REPOSI REGISTRY BROCHURE

THE REPOSI REGISTRY

The REPOSI Registry (REgistro POliteratepie SIMI) is a collaborative project between the Italian Society of Internal Medicine (Società Italiana di Medicina Interna, SIMI), the IRCCS Cà Granda Maggiore Policlinico Hospital Foundation of Milan and the IRCCS Istituto di Ricerche Farmacologiche Mario Negri of Milan.

The REPOSI Registry was designed in 2008 with the purpose of creating a network of internal medicine and geriatric wards in order to evaluate patients affected by multiple diseases and prescribed with polypharmacy. Participation in the network was on a voluntary basis, but in the choice of the participating centers, attention was given to their homogeneous composition in terms of geographic distribution, size and unselected admissions from the territory or the emergency room.

The specific aims of the REPOSI study were:
- to describe the prevalence of co-occurring multiple diseases and treatments in hospitalized elderly patients,
- to correlate clinical characteristics of the patients with type and number of diseases and treatments,
- to evaluate the main clinical outcomes at hospital discharge.

The original study design included two phases: phase one was designed to create the network of internal medicine and geriatric wards, and phase two was intended to activate a registry of patients included in the study. The Figure above shows the study flow chart.

A sample of at least 20 patients aged 65 years and older consecutively admitted to each participating hospital during a period of 4 weeks, 3 months apart each from the other, was enrolled in the study by each participating ward in different years (2008, 2010, 2012, 2014, and from 2015 the Registry become permanent). The study was approved by the Ethical Committee of the IRCCS Cà Granda Maggiore Policlinico Hospital Foundation of Milan and an informed consent was signed by all patients. The Figure at the left side shows the network of REPOSI Italian wards who participated to the study in the period 2008-2016.

A standardized web-based case report form was filled in by the attending physicians for all enrolled patients, including socio-
demographic characteristics, clinical parameters, diagnoses, comorbidity according to the Cumulative Illness Rating Scale (CIRS), basic activities of daily living according to the Barthel Index, cognitive impairment according to the Short Blessed Test, depression according to the Geriatric Depression Scale and medications prescribed at both hospital admission and discharge and clinical events during hospitalization.

Telephone follow-up was performed 3 months (in 2010 and 2012) and 12 months (from 2012) after hospital discharge collecting data on mortality, re-hospitalization, major adverse clinical events, disability and medications.

Until now the Registry has collected a sample of more than 6,000 hospitalized elderly patients. On 2014, a new wave of data collection has been started in 20 Spanish geriatric and internal medicine hospital wards. In the table at right some characteristics of the patients enrolled in 2008, 2010, 2012, 2014 and 2015 are summarized. Starting from May 2015 the Registry become a permanent registry that collect data one index week every 3 months.

During these years, the REPOSI investigators have published 30 original articles and many abstracts/posters/presentations at international and national congresses.

### MAIN RESULTS

#### POLYPHARMACY AND MULTIMORBIDITY

**Effects of polypharmacy on main clinical outcomes.**

Among 1332 elderly patients (aged 65 years or older) recruited in the REPOSI 2008, the prevalence of polypharmacy was 51.9% at hospital admission and 67.0% at discharge. Age, number of drugs at admission, hypertension, ischemic heart disease, heart failure, and chronic obstructive pulmonary disease were independently associated with polypharmacy at discharge. In multivariate analysis, the occurrence of at least one AE while in hospital was the only predictor of prolonged hospitalization (each new AE prolonged hospital stay by 3.57 days, p<0.0001). Age [odds ratio (OR) 1.04; 95% confidence interval (CI) 1.01-1.08; p=0.02], comorbidities (OR 1.18; 95% CI 1.12-1.24; p<0.0001), and AEs (OR 6.80; 95% CI 3.58-12.9; p<0.0001) were significantly associated with in-hospital mortality.

APPRIOPRIATENESS OF DRUG PRESCRIBING

Proton pump inhibitors.
Among 1155 patients, 466 (40.3%) were treated with drugs for GERD or peptic ulcer were at hospital admission and 647 (56.0%) at discharge; 62.4% of patients receiving a drug for peptic ulcer or GERD at admission and 63.2% at discharge were inappropriately treated. Prevalence of inappropriate prescription of drugs for peptic ulcer or GERD remained almost the same at admission and discharge. Inappropriate use of these drugs is related to the concomitant use of other drugs.


Antidepressants.
The number of patients treated with antidepressant medication at hospital admission was 115 (9.9%) and at discharge 119 (10.3%). In a multivariate analysis, a higher number of drugs (OR = 1.2; 95% CI = 1.1-1.3), use of anxiolytic drugs (OR = 2.1; 95% CI = 1.2-3.6 and OR = 3.8; 95% CI = 2.1-6.8), and a diagnosis of dementia (OR = 6.1; 95% CI = 3.1-11.8 and OR = 5.8; 95% CI = 3.3-10.3, respectively, at admission and discharge) were independently associated with antidepressant prescription. A specific diagnosis requiring the use of antidepressants was present only in 66 (57.4%) patients at admission and 76 (66.1%) at discharge.


