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A tool for prediction of risk of rehospitalization and mortality in hospitalized elderly

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ABSTRACT

Objectives: To construct and internally validate a risk score, the "80+ score", for revisits to hospital and mortality for older patients, incorporating aspects of pharmacotherapy. Our secondary aim was to compare the discriminatory ability of the score with that of three validated tools for measuring inappropriate prescribing: Screening Tool of Older Person's Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI).

Setting: Two acute internal medicine wards at Uppsala University hospital. Patient data from a randomized controlled trial, investigating effects of a comprehensive clinical pharmacist intervention, was used.

Participants: Data from 368 patients, aged 80 years and older, admitted to one of the study wards.

Primary outcome measure: Time to rehospitalization or death during the year after discharge from hospital. Candidate variables were selected among a large number of clinical and drug-specific variables. After a selection process, a score for risk-estimation was constructed. The 80+ score was internally validated, and the discriminatory ability of the score and of STOPP, START and MAI was assessed using C-statistics.

Results: Seven variables were selected. Impaired renal function, pulmonary disease, malignant disease, living in nursing home, being prescribed an opioid or being prescribed a drug for peptic ulcer or gastroesophageal reflux disease were associated with an increased risk, while being prescribed an antidepressant drug (tricyclic antidepressants not included) was linked to a lower risk of the outcome. These variables made up the components of the 80+ score. The C-statistics were 0.71 (80+), 0.57 (STOPP), 0.54 (START) and 0.63 (MAI).

Conclusion: We developed and internally validated a score for prediction of risk of rehospitalization and mortality in hospitalized older people. The score discriminated risk better than available tools for inappropriate prescribing. Pending external validation, this score can aid in clinical identification of high-risk patients and targeting of interventions.

ARTICLE SUMMARY

Strengths and limitations

- The 80+ score is based on data from a population on whom there are strong incentives to focus: patients at high risk of hospitalization and also of mortality.

- The score is constructed from a prediction model that includes aspects of pharmacotherapy. The use of drugs can be either positively or negatively causally related to a clinical outcome, and can also be important indicators for a certain condition, disease or circumstance.

- Data from a limited number of patients, being admitted to an acute internal medicine ward at one hospital only, was used in the construction of the score. The generalizability of the score is therefore unknown.

- The 80+ score was internally validated, but external validation is required before general use and recommendation.

BACKGROUND

Hospitalizations of older people pose an increasing economic burden on healthcare systems in the developed world. During recent years, attempts have been made to identify risk factors for hospital readmissions in order to help target interventions and decrease readmission rates [1,2]. Variables tested for their ability to predict readmissions have included patient demographic factors, medical co-morbidity data, laboratory data, social determinants of health, patient functional status, and prior use of health-care services. However, the patients' medication use has rarely been evaluated as potential predictors of readmissions. As adverse drug reactions are the main cause of up to a fourth of hospital admissions [3–5] and are ranked as the fourth to sixth leading cause of death in the United States [6], this is surprising. In older people, multiple co-existing diagnoses and concomitant multi-drug use are common. This group is also, due to pharmacokinetic and pharmacodynamic changes, at increased risk of adverse drug reactions [7,8], and hence hospitalizations and mortality. For this population in particular, the use of medications should be considered as a potential prognostic factor for revisits to hospital and mortality.

There are several tools available for assessment of appropriateness of prescribing in older people [9–16], which can be used prospectively as guides to appropriate prescribing or retrospectively for evaluation of the quality of prescribing [11,17,18]. These tools have mainly been developed through literature search and expert opinion [11–14,19–21]. However, the association between inappropriate medication use in older people and poor health outcomes still remains uncertain. The evidence for a link between the tools and clinical outcomes is not convincing for any of the them [22–25].

The aim of this study was to construct a tool for estimating risk of revisits to hospital or mortality for older people, incorporating aspects of pharmacotherapy. The secondary aim was to compare the discriminatory ability of this tool, or score, with three validated tools for appropriate prescribing: Screening Tool of Older Person's Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI) [11,15], and with the drug list of the Swedish Association of Local Authorities and Regions (SALAR)[16].

METHODS

Study participants and data

Patient data from a prospective randomized controlled study (RCT) was used[26]. The main objective of the RCT was to study the effects of adding a ward-based pharmacist service to the health care team on clinical outcomes (number of revisits to hospital; readmissions or emergency department visits) for elderly patients. Four-hundred patients, aged 80 years and older and acutely admitted to the internal medicine wards at Uppsala University Hospital, were included and randomized into control or intervention group. The patients in the intervention group received an enhanced pharmacist service during the hospital admission. All patients were followed for 12 months after hospital discharge, and the number of and time for revisits to hospital and/or mortality was recorded. Each participant gave written informed consent and the study protocol was approved by the Uppsala Regional Ethics Committee (Trial Registration: clinicaltrials.gov Identifier: NCT00661310). In this study, the group assignment was not taken into consideration in the analyses.

Outcome variables

Time to event (i.e. unplanned rehospitalization [emergency department visit or readmission] or death) from the day of discharge from index admission, was used as outcome variable when constructing the point score system and for goodness-of-fit analyses. For the assessment of discriminatory ability, the occurrence of an event during the 12 months follow-up was used as outcome variable.

Statistical analyses

Identification of risk factors

Candidate variables were selected based on a combination of clinical judgment and statistical properties of the variables. Clinical and drug-specific (drug-disease [i.e. a specific drug in a certain condition], as well as drug) variables were included. The selected clinical variables were: gender, age, renal function (Creatinine clearance [CLcr]), level of social support and medical history (heart failure, diabetes mellitus, pulmonary disease [chronic obstructive pulmonary disease (COPD) or asthma],

arrhythmia, malignant disease [past or present], coronary artery disease, cerebral vascular lesion [past], myocardial infarction [past], hypertension and dementia). As drug-disease variables, STOPP and START criteria (each criterion from each tool individually) were used. The drug variables were the patients' prescribed medications, categorized into groups based on the ATC classification system [27] and on similar effect and risk in elderly people, or categorized according to the SALAR drug list (SALAR drug list presented in eTable 1). In case a SALAR drug variable was the same as an ATC-based category variable, one of them was excluded. Variables with less than 10 patients in the smallest group were excluded from further analyses. In order to detect potential redundancies among the variables, a principal component analysis (PCA) was performed. If two variables were collinear, the variable with the most balanced categories were included for further study. The remaining clinical, drug-disease and drug variables were then subject to a backward stepwise Cox regression likelihood-ratio elimination procedure. To minimize type I errors, the p-value limit for inclusion was set to 0.01. The set of variables extracted from this analysis, i.e. the risk factors, make up the components of our new score.

Development of point score system

We developed a point score system for risk estimation, the "80+ score", following the Framingham Heart Study approach [28,29]. First, the continuous independent variable, CLcr, was organized into categories, and reference values were determined for each category. The remaining independent variables were modeled by sets of dichotomous indicator variables, using their most prevalent category as the base category. We then calculated how far each category was from the base category by dividing the regression unit for the category by a constant ("B") that was common to all variables. The resulting quotient was rounded to the nearest whole number, which was used as the points associated with that category. The point score system is the 80+ score. Last, the risk associated with each level of the score was calculated. For this last step, the following formula was used: Risk estimate = $1 - S_0(t)^{\exp(\Sigma \beta\chi - \Sigma \beta\chi_{mean})}$, where $S_0(t)$ was the average one-year event-free rate, and $\Sigma \beta\chi_{mean}$ was the sum of the variables' regression coefficients (β) multiplied with the means or proportions of the variables in the sample

(Table 3). $\sum \beta\chi$ was approximated from multiplying the constant for the model (B) with the point score and adding back the base value (i.e. the reference value for the base category) for the continuous variable CLcr.

The goodness-of-fit of the 80+ score was assessed by Grønnesby-Borgan test [30] and calibration was assessed by plotting predicted vs observed risk. The discriminatory ability of the 80+ score was assessed using C-statistics. C-statistics, which can range from 0.5 (no discrimination) to 1 (perfect discrimination), provide the ratio of the probability of predicting an event in patients with an event to that in patients without an event. We internally validated the score using an enhanced bootstrap with 1000 iterations, in order to quantify and account for the extent of overoptimism in our prediction model [31]. We present optimism-corrected C-statistics for the 80+ score. The total STOPP, START and MAI scores and the total number of prescribed SALAR drugs were calculated for each patient. Their discriminatory abilities were also assessed using C-statistics, and these were compared to the C-statistic for the 80+ score.

The effect of the pharmacist intervention was not adjusted for in the regression analyses. The reason for this was that the intervention directly affected the results of the STOPP, START and MAI scores as well as the frequency of prescribing of SALAR drugs and the overall number of drugs. As a sensitivity analysis, the C-statistic for the 80+ score was calculated for the control group patients only. Proportionality of hazards was assessed using Schoenfeld's residuals and by inspecting cumulative incidence curves. We investigated the linearity of the association between CLcr and the outcomes by investigating models also including an ordinal variable for CLcr. Two-way interactions between the final set of variables in the score were investigated as deviations from multiplicativity. The score variables were also tested for the association with mortality only. All analyses were performed in IBM SPSS Statistics 21 and STATA version 13.

RESULTS

Out of the 400 included and randomized patients in the RCT, 368 were evaluable for further analyses (27 patients died during the index admission and 5 patients wished to be excluded after the randomization). Table 1 presents baseline characteristics for these patients. Two hundred and fifty (68%) of the patients had an event (i.e. either revisit to hospital or death) during the 12-months follow-up period. In the group of patients that had an event, 212 (85%) were rehospitalized, the rest (15%) died.

Table 1. Baseline characteristics at time of index hospital admission

Baseline characteristics	All patients (n=368)
Age, mean (SD), years	86.7 (4.1)
Female, No (%)	216 (58.7)
Body weight, mean (SD), kg	
Women	61.3 (13.3)
Men	71.3 (12.5)
Laboratory values	
Creatinine clearance, mean (SD), mL/min/1.73m^2	40.3 (18.5)
Hemoglobine level, mean (SD), mg/mL	
Sodium level, No (%)	
Hyponatremia (<137 mEq/L)	112 (30.4)
Within range (137-145 mEq/L)	247 (67.1)
Hypernatremia (>145 mEq/L)	9 (2.4)
Potassium level, No (%)	
Hypokalemia (<3.5 mEq/L)	49 (13.3)
Within range (3.5 -5 mEq/L)	295 (80.2)
Hyperkalemia (>5 mEq/L)	24 (6.5)
Social support, No (%)	
Living alone or with spouse	301 (81.8)
Living in a nursing home	67 (18.2)
Medical history, No (%)	
Heart failure	116 (31.5)
Diabetes	87 (23.6)
Pulmonary disease (asthma or COPD)	44 (12.0)
Arrhythmia	125 (34.0)
Malignant disease (past and present)	54 (14.7)
Coronary artery disease	114 (31.0)
Cerebral vascular lesion (past)	57 (15.5)
Myocardial infarct (past)	87 (23.6)
Hypertension	147 (39.9)
Dementia	47 (12.8)

COPD=chronic obstructive pulmonary disease

Identification of risk factors

eTable 2a-c list all variables taken into consideration in the analysis. Fourteen clinical variables, 14 drug-disease variables and 50 drug variables met the inclusion criteria and

were subject to the PCA. Three variables were excluded after the PCA: "B03B Vitamin B12 and folic acid" (collinear with "STOPP h5; Long-term opiates in patients with recurrent falls"), "G03C Estrogens" and "R03AC Drugs for obstructive airway diseases; selective beta-2-agonists" (both collinear with R03B "Drugs for obstructive airway diseases; anticholinergics +corticosteroids").

Seventy-five variables were entered into the backward stepwise Cox regression. This procedure resulted in seven statistically significant variables, or risk factors, each having an individual association with the outcome variable. Four of the risk factors were clinical while three were drug-specific. Statistical information about the risk factors is presented in Table 2. Past or present malignant disease and presence of pulmonary disease were both associated with an increased risk of rehospitalization or mortality, as was impaired renal function. Further, living in a nursing home was linked to a higher risk of revisits to hospital or death than living alone or with a spouse. Being prescribed a drug for peptic ulcer and gastro-esophageal reflux disease (GERD) was associated with an increased risk (a vast majority of these prescriptions, 115 out of 120 (96%), was of a proton-pump inhibitor), as well as being prescribed a drug from the opioid class. Having an antidepressant drug (tricyclic antidepressants (TCA) not included in this variable) was, conversely, associated with a lower risk.

