



Polypharmacy in older people: lessons from 10 years of experience with the REPOSI register

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Received: 29 June 2018 / Accepted: 27 August 2018 / Published online: 31 August 2018
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Abstract

As a consequence of population aging, we have witnessed in internal medicine hospital wards a progressive shift from a population of in-patients relatively young and mainly affected by a single ailment to one of ever older and more and more complex patients with multiple chronic diseases, followed as out-patients by many different specialists with poor integration and inevitably treated with multiple medications. Polypharmacy (defined as the chronic intake of five or more drugs) is associated with increased risks of drug–drug interactions and related adverse effects, prescription and intake errors, poor compliance, re-hospitalization and mortality. With this background, the Italian Society of Internal Medicine chose to start in 2008 a prospective register called REPOSI (REgistro POLiterapie SIMI, Società Italiana di Medicina Interna) in internal medicine and geriatric hospital wards. The country wide register is an ongoing observatory on multimorbidity and polypharmacy in the oldest old, with the goal to improve prescription appropriateness and, thus to avoid potentially inappropriate medications. The main findings of the register, that has accrued so far, 7005 older patients throughout a 10 year period, are summarized herewith, with special emphasis on the main patterns of poor prescription appropriateness and related risks of adverse events.

Keywords Multimorbidity · Polypharmacy · Inappropriate prescription · Deprescribing · Medication reconciliation

Introduction

Aging is a global issue, not only in high-income countries, but also in more vulnerable economies. According to WHO, older people are the age group in more rapid growth, and in the 2050s, two billion people (one in four) will be older than 60 years, and as many as 80% of them will live in

low-income countries. Planetary aging is good news, owing to the progress of medicine, improved lifestyles and the availability of medications that have changed the course of many ailments. However, aging has a number of negative consequences, such as a proportional decrease of the working class of the countries where more and more people live longer. Furthermore, the gross domestic product of these countries is jeopardized by the burden exerted on welfare by senior citizens with multiple chronic diseases and related disabilities. Italy is one of the countries with higher life expectancy at birth. Within the year 2050, 24% of the population will be older than 65 years and 15% of them will be older than 80 years. Furthermore, the very low fertility rate (1.3 per woman in Italy) is causing a marked disproportion between older people and active citizens. This entails more and more difficulties in sustaining welfare systems, leading to higher out-of-pocket costs for each citizen or their neglect of adequate health care. There are other formidable problems, including those related to the increase in the elderly of frailty, cognitive deficits and disability.

Full list of authors are found in Acknowledgements.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11739-018-1941-8>) contains supplementary material, which is available to authorized users.

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Shifts in internal medicine wards

With this background, Italian internists did progressively realize that during the last 20–30 years of their practice there were dramatic changes in the type of patients acutely admitted to hospital wards. There has been a progressive shift from a population of adult in-patients usually affected by a single acute disease to one of ever older and more and more complex people with multiple chronic diseases, frequently attended before hospital admission by many different specialists, with poor integration of their care and the prescription of multiple medications. Beside taking 5 or more drugs (the most frequent definition of polypharmacy), these patients often need longer and longer hospital stays, not only for the complexity of their clinical conditions but also for the difficulties in planning their home discharge owing to the previous existence or novel onset of many functional and social problems aggravated by acute diseases and hospitalization. We also became aware that so many drugs, prescribed to multimorbid patients on the basis of the evidence stemming from the guidelines for each single disease, were causing new issues and problems.

Polypharmacy and its consequences

According to Marengoni et al. [1], in 2060 “oldest old” people will reach 75 million in Europe (10–15% of the whole continent) and will consume more and more drugs. In Italy, the Italian Medicines Agency (AIFA) reports that 1.5 million of the oldest people (75–85 years) are being prescribed 6 or more daily drugs, and that the number of people on polypharmacy is predicted to reach 6 million in 2050. Older people currently absorb nearly two-thirds of the total budget for drugs provided by the Italian Health Service. Polypharmacy is not only an issue for the increasing costs of medications: it is associated with increased rates of mortality and re-hospitalization, so that polypharmacy itself should be perceived as a disease, often with more serious consequences of the diseases these different drugs have been prescribed for. This is due to the many negative effects of polypharmacy [2, 3]: drug–drug interactions and the related adverse effects, prescription and intake errors by both physicians and patients, poor compliance with prescribed drugs, plus the use in the “oldest old” of drugs that are inappropriate when life expectancy is limited [4, 5].

The limitations of evidence-based medicine

Why is polypharmacy so frequent in the elderly? It is the consequence of the inappropriate fragmentation of their care between multiple specialists, and the application to these

complex multimorbid patients of the guidelines stemming from disease-oriented medicine that in turn stems from the results of randomized clinical trials (RCTs) on single specific diseases [6]. The snag is that RCTs enroll patients very different from the elderly, i.e., younger, usually with only one disease and a low baseline risk of adverse reactions to drugs. Thus, the RCTs provide evidence on drug efficacy, but not on effectiveness in real life, because they investigate the typical disease, not the actual patients with their own complex disease patterns [6]. Regulatory agencies that license drugs are cognizant of this problem; the European Medicines Agency states that “regulators must ensure that the development and evaluation of drugs take into account global demographic changes, so that safe and effective drugs reach the actual patients who ultimately use them” [7]. Taking as an example a complex condition most frequent in the “oldest old” such as heart failure, most RCTs enroll patients who are younger and with no or fewer comorbidities than those seen on real-life hospital wards of internal medicine [8].