Oral anticoagulants in atrial fibrillation.
Among patients with atrial fibrillation, 26.5% at admission and 32.8% at discharge were not on antithrombotic therapy, and 43.7% at admission and 40.9% at discharge were not taking an appropriate therapy according to the CHADS2 score. Among elderly patients admitted with a diagnosis of atrial fibrillation to internal medicine wards, an appropriate antithrombotic prophylaxis was taken by less than 50%, with an underuse of vitamin K antagonist prescription independently of the level of cardio-embolic risk. Hospitalization did not improve the adherence to guidelines.


Effects of cardio-embolic and hemorrhagic scores on warfarin use.
At admission, among 543 patients the median scores (range) were: CHADS2 2 (0-6), CHA2DS2-VASc 4 (1-9), HEMORR2HAGES 3 (0-7), HAS-BLED 2 (1-6). Most of the patients were at high cardio-embolic/high-intermediate bleeding risk (70.5% combining CHADS2 and HEMORR2HAGES, 98.3% combining CHA2DS2-VASc and HAS-BLED). 50-60% of patients were classified in a cardio-embolic risk category higher than the bleeding risk category. In univariate and multivariable analyses, a higher bleeding score was negatively associated with warfarin prescription, and positively associated with aspirin prescription. The cardio-embolic scores were associated with the therapeutic choice only after adjusting for bleeding score or age.

Association between thromboprophylaxis (TP) and venous thromboembolism (VTE), bleeding and death.

Association between TP and VTE, bleeding and death in hospital and during the 3-month post-discharge follow-up were explored by logistic regression and propensity score analysis. Among the 1,380 patients enrolled, 171 (15.2 %) were on TP during the hospital stay (162 on low molecular weight heparins, 9 on fondaparinux). The disability Barthel index was the main independent predictor of TP prescription. Rate of fatal and non-fatal VTE and bleeding during and after hospitalization did not differ between TP and non-TP patients. In-hospital and post-discharge mortality was significantly higher in patients on TP, that however was not an independent predictor of mortality. Among elderly medical patients there was a relatively low rate of TP, that was more frequently prescribed to patients with a higher degree of disability and who had an overall higher mortality.


Potentially inappropriate medications and risk of adverse clinical outcome.

The prevalence of patients receiving at least one PIM was 20.1% and 23.5% according to the 2003 and 2012 versions of the Beers’ criteria, respectively. The 2012 Beers’ criteria identified more patients with at least one PIM than the 2003 version, although a high percentage of those patients (72.2%) were also identified by the criteria updated in 2003. The main difference in the prevalence of patients receiving a PIM according to the two versions of Beers’ criteria involved prescriptions of benzodiazepines for insomnia or agitation, chronic use of non-benzodiazepine hypnotics, prescription of antipsychotics in people with dementia and oral iron at dosage higher than 325 mg/day. Prescription of PIMs was not associated with a higher risk of adverse clinical events, re-hospitalization and all-cause mortality at 3-month follow-up in both univariate and multivariate analysis, after adjusting for age, sex and CIRS comorbidity index.


Inappropriate prescription of allopurinol and febuxostat and risk of adverse events in the elderly: results from the REPOSI registry.

Among the 4035 patients eligible for the analysis, 467 (11.6 %) were treated with allopurinol or febuxostat at hospital admission and 461 (13.2 %) among 3502 patients discharged. At admission, 39 (8.6 %) of patients receiving XO inhibitors and 43 (9.4 %) at discharge were appropriately treated. Among those inappropriately treated, hyperuricemia, polytherapy, chronic renal failure, diabetes, obesity, ischemic cardiomyopathy, heart failure, and cardiac dysrhythmias were associated with greater prescription of XO inhibitors. Prescription of XO inhibitors was associated with a higher risk of adverse clinical events in univariate and multivariate analysis. Prevalence of inappropriate prescription of XO inhibitors remained almost the same at admission and discharge. Inappropriate use of these drugs is principally related to treatment of asymptomatic hyperuricemia and various cardiovascular diseases.


The stigma of low opioid prescription in multimorbid elderly in Italy.

The prevalence of opioid prescription was calculated at hospital admission and discharge. The prevalence of patients prescribed with opioids at admission was 3.8 % in the first run, 3.6 % in the second and 4.1 % in the third, whereas at discharge rates were slightly higher (5.8, 5.3, and 6.6 %). The most frequently
prescribed agents were mild opioids such as codeine and tramadol. The number of total prescribed drugs was positively associated with opioid prescription in the three runs; in the third, dementia and a better functional status were inversely associated with opioid prescription. Finally, as many as 58% of patients with significant pain at discharge were prescribed no analgesic at all. The conservative attitude of Italian physicians to prescribe opioids in elderly patients changed very little between hospital admission and discharge through a period of 5 years. Reasons for such a low opioid prescription should be sought in physicians’ and patients’ concerns and prejudices.


