Clinical Interventions in Aging

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ORIGINAL RESEARCH

Inappropriate pharmacological treatment in older adults affected by cardiovascular disease and other chronic comorbidities: a systematic literature review to identify potentially inappropriate prescription indicators

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
19 October 2017
Number of times this article has been viewed

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Abstract: Avoiding medications in which the risks outweigh the benefits in the elderly patient is a challenge for physicians, and different criteria to identify inappropriate prescription (IP) exist to aid prescribers. Definition of IP indicators in the Italian geriatric population affected by cardiovascular disease and chronic comorbidities could be extremely useful for prescribers and could offer advantages from a public health perspective. The purpose of the present study was to identify IP indicators by means of a systematic literature review coupled with consensus criteria. A systematic search of PubMed, EMBASE, and CENTRAL databases was conducted, with the search structured around four themes and combining each with the Boolean operator "and". The first regarded "prescriptions", the second "adverse events", the third "cardiovascular conditions", and the last was planned to identify studies on "older people". Two investigators independently reviewed titles, abstracts, full texts, and selected articles addressing IP in the elderly affected by cardiovascular condition using the following inclusion criteria: studies on people aged ≥65 years; studies on patients with no restriction on age but with data on subjects aged ≥65 years; and observational effectiveness studies. The database searches produced 5,742 citations. After removing duplicates, titles and abstracts of 3,880 records were reviewed, and 374 full texts were retrieved that met inclusion criteria. Thus, 49 studies reporting 32 potential IP indicators were included in the study. IP indicators regarded mainly drug–drug interactions, cardio- and cerebrovascular risk, bleeding risk, and gastrointestinal risk; among them, only 19 included at least one study that showed significant results, triggering a potential warning for a specific drug or class of drugs in a specific context. This systematic review demonstrates that both cardiovascular and non-cardiovascular drugs increase the risk of adverse drug reactions in older adults with cardiovascular diseases.

Keywords: inappropriate prescriptions, elderly, cardiovascular diseases, chronic diseases, systematic review

Introduction

The world population is aging at a rapid rate, in high- and low-income countries, challenging health care services from both the organizational and the economic point of view. Throughout the world, the number of people over 60 years doubled in the last century and in Europe, for example, the share of older population is expected to peak at up to 30% by 2050.[1] Such epidemiological transition drives the pressing

burden of the increasing prevalence of chronic diseases in this age group.[2] In addition to the complexities related to the clinical management of older people suffering from multiple chronic diseases, one of the challenges physicians are facing is the consequent complication of complex pharmacological regimens.

Even if the potential benefits of pharmacological therapy are unquestionable, the hazards of negative drug-related outcomes often raise relevant concerns in older adults. Polypharmacy increases the risk of drug–drug and drug–disease interactions, and age-related changes in several physiological characteristics, as well as the presence of chronic illnesses (eg, chronic kidney or liver disease), may affect drugs' pharmacokinetics and pharmacodynamics. Such issues potentially increase the risk of adverse drug reactions (ADRs) and explain the significant excess of morbidity, mortality rate, and health care costs within the older population.

In this context, what constitutes an appropriate or inappropriate prescription (IP) in the context of the geriatric population is still debated. Indeed, in order to identify inappropriate pharmacological prescriptions, different criteria have been proposed in recent years. The best known are the Beers criteria,[3] the Screening Tool of Older People's Prescriptions (STOPP), Screening Tool to Alert to Right Treatment (START),[4] as well as the Medication Appropriateness Index (MAI),[5] and the Assessing Care of Vulnerable Elderly (ACOVE)[6] criteria. These criteria and tools are based on expert consensus and are not specifically tailored to any particular disease, even though stroke, myocardial infarction (MI), and other cardiovascular disorders constitute the most frequently treated clinical conditions by physicians in Western countries. Moreover, their impact has not been exhaustively validated toward "hard" end points, and they do not comprise an accurate selection and validation process of drug–drug interactions in light of overlying comorbidities.

Thus, the definition of IP indicators for older adults affected by cardiovascular disease and chronic comorbidities could be extremely useful for the prescriber and might offer advantages from a public health perspective. The aim of the present review was to identify and suggest to the scientific community a list of potential indicators for older adults suffering from cardiovascular diseases and other chronic comorbidities, to be subsequently validated in an ad hoc selected population sample, and eventually proposed as IP indicators. More specifically, we identified all the studies reporting a suspect of drug-related harm in the context of multimorbid older adults suffering from cardiovascular diseases and clustered them according to homogenous groups.

Cardiovascular diseases are defined according to the World Health Organization as

> a group of disorders of the heart and blood vessels and include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism.[60]

Methods

We performed this systematic review in keeping with the *Cochrane Handbook for Systematic Reviews* and reported the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol was registered a priori on PROSPERO (N CRD42017057795).

Data source and search strategy

We conducted a systematic search of PubMed, EMBASE, and CENTRAL databases up to October 2, 2014. A librarian (ZM) structured the search on free text and MESH terms with regard to four different domains: "prescriptions", "adverse events", "cardiovascular conditions", and "older people".

The PubMed search was ((“Drug Prescriptions”[MeSH] OR “Drug Utilization”[MeSH] OR “Adverse Drug Reactions”[tiab] OR “adverse drug events”[tiab] OR “drug safety”[tiab] OR “drug-drug interactions” OR ADRs[tiab] OR “Drug Interactions”[MeSH] OR ((inappropriate*[tiab] OR incorrect*[tiab] OR excess*[tiab] OR harmful*[tiab]) AND (medici*[tiab] OR prescrib*[tiab] OR prescription*[tiab] OR drug*[tiab] OR refill*[tiab] OR claim*[tiab])) OR “Drug-Related Side Effects and Adverse Reactions”[Mesh] OR ((“drug induced”[tiab] OR medication*[ti] OR prescription*[tiab]) AND (“adverse effects” [Subheading:NoExp] OR “adverse effects”[tiab] OR “adverse events”[tiab] OR mortality[sh])))) AND (“Cardiovascular Diseases”[Mesh:noexp] OR “Stroke”[MeSH] OR “Arrhythmias, Cardiac”[MeSH] OR “Hypertension”[MeSH] OR “Heart Diseases”[MeSH] OR “Brain Ischemia”[MeSH] OR “Brain Infarction”[MeSH] OR “Myocardial Ischemia”[MeSH] OR “Peripheral Arterial Disease”[MeSH] OR “Angina Pectoris”[MeSH] OR cardiovascular[tiab] OR “heart disease”[tiab] OR “heart diseases”[tiab] OR “coronary disease”[tiab] OR “coronary diseases”[tiab] OR “heart failure”[tiab] OR “cardiac failure”[tiab] OR “all cause mortality” OR cerebrovascular[tiab])) AND (Aged[Mesh] OR “old people”[tiab] OR “older people”[tiab] OR “old age”[tiab] OR “older age”[tiab] OR “older person”[tiab] OR “old person”[tiab] OR geriatric*[tiab] OR elder*[tiab] OR senior*[tiab]).

