiturates, combinations
	Benzodiazepines	N05BA	Benzodiazepine derivatives
		N05CD	Benzodiazepine derivatives
	Meprobamate	N05BC01	Mebrobamate
		N05BC51	Mebrobamate, combinations
		N05CX01	Mebrobamate, combinations
	Miscellaneous hypnotics	N05CM	Other hypnotics and sedatives
	Paraldehyde	N05CC05	Paraldehyde
Asthma, adult	Anti-inflammatory glucocorticoids	R03BA	Glucocorticoids (inhalant)
		R03AK61	Salmeterol and fluticasone
		R03AK71	Formoterol and beclometasone
		R03AK72	Formoterol and budesonide
	Isoproterenol	R03AB02	Isoprenaline
		R03AB52	Isoprenaline, combinations
		R03AK02	Isoprenaline
		R03CB01	Isoprenaline
		R03CB51	Isoprenaline, combinations
	Bronchodilators	R03A	Adrenergics, inhalants (excl. R03AB02, R03AB52, R03AK02, R03AK61, R03AK71, R03AK72)
		R03C	Adrenergics for systemic use (excl.R03CB01, R03CB51)
		R03DB	Xanthines and adrenergics
	Cromolyn	R03BC01	Cromoglicic acid
	Xanthines	R03DA	Xanthines
	Xanthines	R03DB	Xanthines and adrenergics
Bipolar disorder, adult and pediatric	Lithium	N05AN	Lithium
Cardiac disease, adult	Class I a antiarrhythmics	C01BA	Class I a antiarrhythmics (excl. C01BA01, 02, 03, 51, 71)
	Class I c antiarrhythmics	C01BC	Class I c antiarrhythmics
	Class III antiarrhythmics	C01BD	Class III antiarrhythmics
	Procainamide	C01BA02	Procainamide
	Disopyramide	C01BA03	Disopyramide

	Quinidine	C01BA01	Quinidine
		C01BA51	Quinidine, combinations excl. psycholeptics
		C01BA71	Quinidine, combinations with psycholeptics
	Vasodilator nitrates	C01DA	Organic nitrates
	Diuretic loops	C03C	High-ceiling diuretics
		C03EB	High-ceiling diuretics and potassium-sparing agents
		C03ED*	Aldosterone antagonists and high-ceiling diuretics
Coronary/peripheral vascular disease adult	Antiplatelet agents	B01AC	Platelet aggregation inhibitors excl. heparin
	Oral anticoagulants	B01AA	Vitamin K antagonists
	Trental = pentoxifylline	C04AD03	Pentoxifylline
Cystic fibrosis adult	Anti-inflammatory glucocorticoids[3]	-	-
	Enzymes	R05CB13	Dornase alpha
		A09AA	Digestives
Depression adult	Monoamine oxidase inhibitors	N06AF	Monoamine oxidase inhibitors, non-selective
		N06AG	Monoamine oxidase A inhibitors
	Phenothiazine combinations[4]	-	-
	Tricyclic anti-depressants	N06AA	Non-selective monoamine reuptake inhibitors
	SSRIs	N06AB	Selective serotonin reuptake inhibitors
Diabetes adult	Biguanides	A10BA	Biguanides
		A10BD01	Phenformin and sulfonamides
		A10BD02	Metformin and sulfonamides
		A10BD03	Metformin and rosiglitazone
		A10BD05	Metformin and pioglitazone
		A10BD07	Metformin and sitagliptin
		A10BD08	Metformin and vildagliptin
		A10BD15*	Metformin and glibenclamide
	Insulins	A10A	Insulins and analogues
	Sulfonylureas	A10BB	Sulfonamides, urea derivatives
		A10BD04	Glimepiride and rosiglitazone
		A10BD06	Glimepiride and pioglitazone
		A10BD12	Pioglitazone and sitagliptin
Epilepsy, adult	Anti-convulsants	N03AA	Barbiturates and derivatives
		N03AB	Hydantoin derivatives
		N03AC	Oxazolidine derivatives
		N03AD	Succinimide derivatives
		N03AE	Benzodiazepine derivatives