**Adherence to antibiotic treatment guidelines and outcomes in the hospitalized elderly with different types of pneumonia.**

The empirical antibiotic regimen was defined to be adherent to guidelines if concordant with the treatment regimens recommended by IDSA/ATS for CAP, HAP, and HCAP. A diagnosis of pneumonia was made in 317 patients. Only 38.8% of them received an empirical antibiotic regimen that was adherent to guidelines. However, no significant association was found between adherence to guidelines and outcomes. Having HAP, older age, and higher CIRS severity index were the main factors associated with in-hospital mortality.


**Prevalence and Risk Factors Associated with Use of QT-Prolonging Drugs in Hospitalized Older People.**

Among 3906 patients prescribed with at least one drug at admission, 2156 (55.2%) were taking at least one QT-prolonging drug. Risk factors independently associated with the use of any QT-prolonging drugs were found to be increasing age (OR 1.016 95%CI 1.01-1.026), multimorbidity (OR 2.69 95%CI 2.33-3.10), hypokalemia (OR 2.79 95%CI 1.32-5.89), atrial fibrillation (OR 1.66 95%CI 1.40-1.98), and heart failure (OR 3.17 95%CI 2.49-4.05). Furosemide, alone or in combination, was the most prescribed drug. Amiodarone was the most prescribed drug with a definite risk of TdP. Both the absolute number of QT-prolonging drugs (2890 vs 3549) and the number of patients treated with them (2456 vs 2156) increased at discharge. Among 1808 patients not prescribed QT-prolonging drugs at admission, 35.8% were prescribed with them at discharge. Despite their risk, QT-prolonging drugs are widely prescribed to hospitalized older persons in internal and geriatric wards.


**DRUG-DRUG INTERACTIONS**

**Drug interactions and adverse clinical events.**

Among 2712 patients aged 65 years or older recruited at hospital admission in REPOSI 2008 and 2010, 1642 (60.5%) were exposed to at least one potential DDI and 512 (18.9%) to at least one potentially severe DDI. Among 2314 patients discharged, 1598 (69.1%) were exposed to at least one potential DDI and 1561 (24.2%) to at least one potentially severe DDI. Multivariate analysis found a significant association with an increased risk of mortality at 3 months in patients exposed to at least two potentially severe DDIs (OR 2.62; 95% confidence interval, 1.00–6.68; p = 0.05). Adverse clinical events were potentially related to severe DDIs in 2 patients who died in the hospital, in 5 readmitted, and 1 who died at 3 months after discharge.

Adherence to antithrombotic therapy guidelines improves mortality among elderly patients with atrial fibrillation.

Among 2535 patients, 558 (22.0 %) were discharged with a diagnosis of AF. Based on ESC guidelines, 40.9 % of patients were on guideline-adherent thromboprophylaxis, 6.8 % were overtreated, and 52.3 % were undertreated. Logistic analysis showed that increasing age (p = 0.01), heart failure (p = 0.04), coronary artery disease (p = 0.013), peripheral arterial disease (p = 0.03) and concomitant cancer (p = 0.003) were associated with non-adherence to guidelines. Undertreatment was significantly associated with increasing age (p = 0.001) and cancer (p < 0.001), and inversely associated with HF (p = 0.023). AF patients who were guideline adherent had a lower rate of both all-cause death (p = 0.007) and CV death (p = 0.024) compared to those non-adherent. Kaplan-Meier analysis showed that guideline-adherent patients had a lower cumulative risk for both all-cause (p = 0.002) and CV deaths (p = 0.011). On Cox regression analysis, guideline adherence was independently associated with a lower risk of all-cause and CV deaths (p = 0.019 and p = 0.006).

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**CLUSTER ANALYSIS**

**Effects on in-hospital mortality.**

Patients affected by the clusters including heart failure (HF) and either chronic renal failure (CRF), or chronic obstructive pulmonary disease had a significant association with in-hospital death (OR=4.2;95%CI=1.6-11.4; OR=2.9;95%CI=1.1-8.1, respectively), as well as patients affected by CRF and anaemia (OR=6.0;95%CI=2.3-16.2). The cluster including HF and CRF was also associated with adverse clinical events (OR=3.5;95%CI=1.5-7.7). The effect of both HF and CRF and CRF and anaemia on in-hospital death was additive.