Identical searches were conducted in EMBASE and CENTRAL databases.

Study selection

Two trained investigators (NL and DLV) independently reviewed titles and abstracts, and excluded papers using the following criteria:

1. Studies published in languages other than English
2. Studies on pediatric population
3. Studies regarding exposures other than drugs
4. Studies on diseases other than cardiovascular ones (eg, patients with cancer without cardiovascular disease, with Parkinson without cardiovascular disease, and with diabetes without cardiovascular disease)
5. Non-outcome studies.

The same investigators independently reviewed full texts and selected articles addressing inappropriate prescribing in elderly patients affected by cardiovascular condition using the following inclusion criteria:

1. Studies on people aged ≥65 years
2. Studies on patients with no restriction of age but with data on subjects aged ≥65 years
3. Observational effectiveness studies.

We resolved disagreement by discussion and consensus with a third trained assessor (DLC). Additionally, we reviewed the reference lists of the included studies and previous reviews to identify additional papers that met inclusion criteria.

Data extraction and quality assessment

For each selected study, we extracted the following data: year of publication, study design, drugs, outcomes, country and setting, characteristic of the study population (eg, sample size, age, and gender), information on follow-up, and main results (ie., estimated with corresponding confidence intervals for each outcome) and additional results.

Two investigators (NL and DLC) independently assessed the methodological quality of included studies using the Newcastle–Ottawa Scale (NOS)[7] for case–control and cohort study, the scale proposed by Jadad et al for randomized controlled trials,[8] and the following criteria for case-crossover studies and self-controlled case series:

1. Clearly stated aims
2. Appropriate methods are used
3. Well constituted context of the study
4. Clearly described, valid, and reliable results
5. Clearly described analysis
6. Possible influences of the outcome are considered
7. Conclusion is linked to the aim, analysis, and interpretation of results of the study
8. Limitations on research are identified.

Results

The PRISMA flow diagram of study selection is shown in Figure 1. The database search produced 5,742 citations. After removal of duplicates, we reviewed titles and abstracts of 3880 records, among which 374 met the inclusion criteria and the corresponding full texts were retrieved and reviewed. Subsequently, 325 studies were removed because they did not present analysis for patients aged ≥65 years (258 papers) and had inappropriate study design (50), or for other reasons (6 were not original studies, 4 were on patients without cardiovascular disease, 2 with no safety outcomes, 2 with efficacy outcomes only, 2 were duplicate publications, and 1 was on exposure other than drug).

Supplementary material reports the characteristics of the 49 selected studies grouped according to 32 homogeneous potential IP indicators.[9–57] Briefly, among the selected studies,

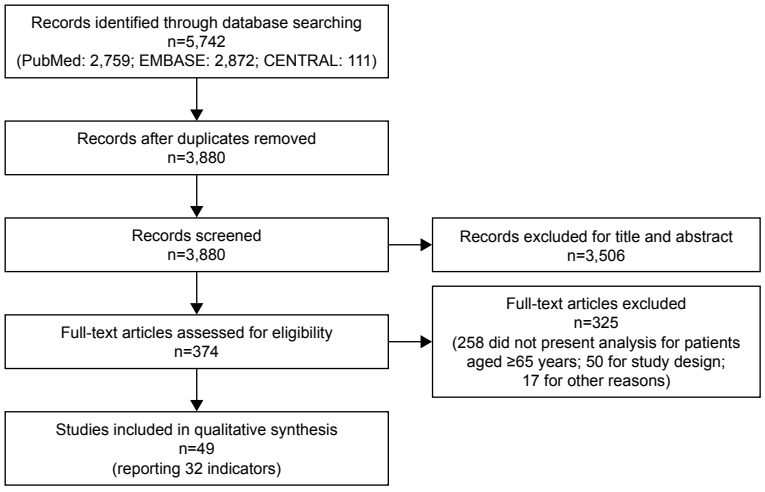

Figure 1 PRISMA flow diagram.

two investigated bisphosphonates; seven investigated statins alone or in combination with ezetimibe and their interactions with other pharmacological agents (clopidogrel, vitamin K antagonists, and macrolides); eight investigated antipsychotics; one investigated long-acting beta-adrenoceptor agonist (LABAs) and long-acting anticholinergic drugs (LAAs); four regarded antidiabetics; one was on aspirin in association with clopidogrel and enoxaparin; two regarded anticholinergic drugs; one was on donepezil and its interactions with the antibacterial clarithromycin; two regarded calcium channel blockers (CCBs; short-acting nifedipine) and their interaction with Cytochrome P450 3A4 (CYP3A4) inhibitors; four regarded clopidogrel and its interactions with proton-pump inhibitors (PPIs); three regarded nonsteroidal anti-inflammatory drugs (NSAID); four regarded oral anticoagulants (OACs); one regarded postmenopausal hormones; one was on opioids; one investigated angiotensin-converting-enzyme (ACE) inhibitors; four investigated antidepressants; one investigated cholinesterase inhibitors; one was on benzodiazepines and benzodiazepine-related drugs; and one investigated the angiotensin receptor blocker olmesartan alone or in combination with other antihypertensive drugs.

Among the 32 homogeneous potential IP indicators, only 19 included at least one study that showed significant and direct association with adverse events (Table 1).