		N03AF	Carboxamide derivatives
		N03AG	Fatty acid derivatives
		N03AX	Other antiepileptics
ESRD, adult	Marrow stimulants[5]	---	
	Human erythropoietin	B03XA	Other antianemic preparations
Gastric acid disorder, adult	Histamine H2 blockers	A02BA	H2-receptor antagonists
	Prostaglandins	A02BB	Prostaglandins
	Proton pump inhibitor	A02BC	Proton pump inhibitors
		A02BD01	Omeprazole, amoxicillin and metronidazole
		A02BD02	Lansoprazole, tetracycline and metronidazole
		A02BD03	Lansoprazole, amoxicillin and metronidazole
		A02BD04	Pantoprazole, amoxicillin and clarithromycin
		A02BD05	Omeprazole, amoxicillin and clarithromycin
		A02BD06	Esomeprazole, amoxicillin and clarithromycin
		A02BD07	Lansoprazole, amoxicillin and clarithromycin
Gout, adult	Colchicine	M04AC01	Colchicine
	Uric acid inhibitors	M04AA	Preparations inhibiting uric acid production
Heart disease/ hypertension, adult	Beta adrenergic blockers	C07AA	Beta blocking agents, non-selective
		C07AB	Beta blocking agents, selective
		C07B	Beta blocking agents and thiazides
		C07C	Beta blocking agents and other diuretics
		C07D	Beta blocking agents, thiazides and other diuretics
		C07E	Beta blocking agents and vasodilators
		C07F	Beta blocking agents and other antihypertensives
		C07G*	Beta blocking agents and other agents
	Dopamine[6]	-	-
	Calcium channel blockers	C08	Calcium channel blockers
		C09BB	ACE inhibitors and calcium channel blockers
		C09DB	Angiotensin II antagonists and calcium channel blockers
		C09DX01	Valsartan, amlodipine and hydrochlorothiazide
		C09DX03	Olmesartan medoxomil, amlodipine and hydrochlorothiazide
		C09XA53	Aliskiren and amlodipine
		C09XA54	Aliskiren, amlodipine and hydrochlorothiazide
		C07FB22*	Metoprolol and nifedipine

		C07FB23*	Atenolol and nifedipine
		C07FB24*	Metoprolol and felodipine
HIV, adult and pediatric	Miscellaneous anti-protozoal	P01AX06	Atovaquone
		P01BD01	Pyrimethamine
	Antivirals	J05AE	Protease inhibitors
		J05AF	Nucleoside and nucleotide reverse transcriptase inhibitors
		J05AG	Non-nucleoside reverse transcriptase inhibitors
		J05AR	Antivirals for treatment of HIV infections, combinations
		J05AX07	Enfuvirtide
		J05AX08	Raltegravir
		J05AX09	Maraviroc
	Pentamidine	P01CX01	Pentamidine isethionate
Hyperlipidemia, adult and pediatric	Antilipemic clofibrate	C10AB01	Clofibrate
		C10BB01*	Clofibrate and nicotinic acid
		C10BB02*	Clofibrate and other lipid modifying agents
	Antilipidemic exchange resins	C10AC	Bile acid sequestrants
	HMG CoA reductase inhibitors	C10AA	HMG CoA reductase inhibitors
		C10BA01	Lovastatin and nicotinic acid
		C10BA02	Simvastatin and ezetimibe
		C10BA03	Pravastatin and fenofibrate
		C10BX	HMG CoA reductase inhibitors, other combinations
Hypertension, adult	ACE inhibitors	C09A	ACE inhibitors, plain
		C09B	ACE inhibitors, combinations
		C09C	Angiotensin II antagonists, plain
		C09D	Angiotensin II antagonists, combinations
	Antihypertensive vasodilators	C02D	Agents acting on arteriolar smooth muscle
		C02C	Antiadrenergic agents, peripherally acting on
	Clonidine	C02AC01	Clonidine
		C02LC01	Clonidine and diuretics
		C02LC51	Clonidine and diuretics, combinations with other drugs
	Ganglionic blockers	C02B	Antiadrenergic agents, ganglion-blocking
	Guanethidine	C02CC02	Guanethidine
		C02LF01	Guanethidine and diuretics
	Methyldopa	C02AB	Methyldopa
		C02LB	Methyldopa and diuretics in combination
	Rauwolfia alkaloids	C02AA	Rauwolfia alkaloids