**Comparison of clusters of 2008 and 2010.**

Data from the REPOSI Registry were used to evaluate and compare patterns of diseases identified with cluster analysis in two samples of hospitalized elderly during 2008 (1,411 subjects enrolled in 38 hospitals wards) and 2010 (1,380 subjects in 66 wards). To analyze patterns of multimorbidity, a cluster analysis was performed including the same diseases (19 chronic conditions with a prevalence >5%) collected at hospital discharge during the two years of the registry. Eight clusters of diseases were identified in 2008 and six in 2010. Several diseases were included in similar clusters in the two years, such as malignancy and liver cirrhosis; anemia, gastric and intestinal diseases; diabetes and coronary heart disease; chronic obstructive pulmonary disease and prostate hypertrophy.


**CLUSTER ANALYSIS AND DRUG UTILIZATION**

Association between clusters of diseases and polypharmacy.
Among clusters of diseases, the highest mean number of drugs (N=8) was found in patients affected by heart failure (HF) plus chronic obstructive pulmonary disease (COPD), HF plus chronic renal failure (CRF), COPD plus coronary heart disease (CHD), diabetes mellitus plus CRF, and diabetes mellitus plus CHD plus cerebrovascular disease (CVD). The strongest association between clusters of diseases and polypharmacy was found for diabetes mellitus plus CHD plus CVD, diabetes plus CHD, and HF plus atrial fibrillation (AF).


Re-hospitalization

Predictors of re-hospitalization.

Nineteen percent of patients were re-admitted at least once within 3 month after discharge. Multivariate logistic regression analysis showed that only AEs during hospitalization, previous hospital admission, and vascular and liver diseases were significantly associated with likelihood of readmission. The results demonstrate the need for increased medical attention towards elderly patients discharged from hospital with characteristics such as AEs during the hospitalization, previous admission, vascular and liver diseases.


Cognitive Impairment

Cognitive impairment and clinical outcomes.

Elderly patients with cognitive impairment were more likely to die during hospitalization with a severity-dependent association. Adverse events may represent an important target of prevention due to their high association with mortality and cognitive impairment.


Anticholinergic properties of drugs and cognitive performance.

Drugs with anticholinergic properties identified by the ACB scale and ARS are associated with worse cognitive and functional performance in elderly patients. The ACB scale might permit a rapid identification of drugs potentially associated with cognitive impairment in a dose-response pattern, but the ARS is better at rating activities of daily living.


Under-detection of delirium and impact of neurocognitive deficits on in-hospital mortality.

Delirium was coded in 2.9%, while deficits in attention, orientation, and memory were found in 35.4%, 29.7% and 77.5% of patients. Inattention and either disorientation or memory deficits were found in 14.1%, while combination of the 3 deficits in 19.8%. Delirium, as per ICD-9 codes, was not a predictor of in-hospital mortality. In contrast, objective deficits of inattention, in combination with orientation and memory disorders, were stronger predictors after adjusting for covariates. The documentation of delirium is poor in medical wards of Italian acute hospitals. Neurocognitive deficits on objective testing (in a pattern
suggestive of undiagnosed delirium) should be used to raise awareness of delirium, given their association with in-hospital mortality.


**PROGNOSTIC MEASURES**

*eGFR and clinical outcomes.*

In a sample of elderly patients (n = 1,363) eGFR was calculated at hospital admission and at discharge by the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Subjects were classified into three groups: 1 normal eGFR (≥60 ml/min/1.73 m², reference group), 2 moderately reduced eGFR (30-59 ml/min/1.73 m²) and 3 severely reduced eGFR (<30 ml/min/1.73 m²). Patients with the lowest eGFR on admission were more likely to be older, to have a greater cognitive and functional impairment and a high rate of comorbidities. Multivariable logistic regression analysis showed that severely reduced eGFR at the time of admission was associated with in-hospital mortality (OR 3.00; 95% CI 1.20-7.39, p = 0.0230), but not with re-hospitalization (OR 0.97; 95% CI 0.54-1.76, p = 0.9156) or mortality at 3 months after discharge (OR 1.93; 95% CI 0.92-4.04, p = 0.1582). On the contrary, an increased risk (OR 2.60; 95% CI 1.13-5.98, p = 0.0813) to die within 3 months after discharge was associated with decreased eGFR measured at the time of discharge.


**Heart failure and chronic kidney disease in a registry of internal medicine wards.**

Of the 1380 patients enrolled, 27.9% had HF (age 80 ± 7, BMI 27 ± 6 kg/m2) and 17.4% CKD (age 81 ± 7, BMI 26.8 ± 6 kg/m2). Both groups were significantly older (P < 0.0001) with BMI higher than the patients without those diagnosis (P < 0.02). Patients with a history of CKD showed higher non-fasting glycaemia (140 ± 86 vs. 125 ± 63 mg/dL, P < 0.001). CKD was significantly associated with HF (P < 0.0001). Patients with HF had an estimated GFR lower than patients without HF (P < 0.0001). Comorbidity and severity indices were significantly higher in subjects with HF (P < 0.0001) and CKD (P < 0.0001) than in those without. Multivariable analysis showed a significant association between HF and age (for five years increase OR 1.13, P < 0.009), BMI (for each 3 kg/m2 increase OR 1.15, P < 0.001), GFR (for each decrease of 10 mL/min increase OR 0.92, P < 0.002) and severity index (SI) (for each 0.25 units increase OR 1.43, P < 0.001). HF on admission is strongly associated with CKD, older age, BMI, and SI.