The rationale for REPOSI

With this background, we chose to tackle to the issue of multimorbidity and related polypharmacy in the Italian older adults by starting and coordinating in 2008 a prospective register called REPOSI, sponsored by the Italian Society of Internal Medicine together with the IRCCS Mario Negri Institute for Pharmacological Research and a large research and teaching hospital in Milan (IRCCS Ospedale Maggiore). The register is based upon a prospective cohort of older patients (at least 65 years of age) acutely admitted to 107 Italian hospital wards of Internal Medicine and Geriatrics. Figure 1 summarizes the setting of the study. At the time of writing, we have already collected data on 7005 patients, and at least one-third of them are older than 85 years, with a mean age of 80 years. Figure 2 shows the flowchart of the patients included so far. Table 1 shows the main characteristics of the actually enrolled patients, who are an accurate and actual picture of the ill people acutely admitted to Italian hospital wards of internal medicine and geriatrics. The main goal of this independent, investigator-driven register is to evaluate the pattern of drug prescription in hospital, in order to improve their appropriateness, and thereby help to avoid or at least reduce adverse reactions. Medication review and deprescribing during hospitalization have been emphasized, in order to avoid unnecessary dispensing and thereby attempting to prevent drug-related problems [9]. The decision to stop unnecessary medications is an important step towards drug optimization, so that deprescribing should be considered a positive, patient-centered intervention, which involves identifying an issue (the use of unnecessary drugs)

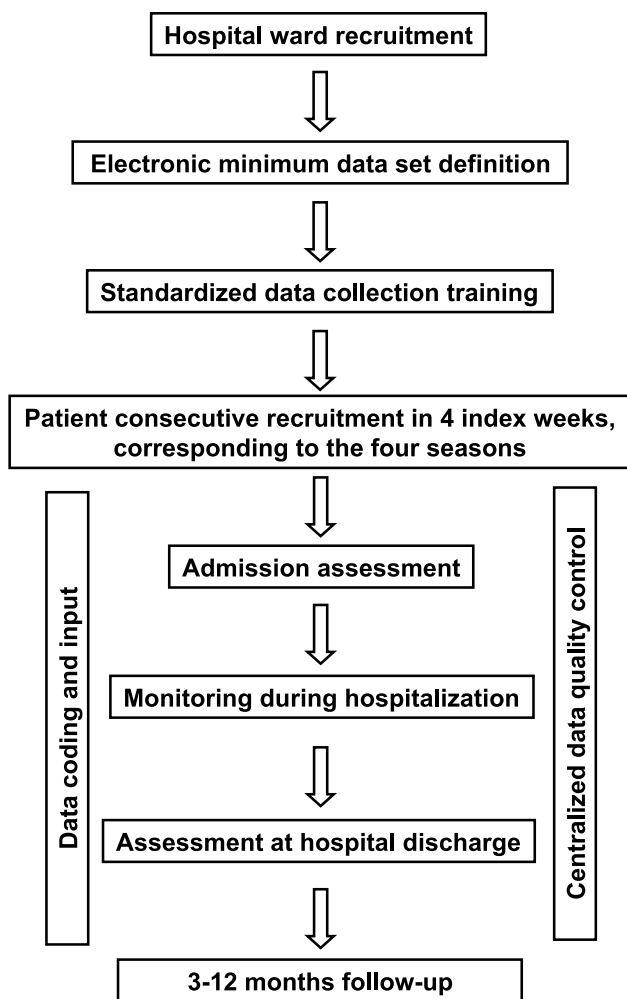
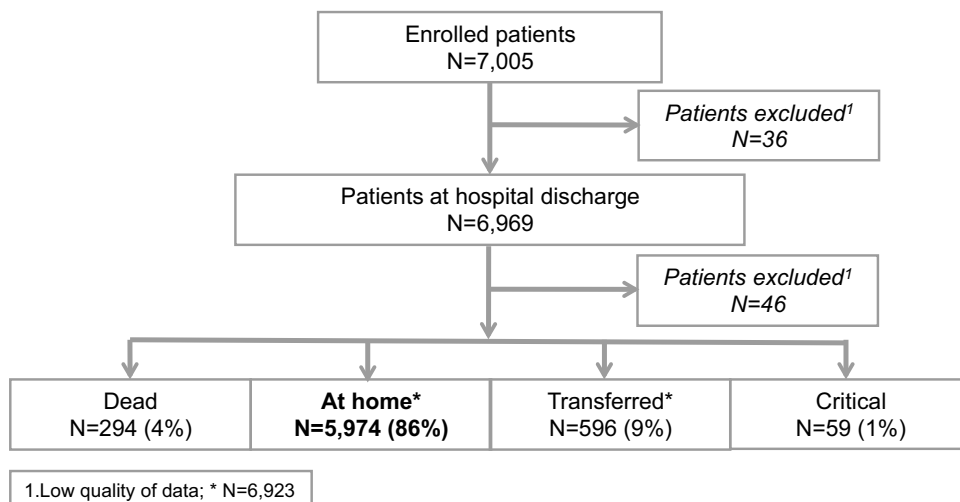


Fig. 1 Flow chart of REPOSI Register

Fig. 2 Overall recruitment and hospital outcomes of REPOSI cohort



and making a therapeutic decision (withdrawing them appropriately and with a close follow-up).