In greater detail, the potentially identified IP indicators were:

1. Anticholinergics (No 1) were associated with cardiac arrhythmia, constipation, delirium, emergency visit, and hospitalization.
2. Anticholinergics in cardiovascular patients (No 2) were associated with hospitalization.
3. Antidepressants (No 3) were associated with attempted suicide/self-harm, epilepsy seizures, falls, fractures, hyponatremia, MI, mortality, stroke/transient ischaemic attack, upper gastrointestinal bleeding, and ventricular arrhythmia.
4. Antidepressants in coronary artery disease (CAD) patients (No 4) were associated with cerebrovascular events.
5. Antidiabetics (No 5) were associated with acute MI, atherosclerotic vascular heart disease, congestive heart failure (HF), and mortality.
6. Antidiabetics in end-stage renal disease or disabled patients (No 6) were associated with HF, mortality, and stroke.
7. Typical antipsychotics (No 7) were associated with cardiovascular death, cerebrovascular events, nervous system disorders, non-cancer death, respiratory disorders, and stroke. Atypical antipsychotics were also associated with mortality and MI.
8. Typical antipsychotics in dementia patients (No 8) were associated with mortality, and MI.
9. Bisphosphonates in fracture patients (No 12) were associated with atrial fibrillation (AF).
10. CCBs in hypertensive patients (No 15) were associated with stroke.
11. Cholinesterase inhibitors in dementia patients (No 16) were associated with bradycardia, hip fractures, permanent pacemaker insertion, and syncope.
12. Clopidogrel + PPIs (No 17) were associated with MI, major cardiovascular events, and/or all-cause mortality.
13. LABA and LAA in chronic obstructive pulmonary disease (COPD) patients (No 19) were associate with acute coronary syndrome and HF. LAA were also associated with cardiac arrhythmia.
14. NSAIDs (No 21) were associated with mortality following upper gastrointestinal events, MI and cerebrovascular events, stroke, acute MI or stroke, or death from coronary heart disease.
15. OACs in CAD patients (No 23) were associated with embolic and hemorrhagic events, gastrointestinal injuries, and mortality.
16. Opioids (No 25) were associated with MI.
17. Statins + Macrolides (No 28) were associated with acute kidney injury, mortality, and rhabdomyolysis.
18. Statins in COPD patients (No 30) were associated with mortality.
19. Warfarin + potentially interacting drugs (No 32) were associated with bleeding.

Studies had a good quality (NOS: 9 or 8/9, quality assessment: 7 or 8/8, Jadad: 4/5) in 14 out of 49 cases (29%), moderate (NOS: 7 or 6/9) in 30 cases (61%), and low (NOS: $<$6/9) in 5 cases (10%).

Discussion

The present systematic review led to the selection of 32 groups of studies indicating potential drug-related harm in older people with cardiovascular diseases. Among them, only 19 included at least one study that showed significant and direct association with adverse events, triggering a potential warning for a specific drug or class of drugs in a specific context. According to the authors of the present review, these 19 groups can be deemed as potential indicators of IP in multimorbid older adults affected by cardiovascular diseases.

The optimization of pharmacological therapy is an essential part of the process of care for an older person. In the past 20 years, several expert panels in Canada, the USA, and Europe have developed different sets of criteria useful

Table 1 Selected characteristics of the 49 articles included in the review based on 32 IP indicators

First author (country, data source) (quality assessment)	Study design	Outcomes	Characteristics of the population	
			Sample size	Estimates (95% CI)
Anticholinergics (no 1)				
Huang et al[25] (China, Longitudinal Health Insurance database of the National Health Insurance Research Database) (NOS 8/9)	Retrospective cohort study Population: elder people aged >65 Exposure: Potentially inappropriate anticholinergics vs no-potentially inappropriate one (the Anticholinergic Risk Scale was the criterion)	(1) Emergency visit (2) Hospitalization (3) Constipation (4) Delirium (5) Cardiac arrhythmia (6) Cognitive impairment	54,888 vs 17,668	(1) 1.85 (1.76–1.95) (2) 1.07 (1.01–1.13) (3) 1.87 (1.72–2.03) (4) 1.51 (1.18–1.93) (5) 1.16 (1.05–1.28)
In cardiovascular patients (no 2)				
Uusvaara et al[50] (Finland, ad hoc data of previous RCT) (NOS 6/9)	Prospective cohort study Population: home-dwelling individuals aged 75–90 years with diagnosis of CardioV disease Exposure: patients users of anticholinergic drugs vs nonusers	(1) Hospitalization (2) Mortality	295 vs 105	(1) 2.08 (1.23–3.51)
Antidepressants (no 3)				
Blanchette et al[12] (USA, Medicare Current Beneficiary Survey) (NOS 8/9)	Historical pooled cohort Population: community residents who are ≥65 years Exposure: users of antidepressant (SSRIs or other) vs nonusers	Acute MI	1,814 vs 10,856 (1,052 SSRI; 762 others)	For SSRI: 1.85 (1.13–3.00)
Coupland et al[15] (UK, supplying data to the QResearch primary care database) (NOS 8/9)	Cohort study Population: patients with a diagnosis of depression and between the ages of 65 and 100 years Exposure: antidepressants users (TCA, SSRI, others) vs nonusers	(1) All-cause mortality (2) Attempted suicide/self-harm (3) MI (4) Stroke/transient ischaemic attack (5) Falls (6) Fractures (7) Upper gatrointestinal bleeding (8) Epilepsy/seizures (9) Road traffic accidents (10) ADRs (11) Hyponatraemia	54,038 vs 6,708 (TCA 21,043; SSRI 29,763; others 3,060)	For TCA: (1) 1.16 (1.10–1.22) (2) 1.70 (1.28–2.25) (5) 1.30 (1.23–1.38) (6) 1.26 (1.16–1.37) (7) 1.29 (1.10–1.51) For SSRI: (1) 1.54 (1.48–1.59) (2) 2.16 (1.71–2.71) (3) 1.15 (1.04–1.27) (4) 1.17 (1.10–1.26) (5) 1.66 (1.58–1.73) (6) 1.58 (1.48–1.68) (7) 1.22 (1.07–1.40) (8) 1.83 (1.49–2.26) (11) 1.52 (1.33–1.75) For others: (1) 1.66 (1.56–1.77) (2) 5.16 (3.90–6.83) (4) 1.37 (1.22–1.55) (5) 1.39 (1.28–1.52)