**Gout, allopurinol intake and clinical outcomes in the hospitalized multimorbid elderly.**

Increased serum uric acid has been considered a cardiovascular risk factor but no study has assessed its relation with hospital mortality or length of stay. The prevalence of gout/hyperuricemia and its association with clinical parameters was evaluated in the REPOSI Registry. Of 1380 patients, 139 (10%) had a diagnosis of gout or were prescribed allopurinol. They had more co-morbidities (7.0 vs 5.6; P<0.0001) and consumed more drugs (6.8 vs 5.0; P<0.0001). The CI3 (co-morbidity index) was worse in these patients (OR 1.28 95% CI 1.15-1.41). Multivariable regression analysis showed that only renal and heart failures were independently associated with gout/allopurinol intake. Moreover, this combined event was associated with
an increased risk of adverse events during hospitalization (OR 1.66, 95% CI 1.16-2.36), but not with the risk of re-hospitalization, length of hospital stay or death.


**Brain and kidney, victims of atrial microembolism in elderly hospitalized patients?**

It is well known that atrial fibrillation (AF) and chronic kidney disease (CKD) are associated with a higher risk of stroke, and new evidence links AF to cognitive impairment, independently from an overt stroke (Cl). Our aim was to investigate, assuming an underlying role of atrial microembolism, the impact of Cl and CKD in elderly hospitalized patients with AF. Among the 1384 patients enrolled, 321 had AF. Patients with AF were older, had worse Cl and disability and higher rates of stroke, hypertension, heart failure, and CKD, and less than 50% were on anticoagulant therapy. Among patients with AF, those with worse Cl and those with lower estimated glomerular filtration rate (eGFR) had a higher mortality risk (odds ratio 1.13, p=0.006). Higher disability levels, older age, higher systolic blood pressure, and higher eGFR were related to lower probability of oral anticoagulant prescription. Lower mortality rates were found in patients on oral anticoagulant therapy.


**Predictors of clinical events occurring during hospital stay among elderly patients admitted to medical wards in Italy.**

During the hospital stay 427 patients (33.7%) experienced at least one ICE and 19 of them died as a consequence of an ICE. The most common ICES were urinary tract infections, pneumonia, anaemia, arrhythmia and fluid electrolyte disorders. Independent predictors of any ICE were being a bladder catheter holder (RR [risk ratio] 1.86, 95% CI 1.52 – 2.27), being on treatment at home with a proton-pump inhibitor (RR 1.25, 95% CI 1.03 – 1.53) or an immunosuppressant therapy (RR 2.10, 95% CI 1.24 – 3.56), after correction for age, sex, comorbidity, cognitive impairment, functional dependence. Three clinical characteristics, easy to be assessed at admission, can be useful to identify older inpatients at a higher risk for ICES during hospital stay.


**GENDER DIFFERENCES**

**Gender-differences in disease distribution and outcome in hospitalized elderly: data from the REPOSI Study.**

Women live longer and outnumber men. On the other hand, older women develop more chronic diseases and conditions such as arthritis, osteoporosis and depression, leading to a greater number of years of living with disabilities. Aim of this study was to describe whether or not there are gender differences in the demographic profile, disease distribution and outcome in a population of hospitalized elderly people.


**Gender difference in drug use in hospitalized elderly patients.**
Polypharmacy (>5 drugs) was more frequent in men both at hospital admission and discharge. At hospital discharge, the number of prescriptions increased in both sexes at all age groups. Neuropsychiatric drugs were significantly more prescribed in women (p<0.0001). At admission men were more likely to be on antiplatelets (41.7% vs 36.7%; p=0.0029), ACE-inhibitors (28.7% vs 24.7%; p=0.0072) and statins (22.9% vs 18.3%; p=0.0008). At discharge, antiplatelets (43.7% vs 37.3%; p=0.0003) and statins (25.2% vs 19.6%; p<0.0001) continued to be prescribed more often in men, while women were given beta-blockers more often than men (21.8% vs 18.9%; p=0.0340). Proton pump inhibitors were the most prescribed drugs regardless of gender. At discharge, the medication pattern did not change according to gender.


Clinical severity, age, and sex overcome cardiometabolic morbidities but not stroke as predictors of mortality in elderly inpatients.

Data from 2,703 individuals were analyze: logistic analysis indicated that diabetes mellitus, IHD, and stroke were not independent predictors of in-hospital and or 3-month mortality. Only stroke had an independent association with mortality at 1- year follow-up. Age, sex, and severity index were strong predictors of mortality, excluding male sex, which was not associated with in-hospital mortality.