Main REPOSI findings

REPOSI has produced a number of reports stemming from the register (at the time of writing, 38 original articles, 5 letters to the Editor and 4 narrative reviews). Table 2 summarizes the main results. We confirm that in our Italian population of patients acutely admitted to internal medicine and geriatric hospital wards there is a high rate of polypharmacy (67% at the time of hospital discharge, more than at admission) [10]. The number of drugs is positively associated with a higher likelihood of re-hospitalization within the 3-month post-discharge follow-up [11]. Potential drug–drug interactions are frequent and associated with a more than twofold increased risk of mortality at 3 months after hospital discharge [12]. According to the 2003 and 2012 Beers criteria on drugs that should be avoided in older people, the prevalence of patients receiving at least one inappropriate medication is relatively high, at 20 and 24%, respectively [13]. Pertaining to the drugs most frequently inappropriately prescribed even according to the available guidelines, there are proton pump inhibitors [14], non-steroidal antiinflammatory drugs (NSAIDs) [15], antibiotics [16], allopurinol [17], such antithrombotic drugs as anticoagulants [18–22] and antiplatelets [23], and, in general, all the classes of drugs active in the central nervous system (antipsychotics, antidepressants, opioids [24–27].) A definite increase in therapeutic duplicates of psychotropic drugs and drugs for peptic ulcer is also observed at hospital discharge, although duplication increases the risk of adverse drug events and costs [28]. Drugs with anticholinergic effects are associated with cognitive and functional impairment [29], and the recognition and management of delirium were rather inadequate in the

Table 1 Main socio-demographic and clinical characteristics of REPOSI patients during the period 2008–September 2017

Years of data collection	2008	2010	2012	2014	2015/2016	2016/2017
Number (<i>N</i>) of patients enrolled	1332	1380	1323	1212	800	958
Females, <i>N</i> (%)	721 (54.1)	696 (50.4)	672 (50.8)	622 (51.3)	442 (55.3)	470 (51.0)
Age (years), mean (SD)	79.3 (7.5)	79.0 (7.3)	79.3 (7.4)	79.1 (7.9)	80.4 (7.7)	80.1 (7.7)
Age class, <i>N</i> (%)						
65–74	409 (30.7)	430 (31.2)	403 (30.5)	365 (30.2)	192 (24.0)	254 (26.5)
75–84	607 (45.6)	650 (47.1)	583 (44.1)	529 (43.8)	350 (43.8)	405 (42.2)
> = 85	316 (23.7)	300 (21.7)	337 (25.5)	315 (26.0)	258 (32.1)	299 (31.2)
Need of caregivers, <i>N</i> (%)	–	772 (56.5)	689 (52.1)	595 (49.0)	386 (48.2)	496 (51.9)
Number of diagnoses at admission, mean (SD)	4.3 (2.3)	5.8 (2.8)	5.7 (2.8)	5.3 (2.9)	6.6 (3.2)	6.1 (2.8)
Number of patients at admission with 5 or more diagnoses, <i>N</i> (%)	571 (42.9)	884 (64.1)	839 (63.4)	640 (55.4)	576 (72.2)	661 (70.9)
Number of drugs at admission, mean (SD)	4.9 (2.8)	5.3 (2.8)	5.4 (3.1)	6.1 (3.1)	5.8 (3.1)	5.7 (3.1)
Number of patients at admission taking 5 or more drugs <i>N</i> (%)	689 (51.7)	805 (58.3)	778 (58.8)	760 (62.7)	516 (64.5)	607 (63.4)
CIRS-Severity index at admission, mean (SD)	–	1.6 (0.3)	1.7 (0.3)	1.7 (0.4)	1.7 (0.3)	1.7 (0.3)
CIRS-Comorbidity index at admission, mean (SD)	–	2.9 (1.7)	3.1 (1.9)	3.1 (2.0)	3.2 (2.0)	3.0 (1.9)
Barthel index at hospital stay, mean (SD)	–	76.8 (30.7)	72.6 (32.4)	70.8 (33.5)	67.5 (33.6)	70.9 (31.8)
Groups according to Barthel Index at hospital stay, <i>N</i> (%)						
Complete dependence (0–24)	–	155 (11.4)	169 (13.4)	176 (14.5)	130 (16.2)	121 (12.9)
Severe dependence (25–49)	–	111 (8.2)	126 (10.0)	104 (8.6)	64 (8.0)	93 (9.9)
Short Blessed test, mean (SD)	–	9.9 (8.2)	9.2 (7.8)	8.4 (7.9)	8.6 (8.1)	8.6 (7.6)
Short Blessed test, Severe (10–28), <i>N</i> (%)	–	637 (47.6)	541 (44.5)	406 (40.4)	276 (41.07)	311 (39.4)
Geriatric Depression Scale, mean (SD)	–	1.4 (1.2)	1.4 (1.2)	1.3 (1.2)	1.3 (1.3)	1.3 (1.3)
Dead, <i>N</i> (%)	66 (5.0)	50 (3.6)	42 (3.0)	68 (5.6)	36 (4.5)	32 (3.5)
Number of patients discharged, <i>N</i> (%)	1155 (86.7)	1159 (84.0)	1159 (87.6)	1053 (86.9)	681(85.2)	778 (81.2)
Number of diagnosis at discharge, mean (SD)	5.9 (2.5)	6.5 (3.0)	6.3 (2.8)	5.9 (3.1)	7.0 (3.3)	7.1 (3.0)
Number of patients at discharge with 5 or more diagnosis, <i>N</i> (%)	796 (68.9)	857 (73.94)	834 (72.0)	637 (60.5)	525 (76.8)	626 (81.1)
Number of drugs at discharge mean (SD)	6.0 (2.9)	6.3 (2.8)	6.4 (3.1)	7.8 (5.5)	6.2 (3.3)	6.5 (3.3)
Number of patients at discharge taking 5 or more drugs <i>N</i> (%)	770 (66.7)	838 (72.3)	838 (72.3)	885 (84.0)	494 (71.0)	573 (73.3)
CIRS-Severity index at discharge, mean (SD)	–	1.7 (0.3)	1.7 (0.3)	1.7 (0.4)	1.7 (0.4)	1.7 (0.3)
CIRS-Cormorbidity index at discharge, mean (SD)	–	3.0 (1.8)	3.2 (2.0)	3.2 (2.1)	3.2 (2.1)	3.2 (2.0)
Hospital stay days, mean (SD)	11.1 (8.5)	10.9 (8.2)	11.4 (8.5)	12.3 (10.5)	12.8 (17.2)	13.4 (17.3)