Table 2. *Statistical information on 80+ score variables.*

	Regression coefficient (SE)	Mean or proportion	p-value	HR	95% CI for HR
Creatinine clearance (per ml/min)	-0.012 (0.004)	40.285	0.001	0.988	0.981-0.995
Social support (living in nursing home *vs* living alone or with spouse)	0.481 (0.162)	0.182	0.003	1.617	1.176-2.224
Pulmonary disease[a] (*vs.* not)	0.607 (0.177)	0.122	0.001	1.834	1.296-2.595
Malignant disease[b] (*vs.* not)	0.506 (0.166)	0.166	0.002	1.659	1.198-2.297
Prescription of drug for peptic ulcer and GERD (*vs.* not)	0.362 (0.135)	0.326	0.008	1.436	1.101-1.872
Prescription of opioid drug (*vs.* not)	0.724 (0.157)	0.179	0.000	2.063	1.517-2.806
Prescription of non-TCA-antidepressant drug (*vs.* not)	-0.558 (0.170)	0.209	0.001	0.573	0.410-0.799

Variables selected from backward stepwise Cox regression
[a]asthma or chronic obstructive pulmonary disease (COPD), [b]past or present
SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease,
TCA=tricyclic antidepressants (TCA)

Table 3. *Data used for calculation of point score system.*

	Proportion of patients in each category	β	W and $W_{ref.}$ for each category	Regression unit for each category	Point score
Creatinine clearance		-0.012			
> 90 ml/min	0.014		105 ml/min = $W_{ref.}$		0
60-89 ml/min	0.128		74.5 ml/min	0.397	1
30-59 ml/min	0.552		54.5 ml/min	0.787	2
< 30 ml/min	0.307		17.5 ml/min	1.138	3
Social support		0.481			
Living alone or with spouse	0.818		0 = W_{ref}	0	0
Nursing home	0.182		1	0.481	1
Pulmonary disease[a]		0.607			
No	0.878		0 = $W_{ref.}$	0	0
Yes	0.122		1	0.607	2
Malignant disease[b]		0.506			
No	0.834		0 = $W_{ref.}$	0	0
Yes	0.166		1	0.506	1
Prescription of drug for peptic ulcer and GERD		0.362			
No	0.674		0 = $W_{ref.}$	0	0
Yes	0.326		1	0.362	1
Prescription of opioid drug		0.724			
No	0.821		0 = $W_{ref.}$	0	0
Yes	0.179		1	0.724	2
Prescription of non-TCA-antidepressant drug		-0.558			
No	0.791		0 = $W_{ref.}$	0	0
Yes	0.209		1	-0.558	-2

The average 1-year event-free rate = 0.3215[c]

[a]*asthma or chronic obstructive pulmonary disease (COPD),* [b]*past or present,* [c]*Kaplan-Meier estimate of the event-free rate at the mean values of the risk factors*
Regression unit for each category = β * (W-W_{ref})
Point score= β(W-Wref)/B

Development of point score system

Table 3 presents reference values (W and W_{ref}) and regression units of each category of each risk factor variable –data that was used for development of point score. CLcr was organized into four levels of renal function, with >90 ml/min considered normal renal function. As reference values for these categories, the midpoints were chosen. For the other risk factor variables, the categories were assigned the values 0 or 1. A referent risk factor profile was determined: a patient with normal renal function, living alone or with a

spouse, without diagnoses for pulmonary disease or malignant disease and with no prescription of drug for peptic ulcer or GERD, no prescription of opioids and no prescription of antidepressant drugs. The constant for the point score system (B) was selected, which was the regression coefficient for the variable "Drugs for peptic ulcer and GERD", 0.362. By dividing the regression unit for each category by B, it was computed how far the categories were from the base category. Hereby, the point scores for each category for each risk factor variable were calculated. The point scores for the 80+ score system, are presented in the right hand column in Table 3.

The point total is the summated score for each patient. For example, a patient with renal function of 65 ml/min, living in a nursing home, diagnosed with COPD and prescribed a drug for peptic ulcer and GERD, would be given a point total of 1+1+2+1=5. The estimated risk associated with each point total in the 80+ score is shown in Table 4. The estimated risk was computed using the formula described in the methods, where the $\sum \beta\chi_{mean}$ was calculated to - 0.106842 and the $\sum \beta\chi$ was approximated by multiplying B with the points and adding back the base value for CLcr (-0.012 * 105 ml/min). An example of risk estimation from the Cox regression as well as from the point score system is illustrated in online-only Supplementary material.

Table 4. *Estimate of risk for each point total*

Point total	Estimate of risk
-2	0.1594
-1	0.2207
0	0.3010
1	0.4021
2	0.5223
3	0.6539
4	0.7821
5	0.8879
6	0.9568
7	0.9890
8	0.9985
9	0.9999
10	>0.9999

The goodness of fit of the 80+ score was good, which is illustrated in Figure 1. This was confirmed by the Grønnesby-Borgan test (p=0.49). A model including both an ordinal and a continuous variable for CLcr did not provide a better fit that a model with only the

continuous variable (likelihood-ratio test p=0.11). There was some evidence of interactions between CLcr and the drug use variables "Drugs for peptic ulcer and GERD" and "Non-TCA-antidepressants" but the groups were very small. No deviations from proportionality were observed (all Schoenfeld's test p>0.21).

When tested for their association with mortality only, the variables Pulmonary disease, Prescription of drug for peptic ulcer and GERD, and Prescription of non-TCA-antidepressant drug were not predictors of this outcome (p>0.05), while the link between social support and this outcome was strong (HR 3.107, 95% confidence interval 2.081-4.640). The remaining variables showed similar predictive ability for the mortality outcome as for the combined outcome (rehospitalization and mortality). Results are presented in eTable 3.

The 80+ score demonstrated a satisfying discriminatory ability of the outcome, with a C-statistic of 0.715 (Figure 2). The optimism was 0.001, rendering an optimism-corrected C-statistic of 0.714 for the 80+ score. This means that a patient with an event (revisit to hospital or death) had a 71% probability to be given a higher risk score than a patient with no event. Figure 2 also shows that STOPP and START scores and the SALAR drug list were basically non-discriminating for the chosen outcome (with C-statistics just above 0.5). When tested in the control group only, the 80+ score had a C-statistic of 0.71, i.e. a similar value as in the whole group.

DISCUSSION

Using a clinical trial database of hospitalized patients, aged 80 years and above, the most relevant factors for identifying those at risk of an adverse outcome were identified. A simple scoring system intended for clinical use was constructed and internally validated, pending validation in an independent cohort. The score is suggested as a tool for identifying patients at highest risk of readmissions and mortality, and ultimately as an aid in clinical decision-making for improving outcomes in these patients. Increasing age, usage of medical services and poor health pose a risk of rehospitalization and mortality [2] and hence, there are strong incentives for focusing on this population.

Various risk factors for rehospitalization and mortality have previously been identified in prediction models based on data from a variety of populations and settings, and with different candidate variables [32–39]. The 80+ risk score has a higher discriminatory ability for risk of rehospitalization and mortality than most other prediction models of today. This is likely due to the fact that we included drug-related variables as candidate variables – the drugs can either be causally related to the outcomes or serve as important proxies for certain conditions, diseases or circumstances. Further, the precision was likely maximized by developing the score using data from a narrowly defined population –these patients were all aged 80 years or older and had been acutely admitted to an internal medicine ward.

The use of drugs deemed inappropriate has been associated with adverse drug events [40,41] and it is often proposed that patients prescribed inappropriate medications should be prioritized for interventions – aimed at improving the quality of prescribing – in order to reduce the risk of unwanted clinical outcomes. However, in this set of patient data, neither the STOPP nor START scores had an ability to discriminate between patients at risk of rehospitalization or mortality that was better than chance. The numbers of prescribed SALAR drugs showed similar results. The MAI, being an implicit, judgment-based score, has a moderate discriminatory ability for risk in this population. However, due to its time-consuming nature, with assessment times per patient of up to 30 minutes, MAI is not suitable as a screening tool for patients in clinical practice. As has already

been stated, none of the STOPP, START and MAI scores or the SALAR drug system, are designed as risk scores. Still, the lack of consistent evidence for their association with clinical outcomes is notable and needs to be further investigated.

The presence of pulmonary disease as well as impaired kidney function are known risk factors for readmissions to hospital [32–35]. These variables also emerged as risk factors in our population. Many nursing home residents have multiple morbidities and are high consumers of health care [42], which explains the prognostic ability of this variable. The unique finding in this study is that three drug-specific variables were individually related to the clinical outcome in the multivariate model: being prescribed a drug for peptic ulcer and GERD or being prescribed an opioid both appeared to increase the risk, while being prescribed an antidepressant drug was associated with a lower risk. The use of proton-pump-inhibitors have in several studies been associated with various adverse events, such as clostridium difficile infections and pneumonia [43], but another explanation for their association with the outcome variable is that the patients being prescribed these drugs have a history of ulcer (which was not among the candidate variables), that is a risk factor itself. This drug group may also function as a proxy for patients with multiple other co-morbidities and polypharmacy since these patients have a potential need for preventive treatment for gastric disorders [43]. Similarly, opioids can, as well as being a risk drug due to their potential to cause adverse drug reactions, be an indicator for pain or frailty (which are potential risk factors in themselves). The prescribing of non-TCA-antidepressants aims to provide relief from psychological symptoms and increase the patient's general well being, which supposedly has a protective effect on rehospitalization and mortality. An alternative explanation for the negative association between this variable and the outcome is that these drugs may be given more often to physically healthier patients with a longer life expectancy. The rationale for exclusion of TCAs in the antidepressant variable, is that the safety profile in elderly people for these drugs differs from that of the other antidepressants. TCA drugs were not a candidate variable in the analyses – since only 5 patients were prescribed these drugs – but were included in the "SALAR a" variable. The strong link between level of social support and mortality is not surprising, since patients often move to nursing homes for the last part of their lives.

Interestingly, pulmonary disease or being prescribed a drug for peptic ulcer or GERD or a non-TCA-antidepressant drug, were predictors mainly for rehospitalization.

A score for risk-identification purposes should have good predictive ability in the target population, and it should use data that is clinically readily available [1,44]. The 80+ score meets these criteria. A simple and user-friendly point score system like this can quickly and easily identify high-risk patients. Yet, in order for this information to be useful, translation into suggested actions for reduction of this risk for these patients is crucial. This undertaking is obviously multifactorial. Nevertheless, by focusing on the patients with the highest risk, a pharmaceutical intervention, or other quality improvement effort, can be targeted more efficiently. For example, patients with COPD or asthma may benefit from a comprehensive patient education [45] and patients being prescribed an opioid or a drug for peptic ulcer or GERD, may benefit from a thorough medication review. In the majority of risk prediction models of today, rehospitalization has been chosen as the outcome measure, but this carries a high risk of bias due to competing risk by death. Therefore, in this study, event-free (i.e. no emergency department visit or readmission) survival was used as endpoint.

The 80+ score was internally validated, but remains to be externally validated in another population before it can be generally recommended. A few limitations with this study need attention. Prior hospital visits have in several studies been associated with risk of rehospitalization [33,34,36,38,39]. This information was not available in this dataset and has therefore not been included as a candidate variable. However, a potential weakness of having prior hospital visits as a variable in a clinical score, is that this information may not be easily available upon the patients admission to hospital. Another limitation is that the 80+ score is based on data from a limited number of patients, being admitted to an acute internal medicine ward at one hospital only. This makes the generalizability unknown and increases the need for external validation. Finally, the limited sample size forced us to use the whole dataset (both intervention and control group patients) for the development of the score.

CONCLUSION

We have developed and internally validated a score intended for use in clinical practice to identify the hospitalized elderly patients at highest risk of rehospitalization and mortality, accounting for pharmacotherapy. The score outperforms scores for inappropriate medication use in risk-prediction ability and can ultimately aid in clinical decision-making for improving outcomes in elderly patients.

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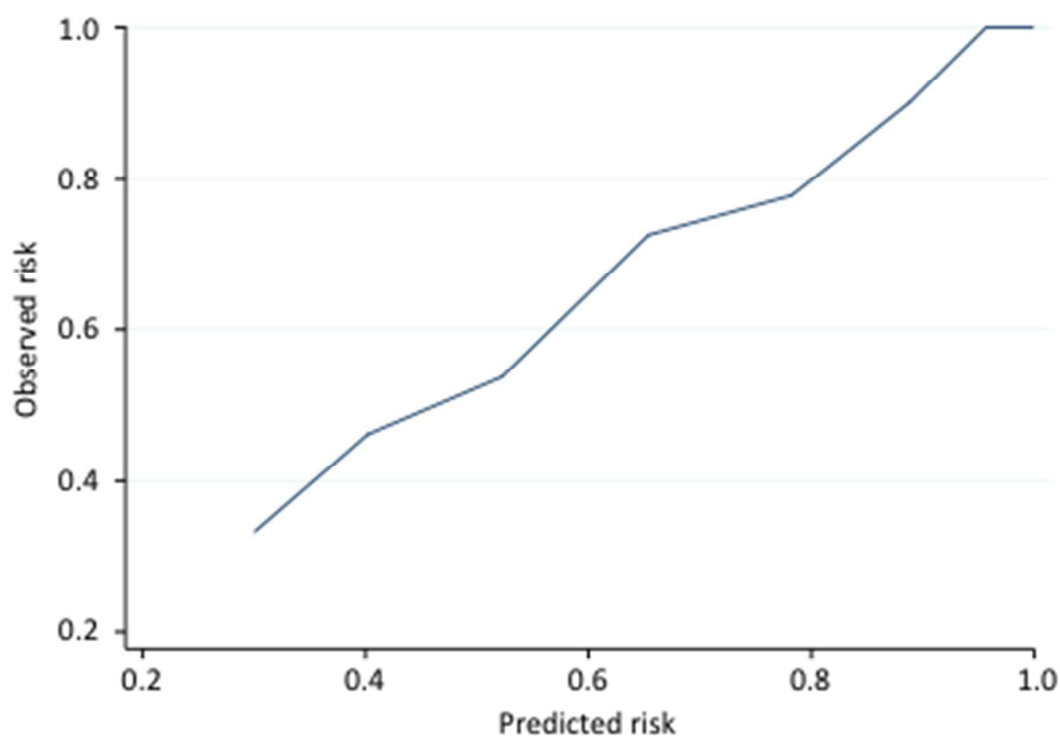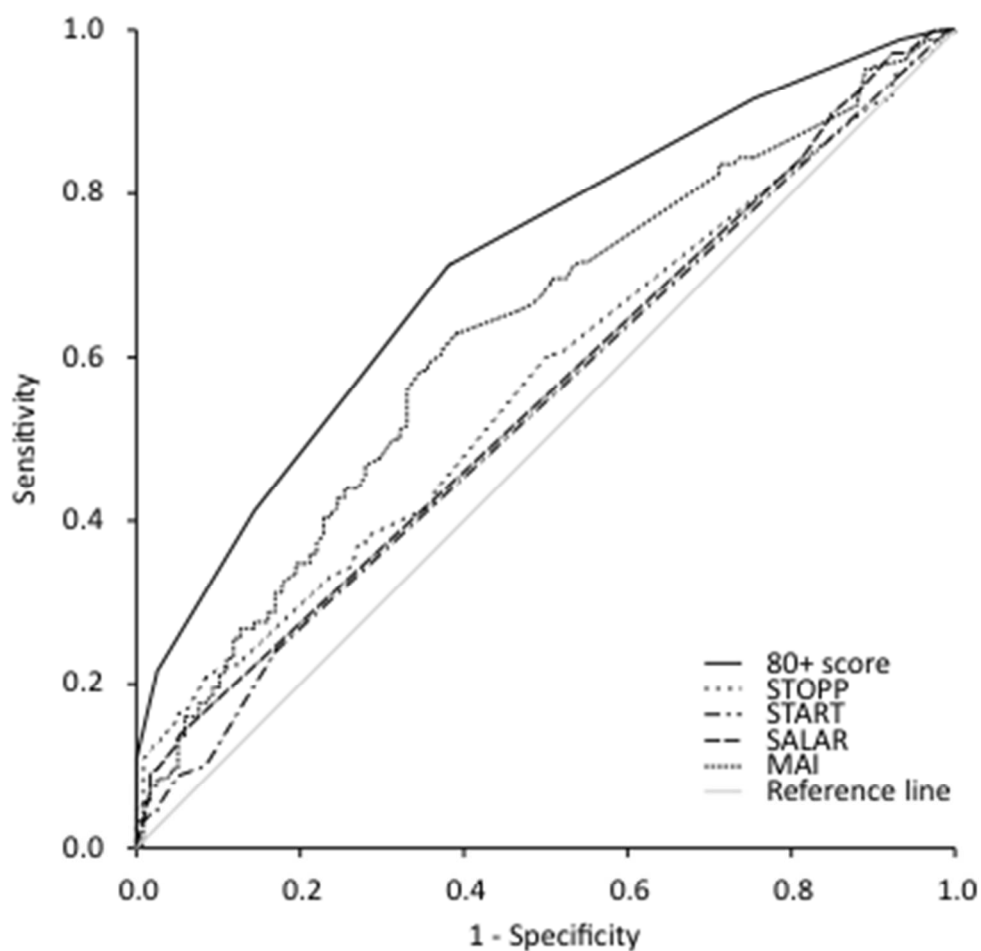*Figure 1. Predicted risk vs observed risk for rehospitalization or death.*

Figure 2. Area under the curve of sensitivity vs. *1-specificity for rehospitalization or death.*

C-statistics: 80+ score=0.72 (95% CI 0.66-0.77), 80+ score (optimism-corrected)=0.71, STOPP score=0.57 (95% CI 0.51-0.63), START score=0.54 (95% CI 0.48-0.60), SALAR drugs=0.55 (95% CI 0.49-0.62), MAI=0.63 (95% CI 0.57-0.69).