(*Continued*)

Table 1 (*Continued*)

First author (country, data source) (quality assessment)	Study design	Outcomes	Characteristics of the population	
			Sample size	Estimates (95% CI)
				(6) 1.64 (1.46–1.84) (7) 1.37 (1.08–1.74) (8) 2.24 (1.60–3.15)
Zivin et al[57] (USA, Veterans Health Administration data) (NOS 7/9)	Cohort study Population: patients with a diagnosis of depression and at least one citalopram or sertraline prescription Exposure: users of citalopram vs users of sertraline	(1) Ventricular arrhythmia (2) All-cause mortality (3) Cardiac mortality (4) Non-cardiac mortality	618,450 vs 365,898 (patients 70–79 years: 71,187 vs 46,585; patients ≥80 years: 54,557 vs 33,487)	Among patients aged 70–79 years, For citalopram: (1) 5.52 (3.97–7.66) (2) 5.99 (5.30–6.77) (3) 28.60 (18.58–44.03) (4) 4.16 (3.66–4.73) For sertraline: (1) 2.99 (2.13–4.21); (2) 8.22 (6.89–9.82); (3) 23.06 (14.27–37.25); (4) 5.98 (4.94–7.24) Among patients aged ≥80 years, for citalopram: (1) 4.59 (3.28–6.41); (2) 9.96 (8.81–11.25); (3) 54.63 (35.50–84.05); (4) 6.38 (5.62–7.26) For sertraline: (1) 2.75 (1.94–3.90); (2) 13.57 (11.36–16.20); (3) 41.81 (25.88–67.54); (4) 9.33 (7.71–11.3)
In CAD patients (no 4)				
Wu et al[55] (Taiwan, National Health Insurance Research database) (Quality Assessment 8/9)	Case-crossover study Population: patients with a hospitalization for a primary diagnosis of CerebroV event Exposure: users of antipsychotics	Hospitalization for CerebroV events	24,214 (16,258 aged ≥65 years)	Among patients aged 65–75 years: 1.48 (1.30–1.68); Among patients aged ≥75 years: 1.56 (1.37–1.78)
Antidiabetics (no 5)				
Margolis et al[37] (UK, The Health Information Network THIN Data) (NOS 7/9)	Retrospective cohort study Population: patients with at least two records for diabetes and at least 40 years old Exposure: users of insulin or sulfonylureas or biguadine or meglitinide or thiazolidinediones or rosiglitazone or pioglitazone vs nonusers	Serious atherosclerotic vascular disease of the heart	63,579 (15,514 patients aged 70–80 years; 6,930 patients aged >80 years)	Among subjects aged 70–80 years: 3.3 (3.0–3.7) Among subjects aged >80 years: 2.8 (2.5–3.2)

Vanasse et al[51] (Canada, Québec's provincial hospital discharge register and Québec's provincial demographic database) (NOS 6/9)	Nested case-control study Population: diabetic patients aged ≥65 years Exposure: users of rosiglitazone	(1) All cause death (2) CV death (3) Hospitalization for acute MI (4) Hospitalization for congestive HF (5) Hospitalization for stroke	18,335 vs 370,866 4,455 vs 89,037 4,274 vs 85,480 4,274 vs 85,480 4,711 vs 94,209	(1) 0.87 (0.76–0.99) (3) 1.41 (1.21–1.65) (4) 1.94 (1.71–2.19)
Winkelmayer et al[54] (USA, New Jersey Pharmaceutical Assistance for the Aged and Disabled program and the Pennsylvania Pharmaceutical Assistance Contract for Elderly program) (NOS 6/9)	Inception cohort study Population: people >65 years with state-sponsored prescription drug benefits who had diabetes mellitus Exposure: patients initiated treatment with rosiglitazone vs pioglitazone	(1) All-cause mortality (2) MI (3) Stroke (4) Hospitalization for congestive HF	14,101 vs 14,260	(1) 1.15 (1.05–1.26) (4) 1.13 (1.01–1.26)
In end-stage renal disease or disabled patients (no 6)				
Graham et al[22] (USA, Medicare) (NOS 7/9)	Retrospective cohort study Population: patients aged ≥65 years who have end-stage renal disease or are disabled Exposure: new users of rosiglitazone vs new users of pioglitazone	(1) Acute MI (2) Stroke (3) HF (4) All-cause mortality (5) Composite end point of acute MI, stroke, HF or death	67,593 vs 159,978	(2) 1.27 (1.12–1.45) (3) 1.25 (1.16–1.34) (4) 1.14 (1.05–1.24) (5) 1.18 (1.12–1.23)
Antipsychotics (no 7)				
Franchi et al[17] (Italy, Drug Administration database of the Lombardy Region) (NOS 6/9)	Retrospective case-control study Population: community-dwelling elderly patients aged between 65 and 94 years Exposure: patients who were given at least two consecutive boxes of antipsychotics (any, typical, atypical)	Hospital discharge diagnosis of CerebroV events	3,855 vs 15,420 (13,805 patients aged ≥75 years)	For typical antipsychotics: 2.4 (1.08–5.5)
Gisev et al[21] (Finland, Finnish National Prescription Register and the Special Reimbursement Register) (NOS 8/9)	Retrospective cohort study Population: community-dwelling older adults (≥65 years) Exposure: users of antipsychotics vs nonusers	Mortality	139 vs 2,085	2.07 (1.73–2.47)
Pratt et al[42] (Australia, Australian Government Department of Veterans' Affairs administrative claims dataset) (Quality Assessment 8/8)	Self-controlled case series Population: elderly users of antipsychotics aged ≥65 years Exposure: users of antipsychotic vs nonusers	Hospitalization for stroke after (1) 1 week (2) 2–4 weeks (3) 5–8 weeks and (4) 8 or more weeks of treatment	514 typical, 564 atypical vs 9,560	For typical antipsychotics: (1) 2.25 (1.32–3.83) (3) 1.62 (1.14–2.32)