CIRS Cumulative Illness Rating Scale

internal medicine wards participating in the register [30]. Importantly, we recently observe that the 27 wards that had regularly participated in the different runs of REPOSI from its onset did improve the rate of polypharmacy compared with the 2010 run. In fact, considering each year of the study period, the proportion of patients prescribed at discharge with 0 to 1 drugs (very low drug use) with respect to those prescribed 2 or more increases from 2.7 to 9.2%, while patients exposed to 5 to 9 drugs decrease from 83.8% in 2010 to 76.8% in 2016 [31]. Furthermore, among hospitalized older patients, we are able to distinguish a gender dimorphism in the demographic and morbidity profiles of hospitalized elderly people [32, 33], different clusters of diseases [34–36] and frailty phenotypes (the healthiest, those with multimorbidity, the functionally

independent women with osteoporosis and arthritis, and the functionally dependent “oldest old” patients with cognitive impairment), differently associated with adverse events [37], emphasizing once more the need for a personalized process of healthcare. Finally, we also observe that the increasing score of the Frailty Index (FI) (according to the model of the age-related accumulation of deficits) is significantly associated with in-hospital and overall mortality, also after adjustment for age and gender. The FI is a simple and useful tool that measures the frailty status of hospitalized older people, and that may thus facilitate their appropriate hospital management, by informing whether or not care should be adapted for the most vulnerable elders at discharge [38]. A full list of the REPOSI published articles has been added in the supplementary material.

Table 2 Summary of main results of REPOSI Register

Drug utilization

High frequency of polypharmacy (67% at discharge) [10]
 A gender difference in overall medication pattern in the hospitalized elderly is found: hospitalization, while increasing the number of prescriptions, does not change drug distribution by gender [33]
 The prevalence of patients with chronic pain prescribed with opioids is low at admission (4%) and increases only slightly at discharge (6%) [26]
 The strongest association between clusters of diseases and polypharmacy is found for diabetes mellitus plus coronary heart disease plus cardiovascular disease, diabetes plus coronary heart disease, and heart failure plus atrial fibrillation [36]
 From 2010 to 2016, there is an increasing number of patients who, on polypharmacy at hospital admission, decrease drug intake at hospital discharge [31]

Appropriateness of drug prescribing

Severe drug-drug interactions are frequent (24%) and associated with an increased risk of 3-month mortality (odds ratio: 2.62) [12]
 The prevalence of patients receiving at least one potentially inappropriate medication is 20 and 24% according to the 2003 and 2012 versions of the Beers' criteria [13]
 The prevalence of patients exposed to at least one therapeutic duplicate rises significantly from hospital admission (2.5%) to discharge (3.4%; $p=0.003$) [28]
 There is a high frequency (63%) of inappropriate prescription of proton pump inhibitors [14]
 Among patients treated with antiplatelet therapy for primary prevention, 52% are inappropriately prescribed (mainly overprescribed, 74%), also with a high rate of inappropriate underprescription in the context of secondary prevention (30%) [18]
 Appropriate antithrombotic prophylaxis has a prevalence of less than 50% in patients with atrial fibrillation, with an underuse of vitamin K antagonists agents independent of the level of cardio-embolic risk [19]
 Non-compliance to guidelines is highly prevalent among elderly patients with atrial fibrillation, despite guideline-compliant treatment being independently associated with lower risk of all-cause and cardiovascular deaths [20]
 Among patients treated with allopurinol more than 90% are treated inappropriately at admission and at discharge [17]
 Despite their risk, QT-prolonging drugs are widely prescribed to hospitalized older persons [44]

Prognostic measures

The number of drugs is significantly associated with the likelihood of readmission at 3 months [11]
 The documentation of delirium is poor (2.9%) on medical wards of Italian acute hospitals [30]
 Patients with cognitive impairment are more likely to die during hospitalization with a severity-dependent association [25]
 Drugs with anticholinergic properties are associated with worse cognitive and functional performance [29]
 Severely reduced eGFR at admission is associated with in-hospital mortality (OR 3.00; $p=0.02$), and a decreased eGFR at hospital discharge is associated with an increased risk (OR 2.60 $p=0.08$) to die within 3 months after discharge [45]
 No difference in predictive power between different e-GFR equations is found [46]
 Mild anemia predicts hospital readmission in older in-patients, while the three-month mortality risk increases proportionally with anemia severity [47]
 Elderly hospitalized patients with pneumonia and clinically significant disability have a higher mortality risk, while diabetes does not represent an important determinant of short and long-term outcome [48]
 Bedridden status, severely reduced kidney function, recent hospital admissions, severe dementia and hypoalbuminemia are associated with higher risk of three-month mortality in non-oncologic patients after discharge [49]
 The increasing score of Frailty Index (according to the age-related accumulation of deficit model) is predictive of both in-hospital (OR 1.61, 95%CI 1.38–1.87) and overall (HR 1.46, 95%CI 1.32–1.62) mortality, also after adjustment for age and gender [38]

Lessons from REPOSI [39]

First of all, REPOSI provides a collaborative clinical network (involving 107 internal medicine and geriatric hospital wards) for more than 300 young internists, who have the opportunity to be associated to an independent, real-life research project. They also have the possibility to learn directly from their clinical practice the appropriate use of drugs, the complexity of hospitalized older adults, and the importance of evaluating such domains as cognitive and functional status, mood disorders and the burden of polypharmacy, perhaps not previously considered by them to

be so cogent. The registry also taught us that Italian hospital internists not only fail to optimally handle the multiple medications prescribed to their older patients, but also fail to improve during the hospital stay prescription patterns through medication reconciliation, medication review and deprescribing, and that these strategies are still far from their usual medicine practice. We also became aware that there is a need for a closer alliance between internists and geriatricians in the management of the oldest patients, and that the internists must become more proficient with the routine use of the tools of the comprehensive geriatric assessment [40]. This also entails the promotion and implementation of

a more interdisciplinary team approach to the hospitalized “oldest old,” including clinical pharmacologists, hospital pharmacists, nurses and involving more than now patients, their relatives, caregivers and family doctors. There is more and more evidence for the crucial role played by the hospital pharmacist to support clinicians for medication reconciliation and review at hospital admission and discharge [41].