		C02LA	Rauwolfia alkaloids and diuretics in combination
	Alpha/ beta blockers	C07AG	Alpha and beta blocking agents
		C07BG	Alpha and beta blocking agents and thiazides
	Diuretic combinations	C02L	Antihypertensives and diuretics in combination
		C03E	Diuretics and potassium-sparing agents in combination
		C07B	Beta blocking agents and thiazides
		C07D	Beta blocking agents and other diuretics
		C08G	Calcium channel blockers and diuretics
		C09BA	ACE inhibitors and diuretics
		C09DA	Angiotensin II antagonists and diuretics
		C09DX01	Valsartan, amlodipine and hydrochlorothiazide
		C09DX03	Olmesartan medoxomil, amlodipine and hydrochlorothiazide
		C09XA52	Aliskiren and hydrochlorothiazide
		C09XA54	Aliskiren, amlodipine and hydrochlorothiazide
	Diuretic K depleting agents	C03A	Low-ceiling diuretics, thiazides
	Diuretic K sparing agents	C03D	Potassium-sparing agents
Irritable bowel syndrome, adult and pediatric	Sulfonamides	A07AB	Sulfonamides
Liver disease, adult and pediatric	Ammonia detoxicants	A06AD61	Lactulose, combinations
		A05BA17*	Ornithine aspartate
		A05BA67*	Ornithine aspartate, combinations
		A06AD12	Lactitol
Malignancies, adult	Leucovorin	V03AF03	Calcium folinate
	Monoclonal	L01XC	Monoclonal antibodies
	Miscellaneous antinauseants	A04AA	Serotonin (5HT3) antagonists
		A04AD12	Aprepitant
	Antineoplastic alkylating	L01A	Alkylating agents
	Antineoplastic antibiotics	L01D	Cytotoxic antibiotics and related substances
	Antineoplastic MAO inhibitors	L01XB	Methylhydrazine
	Antineoplastic progesterones	L02AB	Progestogens
	Antineoplastic pyrimidines	L01BC	Pyrimidine analogues
	Antineoplastics misc.	L01C	Plant alkaloids and other natural products
		L01XA	Platinum compounds
		L01XE	Protein kinase inhibitors
		L01XX	Other neoplastic agents

		L02AE	Gonadotropin releasing hormone analogues
		L02BA	Anti-estrogens
		L02BB	Anti-androgens
		L02BG	Aromatase inhibitors
		L03AB	Interferons
		L03AX15	Mifamurtide
	Bladder protectant	V03AF01	Pentosan polysulfate sodium
		C05BA04	Pentosan polysulfate sodium
	Methotrexate	L01BA01	Methotrexate
		L04AX03	Methotrexate
	Purine antimetabolites	L01BB	Purine analogues
	Colony stimulating factors	L03AA	Colony stimulating factors
Parkinson's disease, adult	Dopamine	N04BA	DOPA and DOPA derivatives
	MAO B inhibitors	N04BD	Monoamine oxidase-B inhibitors
Psychotic illness, adult and pediatric	Miscellaneous antipsychotics	N05AE	Indole derivatives
		N05AG	Diphenylbutylpiperidine derivatives
		N05AH	Diazepines, oxazepines, thiazepines and oxepines
		N05AL	Benzamides
		N05AX	Other antipsychotics
		N06C	Psycholeptics and psychoanaleptics in combination
	Butyrophenones	N05AD	Butyrophenone derivatives
	Phenothiazines	N05AA	Phenothiazines with aliphatic side chain
		N05AB	Phenothiazines with piperazine structure
		N05AC	Phenothiazines with piperidine structure
	Thiothixenes	N05AF	Thioxanthene derivatives
Renal disease, adult	Potassium removing resins	V03AE01	Polystyrene sulfonates
Rheumatoid arthritis, adult and pediatric	Antiinflammatory glucocorticoids	H02AB	Glucocorticoids
		H02BX	Corticosteroids for systemic use, combinations
		M01BA	Antiinflammatory/ antirheumatic agents in combination with corticosteroids
	Gold salts-injectable	M01CB	Gold preparations excl. M01CB03
	Gold salts-oral	M01CB03	Auranofin
Thyroid disorder, adult	Thyroid replacement	H03AA	Thyroid hormones
Transplant, adult	Immunosuppressive agents	L04AA02	Muronab-CD3
		L04AA03	Antilymphocyte immunoglobulin (horse)
		L04AA04	Antilymphocyte immunoglobulin (rabbit)
		L04AA06	Mycophenolic acid