(*Continued*)

Table 1 (*Continued*)

First author (country, data source) (quality assessment)	Study design	Outcomes	Characteristics of the population	
			Sample size	Estimates (95% CI)
Setoguchi et al[48] (USA, General practice database) (NOS 6/9)	Cohort study Population: British Columbia residents aged ≥65 years who were new users of antipsychotics Exposure: new users of atypical antipsychotics agents vs users of conventional agents	(1) Overall non-cancer death (2) CardioV death (3) Out-of-hospital CardioV death (4) Infection (including pneumonia) (5) Respiratory disorders (excluding pneumonia) (6) Nervous system disorders (7) Mental disorders (8) Others disorders	24,359 vs 12,882	For typical antipsychotics: (1) 1.27 (1.18–1.37) (2) 1.23 (1.10–1.36) (3) 1.36 (1.19–1.56) (5) 1.71 (1.35–2.17) (6) 1.42 (1.01–1.86) (8) 1.27 (1.07–1.51)
Vasilyeva et al[52] (Canada, Manitoba Population Health Research Data Repository) (NOS 7/9)	Retrospective cohort study Population: residents in Manitoba aged ≥65 years treated with antipsychotics for the first time Exposure: users of first or second generation antipsychotics	(1) CerebroV events (2) MI (3) Cardiac arrhythmia (4) Congestive HF (5) Mortality	4,655 vs 7,779	For atypical antipsychotics: (2) 1.61 (1.02–2.54)
In dementia patients (no 8)				
Chan et al[14] (Japan, ad hoc data) (NOS 6/9)	Retrospective cohort study Population: patients with vascular and mixed dementia or Alzheimer disease aged ≥65 years Exposure: users of typical and atypical antipsychotic vs nonusers	CerebroV events	72 atypical, 654 typical vs 363 non-user	No association
Liperoti et al[33] (USA, Systematic Assessment of Geriatric drug use via Epidemiology database) (NOS 6/9)	Retrospective cohort study Population: nursing homes residents with dementia, aged ≥65 years, who were new users of antipsychotics Exposure: users of conventional antipsychotics vs users of atypical ones	All cause-mortality	6,524 vs 3,205	For typical antipsychotics: 1.26 (1.13–1.42)
Pariente et al[39] (Canada, Public prescription drug and medical services coverage programs databases) (NOS 7/9)	Retrospective cohort study Population: community-dwelling elderly (≥65 years) patients with dementia, who were new users of cholinesterase inhibitors Exposure: incident antipsychotic users vs antipsychotic nonusers	MI after (1) 30 days (2) 60 days (3) 90 days and (4) 365 days of treatment	10,969 vs 10,969 (17,532 patients aged ≥75 years)	(1) 2.19 (1.11–4.32)
Aspirin + clopidogrel + enoxaparin in NSTE-ACS patients (no 9)				
Heer et al[24] (Germany, Acute Coronary Syndromes Registry) (NOS 5/9)	Observational retrospective multicenter study Population: patients with NSTE-ACSs Exposure: users of aspirin + clopidogrel + enoxaparin vs users of aspirin + UFH	(1) Hospital mortality (2) Non-fatal reinfarction (3) Congestive HF (4) Stroke (5) CABG (6) MACE (7) All bleeding (8) Major bleeding	2,956 (128 vs 760 patients aged ≥75 years)	Among subjects aged ≥75 years: (6) 0.44 (0.20–0.96)

Atorvastatin + ezetimibe + OAC in AF patients (no 10)				
Enajat et al[16] (the Netherlands, ad hoc data) (Jadad 4/5)	Randomized double-blind clinical trial Population: patients aged between 69 and 85 years with chronic or paroxysmal AF with blood cholesterol levels between 4.5 and 7.0 mmol/L Exposure: users of OAC + atorvastatin 40 mg/day + ezetimibe 10 mg/day vs users of OAC + Placebo (target INR of 2.5–3.5)	Major and minor bleeding; intracerebral bleeding; change in median total cholesterol level and low-density lipoprotein cholesterol level	14 vs 17	No association
Benzodiazepines + benzodiazepines-related drugs (no 11)				
Gisev et al[20] (Finland, Finnish National Prescription Register) (NOS 8/9)	Population-based retrospective cohort study Population: community-dwelling people aged ≥65 years Exposure: users of benzodiazepine + benzodiazepine-related drugs (zoplicone and zolpidem) vs nonusers	Mortality	325 vs 1,520	No association
Bisphosphonates				
In fracture patients (no 12)				
Abrahamsen et al[10] (Denmark, National Hospital Discharge Register and National Prescription Database) (NOS 9/9)	Register-based restricted cohort study Population: fractures patients Exposure: new users of bisphosphonates vs nonusers	(1) Probable AF (2) Hospital-treated AF (3) Ischemic stroke (4) MI	14,302 vs 28,731	Among subjects aged >75 years: (1) 1.20 (1.07–1.34) (2) 1.17 (1.02–1.34)
In women with CKD (no 13)				
Hartle et al[23] (USA, EpicCare, Geisinger Medical Center's electronic health records) (NOS 8/9)	Retrospective cohort study Population: women aged 18–88 years who were enrolled for primary care at any Geisinger facility and with baseline CKD Exposure: users of bisphosphonates vs nonusers	(1) Death (2) Composite major CardioV events	3,234 vs 6,370 (5,100 patients aged ≥73 years)	(1) 0.78 (0.66–0.93)
CCBs + CYP3A4 inhibitors in hypertensive patients (no 14)				
Yoshida et al[56] (Japan, Administrative database) (NOS 6/9)	Nested case-control study Population: hypertensive patients treated with CCBs Exposure: users of CCB + CYP3A4 inhibitor or CCB + other drugs (non CYP3A4 inhibitor) vs users of CCBs alone	ADRs	17,430 (Patients >70 years old 30 vs 160)	No association
CCBs in hypertensive patients (no 15)				
Jung et al[27] (Korea, Health Insurance Review and Assessment Service database) (Quality Assessment 7/8)	Observational case-crossover study Population: elderly patients aged ≥65 years with at least one diagnosis of hypertension and at least one prescription of CCBs Exposure: users of nifedipine vs users of other CCBs	(1) Stroke (total risk) (2) Ischemic stroke (3) Hemorrhagic stroke (4) Intracranial hemorrhage (5) Subarachnoid Hemorrhage	373/16,069 (5,546 patients aged 70–74 years)	(1) 2.56 (1.96–3.37) (2) 2.56 (1.89–3.47) (3) 5.16 (2.29–11.66) (4) 3.60 (1.34–9.66) (5) 14.10 (1.84–108.25)