For each prescribed drug, more careful consideration should be given to the number of drugs taken, medication compliance, priorities and life expectancy of each patient, the time to benefit of each treatment, and the goals of care and treatment targets should be more accurately considered for a more rational prescribing. Patients may be more willing to stop unnecessary medications than their physicians believe [42]. Emphasizing the positive aspects of stopping medicines, reducing the burden of daily pills, improving compliance, and reducing the risk of drug–drug interactions and the associated adverse reactions are an approach that internists should pursue and emphasize in conversations with patients and relatives during the hospital stay and at discharge, involving in these choices the family doctors [43].

The future of REPOSI

There is a need for more research tailored to the peculiar features and needs of the multimorbid older patients on polypharmacy. For instance, RCT should be based on outcomes centered on the features and needs of people with a limited life expectancy (for instance, cognitive and physical function, emotional well-being and social connectivity) rather than on more traditional outcomes such as mortality, re-hospitalization and institutionalization. Because we are using multiple drugs that were originally evaluated and licensed in the frame of RCT of single drugs for single ailments, it is imperative to develop designs of new pragmatic trials, involving patients randomized to drug combinations chosen more rationally than hitherto, for instance in relation to disease clusters [34, 35]. Other research approaches in this population are to implement new designs of drug studies, such as network analysis, N-of-1 trials, narrative medicine and systems medicine.

Conclusions

We envisage REPOSI as a permanent observatory on multimorbidity and polypharmacy in the elderly, with the main goal being to improve prescription appropriateness and, thus, to avoid potentially inappropriate medications. This goal should be pursued by means of medication reconciliation, with regular reviews of the list of drugs and deprescribing those that are useless, dangerous or inappropriate when the life expectancy of the oldest patients is considered. The

huge available database of REPOSI is a still poorly explored source of information. We emphasize that the database is being made available and shared with those who are contributing to data collection, and are willing to test their own scientific projects, provided these are compatible and feasible with the available limited dataset. Finally, we point out that REPOSI is a rather unique endeavor, but with the limitation of depicting the situation of one European country only. We believe that similar registries should be considered in the frame of Internal Medicine settings in other countries, with the obvious advantage of accruing real-life data on the growing population of older patients.

Acknowledgements We would like to Silvio Garattini, the director of the IRCCS Mario Negri Institute, the 2008–2018 presidents of the Italian Society of Internal Medicine (Giuseppe Licata, Francesco Violi, Roberto Corazza, Francesco Perticone), the Scientific Director of the IRCCS Ca’ Granda Maggiore Policlinico Hospital Foundation Silvano Bosari and, importantly, the physicians of the Italian hospital wards who did participate in REPOSI). Collaborators and co-authors of the REPOSI (REGistro POLiterapie SIMI, Società Italiana di Medicina Interna) Study Group are as follows: Steering Committee: Pier Mannuccio Mannucci (Chair, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano), Alessandro Nobili (co-chair, IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano), Mauro Tettamanti, Luca Pasina, Carlotta Franchi (IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano), Salvatore Corrao (ARNAS Civico, Di Cristina, Benfratelli, DiBiMIS, Università di Palermo, Palermo), Alessandra Marengoni (Spedali Civili di Brescia, Brescia), Francesco Salerno (IRCCS Policlinico San Donato Milanese, Milano), Matteo Cesari (UO Geriatria, Università degli Studi di Milano), Francesco Perticone (Presidente SIMI), Giuseppe Licata (Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Medicina Interna e Cardioangiologia), Francesco Violi (Policlinico Umberto I, Roma, Prima Clinica Medica), Gino Roberto Corazza, (Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I). Clinical data monitoring and revision: Carlotta Franchi, Laura Cortesi (IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano). Database Management and Statistics: Mauro Tettamanti, Laura Cortesi, Ilaria Ardoino (IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano). Investigators: Italian Hospitals: Domenico Prisco, Elena Silvestri, Caterina Cenci, Giacomo Emmi (Azienda Ospedaliera Universitaria Careggi Firenze, Medicina Interna Interdisciplinare); Gianni Biolo, Michela Zanetti, Martina Guadagni, Michele Zaccari (Azienda Sanitaria Universitaria Integrata di Trieste, Clinica Medica Generale e Terapia Medica); Massimo Vanoli, Giulia Grignani, Edoardo Alessandro Pulixi (Azienda Ospedaliera della Provincia di Lecco, Ospedale di Merate, Lecco, Medicina Interna); Mauro Bernardi, Silvia Li Bassi, Luca Santi, Giacomo Zaccherini (Azienda Ospedaliera Policlinico Sant’Orsola-Malpighi, Bologna, Semeiotica Medica Bernardi); Elmo Mannarino, Graziana Lupattelli, Vanessa Bianconi, Francesco Paciullo (Azienda Ospedaliera Santa Maria della Misericordia, Perugia, Medicina Interna); Ranuccio Nuti, Roberto Valenti, Martina Ruvio, Silvia Cappelli, Alberto Palazzuoli (Azienda Ospedaliera Università Senese, Siena, Medicina Interna I); Oliviero Olivieri, Domenico Girelli, Thomas Matteazzi (Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Medicina Generale a indirizzo Immuno-Ematologico e Emocoagulativo); Mario Barbagallo, Ligia Dominguez, Floriana Cocita, Vincenza Beneduce, Lidia Plances (Azienda Ospedaliera Universitaria Policlinico Giaccone Policlinico di Palermo, Palermo, Unità Operativa di Geriatria e Lungodegenza); Marco Zoli, Ilaria Lazzari, Mattia Brunori (Azienda Ospedaliera Universitaria Policlinico S. Orsola-Malpighi, Bologna, Unità Operativa di