		L04AA10	Sirolimus
		L04AA18	Everolimus
		L04AA19	Gusperimus
		L04AA28	Belatacept
		L04AC01	Daclizumab
		L04AC02	Basiliximab
		L04AD	Calcineurin inhibitors
		L04AX01	Azathioprine
Tuberculosis, adult	Anti-tuberculosis antibiotics	J04AB	Anti-tuberculosis antibiotics
	Isoniazide	J04AC01	Isoniazide
		J04AC51	Isoniazide, combinations
		J04AM	Isoniazide, combinations

ACE: angiotensin-converting enzyme, DOPA: dihydroxyphenylalanine, HIV: human immonudeficiency virus, HMG CoA: hydroxy-methylglutaryl coenzyme A, MAO: monoamine oxidase, SSRI: selective serotonin reuptake inhibitors.

*ATC according to: Deutsches Institut für Medizinische Dokumentation und Information. Anatomisch-therapeutisch-chemische-Klassifikation mit Tagesdosen. Amtliche Fassung des ATC-Index mit DDD-Angaben für Deutschland im Jahr 2014. Available at: http://www.dimdi.de.

[1] Fishman PA, Goodman MJ, Hornbrook MC, Meenan RT, Bachman DJ, O'Keeffe Rosetti MC. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. Med Care 2003;41:84-99.

[2] Not indicated for anxiety and tension.

[3] Systemic anti-inflammatory glucocorticoids are listed in RxRisk Class "rheumatoid arthritis".

[4] Not indicated for depression.

[5] See human erythropoietin.

[6] Not indicated for heart disease or hypertension.

Table S7: Distribution of severity of the medCDS score in the different cohorts.

Cohort	medCDS score risk groups		
	Low risk (≤ 5 score points) n (%)	Medium risk (6 score points) n (%)	High risk (≥ 7 score points) n (%)
MultiCare (n = 3163)	2810 (88.8 %)	175 (5.5 %)	178 (5.6 %)
KORA-Age (n = 4127)	3787 (91.8 %)	179 (4.3 %)	161 (3.9 %)
ESTHER (n = 2703)	2588 (95.7 %)	58 (2.1 %)	57 (2.1 %)

Development and validation of a medication-based chronic disease score (medCDS)

Quinzler et al.

What is new?

1. In a prospective cohort of older patients with multiple morbidities, a new medication-based, disease-oriented score (medCDS) was developed on the basis of current treatment guidelines for the most prevalent chronic diseases in older patients.
2. medCDS more accurately predicted mortality than established medication-based scores (e.g. RxRisk or CDS), which are still used for morbidity assessment.
3. The score was validated in two independent large longitudinal cohorts of community-dwelling older patients and performed similarly well.
4. medCDS is designed to allow easy maintenance and expansion of the score as new and effective medicines become available.
5. In its current form, it performed better than an empirical score that used a set of selected anatomical-therapeutic-chemical (ATC) codes or only age and sex.

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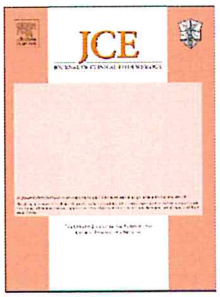

A novel superior medication-based chronic disease score (medCDS) predicted all-cause mortality in independent geriatric cohorts

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