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Table 1 (*Continued*)

First author (country, data source) (quality assessment)	Study design	Outcomes	Characteristics of the population	
			Sample size	Estimates (95% CI)
Cholinesterase inhibitors in dementia patients (no 16)				
Gill et al[19] (Canada, Ontario administrative healthcare databases) (NOS 689)	Population-based cohort study Population: community-dwelling patients aged ≥66 years with a prior diagnosis of dementia Exposure: users of cholinesterase inhibitors vs nonusers	(1) Hospital visits for syncope (2) Hospital visits for bradycardia (3) Permanent pacemaker insertion (4) Hospitalization for hip fracture	19,803 vs 61,499	(1) 1.76 (1.57–1.98) (2) 1.69 (1.32–2.15) (3) 1.49 (1.12–2.00) (4) 1.18 (1.04–1.34)
Clopidogrel + PPIs (no 17)				
Juurlink et al[28] (Canada, Ontario Public Drug Program) (NOS 7/9)	Nested case-control study Population: subjects ≥66 years with a prescription of clopidogrel within 3 days after hospital discharge following treatment for acute MI Exposure: users PPIs	(1) Recurrent MI <90 days (2) Death <90 days (3) Recurrent MI <1 year (4) Death <1 year	734 vs 2,057	(1) 1.27 (1.03–1.57) (3) 1.23 (1.01–1.49)
Mahabaleshwarkar et al[36] (USA, Medicare) (NOS 6/9)	Nested case-control study Population: subjects ≥65 years who had initiated clopidogrel therapy and with no gap of 30 days or more between clopidogrel prescription fills Exposure: users of PPIs	(1) Major CardioV events or all-cause mortality (composite) (2) Acute MI (3) Stroke (4) CABG (5) PCI (6) All-cause mortality (7) Any major CardioV events	9,908 vs 9,908	(1) 1.26 (1.18–1.34) (6) 1.40 (1.29–1.53)
Rassen et al[43] (USA, Provincial health care system funded by the British Columbia government, Pharmaceutical Assistance Contract for the Elderly in Pennsylvania and Pharmaceutical Assistance to the Aged and Disabled in New Jersey) (NOS 7/9)	Cohort study Population: subjects that underwent PCI or hospitalized for ACS and were new users of clopidogrel Exposure: concurrent users of PPIs vs nonusers	MI hospitalization or death; MI hospitalization; all-cause death; revascularization	Cohort 1: 1,353 vs 9,038 Cohort 2: 1,352 vs 2,824 Cohort 3: 1,291 vs 2,707	No association
Rossini et al[44] (Italy, Administrative database) (NOS 7/9)	Observational study Population: patients that underwent PCI and drug-eluting stents implantation treated with aspirin and clopidogrel Exposure: concurrent users of PPIs vs nonusers	MACE; bleeding; death; any stent thrombosis	1,158 vs 170	No association
Donepezil + clarithromycin (no 18)				
Hutson et al[26] (Canada, Ontario Provincial healthcare database) (NOS 6/9)	Nested case-control study Population: residents aged ≥66 years and users of antibacterial agents for respiratory tract infections Exposure: recent users of antibacterial agents	Hospitalization for CardioV events	59 vs 295	No association

LABA and LAA in COPD patients (no 19)				
Gershon et al[18] (Canada, Ontario health care database) (NOS 6/9)	Nested case-control study Population: individuals aged ≥66 with COPD Exposure: new users of inhaled LABAs or LAAs	(1) Hospitalization or emergency department visit for ACS (2) HF (3) Cardiac arrhytmia (4) Ischemic stroke	26,628 vs 26,628	For LAAs: (1) 1.30 (1.04–1.62) (2) 1.31 (1.08–1.60) (4) 0.68 (0.50–0.91) For LABAs: (1) 1.43 (1.08–1.89) (2) 1.42 (1.10–1.83)
New ACE inhibitors in AF patients (no 20)				
Mujib et al[38] (USA, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) (NOS 7/9)	Cohort study Population: patients aged ≥65 years with HF and preserved ejection fraction ≥40% Exposure: users of ACE inhibitors vs nonusers	(1) Composite outcome (all-cause mortality or HF hospitalization) (2) All-cause mortality (3) HF hospitalization (4) All-cause hospitalization	After propensity score matching: 1,337 vs 1,337	(1) 0.91 (0.84–0.99)
NSAIDs (no 21)				
Abraham et al[9] (USA, Veterans Affairs – Pharmacy Benefits Management) (NOS 8/9)	Retrospective cohort study Population: veterans >65 years prescribed an NSAID at any Veterans Affairs facility Exposure: users of NSAIDs, NSAIDs + PPIs, coxib, coxib + PPIs, PPIs vs NSAIDs nonusers	All-cause mortality following (1) Upper GI events (2) MI (3) CerebroV events	474,495	(1) 3.3 (2.8–3.4) (2) 10.3 (9.2–11.6) (3) 12.4 (10.9–14.3)
Caughey et al[13] (Australia, Administrative database) (NOS 7/9)	Retrospective cohort study Population: Australian veterans with incident dispensing of an NSAIDs Exposure: users of NSAIDs	(1) All stroke (2) Ischaemic stroke (3) Hemorrhagic stroke	162,065	(1) 1.88 (1.70–2.08) (2) 1.90 (1.65–2.18) (3) 2.19 (1.74–2.77)
Roumie et al[45] (USA, Tennesee Medicaid program) (NOS 7/9)	Retrospective Observational Study Population: non-institutionalized person aged 35–94 years who did not have evidence of any non-cardiovascular serious medical illness prior to cohort entry Exposure: users of NSAIDs vs nonusers, with CardioV or not	Hospitalization for acute MI, stroke, or death from coronary heart disease	NSAIDs users with history of CardioV disease: – Colecoxib 1,882 – Rofecoxib 1,354 – Valdecoxib 394 – Ibuprofen 6,236 – Naproxen 7,249 – Indomethacin 1,361 – Diclofenac 496 NSAIDs non–users with history of CardioV disease: 60,784 NSAIDs users without history of CardioV disease: – Colecoxib 7,117 – Rofecoxib 6,840 – Valdecoxib 1,742 – Ibuprofen 44,261	In patients aged ≥65 years and among subjects without CVD history, for rofecoxib: 1.26 (1.05–1.51) for valdecoxib: 1.40 (1.05–1.87) for indomethacin: 1.57 (1.15–2.14)