Medicina Interna); Franco Laghi Pasini, Pier Leopoldo Capecci, (Azienda Ospedaliera Universitaria Senese, Siena, Unità Operativa Complessa Medicina 2); Giuseppe Palasciano, Maria Ester Modeo, Carla Di Gennaro (Azienda Ospedaliero-Universitaria Consorziata Policlinico di Bari, Bari, Medicina Interna Ospedaliera “L. D’Agostino”, Medicina Interna Universitaria “A. Murri”); Maria Domenica Cappellini, Diletta Maira, Valeria Di Stefano, Giovanna Fabio, Sonia Seghezzi, Marta Mancarella (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Unità Operativa Medicina Interna IA); Matteo Cesari, Paolo Dionigi Rossi, Sarah Damanti, Marta Clerici, Federica Conti (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Geriatria); Gino Roberto Corazza, Emanuela Miceli, Marco Vincenzo Lenti, Martina Pisati, Costanza Caccia Dominioni (Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I); Giovanni Murialdo, Alessio Marra, Federico Cattaneo (IRCS Azienda Ospedaliera Universitaria San Martino-IST di Genova, Genova, Clinica di Medicina Interna 2); Maria Beatrice Secchi, Davide Ghelfi (Ospedale Bassini di Cinisello Balsamo, Milano, Divisione Medicina); Luigi Anastasio, Lucia Sofia, Maria Carbone (Ospedale Civile Jazzolino di Vibo Valentia, Vibo Valentia, Medicina interna); Francesco Cipollone, Maria Teresa Guagnano, Ermanno Angelucci, Emanuele Valeriani (Ospedale Clinicizzato SS. Annunziata, Chieti, Clinica Medica); Gerardo Mancuso, Daniela Calipari, Mosè Bartone (Ospedale Giovanni Paolo II Lamezia Terme, Catanzaro, Unità Operativa Complessa Medicina Interna); Giuseppe Delitala, Maria Berria (Azienda ospedaliero-universitaria di Sassari, Clinica Medica); Maurizio Muscaritoli, Alessio Molfino, Enrico Petrillo (Policlinico Umberto I, Sapienza Università di Roma, Medicina Interna e Nutrizione Clinica Policlinico Umberto I); Giuseppe Zuccalà, Gabriella D’Aurizio (Policlinico Universitario A. Gemelli, Roma, Roma, Unità Operativa Complessa Medicina d’Urgenza e Pronto Soccorso). Giuseppe Romanelli, Alessandra Marengoni, Alberto Zucchelli (Spedali Civili di Brescia, Brescia, Geriatria); Antonio Picardi, Umberto Vespasiani Gentilucci, Paolo Gallo, Chiara Dell’Unto (Università Campus Bio-Medico, Roma, Medicina Clinica-Epatologia); Giorgio Annoni, Maurizio Corsi, Giuseppe Bellelli, Sara Zazzetta, Paolo Mazzola, Hajnalka Szabo, Alessandra Bonfanti (Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza, Unità Operativa di Geriatria); Franco Arturi, Elena Succurro, Mariangela Rubino (Università degli Studi Magna Grecia, Policlinico Mater Domini, Catanzaro, Unità Operativa Complessa di Medicina Interna); Maria Grazia Serra, Maria Antonietta Bleve (Azienda Ospedaliera “Cardinale Panico” Tricase, Lecce, Unità Operativa Complessa Medicina); Laura Gasbarrone, Maria Rosaria Sajeva (Azienda Ospedaliera Ospedale San Camillo Forlanini, Roma, Medicina Interna I); Antonio Bruccato, Silvia Ghidoni (Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Medicina I); Fabrizio Fabris, Irene Bertozzi, Giulia Bogoni, Maria Victoria Rabuini, Elisabetta Così (Azienda Ospedaliera Università di Padova, Padova, Clinica Medica I); Roberto Manfredini, Fabio Fabbian, Benedetta Boari, Alfredo De Giorgi, Ruana Tiseo (Azienda Ospedaliero—Universitaria Sant’Anna, Ferrara, Unità Operativa Clinica Medica); Giuseppe Paolisso, Maria Rosaria Rizzo, (Azienda Ospedaliera Universitaria della Seconda Università degli Studi di Napoli, Napoli, VI Divisione di Medicina Interna e Malattie Nutrizionali dell’Invecchiamento); Claudio Borghi, Enrico Strocchi, Valeria De Sando, Ilenia Pareo (Azienda Ospedaliera Universitaria Policlinico S. Orsola-Malpighi, Bologna, Unità Operativa di Medicina Interna Borghi); Carlo Sabbà, Francesco Saverio Vella, Patrizia Suppressa, Pasquale Agosti, Andrea Schilardi, Francesca Loparco (Azienda Ospedaliero-Universitaria Consorziata Policlinico di Bari, Bari, Medicina Interna Universitaria C. Frugoni); Luigi Fenoglio, Christian Bracco, Alessia Valentina Giraudo (Azienda Sanitaria Ospedaliera Santa Croce e Carle di Cuneo, Cuneo, S. C. Medicina Interna); Silvia Fargion, Giulia Periti, Marianna Porzio, Slivia Tiraboschi (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna 1B); Flora Peyvandi, Raffaella Rossio, Barbara Ferrari, Giulia Colombo

(Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna 2); Valter Monzani, Valeria Savojardo, Christian Folli, Giuliana Ceriani (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna Alta Intensità); Francesco Salerno, Giada Pallini (IRCCS Policlinico San Donato e Università di Milano, San Donato Milanese, Medicina Interna); Franco Dallegri, Luciano Ottonello, Luca Liberale, Lara Caserza, Kassem Salam (Università di Genova, Genova, Medicina Interna I); Nicola Lucio Liberato, Tiziana Tognin (ASST di Pavia, UOSD Medicina Interna, Ospedale di Casorate Primo, Pavia); Giovanni Battista Bianchi, Sabrina Giaquinto (Ospedale “SS Gerosa e Capitanio” di Lovere, Bergamo, Unità Operativa Complessa di Medicina Generale, Azienda Ospedaliera “Bolognini” di Seriate, Bergamo); Francesco Purrello, Antonino Di Pino, Salvatore Piro (Ospedale Garibaldi Nesima, Catania, Unità Operativa Complessa di Medicina Interna); Renzo Rozzini, Lina Falanga, Elena Spazzini, Camillo Ferrandina (Ospedale Poliambulanza, Brescia, Medicina Interna e Geriatria); Giuseppe Montrucchio, Paolo Petitti (Dipartimento di Scienze Mediche, Università di Torino, Città della Scienza e della Salute, Torino, Medicina Interna 2 U. Indirizzo d’Urgenza); Raffaella Salmi, Piergiorgio Gaudenzi (Azienda Ospedaliero-Universitaria S. Anna, Ferrara, Unità Operativa di Medicina Ospedaliera II); Francesco Violi, Ludovica Perri (Policlinico Umberto I, Roma, Prima Clinica Medica); Raffaele Landolfi, Massimo Montalto, Antonio Mirijello (Policlinico Universitario A. Gemelli, Roma, Clinica Medica); Luigina Guasti, Luana Castiglioni, Andrea Maresca, Alessandro Squizzato, Marta Molaro, Alessandra Grossi (Università degli Studi dell’Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Medicina Interna I); Marco Bertolotti, Chiara Mussi, Maria Vittoria Libbra, Giulia Dondi, Elisa Pellegrini, Lucia Carulli (Università di Modena e Reggio Emilia, AUSL di Modena, Modena, Nuovo Ospedale Civile, Unità Operativa di Geriatria e U.O. di Medicina a indirizzo Metabolico Nutrizionistico); Francesco Peticone, Lidia Colangelo, Tania Falbo (Università Magna Grecia Policlinico Mater Domini, Catanzaro, Unità Operativa Malattie Cardiovascolari Geriatriche); Vincenzo Stanghellini, Roberto De Giorgio, Eugenio Ruggeri, Sara del Vecchio (Dipartimento di Scienze Mediche e Chirurgiche, Unità Operativa di Medicina Interna, Università degli Studi di Bologna/Azienda Ospedaliero-Universitaria S.Orsola-Malpighi, Bologna); Andrea Salvi, Roberto Leonardi, Giampaolo Damiani (Spedali Civili di Brescia, U.O. 3a Medicina Generale); Armando Gabrielli, William Capeci, Massimo Mattioli, Giuseppe Pio Martino, Lorenzo Biondi, Pietro Pettinari (Clinica Medica, Azienda Ospedaliera Universitaria—Ospedali Riuniti di Ancona); Riccardo Ghio, Anna Dal Col (Azienda Ospedaliera Università San Martino, Genova, Medicina III); Salvatore Minisola, Luciano Colangelo (Policlinico Umberto I, Roma, Medicina Interna F e Malattie Metaboliche dell’osso); Antonella Afeltra, Benedetta Marigliano, Maria Elena Pipita (Policlinico Campus Biomedico Roma, Roma, Medicina Clinica); Pietro Castellino, Julien Blanco, Luca Zanoli, Samuele Pignataro (Azienda Ospedaliera Universitaria Policlinico—V. Emanuele, Catania, Dipartimento di Medicina); Valter Saracco, Marisa Fogliati, Carlo Bussolino (Ospedale Cardinal Massaia Asti, Medicina A); Francesca Mete, Miriam Gino (Ospedale degli Infermi di Rivoli, Torino, Medicina Interna). Antonio Cittadini, Carlo Vigorito, Michele Arcopinto, Andrea Salzano, Emanuele Bobbio, Alberto Maria Marra, Domenico Sirico (Azienda Policlinico Universitario Federico II di Napoli, Napoli, Medicina Interna e Riabilitazione Cardiologica); Guido Moreo, Francesca Gasparini, Silvia Prolo, Gloria Pina (Clinica San Carlo Casa di Cura Polispecialistica, Paderno Dugnano, Milano, Unità Operativa di Medicina Interna); Alberto Ballestrero, Fabio Ferrando (Clinica Di Medicina Interna ad Indirizzo Oncologico, Azienda Ospedaliera Università San Martino di Genova); Sergio Berra, Simonetta Dassi, Maria Cristina Nava (Medicina Interna, Azienda Ospedaliera Guido Salvini, Garnagnate, Milano); Bruno Graziella, Stefano Baldassarre, Salvatore Fragapani, Gabriella Gruden (Medicina Interna III, Ospedale S. Giovanni Battista Molinette, Torino); Giorgio Galanti, Gabriele Mascherini, Cristian Petri, Laura Stefani (Agenzia di