On-line only Supplemental Material

eTable 1. Swedish Associations of Local Authorities and Regions (SALAR) drug list

Drug classes	Example
Anticholinergic agents (SALAR a)	*Alimemazine, hydroxizine, prometiazine, tolterodine, tricyclic antidepressants*
Long-acting benzodiazepine derivates (SALAR b)	*Diazepam, flunitrazepam, nitrazepam*
Neuroleptics (SALAR n)	*Haloperidol, olanzapine. quetiapine risperidone*
Oral nonsteoridal anti-inflammatory drugs (NSAIDs) (SALAR s)	*Diclofenac, ibuprofen, naproxen*
Tradolan (SALAR t)	*Tramadol*
Propiomazin (SALAR p)	*Propiomazine*

eTable 2a. Variable selection. Clinical variables

Variable	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
Age, years (cont.)	-	Yes		Yes
Female, (man/woman)	-	Yes		Yes
Creatinine clearance, ml/min (cont.)	-	Yes		Yes
Social support (living alone or with spouse /living in nursing home)	301[a]	Yes		Yes
Heart failure (yes/no)	141	Yes		Yes
Diabetes (yes/no)	88	Yes		Yes
Pulmonary disease (yes/no)	45	Yes		Yes
Arrhythmia (yes/no)	142	Yes		Yes
Malignant disease -past and present (yes/no)	61	Yes		Yes
Coronary artery disease (yes/no)	114	Yes		Yes
Cerebral vascular lesion –past (yes/no)	72	Yes		Yes
Myocardial infarct –past (yes/no)	98	Yes		Yes
Hypertension (yes/no)	147	Yes		Yes
Dementia (yes/no)	51	Yes		Yes

[a] (no of patients living alone or with spouse). PCA=principal component analysis)

eTable 2b. Variable selection. Drug-disease variables.

Variable	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
STOPP a1	29	Yes		Yes
STOPP a2	8			
STOPP a4	1			
STOPP a6	1			
STOPP a7	2			
STOPP a8	3			
STOPP a11	3			
STOPP a12	48	Yes		Yes
STOPP a13	7			
STOPP b1	2			
STOPP b3	2			
STOPP b7	11	Yes		Yes
STOPP b8	6			
STOPP b9	2			
STOPP b12	3			
STOPP b13	3			
STOPP c1	3			
STOPP c4	23	Yes		Yes
STOPP e1	2			
STOPP e2	3			
STOPP e3	2			
STOPP e4	5			
STOPP e6	2			
STOPP e7	8			
STOPP f1	2			
STOPP f2	1			
STOPP f5	1			
STOPP g1	8			
STOPP g3	3			
STOPP g4	12	Yes		Yes
STOPP h1	158	Yes		Yes
STOPP h2	28	Yes		Yes
STOPP h3	10	Yes		Yes
STOPP h4	13	Yes		Yes
STOPP h5	49	Yes		Yes
STOPP i2	2			
STOPP j	9			
START a1	7			
START a3	11	Yes		Yes
START a5	1			
START a6	26	Yes		Yes
START a7	9			
START a8	10	Yes		Yes
START b1	5			
START e2	6			
START e3	12	Yes		Yes
START f1	1			
START f2	5			
START f3	3			

No patients scored positive on the STOPP criteria a3, a5, a9, a10, a14, a15, a16, 17, b2, b4, b5, b6, b10, b11, c2, c3, c5, d1, d2, d3, e5, e8, f3, f4, f6, g2, i1, i3 and START criteria a2, a4, b2, b3, c1, c2, c3, d1, d2, e1, f4. PCA=principal component analysis

eTable 2c. Variable selection. Drug variables, i.e. the medications used by patients, categorized according to ATC classification system or SALAR drug classes.

ATC code class / SALAR drug class	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
A02A	Antacid drugs	4			
A02B (A02BA + A02BC)	Drugs for peptic ulcer and gastro-esophageal reflux disease	120	Yes		Yes
A03AX13	Drugs for functional gastrointestinal disorders; Dimetikon	4			
A03FA01	Propulsives; Metoclopramide	13	Yes		Yes
A06AB	Laxatives (contact)	32	Yes		Yes
A06AC+A06AD	Laxatives (bulk-forming and osmotically acting)	129	Yes		Yes
A07DA03	Antipropulsives; Loperamid	8			
A07EC	Intestinal antiinflammatory agents; aminsosalicylic acid and similar	4			
A09A	Digestives	2			
A10A	Insulins and analogues	54	Yes		Yes
A10BA02	Oral blood glucose lowering drugs, excl. insulins; Metformin	15	Yes		Yes
A10BB	Oral blood glucose lowering drugs, excl insulines; Sulfonureids	39	Yes		Yes
A10BX	Oral blood glucose lowering drugs, excl. insulins; Other	2			
A11	Vitamins	27	Yes		Yes
A12A	Calcium supplement	64	Yes		Yes
A12B	Potassium supplement	19	Yes		Yes
A12C	Other mineral supplements	11	Yes		Yes
B01AA03	Antithrombotic agents – Warfarin	44	Yes		Yes
B01AB	Antithrombotic agents – Heparin group	7			
B01AC	Antithrombotic agents –Platelet aggregation inhibitors excl heparin	234	Yes		Yes
B03A	Iron preparations	38	Yes		Yes
B03B	Vitamin B12 and folic acid	190	Yes	Yes[*]	
B03X	Other antianemic preparations	13	Yes		Yes
C01A	Cardiac glycosides	71	Yes		Yes
C01B	Antiarrhythmics	4			
C01CX	Cardiac stiumulants excl. cardiac glycosides; Levosimendan	1			
C01DA	Vasodilators used in cardiac diseases; organic nitrates	195	Yes		Yes
C02CA	Antihypertensives; alfa-adrenoreceptor blockers	2			
C03	Diuretics	318	Yes		Yes
C05A	Agents for treatment of hemorrhoids and anal fissures	2			
C07A	Beta blocking agents	191	Yes		Yes

3

ATC code class / SALAR drug class	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-analysis
C08	Calcium channel blockers	69	Yes		Yes
C09	Agents acting on the renin-angiotensin system	189	Yes		Yes
C10	Lipid modifying agents	33	Yes		Yes
G03C	Estrogens	27	Yes	Yes[**]	
G04BD	Other urologicals; drugs used in urinary incontince	5			
G04C	Drugs used in benign prostata hyperplasi	17	Yes		Yes
H02A	Corticosteroids for systemic use	36	Yes		Yes
H03	Thyroid preparations	45	Yes		Yes
J01	Antibacterials for systemic use	7			
L01BA	Cytostatic/cytotoxics; Folic acid analoges	1			
L02B	Endocrine therapy; Hormone antagonists and related agents	5			
L04A	Immunosuppressants	1			
M01A	Anti-inflammatory and antirheumatic products, non steroids	19	Yes		Yes
M04A	Anti-gout preparations	30	Yes		Yes
M05BA	Drugs affecting bone structure and mineralization; Bisfosfonates	15	Yes		Yes
N02A	Analgesics; Opioids	68	Yes		Yes
N02B	Analgesics; other analgetics	177	Yes		Yes
N02C	Analgesics; antimigraine preparations	2			
N03A	Antiepileptics	5			
N04A+B	Antiparkinson drugs	19	Yes		Yes
N05A	Antipsychotics	34	Yes		Yes
N05BA	Anxiolytics; Bensodiazapine derivates	64	Yes		Yes
N05BB01	Anxiolytics; Hydroxizin	5			
N05CD	Hypnotics and sedatives; Benzodiazepine derivates	12			
N05CF	Hypnotics and sedatives; Benzodiazepine related agents	113	Yes		Yes
N05CM	Hypnotics and sedatives; Others	28	Yes		Yes
N06AC	Antidepressants; Tricyclic antidepressants	5			
N06AB+AX	Antidepressants; SSRI+others	83	Yes		Yes
N06B	Psychostimulants	1			
N06D	Anti-dementia drugs	12	Yes		Yes
R03AC	Drugs for obstructive airway diseases; Selective beta-2-stimulating agents	46	Yes	Yes	
R03B	Drugs for obstructive airway diseases; Anticholinergic +corticosteroids	51	Yes		Yes
R03D	Drugs for obstructive airway diseases; Other (systemic)	1			
R05	Cough and cold preparations	46	Yes		Yes

ATC code class / SALAR drug class	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-analysis
R06A	Antihistamines for systemic use	12	Yes		Yes
S01B	Opthalmologicals	39	Yes		Yes
SALAR a	Anticholinergic agents	34	Yes		Yes
SALAR b	Long-acting benzodiazepine derivates	12	Yes		Yes
SALAR n	Neuroleptics	26	Yes		Yes
SALAR s	Oral NSAID	14	Yes		Yes
SALAR t	Tradolan	27	Yes		Yes
SALAR p	Propavan	16	Yes		Yes

*Redundant with STOPP h5 **Redundant with R03B

PCA=principal component analysis

Supplementary Material: Risk estimation from Cox model and from score sheet

Formula

$$\text{Estimate of risk} = 1 - S_0(t)^{\exp(\Sigma \beta\chi - \Sigma \beta\chi_{mean})}$$

$S_0(t) = 0.3215$ (the average 1-year event-free time)
$\Sigma \beta\chi$ = the sum of the variables' regression coefficients multiplied with actual value
$\Sigma \beta\chi\text{mean}$ = the sum of the variables' regression coefficients multiplied with mean/proportions

Example

A patient living in a nursing home with pulmonary disease and a kidney function of 55 ml/min, being prescribed a proton-pump-inhibitor.

1. Risk estimate based on the Cox model:

$\Sigma \beta\chi = -0.012 * \mathbf{55} + 0.481 * \mathbf{1} + 0.607 * \mathbf{1} + 0.506 * \mathbf{0} + 0.362 * \mathbf{1} + 0.724 * \mathbf{0} - 0.558 * \mathbf{0} = 0.79$

$\Sigma \beta\chi\text{mean} = -0.012 * 40.285 + 0.481 * 0.182 + 0.607 * 0.122 + 0.506 * 0.166 + 0.362 * 0.326 + 0.724 * 0.179 - 0.558 * 0.209 = -0.106842$

Estimate of risk $= 1 - 0.3215^{\exp(0.79 + 0.106842)} = 0.938$

2. Risk estimate based on the point score system:

1 point (nursing home) + 2 points (pulmonary disesase) + 2 points (GFR 55 ml/min) + 1 points (drugs for peptic ulcer and GERD) = 6 points.

Estimate of risk = 0.9568 (Table 4)

The points system gives a 1-year estimate of risk for rehospitalization or death of 96%, while using the Cox model directly gives an estimated risk of 94%.

eTable 3. Statistical information of the 80+ score variables when tested for association with mortality

	Regression coefficient (SE)	Mean or proportion	p-value	HR	95% CI for HR
Creatinine clearance (per ml/min)	-0.017 (0.006)	40.285	0.004	0.983	0.972-0.994
Social support (living in nursing home *vs* living alone or with spouse)	1.134 (0.205)	0.182	0.000	3.107	2.081-4.640
Pulmonary disease[a] (*vs.* not)	0.108 (0.283)	0.122	0.701	1.114	0.641-1.939
Malignant disease[b] (*vs.* not)	0.619 (0.223)	0.166	0.005	1.858	1.200-2.875
Prescription of drug for peptic ulcer and GERD (*vs.* not)	0.236 (0.194)	0.326	0.225	1.266	0.865-1.852
Prescription of opioid drug (*vs.* not)	0.527 (0.216)	0.179	0.015	1.694	1.109-2.587
Prescription of non-TCA-antidepressant drug (*vs.* not)	-0.209 (0.208)	0.209	0.315	0.812	0.540-1.219

[a]*asthma or chronic obstructive pulmonary disease (COPD)*, [b]*past or present*

SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease, TCA=tricyclic antidepressants (TCA)

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A tool for prediction of risk of rehospitalization and mortality in hospitalized elderly: secondary analysis of clinical trial data

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A tool for prediction of risk of rehospitalization and mortality in hospitalized elderly: secondary analysis of clinical trial data

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1

ABSTRACT

Objectives: To construct and internally validate a risk score, the "80+ score", for revisits to hospital and mortality for older patients, incorporating aspects of pharmacotherapy. Our secondary aim was to compare the discriminatory ability of the score with that of three validated tools for measuring inappropriate prescribing: Screening Tool of Older Person's Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI).