MANUSCRIPTS IN PROGRESS

Anemia in hospitalized elderly patients: the REPOSI study

Several studies have demonstrated a high prevalence of anemia in elderly community-dwelling individuals, but few previous studies have focused on hospitalized elderly patients. Anemia, even mild, is associated with negative outcomes, including prolonged hospital stay and in-hospital mortality. The aims of this study were to evaluate: (i) the prevalence of anemia in elderly patients acutely admitted to internal medicine and geriatric wards; (ii) the association between anemia and comorbidity, polypharmacy at admission and some diseases (chronic obstructive pulmonary disease, cardio-cerebral vascular diseases, neoplasms, chronic renal failure, gastrointestinal disorders, diabetes) and their correlation with severity of anemia; (iii) the role of anemia in predicting the length of hospital stay and in-hospital mortality.

Prevalence and characteristics of the use of lipid-lowering agents in a population of elderly hospitalized patients

A total of 2171 subjects older than 65 were enrolled (1057 males, 1114 females, mean age 78.6 yr). The number of patients treated with lipid lowering drugs was 508 (23.4%) with no gender difference. Among statin-treated patients, atorvastatin (39.3%) and simvastatin (34.0%) were the most used drugs. The prevalence of drug use was higher in patients under polypharmacological treatment (≥ 5 drugs) and with a higher CIRS score. At logistic regression analysis the presence of coronary heart disease, peripheral vascular disease and hypertension were significantly correlated with lipid lowering drug use, whereas age showed an inverse correlation. Diabetes was not associated with drug treatment.
Antipsychotic prescription in older persons and mortality during hospitalization and 3 months after discharge

Among 2703 patients included in the study, 135 (5%) received new prescriptions of antipsychotic drugs. The most frequently prescribed antipsychotics during hospitalization and eventually maintained at discharge were: haloperidol (38 and 36% of cases, respectively), promazine (28 and 20%) and quietapine (12 and 11%). Antipsychotics-group patients were older and had a higher CIRS comorbidity index both at admission and at discharge compared to those not prescribed with antipsychotics. Seventy-one percent of those prescribed with antipsychotics had a SBT score ≥10 (indicative of dementia); 12% a SBT score from 5 to 9 (indicative of questionable dementia); and 17% a SBT score <5 (indicative of normal cognition). In-hospital mortality was slightly higher in patients prescribed with antipsychotic drugs (14.3% vs. 9.4%; p=0.109), but in multivariate analysis only a higher CIRS and SBT scores were significantly related to mortality during hospitalization. At follow-up, male sex, older age, and higher SBT scores were the only factors associated with mortality.

Defining aging phenotypes and related outcomes: clues to recognize frailty in hospitalized older patients

2841 patients were included in the statistical analyses. Four clusters were identified: the healthiest (I); the patients with multimorbidity (II); the functionally independent females with osteoporosis and arthritis (III); the functionally dependent oldest old patients with cognitive impairment (IV). There was a significantly higher in-hospital mortality in Cluster II (OR 2.27, 95% CI 1.15-4.46) and Cluster IV (OR 5.15, 95% CI 2.58-10.26) and a higher 3-month mortality in Cluster II (OR 1.66, 95% CI 1.13-2.44) and in Cluster IV (OR 1.86, 95% CI 1.15-3.00) than in Cluster I. Using alternative analytical techniques, among hospitalized older patients, we could distinguish different frailty phenotypes, differently associated with adverse events. The identification of different patients profiles can help defining the best care strategy according to specific patients needs.

Therapeutic duplicates in a cohort of hospitalized elderly patients: results from the REPOSI study

Explicit criteria for potentially inappropriate prescription in the elderly recommend to avoid any duplicate drug class prescription and optimize monotherapy within a single drug class before considering a new agent. Therapeutic duplicates were defined as prescribing at least two drugs of the same therapeutic class simultaneously to the same patients. The study sample comprised 5,821 patients admitted and 4,983 discharged. In all, 143 therapeutic duplicates were found at admission and 170 at discharge. The prevalence of patients exposed to at least one therapeutic duplicate rose significantly from hospital admission (2.5%) to discharge (3.4%; p=0.0032). Psychotropic drugs and drugs for peptic ulcer or gastroesophageal reflux disease were the most frequent drugs involved. Among the patients discharged with at least one therapeutic duplicate 86.8% still had them at the three-month follow-up.

Risk factors for 3-months mortality after discharge in a cohort of non-oncological hospitalized elderly patients.