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Table 1 (*Continued*)

First author (country, data source) (quality assessment)	Study design	Outcomes	Characteristics of the population	
			Sample size	Estimates (95% CI)
			– Naproxen 48,103 – Indomethacin 6,730 – Diclofenac 3,420 NSAIDs non–users without history of CardioV disease: 380,434	
OACs (no 22)				
Poli et al[41] (Italy, Elderly Patients followed by Italian Centres for Anticoagulation study) (NOS 5/9)	Multicenter prospective observational study Population: old patients who started vitamin K antagonist treatment after 80 years of age for thromboprophylaxis of AF or venous thromboembolism Exposure: users vitamin K antagonist	Major bleedings	4,093	NA
In CAD patients (no 23)				
Ruiz Ortiz et al[46] (Spain, Administrative database) (NOS 7/9)	Observational study Population: patients aged ≥80 years with non-valvular AF treated Exposure: users of OAC vs nonusers	(1) Embolic events (2) Severe bleeding (3) All embolic and hemorrhagic events (4) All-cause death	164 vs 105 (196 patients aged 80–84 years; 57 patients aged 85–89 years; 16 patients aged ≥90 years)	(1) 0.17 (0.07–0.41) (3) 0.46 (0.25–0.83) (4) 0.52 (0.31–0.88)
Tanaka et al[49] (Japan, Administrative database) (NOS 2/9)	Retrospective case-control study Population: patients treated with antithrombotic drugs Exposure: users of OACs	GI injuries, including gastric ulcers, duodenal ulcers, and hemorrhagic injuries	172 vs 3,099 (39 vs 156 patients aged 60–69 years; 102 vs 408 patients aged ≥70 years)	Among patients aged 60–69 years, for clopidogrel: 4.41 (1.56–12.43) for NSAIDs: 4.01 (1.83–8.86) Among patients aged ≥70 years, for low–dose aspirin: 1.91 (1.17–3.16) for clopidogrel: 3.07 (1.62–5.77) for warfarin: 2.45 (1.35–4.43) for NSAIDs: 4.26 (2.65–6.93)
Olmesartan medoxomil in hypertensive patients (no 24)				
Saito et al[47] (Japan, ad hoc database) (NOS 2/9)	Prospective cohort study Population: olmesartan-naïve hypertensive patients aged ≥65 years Exposure: olmesartan alone, in combination with drugs, or by switching from other antihypertensive medications	Blood pressure; Clinical laboratory tests; ADRs	550 (280 young-old patients 65–74 years; 270 older-old patients ≥75 years)	No association

Opioids (no 25)				
Li et al[32] (UK, General Practice Research Database) (NOS 6/9)	Nested case-control study Population: non-cancer pain patients who had a record for at least one opioid prescription Exposure: users of opioids	MI	11,693 vs 44,897	Among patients aged 71–80 years old, for male: 1.46 (1.23–1.75) for female: 1.34 (1.12–1.61)
Postmenopausal hormones (no 26)				
Løkkegaard et al[34] (Denmark, Danish Sex Hormone Register Study) (NOS 8/9)	Retrospective cohort study Population: healthy Danish women aged 51–69 years Exposure: users of hormone therapy vs nonusers	MI	Patients aged 65–69 years: – Previous use 27,338; – Current use 75,473	For patients aged 65–69 years, for past use: 0.77 (0.60–0.99)
Statins + clopidogrel in PCI patients (no 27)				
Blagojevic et al[11] (Canada, Health Insurance databases of Quebec) (NOS 6/9)	Population-based cohort study Population: PCI patients aged ≥66 years and receiving their first post discharge clopidogrel prescription within 5 days of the hospital discharge date Exposure: users of clopidogrel + non-CYP3A4-metabolized statins, or clopidogrel + CYP3A4-metabolized statins vs clopidogrel and no statins	Death; MI; unstable angina; hospitalization with repeat revascularization; CerebroV events	8,417 vs 2,074	No association
Statins + macrolides (no 28)				
Patel et al[40] (Canada, Ontario Drug Benefit database, Canadian Institute for health Information Discharge Abstract database, Ontario Health Insurance Plan database, and Registered persons database of Ontario) (NOS 7/9)	Population-based cohort study Population: continuous statin users >65 years with macrolide antibiotic co-prescription Exposure: users of statin + clarithromycin or erythromycin vs users of statin + azithromycin	(1) Hospitalization for rhabdomyolysis (2) Hospitalization for acute kidney injury (3) Hospitalization for hyperkalemia (4) All-cause mortality	75,858 vs 68,478	(1) 2.17 (1.03 to 4.52) (2) 1.83 (1.52 to 2.19) (4) 1.57 (1.37 to 1.82)
Statins **In CAD patients (no 29)**				
Kulik et al[29] (USA, Medicare, Pennsylvania Pharmaceutical Assistance Contract for the Elderly program, and the New Jersey Pharmaceutical Assistance to the Aged and Disabled program) (NOS 7/9)	Observational population-based study Population: patients ≥65 years old who had been hospitalized for acute MI or coronary revascularization Exposure: users of statins vs nonusers	New-onset AF	8,450 vs 20,638	0.90 (0.85–0.96) In PCI cohort: 0.89 (0.82–0.96) In MI cohort: 0.84 (0.76–0.92)