Setting: Two acute internal medicine wards at Uppsala University hospital. Patient data from a randomized controlled trial, investigating effects of a comprehensive clinical pharmacist intervention, was used.

Participants: Data from 368 patients, aged 80 years and older, admitted to one of the study wards.

Primary outcome measure: Time to rehospitalization or death during the year after discharge from hospital. Candidate variables were selected among a large number of clinical and drug-specific variables. After a selection process, a score for risk-estimation was constructed. The 80+ score was internally validated, and the discriminatory ability of the score and of STOPP, START and MAI was assessed using C-statistics.

Results: Seven variables were selected. Impaired renal function, pulmonary disease, malignant disease, living in nursing home, being prescribed an opioid or being prescribed a drug for peptic ulcer or gastroesophageal reflux disease were associated with an increased risk, while being prescribed an antidepressant drug (tricyclic antidepressants not included) was linked to a lower risk of the outcome. These variables made up the components of the 80+ score. The C-statistics were 0.71 (80+), 0.57 (STOPP), 0.54 (START) and 0.63 (MAI).

Conclusion: We developed and internally validated a score for prediction of risk of rehospitalization and mortality in hospitalized older people. The score discriminated risk better than available tools for inappropriate prescribing. Pending external validation, this score can aid in clinical identification of high-risk patients and targeting of interventions.

ARTICLE SUMMARY

Strengths and limitations

- The 80+ score is based on data from a population on whom there are strong incentives to focus: patients at high risk of hospitalization and also of mortality.

- The score is constructed from a prediction model that includes aspects of pharmacotherapy. The use of drugs can be either positively or negatively causally related to a clinical outcome, and can also be important indicators for a certain condition, disease or circumstance.

- Data from a limited number of patients, being admitted to an acute internal medicine ward at one hospital only, was used in the construction of the score. The generalizability of the score is therefore unknown.

- The 80+ score was internally validated, but external validation is required before general use and recommendation.

BACKGROUND

Hospitalizations of older people pose an increasing economic burden on healthcare systems in the developed world. During recent years, attempts have been made to identify risk factors for hospital readmissions in order to help target interventions and decrease readmission rates [1,2]. Variables tested for their ability to predict readmissions have included patient demographic factors, medical co-morbidity data, laboratory data, social determinants of health, patient functional status, and prior use of health-care services. However, the patients' medication use has rarely been evaluated as potential predictors of readmissions. As adverse drug reactions are the main cause of up to a fourth of hospital admissions [3–5] and are ranked as the fourth to sixth leading cause of death in the United States [6], this is surprising. In older people, multiple co-existing diagnoses and concomitant multi-drug use are common. This group is also, due to pharmacokinetic and pharmacodynamic changes, at increased risk of adverse drug reactions [7,8], and hence hospitalizations and mortality. For this population in particular, the use of medications should be considered as a potential prognostic factor for revisits to hospital and mortality.

There are several tools available for assessment of appropriateness of prescribing in older people [9–16], which can be used prospectively as guides to appropriate prescribing or retrospectively for evaluation of the quality of prescribing [11,17,18]. The tools are either checklist-based or judgment-based. Examples of checklist-based tools are STOPP (Screening Tool of Older Person's Prescriptions), identifying drugs that should be avoided in certain situations, and START (Screening Tool to Alert doctors to Right Treatment), identifying irrational prescribing omissions [11]. Medication Appropriateness Index (MAI) [15] is a validated judgment-based tool and includes ten aspects of appropriateness of prescribing: indication, effectiveness, dosage, correct and practical directions, drug-drug and drug-disease interactions, duplication, duration and costs. These tools have mainly been developed through literature search and expert opinion [11–14,19–21]. However, the association between inappropriate medication use in older people and poor health outcomes still remains uncertain. The evidence for a link between the tools and clinical outcomes is not convincing for any of the them [22–25]. In Sweden, as an attempt to improve quality of prescribing and reduce drug-related morbidity, a number of drugs and drug classes been recognized as inappropriate to elderly people ("Swedish Association of Local Authorities and Regions (SALAR) drugs") [16], and there is a national initiative aiming to reduce prescribing of these drugs with economic reimbursement as incentives. The association between the prescribing of these drugs and negative clinical outcome has not been investigated.

The aim of this study was to construct a tool for estimating risk of revisits to hospital or mortality for older people, incorporating aspects of pharmacotherapy. The secondary aim was to compare the discriminatory ability of this tool, or score, with three validated tools for appropriate prescribing: STOPP, START and the MAI. and with the SALAR drug list.

METHODS

Study participants and data

Patient data from a prospective randomized controlled study (RCT) was used [22,26]. The main objective of the RCT was to study the effects of adding a ward-based pharmacist service to the health care team on clinical outcomes (number of rehospitalizations; readmissions or emergency department visits) for elderly patients. Four-hundred patients, aged 80 years and older and acutely admitted to the internal medicine wards at Uppsala University Hospital, were included and randomized into control or intervention group. The patients in the intervention group received an enhanced pharmacist service during the hospital admission. All patients were followed for 12 months after hospital discharge, and the number of and time for revisits to hospital and/or mortality was recorded. Each participant gave written informed consent and the study protocol was approved by the Uppsala Regional Ethics Committee (Trial Registration: clinicaltrials.gov Identifier: NCT00661310). In this study, the group assignment was not taken into consideration in the analyses.

Outcome variables

A composite variable (combining the event of an unplanned rehospitalization [emergency department visit or readmission] or death during the 12-months follow-up period) was chosen as the endpoint for the analysis. The outcome variable in the regression analysis and the goodness-of-fit analysis was the time to the endpoint from the day of discharge from index admission. The outcome variable in the assessment of discriminatory ability was the occurrence of an event (i.e the endpoint).

Statistical analyses

Identification of risk factors

Candidate variables were selected based on a combination of clinical judgment and statistical properties of the variables. Clinical and drug variables were included. The selected clinical variables were: gender, age, renal function (estimated glomerular filtration rate [eGFR]), level of social support and medical history (heart failure, diabetes mellitus, pulmonary disease [chronic obstructive pulmonary disease (COPD) or asthma],

arrhythmia, malignant disease [past or present], coronary artery disease, cerebral vascular lesion [past], myocardial infarction [past], hypertension and dementia). The drug variables were the patients' prescribed medications, categorized into groups based on the ATC classification system [27] and on similar effect and risk in elderly people, or categorized according to the SALAR drug list (SALAR drug list presented in eTable 1). In case a SALAR drug variable was the same as an ATC-based category variable, one of them was excluded. The drug variables were also potentially inappropriate medications (identified by STOPP) and potential prescription omissions (identified by START). Variables with less than 10 patients in the smallest group were excluded from further analyses. In order to detect potential redundancies among the variables, a principal component analysis (PCA) was performed. If two variables were collinear, the variable with the most balanced categories were included for further study. The remaining clinical, drug-disease and drug variables were then subject to a backward stepwise Cox regression likelihood-ratio elimination procedure. To minimize type I errors, the p-value limit for inclusion was set to 0.01. The set of variables extracted from this analysis, i.e. the risk factors, make up the components of our new score.

Development of point score system

We developed a point score system for risk estimation, the "80+ score", following the Framingham Heart Study approach [28,29]. First, the continuous independent variable, eGFR, was organized into categories representing different levels of renal function. Reference values were determined for each of these categories. The remaining independent variables were modelled by sets of dichotomous indicator variables. For each variable, a base category was determined (using their most prevalent category). We then calculated how far each category was from the base category by dividing the regression unit for the category by a constant ("B") that was common to all variables. The resulting quotient was rounded to the nearest whole number, which was used as the points associated with that category. The point score system is the 80+ score. Last, the risk associated with each level of the score was calculated. For this last step, the following formula was used: Risk estimate = $1 - S_0(t)^{\exp(\Sigma \beta \chi - \Sigma \beta \chi_{mean})}$, where $S_0(t)$ was the average one-year event-free rate, and $\Sigma \beta \chi_{mean}$ was the sum of the variables'

regression coefficients (β) multiplied with the means or proportions of the variables in the sample (Table 3). $\sum \beta\chi$ was approximated from multiplying the constant for the model (B) with the point score and adding back the base value (i.e. the reference value for the base category) for the continuous variable eGFR.

The goodness-of-fit of the 80+ score was assessed by Grønnesby-Borgan test [30] and calibration was assessed by plotting predicted vs observed risk. The discriminatory ability of the 80+ score was assessed using C-statistics. C-statistics, which can range from 0.5 (no discrimination) to 1 (perfect discrimination), provide the probability of the model giving a higher predicted risk to the patient that will have an event than the one that will not. We internally validated the score using an enhanced bootstrap with 1000 iterations, in order to quantify and account for the extent of overoptimism in our prediction model [31]. We present optimism-corrected C-statistics for the 80+ score. The total STOPP, START and MAI scores and the total number of prescribed SALAR drugs were calculated for each patient. Their discriminatory abilities were also assessed using C-statistics, and these were compared to the C-statistic for the 80+ score.

The effect of the pharmacist intervention was not adjusted for in the regression analyses. The reason for this was that the intervention directly affected the results of the STOPP, START and MAI scores as well as the frequency of prescribing of SALAR drugs and the overall number of drugs. As a sensitivity analysis, the C-statistic for the 80+ score was calculated for the control group patients only. Proportionality of hazards was assessed using Schoenfeld's residuals and by inspecting cumulative incidence curves. We investigated the linearity of the association between eGFR and the outcomes by investigating models also including an ordinal variable for eGFR. Two-way interactions between the final set of variables in the score were investigated as deviations from multiplicativity. The score variables were also tested for the association with mortality only. All analyses were performed in IBM SPSS Statistics 21 and STATA version 13.

RESULTS

Out of the 400 included and randomized patients in the RCT, 368 were evaluable for further analyses (27 patients died during the index admission and 5 patients wished to be excluded after the randomization). Table 1 presents baseline characteristics for these patients. Two hundred and fifty (68%) of the patients had an event (i.e. either revisit to hospital or death) during the 12-months follow-up period. In the group of patients that had an event, 212 (85%) were rehospitalized, the rest (15%) died.

Table 1. *Baseline characteristics at time of index hospital admission*

Baseline characteristics	All patients (n=368)
Age, mean (SD), years	86.7 (4.1)
Female, No (%)	216 (58.7)
Body weight, mean (SD), kg	
Women	61.3 (13.3)
Men	71.3 (12.5)
Laboratory values	
eGFR[a], mean (SD), mL/min/1.73m^2	40.3 (18.5)
Hemoglobine level, mean (SD), mg/mL	
Sodium level, No (%)	
Hyponatremia (<137 mEq/L)	112 (30.4)
Within range (137-145 mEq/L)	247 (67.1)
Hypernatremia (>145 mEq/L)	9 (2.4)
Potassium level, No (%)	
Hypokalemia (<3.5 mEq/L)	49 (13.3)
Within range (3.5 -5 mEq/L)	295 (80.2)
Hyperkalemia (>5 mEq/L)	24 (6.5)
Social support, No (%)	
Living alone or with spouse	301 (81.8)
Living in a nursing home	67 (18.2)
Medical history, No (%)	
Heart failure	116 (31.5)
Diabetes	87 (23.6)
Pulmonary disease (asthma or COPD)	44 (12.0)
Arrhythmia	125 (34.0)
Malignant disease (past and present)	54 (14.7)
Coronary artery disease	114 (31.0)
Cerebral vascular lesion (past)	57 (15.5)
Myocardial infarct (past)	87 (23.6)
Hypertension	147 (39.9)
Dementia	47 (12.8)
Annual incidence of rehospitalizations (95% CI)	1.15 (1.01-1.32)
Annual incidence of mortality (95% CI)	0.40 (0.33-0.48)

[a]*Cockroft –Gault formula estimated glomerular filtration rate*
COPD=chronic obstructive pulmonary disease
CI=confidence interval

Identification of risk factors

eTable 2a-b list all variables taken into consideration in the analysis. Fourteen clinical variables and 64 drug variables met the inclusion criteria and were subject to the PCA. Three variables were excluded after the PCA: "B03B Vitamin B12 and folic acid" (collinear with "STOPP h5; Long-term opiates in patients with recurrent falls"), "G03C Estrogens" and "R03AC Drugs for obstructive airway diseases; selective beta-2-agonists" (both collinear with R03B "Drugs for obstructive airway diseases; anticholinergics +corticosteroids").

Seventy-five variables were entered into the backward stepwise Cox regression. This procedure resulted in seven statistically significant variables, or risk factors, each having an individual association with the outcome variable. Four of the risk factors were clinical while three were drug-specific. Statistical information about the risk factors is presented in Table 2. Past or present malignant disease and presence of pulmonary disease were both associated with an increased risk of rehospitalization or mortality, as was impaired renal function. Further, living in a nursing home was linked to a higher risk of revisits to hospital or death than living alone or with a spouse. Being prescribed a drug for peptic ulcer and gastro-esophageal reflux disease (GERD) was associated with an increased risk (a vast majority of these prescriptions, 115 out of 120 (96%), was of a proton-pump inhibitor), as well as being prescribed a drug from the opioid class. Having an antidepressant drug (tricyclic antidepressants (TCA) not included in this variable) was, conversely, associated with a lower risk.