Short-term prognosis, e.g. mortality at 3 months, has many important implications in planning the overall management of patients, but to assess this short-term-prognosis is difficult, particularly in non-oncological patients. Performance status is a potent predictor of mortality. The sample included all patients with 3-months follow-up data. Bedridden condition was defined as the inability to walk or stand upright during all the hospitalization. The following parameters were also recorded: estimated GFR ≤ 29 ml/min/1.73 m²; severe dementia; albuminemia <2.5 g/dL; hospital admissions in the six months before the index admission.
REPOSI REGISTRY BROCHURE

Among 3,915 patients eligible for the analysis data about 3-months follow-up were available for 2,058 patients and were included in the study. 181 (8.8%) patients died between discharge and 3-months follow-up. Bedridden patients were 112 and the absolute risk difference of mortality was 0.13 (CI 95% 0.08-0.19, p< 0.0001). Patients with at least one risk factor considered in the study were 882 (42.6%). Mortality was significantly higher among these patients (12.9% vs 4.1%. p<0.0001). Logistic regression analysis adjusted for age, sex, number of drugs and comorbidity index found that bedridden condition, severely reduced kidney function, hospital admission in the previous 6 months and severe dementia with total or severe level of physical dependence were associated with a higher risk of 3-month mortality. Results were confirmed in the analysis on the sample of patients with measure of serum albumin.

POINTS OF VIEW

Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium

The pattern of patients admitted to internal medicine wards has dramatically changed in the last 20–30 years. Elderly people are now the most rapidly growing proportion of the patient population in the majority of Western countries, and aging seldom comes alone, often being accompanied by chronic diseases, comorbidity, disability, frailty, and social isolation. Multiple diseases and multimorbidity inevitably lead to the use of multiple drugs, a condition known as polypharmacy. Over the last 20–30 years, problems related to aging, multimorbidity, and polypharmacy have become a prominent issue in global healthcare.

This review discusses how internists might tackle these new challenges of the aging population. Internists are called to play a primary role in promoting a new, integrated, and comprehensive approach to the care of elderly people, which should incorporate age-related issues into routine clinical practice and decisions. The development of new approaches in the frame of undergraduate and postgraduate training and of clinical research is essential to improve and implement suitable strategies meant to evaluate and manage frail elderly patients with chronic diseases, comorbidity, and polypharmacy.

Internal and geriatric medicine: an alliance for the challenges of the elderly.

It is now time for the renaissance of an internal medicine able to deal optimally with the changing demography, tackle the challenges of the complexity of patients admitted to internal medicine hospital wards, and ensure the integration and continuity of care between the network of health and social services. This new era of internal medicine provides the opportunity for a renaissance of our practice, to overcome the risk of feeling overwhelmed and avoid the nihilism of the routine daily clinical activity. Current health care structures where the internists practice medicine do not facilitate the multidimensional approach to the elderly with multimorbidity, and encourage to measure outcomes related to single diseases, whereas the challenge is to delivery patient-centered care to complex chronic patients with multimorbidities. With their basic training designed to acquire a holistic approach to clinical problems, internists are fortunately in an optimal position to acquire this new knowledge and expertise, even though this acquisition requires some degree of humility joined with awareness of the ongoing change of their mission.


Multimorbidity and polypharmacy in the elderly: lessons from REPOSI.

The dramatic demographic changes that are occurring in the third millennium are modifying the mission of generalist professionals such as primary care physicians and internists. Multiple chronic diseases and the related prescription of multiple medications are becoming typical problems and present many challenges. Unfortunately, the available evidence regarding the efficacy of medications has been generated by clinical trials involving patients completely different from those currently admitted to internal medicine: much younger, affected by a single disease and managed in a highly controlled research environment. Because only registries can provide information on drug effectiveness in real-life conditions, REPOSI started in 2008 with the goal of acquiring data on elderly people acutely admitted to medical or geriatric hospital wards in Italy. The main goals of the registry were to evaluate drug prescription appropriateness, the relationship between multimorbidity/polypharmacy and such cogent outcomes as hospital mortality and re-hospitalization, and the identification of disease clusters that most often concomitantly occur in the elderly. The findings of 3-yearly REPOSI runs (2008, 2010, 2012) suggest the following pertinent tasks for the internist in order to optimally handle their elderly patients: the management of multiple medications, the need to become acquainted with geriatric multidimensional tools, the promotion and implementation of a multidisciplinary team approach to patient health and care and the corresponding involvement of patients and their relatives and caregivers. There is also a need for more research, tailored to the peculiar features of the multimorbid elderly patient.


THE SPANISH REPOSI REGISTRY

Starting from 2014, the REPOSI Registry became an international network. Thanks to support of the "Hospital Universitario Virgen del Rocio, Sevilla", 27 internal medicine wards of Spanish hospitals have been involved in the study. In each wards during the same four index week will be enrolled at least five patients with the same criteria applied in the Italian REPOSI network. PROFUND Index, Polypathology Index and
SPMQS (Short Portable Mental Status Questionnaire) have been added to the electronic clinical record form.