Medicina dello Sport, AOUC Careggi, Firenze); Margherita Girino, Valeria Piccinelli (Medicina Interna, Ospedale S. Spirito Casale Monferrato, Alessandria); Francesco Nasso, Vincenza Gioffrè, Maria Pasquale (Struttura Operativa Complessa di Medicina Interna, Ospedale Santa Maria degli Ungheresi, Reggio Calabria); Giuseppe Scattolin, Sergio Martinelli, Mauro Turrin (Medicina Interna, Ospedale di Monselice, Padova); Leonardo Sechi, Cristina Catena, Gianluca Colussi (Clinica Medica, Azienda Ospedaliera Universitaria, Udine). Nicola Passariello, Luca Rinaldi (Presidio Medico di Marciacise, Napoli, Medicina Interna); Franco Berti, Giuseppe Famularo, Tarsitani Patrizia (Azienda Ospedaliera San Camillo Forlanini, Roma, Medicina Interna II); Roberto Castello, Michela Pasino (Ospedale Civile Maggiore Borgo Trento, Verona, Medicina Generale e Sezione di Decisione Clinica); Gian Paolo Ceda, Marcello Giuseppe Maggio, Simonetta Morganti, Andrea Artoni (Azienda Ospedaliera Universitaria di Parma, U.O.C Clinica Geriatrica); Stefano Del Giacco, Davide Firinu, Francesca Losa, Giovanni Paoletti (Policlinico Universitario Dulio Casula, Azienda Ospedaliero-Universitaria di Cagliari, Cagliari, Medicina Interna, Allergologia ed Immunologia Clinica); Giuseppe Montalto, Anna Licata, Valentina Malerba (Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, U.O.S Prevenzione Malattie Epato biliari); Lasco Antonino, Giorgio Basile, Catalano Antonino (Azienda Ospedaliera Universitaria Policlinico G. Martino, Messina, Unità Operativa di Geriatria); Lorenzo Malatino, Benedetta Stancanelli, Valentina Terranova, Salvatore Di Marca (Azienda Ospedaliera per l’Emergenza Cannizzaro, Catania, (Clinica Medica Università di Catania); Patrizia Mecocci, Carmelinda Ruggiero, Virginia Boccardi (Università degli Studi di Perugia-Azienda Ospedaliera S.M. della Misericordia, Perugia, Struttura Complessa di Geriatria); Tiziana Meschi, Fulvio Lauretani, Andrea Ticinesi (Azienda Ospedaliera Universitaria di Parma, U.O Medicina Interna e Lungodegenza Critica); Pietro Minuz, Luigi Fondrieschi (Azienda Ospedaliera Universitaria Verona, Policlinico GB Rossi, Verona, Medicina Generale per lo Studio ed il Trattamento dell’Ipertensione Arteriosa); Mario Pirisi, Gian Paolo Fra, Daniele Sola (Azienda Ospedaliera Universitaria Maggiore della Carità, Medicina Interna 1); Massimo Porta, Piero Riva (Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Medicina Interna IU); Roberto Quadri (Ospedale di Ciriè, ASL TO4, Torino, S.C. Medicina Interna); Giorgio Scanzi, Caterina Mengoli, Stella Provini, Laura Ricevuti (ASST Lodi, Presidio di Codogno, Milano, Medicina); Emilio Simeone, Rosa Scurti, Fabio Tolloso (Ospedale Spirito Santo di Pescara, Geriatria); Roberto Tarquini, Alice Valoriani, Silvia Dolenti, Giulia Vannini (Ospedale San Giuseppe, Empoli, USL Toscana Centro, Firenze, Medicina Interna I); Alberto Tedeschi, Lucia Trotta (ASST Fatebenefratelli—Sacco, Milano, Medicina Interna a indirizzo Pneumologico); Riccardo Volpi, Pietro Bocchi, Alessandro Vignali (Azienda Ospedaliera Universitaria di Parma, Clinica e Terapia Medica). Sergio Harari, Chiara Lonati, Mara Cattaneo (Ospedale San Giuseppe Multimedita Spa, U.O. Medicina Generale). Ramirez Duque Nieves (Hospital Universitario Virgen del Rocío, Sevilla); Muela Molinero Alberto (Hospital de Leon); Abad Requejo Pedro, Lopez Pelaez Vanessa, Tamargo Lara (Hospital del Oriente de Asturias, Arriendas); Corbella Viros Xavier, Formiga Francesc (Hospital Universitario de Bellvitge); Diez Manglano Jesus, Bejarano Tello Esperanza, Del Corral Behamonte Esther, Sevil Puras Maria (Hospital Rojo Villanova, Zaragoza); Manuel Romero (Hospital Infanta Elena Huelva); Pinilla Llorente Blanca, Lopez Gonzalez-Cobos Cristina, Villalba Garcia M. Victoria (Hospital Gregorio Marañon Madrid); Lopez Saez, Juan Bosco (Hospital Universitario de Puerto Real, Cadiz); Sanz Baena Susana, Arroyo Gallego Marta (Hospital Del Henares De Coslada, Madrid); Gonzalez Becerra Concepcion, Fernandez Moyano Antonio, Mercedes Gomez Hernandez, Manuel Payoto Borrego (Hospital San Juan De Dios Del Aljarafe, Sevilla); Pacheco Cuadros Raquel, Perez Rojas Florencia, Garcia Olid Beatriz, Carrascosa Garcia Sara (Hospital Virgen De La Torre De Madrid); Gonzalez-Cruz Cervellera Alfonso, Peinado Martinez Marta, Sara Carrascosa

Garcia (Hospital General Universitario De Valencia); Ruiz Cantero Alberto, Albarracín Arraigosa Antonio, Godoy Guerrero Montserrat, Barón Ramos Miguel Ángel (Hospital De La Serrania De Ronda); Machin Jose Manuel (Hospital Universitario De Guadalajara); Novo Veleiro Ignacio, Alveta Suarez Lucia (Hospital Universitario De Santiago De Compostela); Lopez Alfonso, Rubal Bran David, Iñiguez Vazquez Iria (Hospital Lucus Augusti De Lugo); Rios Prego Monica (Hospital Universitario De Pontevedra).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Statement of human and animal rights REPOSI was accepted by the ethical committees of all participant hospitals.

Informed consent Each patient supplied informed consent.

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