Table 2. *Statistical information on 80+ score variables.*

	Regression coefficient (SE)	Mean or proportion	p-value	HR	95% CI for HR
eGFR[a] (per mL/min/1.73m^2)	-0.012 (0.004)	40.285	0.001	0.988	0.981-0.995
Social support (living in nursing home *vs* living alone or with spouse)	0.481 (0.162)	0.182	0.003	1.617	1.176-2.224
Pulmonary disease[b] (*vs.* not)	0.607 (0.177)	0.122	0.001	1.834	1.296-2.595
Malignant disease[c] (*vs.* not)	0.506 (0.166)	0.166	0.002	1.659	1.198-2.297
Prescription of drug for peptic ulcer and GERD (*vs.* not)	0.362 (0.135)	0.326	0.008	1.436	1.101-1.872
Prescription of opioid drug (*vs.* not)	0.724 (0.157)	0.179	0.000	2.063	1.517-2.806
Prescription of non-TCA-antidepressant drug (*vs.* not)	-0.558 (0.170)	0.209	0.001	0.573	0.410-0.799

Variables selected from backward stepwise Cox regression

[a]Cockroft –Gault formula estimated glomerular filtration rate, [b]asthma or chronic obstructive pulmonary disease (COPD), [c]past or present
SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease, TCA=tricyclic antidepressants (TCA)

Table 3. *Data used for calculation of point score system.*

	Proportion of patients in each category	β	W and $W_{ref.}$ for each category	Regression unit for each category	Point score
		-0.012			
eGFR[a]					
> 90 ml/min	0.014		105 ml/min = $W_{ref.}$		0
60-89 ml/min	0.128		74.5 ml/min	0.397	1
30-59 ml/min	0.552		54.5 ml/min	0.787	2
< 30 ml/min	0.307		17.5 ml/min	1.138	3
Social support		0.481			
Living alone or with spouse	0.818		0 = W_{ref}	0	0
Nursing home	0.182		1	0.481	1
Pulmonary disease[b]		0.607			
No	0.878		0 = $W_{ref.}$	0	0
Yes	0.122		1	0.607	2
Malignant disease[c]		0.506			
No	0.834		0 = $W_{ref.}$	0	0
Yes	0.166		1	0.506	1
Prescription of drug for peptic ulcer and GERD		0.362			
No	0.674		0 = $W_{ref.}$	0	0
Yes	0.326		1	0.362	1
Prescription of opioid drug		0.724			
No	0.821		0 = $W_{ref.}$	0	0
Yes	0.179		1	0.724	2
Prescription of non-TCA-antidepressant drug		-0.558			
No	0.791		0 = $W_{ref.}$	0	0
Yes	0.209		1	-0.558	-2

The average 1-year event-free rate = 0.3215[d]

[a]Cockroft –Gault formula estimated glomerular filtration rate, [b]asthma or chronic obstructive pulmonary disease (COPD), [c]past or present, [d]Kaplan-Meier estimate of the event-free rate at the mean values of the risk factors
Regression unit for each category = $\beta * (W-W_{ref})$
Point score= $\beta(W-W_{ref})/B$

Development of point score system

Table 3 presents reference values (W and W_{ref}) and regression units of each category of each risk factor variable –data that was used for development of point score. eGFR was organized into four levels of renal function, with >90 ml/min considered normal renal function. As reference values for these categories, the midpoints were chosen. For the other risk factor variables, the categories were assigned the values 0 or 1. A referent risk factor profile was determined: a patient with normal renal function, living alone or with a spouse, without diagnoses for pulmonary disease or malignant disease and with no prescription of drug for peptic ulcer or GERD, no prescription of opioids and no prescription of antidepressant drugs. The constant for the point score system (B) was selected, which was the regression coefficient for the variable "Drugs for peptic ulcer and GERD", 0.362. By dividing the regression unit for each category by B, it was computed how far the categories were from the base category. Hereby, the point scores for each category for each risk factor variable were calculated. The point scores for the 80+ score system, are presented in the right hand column in Table 3.

The point total is the summated score for each patient. For example, a patient with renal function of 65 ml/min, living in a nursing home, diagnosed with COPD and prescribed a drug for peptic ulcer and GERD, would be given a point total of 1+1+2+1=5. The estimated risk associated with each point total in the 80+ score is shown in Table 4. The estimated risk was computed using the formula described in the methods, where the $\sum \beta\chi_{mean}$ was calculated to - 0.106842 and the $\sum \beta\chi$ was approximated by multiplying B with the points and adding back the base value for eGFR (-0.012 * 105 ml/min). An example of risk estimation from the Cox regression as well as from the point score system is illustrated in online-only Supplementary material.

Table 4. Estimate of risk for each point total

Point total	Estimate of risk
-2	0.1594
-1	0.2207
0	0.3010
1	0.4021
2	0.5223
3	0.6539
4	0.7821
5	0.8879
6	0.9568
7	0.9890
8	0.9985
9	0.9999
10	>0.9999

The goodness of fit of the 80+ score was good, which is illustrated in Figure 1. This was confirmed by the Grønnesby-Borgan test (p=0.49). A model including both an ordinal and a continuous variable for eGFR did not provide a better fit than a model with only the continuous variable (likelihood-ratio test p=0.11). There was some evidence of interactions between eGFR and the drug use variables "Drugs for peptic ulcer and GERD" and "Non-TCA-antidepressants" but the groups were very small. No deviations from proportionality were observed (all Schoenfeld's test p>0.21).

When tested for their association with mortality only, the variables Pulmonary disease, Prescription of drug for peptic ulcer and GERD, and Prescription of non-TCA-antidepressant drug were not predictors of this outcome (p>0.05), while the link between social support and this outcome was strong (HR 3.107, 95% confidence interval 2.081-4.640). The remaining variables showed similar predictive ability for the mortality outcome as for the combined outcome (rehospitalization and mortality). Results are presented in eTable 3.

A logistic regression model with the seven variables of the 80+ score as independent variables had a pseudo-R^2 of 0.13. The 80+ score demonstrated a satisfying discriminatory ability of the outcome, with a C-statistic of 0.715 (Figure 2). The optimism was 0.001, rendering an optimism-corrected C-statistic of 0.714 for the 80+ score. This means that a patient with an event (revisit to hospital or death) had a 71% probability to be given a higher risk score than a patient with no event. Figure 2 also

shows that STOPP and START scores and the SALAR drug list were basically non-discriminating for the chosen outcome (with C-statistics just above 0.5). When tested in the control group only, the 80+ score had a C-statistic of 0.71, i.e. a similar value as in the whole group.

DISCUSSION

Using a clinical trial database of hospitalized patients, aged 80 years and above, the most relevant factors for identifying those at risk of an adverse outcome were identified. A simple scoring system intended for clinical use was constructed and internally validated, pending validation in an independent cohort. The score is suggested as a tool for identifying patients at highest risk of readmissions and mortality, and ultimately as an aid in clinical decision-making for improving outcomes in these patients. Increasing age, usage of medical services and poor health pose a risk of rehospitalization and mortality [2] and hence, there are strong incentives for focusing on this population.

Various risk factors for rehospitalization and mortality have previously been identified in prediction models based on data from a variety of populations and settings, and with different candidate variables [32–39]. The 80+ risk score has a higher discriminatory ability for risk of rehospitalization and mortality than most other prediction models of today. This is likely due to the fact that we included drug variables as candidate variables – the drugs can either be causally related to the outcomes or serve as important proxies for certain conditions, diseases or circumstances. Further, the precision was likely maximized by developing the score using data from a narrowly defined population –these patients were all aged 80 years or older and had been acutely admitted to an internal medicine ward. In the majority of risk prediction models of today, rehospitalization has been chosen as the outcome measure, but this carries a high risk of bias due to competing risk by death. Therefore, in this study, event-free (i.e. no emergency department visit or readmission) survival was used as endpoint.

The use of drugs deemed inappropriate has been associated with adverse drug events [40,41] and it is often proposed that patients prescribed inappropriate medications should be prioritized for interventions – aimed at improving the quality of prescribing – in order to reduce the risk of unwanted clinical outcomes. However, in this set of patient data, neither the STOPP nor START tools had an ability to discriminate between patients at risk of rehospitalization or mortality that was better than chance. The numbers of prescribed SALAR drugs showed similar results. The MAI, being an judgment-based tool, has a moderate discriminatory ability for risk in this population. However, due to its time-consuming nature, with assessment times per patient of up to 30 minutes, MAI is not suitable as a screening tool for patients in clinical practice. As has already been stated, none of the STOPP, START and MAI scores or the SALAR drug system, are designed as risk scores. Still, the lack of consistent evidence for their association with clinical outcomes is notable and needs to be further investigated.

The presence of pulmonary disease as well as impaired renal function are known risk factors for readmissions to hospital [32–35]. These variables also emerged as risk factors in our population. Many nursing home residents have multiple morbidities and are high consumers of health care [42], which explains the prognostic ability of this variable. The unique finding in this study is that three drug variables were individually related to the clinical outcome in the multivariate model: being prescribed a drug for peptic ulcer and GERD or being prescribed an opioid both appeared to increase the risk, while being prescribed an antidepressant drug was associated with a lower risk. The use of proton-pump-inhibitors have in several studies been associated with various adverse events, such as clostridium difficile infections and pneumonia [43], but another explanation for their association with the outcome variable is that the patients being prescribed these drugs have a history of ulcer (which was not among the candidate variables), that is a risk factor itself. This drug group may also function as a proxy for patients with multiple other co-morbidities and polypharmacy since these patients have a potential need for preventive treatment for gastric disorders [43]. Similarly, opioids can, as well as being a risk drug due to their potential to cause adverse drug reactions, be an indicator for pain or frailty (which are potential risk factors in themselves). The prescribing of non-TCA-

antidepressants aims to provide relief from psychological symptoms and increase the patient's general wellbeing, which supposedly has a protective effect on rehospitalization and mortality. An alternative explanation for the negative association between this variable and the outcome is that these drugs may be given more often to physically healthier patients with a longer life expectancy. The rationale for exclusion of TCAs in the antidepressant variable, is that the safety profile in elderly people for these drugs differs from that of the other antidepressants. TCA drugs were not a candidate variable in the analyses – since only 5 patients were prescribed these drugs – but were included in the "SALAR a" variable. The strong link between level of social support and mortality is not surprising, since patients often move to nursing homes for the last part of their lives. Interestingly, pulmonary disease or being prescribed a drug for peptic ulcer or GERD or a non-TCA-antidepressant drug, were predictors mainly for rehospitalization.

A score for risk-identification purposes should have a satisfying predictive ability in the target population, and it should use data that is clinically readily available [1,44]. The 80+ score meets these criteria. A simple and user-friendly point score system like this can quickly and easily identify high-risk patients. Yet, in order for this information to be useful, translation into suggested actions for reduction of this risk for these patients is crucial. This undertaking is obviously multifactorial. Nevertheless, by focusing on the patients with the highest risk, a pharmaceutical intervention, or other quality improvement effort, can be targeted more efficiently. For example, patients with COPD or asthma may benefit from a comprehensive patient education [45] and patients being prescribed an opioid or a drug for peptic ulcer or GERD, may benefit from a thorough medication review.

The 80+ score was internally validated, but remains to be externally validated in another population before it can be generally recommended. A few limitations with this study need attention. Prior hospital visits have in several studies been associated with risk of rehospitalization [33,34,36,38,39]. This information was not available in this dataset and has therefore not been included as a candidate variable. However, a potential weakness of having prior hospital visits as a variable in a clinical score, is that this information may

not be easily available upon the patients admission to hospital. Another limitation is that the 80+ score is based on data from a limited number of patients, being admitted to an acute internal medicine ward at one hospital only. This makes the generalizability unknown and increases the need for external validation. Finally, the limited sample size forced us to use the whole dataset (both intervention and control group patients) for the development of the score. In this paper we have discussed the role of prescribed drugs as potential risk factors for adverse clinical outcomes. However, it should be noted that the analyses do not take the potential risks of suboptimal use of drugs into consideration. Suboptimal drug use, such as patient non-adherence to treatment or lack of correct and complete transfer of information when patients are transitioned between different levels of health care, can cause adverse drug events and are risk factors of drug-related morbidity [46–48].

CONCLUSION

We have developed and internally validated a score intended for use in clinical practice to identify the hospitalized elderly patients at highest risk of rehospitalization and mortality, accounting for pharmacotherapy. The score outperforms scores for inappropriate medication use in risk-prediction ability and can ultimately aid in clinical decision-making for improving outcomes in elderly patients.

Contributorship statement: Study concepts and design: AA, JS, MB, HS; Acquisition, analysis, or interpretation of data: AA, JS, MB, UG, HM, MHU; Drafting of the manuscript: AA, JS; Critical revision of the manuscript for important intellectual content: AA, HM, MHU, MB, UG, JS; Statistical analysis: AA, JS, MB; Obtained funding: HM, AA; Administrative, technical, or material support: HM, UG; Study supervision: JS, HM, MHU, UG

AA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

FIGURES

Figure 1. Predicted risk vs observed risk for rehospitalization or death.
Figure 2. Area under the curve of sensitivity vs. *1-specificity for rehospitalization or death.*

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A tool for prediction of risk of rehospitalization and mortality in hospitalized elderly: secondary analysis of clinical trial data

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ABSTRACT

Objectives: To construct and internally validate a risk score, the "80+ score", for revisits to hospital and mortality for older patients, incorporating aspects of pharmacotherapy. Our secondary aim was to compare the discriminatory ability of the score with that of three validated tools for measuring inappropriate prescribing: Screening Tool of Older Person's Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI).

Setting: Two acute internal medicine wards at Uppsala University hospital. Patient data from a randomized controlled trial, investigating effects of a comprehensive clinical pharmacist intervention, was used.

Participants: Data from 368 patients, aged 80 years and older, admitted to one of the study wards.

Primary outcome measure: Time to rehospitalization or death during the year after discharge from hospital. Candidate variables were selected among a large number of clinical and drug-specific variables. After a selection process, a score for risk-estimation was constructed. The 80+ score was internally validated, and the discriminatory ability of the score and of STOPP, START and MAI was assessed using C-statistics.

Results: Seven variables were selected. Impaired renal function, pulmonary disease, malignant disease, living in nursing home, being prescribed an opioid or being prescribed a drug for peptic ulcer or gastroesophageal reflux disease were associated with an increased risk, while being prescribed an antidepressant drug (tricyclic antidepressants not included) was linked to a lower risk of the outcome. These variables made up the components of the 80+ score. The C-statistics were 0.71 (80+), 0.57 (STOPP), 0.54 (START) and 0.63 (MAI).

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Conclusion: We developed and internally validated a score for prediction of risk of rehospitalization and mortality in hospitalized older people. The score discriminated risk better than available tools for inappropriate prescribing. Pending external validation, this score can aid in clinical identification of high-risk patients and targeting of interventions.

ARTICLE SUMMARY

Strengths and limitations

- The 80+ score is based on data from a population on whom there are strong incentives to focus: patients at high risk of hospitalization and also of mortality.
- The score is constructed from a prediction model that includes aspects of pharmacotherapy. The use of drugs can be either positively or negatively causally related to a clinical outcome, and can also be important indicators for a certain condition, disease or circumstance.
- Data from a limited number of patients, being admitted to an acute internal medicine ward at one hospital only, was used in the construction of the score. The generalizability of the score is therefore unknown.
- The 80+ score was internally validated, but external validation is required before general use and recommendation.