**PROFUND INDEX**

The PROFUND index includes nine easy-to-achieve variables: one demographical (age ≥ 85 years, 3 points), four clinical (presence of active neoplasia, 6 points; dementia, 3 points; disabling dyspnea by means of III–IV functional class on New York Heart Association and/or Medical Research Council, 3 points; delirium during last hospital admission, 3 points), one laboratory (hemoglobinemia < 10 g/dL, 3 points), one functional (Barthel index < 60 points, 4 points), one sociofamilial (caregiver other than spouse or no caregiver; 2 points), and one care (number of hospital admissions in last 12 months ≥ 4, 3 points) variable.

PROFUND Index was validated in a multicenter prospective cohort-study recruiting 1.632 polypathological patients (PP) after hospital discharge, outpatient clinics, or home hospitalization, from 33 hospitals. Potential risk factors were obtained in the 1.525 PP who completed follow-up. Each factor independently associated with mortality in the derivation cohort (757 PP from western hospitals) was assigned a weight, and risk scores were calculated by adding the points of each factor. Accuracy was assessed in the validation cohort (768 PP from eastern hospitals) by risk quartiles calibration, and discrimination power, by ROC curves. Finally, accuracy of the PROFUND index was compared with that of the Charlson index. One year mortality rates were as follows: 0–2 points: 12.1%; 3–6 points: 21.5%; 7–10 points: 45%; and 11 or more points: 68%.


**SUMMARY OF PATIENTS ENROLLED IN REPOSI REGISTRY (2008-2016)**

[Image of study flow chart]

- Enrolled patients N=6,157
- Patients excluded¹ N=36
- Patients at hospital discharge N=6,121
- Patients excluded² N=111
- Dead N=262
- At home N=5,194
- Transferred N=499
- Critical N=55
The goals and challenge of this International Seminar are to promote more effective and focused clinical and research approaches to multimorbidity in the oldest old, taking into account different European healthcare scenarios, experiences and expertises.

In the European Union (EU) the number of people aged >75 years is projected to double by the year 2060, comprising 20% of the total population. These changes will lead to an increase of 20 to 40% of the costs necessary to maintain the existing quality of healthcare services.

Multimorbidity is almost constant in the oldest old and has such adverse consequences as higher mortality, poorer quality of life and functional status. Elderly people with multimorbidity are usually treated with multiple medications, and polypharmacy leads to drug interactions, adverse reactions, poor compliance, heightened health service use, inadequate coordination of care and higher treatment burden. Current therapeutic guidelines are based upon randomized clinical trials, that enrol only highly selected, relatively young patients suffering from a single disease. This population is obviously very different from the oldest old and very few of the available guidelines take into due account multimorbidity and overall medication burden. This background highlights the need of making drug prescription more appropriate and personalized, also ensuring that decision making takes into account patients’ life expectancy, concerns and priorities. There is also a need to bolster a patient-centered approach instead of the current disease-focused efforts, that inevitably lead to fragmentation of healthcare of the elderly and inappropriate use of facilities. (http://www.reposi2013.org/).

To download the Speakers’ Presentations, please, click here: http://www.reposi2013.org/reposi-2013-speakers-presentations/
With some Italian medical institutions we have developed since 2008 a registry called REPOSI with the goal to collect data meant to improve the appropriateness of prescription of the multiple drugs often given to the elderly. If you want to get more information on our activities, we take the liberty to include two relatively recent review articles that depict our activities since 2008.

With this background, we organize each year a Seminar on multimorbidity and related polypharmacy in the elderly, that at alternate years also involves includes an international faculty. In 2015, the meeting will take place in Milan, starting in the early afternoon of September 24 and ending in the late morning or early afternoon of September 25.

REPOSI EDUCATION

In the third millennium, internists and geriatricians must acquire a leading role, together with primary care physicians, in order to make health care systems fit for the management of an aging population. Are we ready for this formidable task?
THE FUTURE

In the next few years, REPOSI should be able to propose new lines of research in patients with multimorbidity and polypharmacy.

In particular:

- designing clinical trials based upon patient-centred outcomes (cognitive and physical function, emotional well-being and social connectivity) rather than on outcomes such as death, re-hospitalization and institutionalization
- designing pragmatic clinical trials in which, for instance, patients are randomized in relation to disease clusters to receive or not receive a specific treatment,
- promoting and implementing a multidisciplinary team approach to patient health and care and involving patients and their relatives or caregivers,
- implementing new approaches of data analysis or study design (network analysis, N-of-1 trials, narrative medicine).

THE FUTURE

- A permanent observatory on multimorbidity and polypharmacy in the elderly
- A joint effort between Italian and Spanish internists
- Other European internal medical societies are welcome to join
- Promotion of prescription appropriateness in order to avoid potentially inappropriate medication (PIM)
- Development of new research approaches to evaluate more rational prescription of multiple drugs
ITALIAN REPOSI STUDY COORDINATING GROUP

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