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BACKGROUND

Hospitalizations of older people pose an increasing economic burden on healthcare systems in the developed world. During recent years, attempts have been made to identify risk factors for hospital readmissions in order to help target interventions and decrease readmission rates [1,2]. Variables tested for their ability to predict readmissions have included patient demographic factors, medical co-morbidity data, laboratory data, social determinants of health, patient functional status, and prior use of health-care services. However, the patients' medication use has rarely been evaluated as potential predictors of readmissions. As adverse drug reactions are the main cause of up to a fourth of hospital admissions [3–5] and are ranked as the fourth to sixth leading cause of death in the United States [6], this is surprising. In older people, multiple co-existing diagnoses and concomitant multi-drug use are common. This group is also, due to pharmacokinetic and pharmacodynamic changes, at increased risk of adverse drug reactions [7,8], and hence hospitalizations and mortality. For this population in particular, the use of medications should be considered as a potential prognostic factor for revisits to hospital and mortality.

There are several tools available for assessment of appropriateness of prescribing in older people [9–16], which can be used prospectively as guides to appropriate prescribing or

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retrospectively for evaluation of the quality of prescribing [11,17,18]. The tools are either checklist-based or judgment-based. Examples of checklist-based tools are STOPP (Screening Tool of Older Person's Prescriptions), identifying drugs that should be avoided in certain situations, and START (Screening Tool to Alert doctors to Right Treatment), identifying irrational prescribing omissions [11]. Medication Appropriateness Index (MAI) [15] is a validated judgment-based tool and includes ten aspects of appropriateness of prescribing: indication, effectiveness, dosage, correct and practical directions, drug-drug and drug-disease interactions, duplication, duration and costs. These tools have mainly been developed through literature search and expert opinion [11–14,19–21]. However, the association between inappropriate medication use in older people and poor health outcomes still remains uncertain. The evidence for a link between the tools and clinical outcomes is not convincing for any of the them [22–25]. In Sweden, as an attempt to improve quality of prescribing and reduce drug-related morbidity, a number of drugs and drug classes have been recognized as inappropriate to elderly people ("Swedish Association of Local Authorities and Regions (SALAR) drugs") [16], and there is a national initiative aiming to reduce prescribing of these drugs with economic reimbursement as incentives. The association between the prescribing of these drugs and negative clinical outcome has not been investigated.

The aim of this study was to construct a tool for estimating risk of revisits to hospital or mortality for older people, incorporating aspects of pharmacotherapy. The secondary aim was to compare the discriminatory ability of this tool, or score, with three validated tools for appropriate prescribing: STOPP, START and the MAI~~Screening Tool of Older Person's Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI) [11,15]~~, and with the SALAR drug list ~~of the Swedish Association of Local Authorities and Regions (SALAR)~~ [16].

METHODS

Study participants and data

Patient data from a prospective randomized controlled study (RCT) was used [22,26][26]. The main objective of the RCT was to study the effects of adding a ward-based pharmacist service to the health care team on clinical outcomes (number of revisits to hospitalizations; readmissions or emergency department visits) for elderly patients. Four-hundred patients, aged 80 years and older and acutely admitted to the internal medicine wards at Uppsala University Hospital, were included and randomized into control or intervention group. The patients in the intervention group received an enhanced pharmacist service during the hospital admission. All patients were followed for 12 months after hospital discharge, and the number of and time for revisits to hospital and/or mortality was recorded. Each participant gave written informed consent and the study protocol was approved by the Uppsala Regional Ethics Committee (Trial Registration: clinicaltrials.gov Identifier: NCT00661310). In this study, the group assignment was not taken into consideration in the analyses.

Outcome variables

A composite variable Time to event (combining the event of ani.e. unplanned rehospitalization [emergency department visit or readmission] or death during the 12-months follow-up period) was chosen as the endpoint for the analysis. The outcome variable in the regression analysis and the goodness-of-fit analysis was the time to the endpoint from the day of discharge from index admission, was used as outcome variable when constructing the point score system and for goodness-of-fit analyses. The outcome variable in For the assessment of discriminatory ability was, the occurrence of an event during the 12 months follow-up(i.e the endpoint) was used as outcome variable.

Statistical analyses

Identification of risk factors

Candidate variables were selected based on a combination of clinical judgment and statistical properties of the variables. Clinical and drug-specific (drug-disease [i.e. a specific drug in a certain condition], as well as drug) variables were included. The selected clinical variables were: gender, age, renal function (Creatinine clearanceestimated glomerular filtration rate [eGFRCLcr]), level of social support and

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medical history (heart failure, diabetes mellitus, pulmonary disease [chronic obstructive pulmonary disease (COPD) or asthma], arrhythmia, malignant disease [past or present], coronary artery disease, cerebral vascular lesion [past], myocardial infarction [past], hypertension and dementia). ~~As drug-disease variables, STOPP and START criteria (each criterion from each tool individually) were used.~~ The drug variables were the patients' prescribed medications, categorized into groups based on the ATC classification system [27] and on similar effect and risk in elderly people, or categorized according to the SALAR drug list (SALAR drug list presented in eTable 1). In case a SALAR drug variable was the same as an ATC-based category variable, one of them was excluded. The drug variables were also potentially inappropriate medications (identified by STOPP) and potential prescription omissions (identified by START). Variables with less than 10 patients in the smallest group were excluded from further analyses. In order to detect potential redundancies among the variables, a principal component analysis (PCA) was performed. If two variables were collinear, the variable with the most balanced categories were included for further study. The remaining clinical, drug-disease and drug variables were then subject to a backward stepwise Cox regression likelihood-ratio elimination procedure. To minimize type I errors, the p-value limit for inclusion was set to 0.01. The set of variables extracted from this analysis, i.e. the risk factors, make up the components of our new score.

Development of point score system

We developed a point score system for risk estimation, the "80+ score", following the Framingham Heart Study approach [28,29]. First, the continuous independent variable, ~~CLcr~~eGFR, was organized into categories representing different levels of renal function. ~~R, and r~~eference values ~~s~~ were determined for each of these catego~~ry~~ries. The remaining independent variables were modelled by sets of dichotomous indicator variables. For each variable, a base category was determined (~~, using~~ using the~~ir~~ir most prevalent category). We then ~~as the base category. We then~~ calculated how far each category was from the base category by dividing the regression unit for the category by a constant ("B") that was common to all variables. The resulting quotient was rounded to the nearest whole number, which was used as the points associated with that category. The point

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score system is the 80+ score. Last, the risk associated with each level of the score was calculated. For this last step, the following formula was used: Risk estimate = $1 - S_0(t)^{\exp(\Sigma \beta\chi - \Sigma \beta\chi_{mean})}$, where $S_0(t)$ was the average one-year event-free rate, and $\Sigma \beta\chi_{mean}$ was the sum of the variables' regression coefficients (β) multiplied with the means or proportions of the variables in the sample (Table 3). $\Sigma \beta\chi$ was approximated from multiplying the constant for the model (B) with the point score and adding back the base value (i.e. the reference value for the base category) for the continuous variable ~~CLcr~~eGFR.

The goodness-of-fit of the 80+ score was assessed by Grønnesby-Borgan test [30] and calibration was assessed by plotting predicted vs observed risk. The discriminatory ability of the 80+ score was assessed using C-statistics. C-statistics, which can range from 0.5 (no discrimination) to 1 (perfect discrimination), provide the ~~ratio of the~~ probability of the model giving a higher predicted risk to the patient that will have an event than the one that will not~~predicting an event in patients with an event to that in patients without an event~~. We internally validated the score using an enhanced bootstrap with 1000 iterations, in order to quantify and account for the extent of overoptimism in our prediction model [31]. We present optimism-corrected C-statistics for the 80+ score. The total STOPP, START and MAI scores and the total number of prescribed SALAR drugs were calculated for each patient. Their discriminatory abilities were also assessed using C-statistics, and these were compared to the C-statistic for the 80+ score.

The effect of the pharmacist intervention was not adjusted for in the regression analyses. The reason for this was that the intervention directly affected the results of the STOPP, START and MAI scores as well as the frequency of prescribing of SALAR drugs and the overall number of drugs. As a sensitivity analysis, the C-statistic for the 80+ score was calculated for the control group patients only. Proportionality of hazards was assessed using Schoenfeld's residuals and by inspecting cumulative incidence curves. We investigated the linearity of the association between ~~CLcr~~ eGFR and the outcomes by investigating models also including an ordinal variable for ~~CLcr~~eGFR. Two-way interactions between the final set of variables in the score were investigated as deviations from multiplicativity. The score variables were also tested for the association with

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mortality only. All analyses were performed in IBM SPSS Statistics 21 and STATA version 13.

RESULTS

Out of the 400 included and randomized patients in the RCT, 368 were evaluable for further analyses (27 patients died during the index admission and 5 patients wished to be excluded after the randomization). Table 1 presents baseline characteristics for these patients. Two hundred and fifty (68%) of the patients had an event (i.e. either revisit to hospital or death) during the 12-months follow-up period. In the group of patients that had an event, 212 (85%) were rehospitalized, the rest (15%) died.

Table 1. *Baseline characteristics at time of index hospital admission*

Baseline characteristics	All patients (n=368)
Age, mean (SD), years	86.7 (4.1)
Female, No (%)	216 (58.7)
Body weight, mean (SD), kg	
Women	61.3 (13.3)
Men	71.3 (12.5)
Laboratory values	
Creatinine clearanceeGFR[a], mean (SD), mL/min/1.73m²	40.3 (18.5)
Hemoglobine level, mean (SD), mg/mL	
Sodium level, No (%)	
Hyponatremia (<137 mEq/L)	112 (30.4)
Within range (137-145 mEq/L)	247 (67.1)
Hypernatremia (>145 mEq/L)	9 (2.4)
Potassium level, No (%)	
Hypokalemia (<3.5 mEq/L)	49 (13.3)
Within range (3.5 -5 mEq/L)	295 (80.2)
Hyperkalemia (>5 mEq/L)	24 (6.5)
Social support, No (%)	
Living alone or with spouse	301 (81.8)
Living in a nursing home	67 (18.2)
Medical history, No (%)	
Heart failure	116 (31.5)
Diabetes	87 (23.6)
Pulmonary disease (asthma or COPD)	44 (12.0)

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Arrhythmia	125 (34.0)
Malignant disease (past and present)	54 (14.7)
Coronary artery disease	114 (31.0)
Cerebral vascular lesion (past)	57 (15.5)
Myocardial infarct (past)	87 (23.6)
Hypertension	147 (39.9)
Dementia	47 (12.8)
Annual incidence of rehospitalizations (95% CI)	1.15 (1.01-1.32)
Annual incidence of mortality (95% CI)	0.40 (0.33-0.48)

[a]*Cockroft –Gault formula estimated glomerular filtration rate*
COPD=chronic obstructive pulmonary disease
CI=confidence interval

Identification of risk factors

eTable 2a-be list all variables taken into consideration in the analysis. Fourteen clinical variables and , 6414 drug-disease variables and 50 drug variables met the inclusion criteria and were subject to the PCA. Three variables were excluded after the PCA: "B03B Vitamin B12 and folic acid" (collinear with "STOPP h5; Long-term opiates in patients with recurrent falls"), "G03C Estrogens" and "R03AC Drugs for obstructive airway diseases; selective beta-2-agonists" (both collinear with R03B "Drugs for obstructive airway diseases; anticholinergics +corticosteroids").

Seventy-five variables were entered into the backward stepwise Cox regression. This procedure resulted in seven statistically significant variables, or risk factors, each having an individual association with the outcome variable. Four of the risk factors were clinical while three were drug-specific. Statistical information about the risk factors is presented in Table 2. Past or present malignant disease and presence of pulmonary disease were both associated with an increased risk of rehospitalization or mortality, as was impaired renal function. Further, living in a nursing home was linked to a higher risk of revisits to hospital or death than living alone or with a spouse. Being prescribed a drug for peptic ulcer and gastro-esophageal reflux disease (GERD) was associated with an increased risk (a vast majority of these prescriptions, 115 out of 120 (96%), was of a proton-pump inhibitor), as well as being prescribed a drug from the opioid class. Having an antidepressant drug (tricyclic antidepressants (TCA) not included in this variable) was, conversely, associated with a lower risk.

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Table 2. Statistical information on 80+ score variables.

	Regression coefficient (SE)	Mean or proportion	p-value	HR	95% CI for HR
~~Creatinine clearance~~eGFR[a] (per mL~~L~~/min/1.73m^2)	-0.012 (0.004)	40.285	0.001	0.988	0.981-0.995
Social support (living in nursing home *vs* living alone or with spouse)	0.481 (0.162)	0.182	0.003	1.617	1.176-2.224
Pulmonary disease[ba] (*vs.* not)	0.607 (0.177)	0.122	0.001	1.834	1.296-2.595
Malignant disease[cb] (*vs.* not)	0.506 (0.166)	0.166	0.002	1.659	1.198-2.297
Prescription of drug for peptic ulcer and GERD (*vs.* not)	0.362 (0.135)	0.326	0.008	1.436	1.101-1.872
Prescription of opioid drug (*vs.* not)	0.724 (0.157)	0.179	0.000	2.063	1.517-2.806
Prescription of non-TCA-antidepressant drug (*vs.* not)	-0.558 (0.170)	0.209	0.001	0.573	0.410-0.799

Variables selected from backward stepwise Cox regression
[a]Cockroft –Gault formula estimated glomerular filtration rate.
[ba]asthma or chronic obstructive pulmonary disease (COPD), [cb]past or present
SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease,
TCA=tricyclic antidepressants (TCA)

Table 3. Data used for calculation of point score system.

	Proportion of patients in each category	β	W and W$_{ref.}$ for each category	Regression unit for each category	Point score
~~Creatinine clearance~~eGFR[a]		-0.012			
> 90 ml/min	0.014		105 ml/min = W$_{ref.}$	0	0
60-89 ml/min	0.128		74.5 ml/min	0.397	1
30-59 ml/min	0.552		54.5 ml/min	0.787	2
< 30 ml/min	0.307		17.5 ml/min	1.138	3
Social support					
Living alone or with spouse	0.818	0.481	0 = W$_{ref}$	0	0
Nursing home	0.182		1	0.481	1
Pulmonary disease[ba]		0.607			
No	0.878		0 = W$_{ref.}$	0	0
Yes	0.122		1	0.607	2
Malignant disease[cb]		0.506			
No	0.834		0 = W$_{ref.}$	0	0
Yes	0.166		1	0.506	1
Prescription of drug for peptic ulcer and GERD		0.362			
No	0.674		0 = W$_{ref.}$	0	0
Yes	0.326		1	0.362	1
Prescription of opioid drug		0.724			
No	0.821		0 = W$_{ref.}$	0	0
Yes	0.179		1	0.724	2

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Prescription of non-TCA-antidepressant drug		-0.558		
No	0.791	0 = $W_{ref.}$	0	0
Yes	0.209	1	-0.558	-2

The average 1-year event-free rate = 0.3215[de]

[a]*Cockroft –Gault formula estimated glomerular filtration rate,* [b]*asthma or chronic obstructive pulmonary disease (COPD),* [c]*past or present,* [d]*Kaplan-Meier estimate of the event-free rate at the mean values of the risk factors*
*Regression unit for each category = β * (W-W$_{ref}$)*
Point score= β(W-Wref)/B

Development of point score system

Table 3 presents reference values (W and W$_{ref}$) and regression units of each category of each risk factor variable –data that was used for development of point score. CLcr eGFR was organized into four levels of renal function, with >90 ml/min considered normal renal function. As reference values for these categories, the midpoints were chosen. For the other risk factor variables, the categories were assigned the values 0 or 1. A referent risk factor profile was determined: a patient with normal renal function, living alone or with a spouse, without diagnoses for pulmonary disease or malignant disease and with no prescription of drug for peptic ulcer or GERD, no prescription of opioids and no prescription of antidepressant drugs. The constant for the point score system (B) was selected, which was the regression coefficient for the variable "Drugs for peptic ulcer and GERD", 0.362. By dividing the regression unit for each category by B, it was computed how far the categories were from the base category. Hereby, the point scores for each category for each risk factor variable were calculated. The point scores for the 80+ score system, are presented in the right hand column in Table 3.

The point total is the summated score for each patient. For example, a patient with renal function of 65 ml/min, living in a nursing home, diagnosed with COPD and prescribed a drug for peptic ulcer and GERD, would be given a point total of 1+1+2+1=5. The estimated risk associated with each point total in the 80+ score is shown in Table 4. The estimated risk was computed using the formula described in the methods, where the $\sum \beta\chi_{mean}$ was calculated to - 0.106842 and the $\sum \beta\chi$ was approximated by multiplying B with the points and adding back the base value for CLcr eGFR (-0.012 * 105 ml/min). An

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example of risk estimation from the Cox regression as well as from the point score system is illustrated in online-only Supplementary material.

Table 4. *Estimate of risk for each point total*

Point total	Estimate of risk
-2	0.1594
-1	0.2207
0	0.3010
1	0.4021
2	0.5223
3	0.6539
4	0.7821
5	0.8879
6	0.9568
7	0.9890
8	0.9985
9	0.9999
10	>0.9999

The goodness of fit of the 80+ score was good, which is illustrated in Figure 1. This was confirmed by the Grønnesby-Borgan test (p=0.49). A model including both an ordinal and a continuous variable for ~~CLcr~~ eGFR did not provide a better fit tha~~nt~~ a model with only the continuous variable (likelihood-ratio test p=0.11). There was some evidence of interactions between ~~CLcr~~ eGFR and the drug use variables "Drugs for peptic ulcer and GERD" and "Non-TCA-antidepressants" but the groups were very small. No deviations from proportionality were observed (all Schoenfeld's test p>0.21).

When tested for their association with mortality only, the variables Pulmonary disease, Prescription of drug for peptic ulcer and GERD, and Prescription of non-TCA-antidepressant drug were not predictors of this outcome (p>0.05), while the link between social support and this outcome was strong (HR 3.107, 95% confidence interval 2.081-4.640). The remaining variables showed similar predictive ability for the mortality outcome as for the combined outcome (rehospitalization and mortality). Results are presented in eTable 3.

A logistic regression model with the seven variables of the 80+ score as independent variables had a pseudo-R^2 of 0.13. The 80+ score demonstrated a satisfying

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discriminatory ability of the outcome, with a C-statistic of 0.715 (Figure 2). The optimism was 0.001, rendering an optimism-corrected C-statistic of 0.714 for the 80+ score. This means that a patient with an event (revisit to hospital or death) had a 71% probability to be given a higher risk score than a patient with no event. Figure 2 also shows that STOPP and START scores and the SALAR drug list were basically non-discriminating for the chosen outcome (with C-statistics just above 0.5). When tested in the control group only, the 80+ score had a C-statistic of 0.71, i.e. a similar value as in the whole group.

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DISCUSSION

Using a clinical trial database of hospitalized patients, aged 80 years and above, the most relevant factors for identifying those at risk of an adverse outcome were identified. A simple scoring system intended for clinical use was constructed and internally validated, pending validation in an independent cohort. The score is suggested as a tool for identifying patients at highest risk of readmissions and mortality, and ultimately as an aid in clinical decision-making for improving outcomes in these patients. Increasing age, usage of medical services and poor health pose a risk of rehospitalization and mortality [2] and hence, there are strong incentives for focusing on this population.

Various risk factors for rehospitalization and mortality have previously been identified in prediction models based on data from a variety of populations and settings, and with different candidate variables [32–39]. The 80+ risk score has a higher discriminatory

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ability for risk of rehospitalization and mortality than most other prediction models of today. This is likely due to the fact that we included drug-related variables as candidate variables – the drugs can either be causally related to the outcomes or serve as important proxies for certain conditions, diseases or circumstances. Further, the precision was likely maximized by developing the score using data from a narrowly defined population – these patients were all aged 80 years or older and had been acutely admitted to an internal medicine ward. In the majority of risk prediction models of today, rehospitalization has been chosen as the outcome measure, but this carries a high risk of bias due to competing risk by death. Therefore, in this study, event-free (i.e. no emergency department visit or readmission) survival was used as endpoint.

The use of drugs deemed inappropriate has been associated with adverse drug events [40,41] and it is often proposed that patients prescribed inappropriate medications should be prioritized for interventions – aimed at improving the quality of prescribing – in order to reduce the risk of unwanted clinical outcomes. However, in this set of patient data, neither the STOPP nor START scores tools had an ability to discriminate between patients at risk of rehospitalization or mortality that was better than chance. The numbers of prescribed SALAR drugs showed similar results. The MAI, being an implicit, judgment-based toolscore, has a moderate discriminatory ability for risk in this population. However, due to its time-consuming nature, with assessment times per patient of up to 30 minutes, MAI is not suitable as a screening tool for patients in clinical practice. As has already been stated, none of the STOPP, START and MAI scores or the SALAR drug system, are designed as risk scores. Still, the lack of consistent evidence for their association with clinical outcomes is notable and needs to be further investigated.

The presence of pulmonary disease as well as impaired renalkidney function are known risk factors for readmissions to hospital [32–35]. These variables also emerged as risk factors in our population. Many nursing home residents have multiple morbidities and are high consumers of health care [42], which explains the prognostic ability of this variable. The unique finding in this study is that three drug-specific variables were individually related to the clinical outcome in the multivariate model: being prescribed a drug for

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peptic ulcer and GERD or being prescribed an opioid both appeared to increase the risk, while being prescribed an antidepressant drug was associated with a lower risk. The use of proton-pump-inhibitors have in several studies been associated with various adverse events, such as clostridium difficile infections and pneumonia [43], but another explanation for their association with the outcome variable is that the patients being prescribed these drugs have a history of ulcer (which was not among the candidate variables), that is a risk factor itself. This drug group may also function as a proxy for patients with multiple other co-morbidities and polypharmacy since these patients have a potential need for preventive treatment for gastric disorders [43]. Similarly, opioids can, as well as being a risk drug due to their potential to cause adverse drug reactions, be an indicator for pain or frailty (which are potential risk factors in themselves). The prescribing of non-TCA-antidepressants aims to provide relief from psychological symptoms and increase the patient's general well-being, which supposedly has a protective effect on rehospitalization and mortality. An alternative explanation for the negative association between this variable and the outcome is that these drugs may be given more often to physically healthier patients with a longer life expectancy. The rationale for exclusion of TCAs in the antidepressant variable, is that the safety profile in elderly people for these drugs differs from that of the other antidepressants. TCA drugs were not a candidate variable in the analyses – since only 5 patients were prescribed these drugs – but were included in the "SALAR a" variable. The strong link between level of social support and mortality is not surprising, since patients often move to nursing homes for the last part of their lives. Interestingly, pulmonary disease or being prescribed a drug for peptic ulcer or GERD or a non-TCA-antidepressant drug, were predictors mainly for rehospitalization.

A score for risk-identification purposes should have ~~good~~ a satisfying predictive ability in the target population, and it should use data that is clinically readily available [1,44]. The 80+ score meets these criteria. A simple and user-friendly point score system like this can quickly and easily identify high-risk patients. Yet, in order for this information to be useful, translation into suggested actions for reduction of this risk for these patients is crucial. This undertaking is obviously multifactorial. Nevertheless, by focusing on the

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patients with the highest risk, a pharmaceutical intervention, or other quality improvement effort, can be targeted more efficiently. For example, patients with COPD or asthma may benefit from a comprehensive patient education [45] and patients being prescribed an opioid or a drug for peptic ulcer or GERD, may benefit from a thorough medication review.

~~In the majority of risk prediction models of today, rehospitalization has been chosen as the outcome measure, but this carries a high risk of bias due to competing risk by death. Therefore, in this study, event-free (i.e. no emergency department visit or readmission) survival was used as endpoint.~~

The 80+ score was internally validated, but remains to be externally validated in another population before it can be generally recommended. A few limitations with this study need attention. Prior hospital visits have in several studies been associated with risk of rehospitalization [33,34,36,38,39]. This information was not available in this dataset and has therefore not been included as a candidate variable. However, a potential weakness of having prior hospital visits as a variable in a clinical score, is that this information may not be easily available upon the patients admission to hospital. Another limitation is that the 80+ score is based on data from a limited number of patients, being admitted to an acute internal medicine ward at one hospital only. This makes the generalizability unknown and increases the need for external validation. Finally, the limited sample size forced us to use the whole dataset (both intervention and control group patients) for the development of the score. In this paper we have discussed the role of prescribed drugs as potential risk factors for adverse clinical outcomes. However, it should be noted that the analyses do not take the potential risks of suboptimal use of drugs into consideration. Suboptimal drug use, such as patient non-adherence to treatment or lack of correct and complete transfer of information when patients are transitioned between different levels of health care, can cause adverse drug events and are risk factors of drug-related morbidity [46–48].

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CONCLUSION

We have developed and internally validated a score intended for use in clinical practice to identify the hospitalized elderly patients at highest risk of rehospitalization and mortality, accounting for pharmacotherapy. The score outperforms scores for inappropriate medication use in risk-prediction ability and can ultimately aid in clinical decision-making for improving outcomes in elderly patients.

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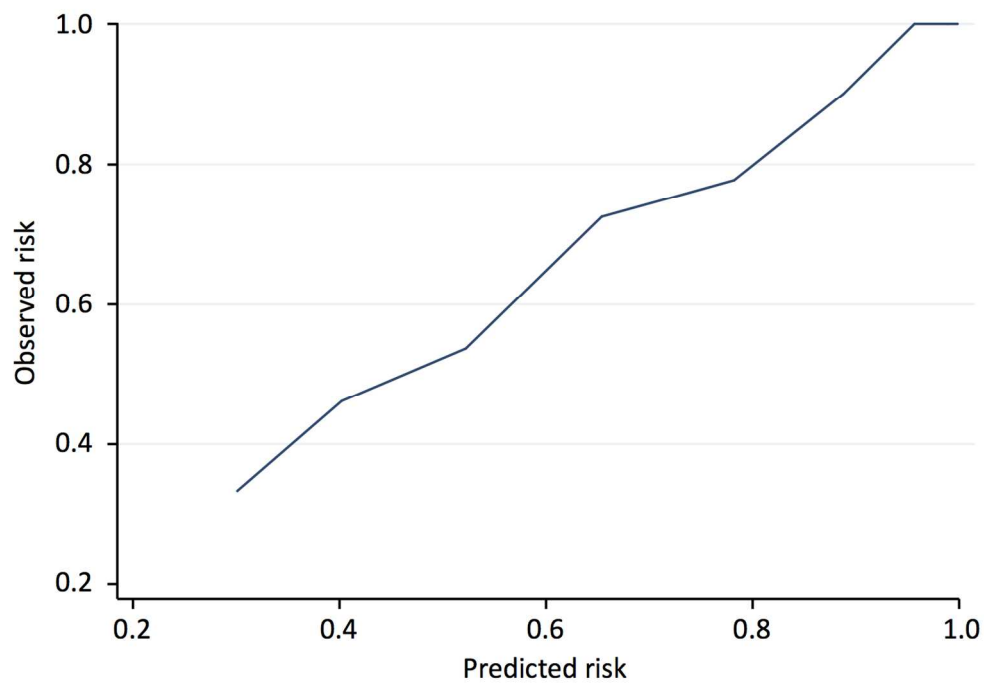
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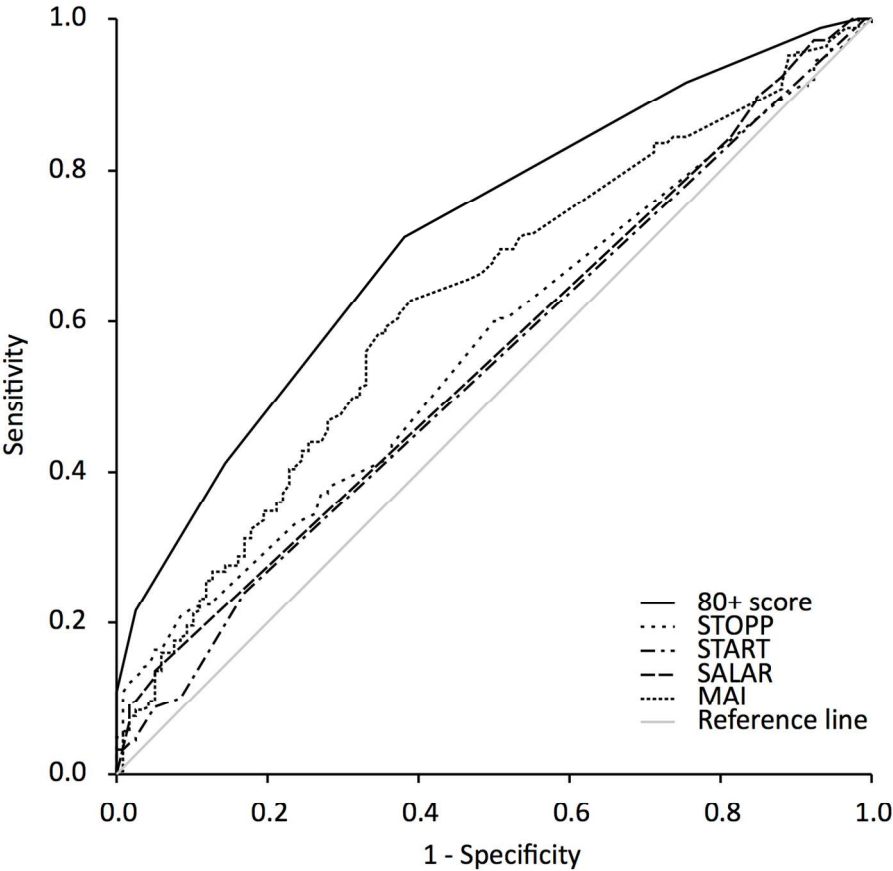
C-statistics: 80+ score=0.72 (95% CI 0.66-0.77), 80+ score (optimism-corrected)=0.71, STOPP score=0.57 (95% CI 0.51-0.63), START score=0.54 (95% CI 0.48-0.60), SALAR drugs=0.55 (95% CI 0.49-0.62), MAI=0.63 (95% CI 0.57-0.69).

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On-line only Supplemental Material

eTable 1. Swedish Associations of Local Authorities and Regions (SALAR) drug list

Drug classes	Example
Anticholinergic agents (SALAR a)	*Alimemazine, hydroxizine, prometiazine, tolterodine, tricyclic antidepressants*
Long-acting benzodiazepine derivates (SALAR b)	*Diazepam, flunitrazepam, nitrazepam*
Neuroleptics (SALAR n)	*Haloperidol, olanzapine. quetiapine risperidone*
Oral nonsteoridal anti-inflammatory drugs (NSAIDs) (SALAR s)	*Diclofenac, ibuprofen, naproxen*
Tradolan (SALAR t)	*Tramadol*
Propiomazin (SALAR p)	*Propiomazine*

eTable 2a. Variable selection. Clinical variables

Variable	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
Age, years (cont.)	-	Yes		Yes
Female, (man/woman)	-	Yes		Yes
Creatinine clearance, ml/min (cont.)	-	Yes		Yes
Social support (living alone or with spouse /living in nursing home)	301[a]	Yes		Yes
Heart failure (yes/no)	141	Yes		Yes
Diabetes (yes/no)	88	Yes		Yes
Pulmonary disease (yes/no)	45	Yes		Yes
Arrhythmia (yes/no)	142	Yes		Yes
Malignant disease -past and present (yes/no)	61	Yes		Yes
Coronary artery disease (yes/no)	114	Yes		Yes
Cerebral vascular lesion –past (yes/no)	72	Yes		Yes
Myocardial infarct –past (yes/no)	98	Yes		Yes
Hypertension (yes/no)	147	Yes		Yes
Dementia (yes/no)	51	Yes		Yes

[a] *(no of patients living alone or with spouse). PCA=principal component analysis)*

eTable 2b. Variable selection. Drug variables (the medications used by patients, categorized according to ATC classification system or SALAR drug classes; STOPP START criteria).

Variable (ATC code class/SALAR drug class/ STOPP and START criteria)	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
A02A	Antacid drugs	4			
A02B *(A02BA + A02BC)*	Drugs for peptic ulcer and gastro-esophageal reflux disease	120	Yes		Yes
A03AX13	Drugs for functional gastrointestinal disorders; Dimetikon	4			
A03FA01	Propulsives; Metoclopramide	13	Yes		Yes
A06AB	Laxatives (contact)	32	Yes		Yes
A06AC+A06AD	Laxatives (bulk-forming and osmotically acting)	129	Yes		Yes
A07DA03	Antipropulsives; Loperamid	8			
A07EC	Intestinal antiinflammatory agents; aminsosalicylic acid and similar	4			
A09A	Digestives	2			
A10A	Insulins and analogues	54	Yes		Yes
A10BA02	Oral blood glucose lowering drugs, excl. insulins; Metformin	15	Yes		Yes
A10BB	Oral blood glucose lowering drugs, excl insulines; Sulfonureids	39	Yes		Yes
A10BX	Oral blood glucose lowering drugs, excl. insulins; Other	2			
A11	Vitamins	27	Yes		Yes
A12A	Calcium supplement	64	Yes		Yes
A12B	Potassium supplement	19	Yes		Yes
A12C	Other mineral supplements	11	Yes		Yes
B01AA03	Antithrombotic agents – Warfarin	44	Yes		Yes
B01AB	Antithrombotic agents – Heparin group	7			
B01AC	Antithrombotic agents – Platelet aggregation inhibitors excl heparin	234	Yes		Yes
B03A	Iron preparations	38	Yes		Yes
B03B	Vitamin B12 and folic acid	190	Yes	Yes[*]	
B03X	Other antianemic preparations	13	Yes		Yes
C01A	Cardiac glycosides	71	Yes		Yes
C01B	Antiarrhythmics	4			
C01CX	Cardiac stiumulants excl. cardiac glycosides; Levosimendan	1			
C01DA	Vasodilators used in cardiac diseases; organic nitrates	195	Yes		Yes
C02CA	Antihypertensives; alfa-adrenoreceptor blockers	2			

Variable (ATC code class/SALAR drug class/ STOPP and START criteria)	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
C03	Diuretics	318	Yes		Yes
C05A	Agents for treatment of hemorrhoids and anal fissures	2			
C07A	Beta blocking agents	191	Yes		Yes
C08	Calcium channel blockers	69	Yes		Yes
C09	Agents acting on the renin-angiotensin system	189	Yes		Yes
C10	Lipid modifying agents	33	Yes		Yes
G03C	Estrogens	27	Yes	Yes[**]	
G04BD	Other urologicals; drugs used in urinary incontince	5			
G04C	Drugs used in benign prostata hyperplasi	17	Yes		Yes
H02A	Corticosteroids for systemic use	36	Yes		Yes
H03	Thyroid preparations	45	Yes		Yes
J01	Antibacterials for systemic use	7			
L01BA	Cytostatic/cytotoxics; Folic acid analoges	1			
L02B	Endocrine therapy; Hormone antagonists and related agents	5			
L04A	Immunosuppressants	1			
M01A	Anti-inflammatory and antirheumatic products, non steroids	19	Yes		Yes
M04A	Anti-gout preparations	30	Yes		Yes
M05BA	Drugs affecting bone structure and mineralization; Bisfosfonates	15	Yes		Yes
N02A	Analgesics; Opioids	68	Yes		Yes
N02B	Analgesics; other analgetics	177	Yes		Yes
N02C	Analgesics; antimigraine preparations	2			
N03A	Antiepileptics	5			
N04A+B	Antiparkinson drugs	19	Yes		Yes
N05A	Antipsychotics	34	Yes		Yes
N05BA	Anxiolytics; Bensodiazapine derivates	64	Yes		Yes
N05BB01	Anxiolytics; Hydroxizin	5			
N05CD	Hypnotics and sedatives; Benzodiazepine derivates	12			
N05CF	Hypnotics and sedatives; Benzodiazepine related agents	113	Yes		Yes
N05CM	Hypnotics and sedatives; Others	28	Yes		Yes
N06AC	Antidepressants; Tricyclic antidepressants	5			
N06AB+AX	Antidepressants; SSRI+others	83	Yes		Yes
N06B	Psychostimulants	1			
N06D	Anti-dementia drugs	12	Yes		Yes

Variable (ATC code class/SALAR drug class/ STOPP and START criteria)	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
R03AC	Drugs for obstructive airway diseases; Selective beta-2-stimulating agents	46	Yes	Yes	
R03B	Drugs for obstructive airway diseases; Anticholinergic +corticosteroids	51	Yes		Yes
R03D	Drugs for obstructive airway diseases; Other (systemic)	1			
R05	Cough and cold preparations	46	Yes		Yes
R06A	Antihistamines for systemic use	12	Yes		Yes
S01B	Opthalmologicals	39	Yes		Yes
SALAR a	Anticholinergic agents	34	Yes		Yes
SALAR b	Long-acting benzodiazepine derivates	12	Yes		Yes
SALAR n	Neuroleptics	26	Yes		Yes
SALAR s	Oral NSAID	14	Yes		Yes
SALAR t	Tradolan	27	Yes		Yes
SALAR p	Propavan	16	Yes		Yes
STOPP a1		29	Yes		Yes
STOPP a2		8			
STOPP a4		1			
STOPP a6		1			
STOPP a7		2			
STOPP a8		3			
STOPP a11		3			
STOPP a12		48	Yes		Yes
STOPP a13		7			
STOPP b1		2			
STOPP b3		2			
STOPP b7		11	Yes		Yes
STOPP b8		6			
STOPP b9		2			
STOPP b12		3			
STOPP b13		3			
STOPP c1		3			
STOPP c4		23	Yes		Yes
STOPP e1		2			
STOPP e2		3			
STOPP e3		2			
STOPP e4		5			
STOPP e6		2			
STOPP e7		8			
STOPP f1		2			
STOPP f2		1			
STOPP f5		1			
STOPP g1		8			
STOPP g3		3			
STOPP g4		12	Yes		Yes
STOPP h1		158	Yes		Yes
STOPP h2		28	Yes		Yes
STOPP h3		10	Yes		Yes
STOPP h4		13	Yes		Yes
STOPP h5		49	Yes		Yes

Variable (ATC code class/SALAR drug class/ STOPP and START criteria)	Drug	No of cases	Subject for PCA	Excl. after PCA	Subject for backward stepwise Cox-regression
STOPP i2		2			
STOPP j		9			
START a1		7			
START a3		11	Yes		Yes
START a5		1			
START a6		26	Yes		Yes
START a7		9			
START a8		10	Yes		Yes
START b1		5			
START e2		6			
START e3		12	Yes		Yes
START f1		1			
START f2		5			
START f3		3			

*Redundant with STOPP h5 **Redundant with R03B

PCA=principal component analysis

No patients scored positive on the STOPP criteria a3, a5, a9, a10, a14, a15, a16, 17, b2, b4, b5, b6, b10, b11, c2, c3, c5, d1, d2, d3, e5, e8, f3, f4, f6, g2, i1, i3 and START criteria a2, a4, b2, b3, c1, c2, c3, d1, d2, e1, f4.

Supplementary Material: Risk estimation from Cox model and from score sheet

Formula

Estimate of risk = $1 - S_0(t)^{\exp(\Sigma \beta \chi - \Sigma \beta \chi_{mean})}$

$S_0(t) = 0.3215$ (the average 1-year event-free time)

$\Sigma \beta \chi$ = the sum of the variables' regression coefficients multiplied with actual value

$\Sigma \beta \chi mean$ = the sum of the variables' regression coefficients multiplied with mean/proportions

Example

A patient living in a nursing home with pulmonary disease and a kidney function of 55 ml/min, being prescribed a proton-pump-inhibitor.

1. Risk estimate based on the Cox model:

$\Sigma \beta \chi = -0.012 * \mathbf{55} + 0.481 * \mathbf{1} + 0.607 * \mathbf{1} + 0.506 * \mathbf{0} + 0.362 * \mathbf{1} + 0.724 * \mathbf{0} - 0.558 * \mathbf{0} = 0.79$

$\Sigma \beta \chi mean = -0.012 * 40.285 + 0.481 * 0.182 + 0.607 * 0.122 + 0.506 * 0.166 + 0.362 * 0.326 + 0.724 * 0.179 - 0.558 * 0.209 = -0.106842$

Estimate of risk = $1 - 0.3215^{\exp(0.79 + 0.106842)} = 0.938$

2. Risk estimate based on the point score system:

1 point (nursing home) + 2 points (pulmonary disesase) + 2 points (GFR 55 ml/min) + 1 points (drugs for peptic ulcer and GERD) = 6 points.

Estimate of risk = 0.9568 (Table 4)

The points system gives a 1-year estimate of risk for rehospitalization or death of 96%, while using the Cox model directly gives an estimated risk of 94%.

eTable 3. Statistical information of the 80+ score variables when tested for association with mortality

	Regression coefficient (SE)	Mean or proportion	p-value	HR	95% CI for HR
eGFR[a] (per mL/min/1.73m^2)	-0.017 (0.006)	40.285	0.004	0.983	0.972-0.994
Social support (living in nursing home *vs* living alone or with spouse)	1.134 (0.205)	0.182	0.000	3.107	2.081-4.640
Pulmonary disease[b] (*vs.* not)	0.108 (0.283)	0.122	0.701	1.114	0.641-1.939
Malignant disease[c] (*vs.* not)	0.619 (0.223)	0.166	0.005	1.858	1.200-2.875
Prescription of drug for peptic ulcer and GERD (*vs.* not)	0.236 (0.194)	0.326	0.225	1.266	0.865-1.852
Prescription of opioid drug (*vs.* not)	0.527 (0.216)	0.179	0.015	1.694	1.109-2.587
Prescription of non-TCA-antidepressant drug (*vs.* not)	-0.209 (0.208)	0.209	0.315	0.812	0.540-1.219

[a]*Cockroft –Gault formula estimated glomerular filtration rate,* [b]*asthma or chronic obstructive pulmonary disease (COPD),* [c]*past or present*

SE=standard error, HR=hazard ratio, CI=confidence interval, GERD=gastroesophageal reflux disease, TCA=tricyclic antidepressants (TCA)