(*Continued*)

Table 1 (*Continued*)

First author (country, data source) (quality assessment)	Study design	Outcomes	Characteristics of the population	
			Sample size	Estimates (95% CI)
Macchia et al[35] (Italy, Administrative database) (NOS 7/9)	Observational retrospective cohort study Population: patients discharged alive with a first diagnosis of MI treated with statins Exposure: users of statins + n–3 PUFA vs users of statins	(1) All-cause death (2) Death or MI (3) Death or AF (4) Death or congestive HF (5) Death or stroke	4,302 vs 7,230 (4,812 patients aged ≥70 years)	(1) 0.59 (0.52–0.66) (3) 0.78 (0.71–0.86) (4) 0.81 (0.74–0.88) (5) 0.66 (0.59–0.74) In paired–matched cohort: (1) 0.63 (0.56–0.72) (3) 0.82 (0.75–0.90) (4) 0.86 (0.79–0.95) (5) 0.65 (0.58–0.73)
In COPD patients (no 30)				
Lawes et al[31] (New Zeland, Administrative database) (NOS 7/9)	Retrospective cohort study Population: patients with 50–80 years discharged from hospital with a first admission of COPD Exposure: users of statins vs nonusers	All-cause mortality	596 vs 1,091; (patients aged 70–79: 354 vs 593)	2.22 (1.60–3.07)
In women (no 31)				
LaCroix et al[30] (USA, Women's Health Initiative Observational Study) (NOS 4/9)	Prospective Study Population: women aged 65–79 years who did not have frailty at baseline Exposure: users of statin vs nonusers	Intermediate frailty; Frail	2,122 vs 23,256	No association
Warfarin + potentially interacting drugs (no 32)				
Vitry et al[53] (Australia, Australian Department of Veterans' Affairs administrative claims database) (NOS 6/9)	Retrospective cohort study Population: veterans aged ≥65 years who were new users of warfarin Exposure: users of Warfarin + potentially interacting drugs vs users of warfarin	Bleeding-related hospitalization	17,661	For clopidogrel: 2.23 (1.48–3.36) for clopidogrel + aspirin: 3.44 (1.28–9.23) for amiodarone: 3.33 (1.38–8.00) for antibiotics: 2.34 (1.55–3.54) for macrolides: 3.07 (1.37–6.90) for trimetoprim or cotrimoxazole: 5.08 (2.00–12.88)

Abbreviations: ACE, angiotensin-converting-enzyme; ACS, acute coronary syndromes; ADR, adverse drug reaction; AF, atrial fibrillation; CardioV, cardiovascular; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CerebroV, cerebrovascular; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, CardioV disease; CYP3A4, Cytochrome P450 3A4; GI, gastrointestinal; HF, heart failure; INR, international normalized ratio; LAA, long-acting anticholinergic; LABA, long-acting beta-agonist; MACE, major adverse cardiac events; MI, myocardial infraction; NA, no association; NOS, Newcastle Ottawa Scale; NSAID, nonsteroidal anti-inflammatory drug; NSTE, non-ST segment elevation; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PUFA, polyunsaturated fatty acid; TCA, tricyclic antidepressants; UFH, unfractionated heparin; SSRI, selective serotonin reuptake inhibitor.

for making quality assessments of prescribing practices and medication use in older adults and potentially helpful during the process of medication review. The most widely used criteria for inappropriate medications are the Beers criteria,[3] initially developed in 1991 in the USA to target nursing home residents and then revised in 1997, 2003, 2012, and most recently in 2015. These criteria include more than 50 medications assigned to one of three possible categories: those that should always be avoided, those that are potentially inappropriate in older adults with particular health conditions or syndromes, and those that should be used with caution. It has been shown that potentially inappropriate medications included in the Beers criteria are associated with poor health outcomes such as confusion, falls, and mortality. Another important set of criteria is represented by START/STOPP[4] which were first published in 2008 and last updated in 2014. STOPP criteria identify prescriptions that are potentially inappropriate to use in patients aged ≥65 years, while START criteria list drug therapies that should be considered where no contraindication to prescription exists in the same group of patients. Beers and START/STOPP criteria overlap in several areas, making them able to predict ADRs, but often with different reliability.[58,59]

The list of indicators provided in the present review is intended as a set of potential indicators of IP that need to be tested in the real world through a validation process based on tailored studies to explore health outcomes in different older populations and across different care settings. Eventually, these validation studies might lead to a structural proposal for a new set of criteria of IP in older adults suffering from multiple chronic conditions and affected by cardiovascular diseases. This systematic review represents the first step in the process of validation of new indicators, granted by the Italian Medicine Agency (AIFA) and carried out by the I-GrADE consortium.

Our list of potential indicators partially overlaps those proposed by the Beers and STOPP criteria. Several drugs highlighted in this review, including anticoagulants, antiplatelet, blood pressure lowering medications, and many psychotropic drugs, are listed by at least one of the aforementioned criteria. However, this can be no more than an indirect comparison, considering that this review specifically focuses on multimorbid older people suffering from cardiovascular diseases. However, when the attention of such criteria is focused on specific conditions, the agreement intensifies. For example, Beers criteria include a section of recommendations valid in specific contexts and make the case of HF. They point out NSAIDs, CCBs, thiazolidinediones, cilostazol, and dronedarone as potentially inappropriate medications in older adults suffering from HF. Interestingly, three out of five of these drugs have been included in our list. Several selection criteria beyond the specific selection of a population affected by cardiovascular diseases, and the decision-making process itself, might explain these and other discrepancies.

Several drugs not recommended for the treatment of cardiovascular diseases (but that have a potential role in determining ADRs in people with heart diseases) have been included in our list. Some of them are proposed here for the first time as potentially inappropriate. For example, in the study from Abrahamsen et al[10] bisphosphonates showed a possible correlation with AF in patients with an underling cardiac disease. This finding, considering the high prevalence of both osteoporosis and cardiovascular diseases in the older population, represents an interesting area of future research, especially when considering the broad set of bisphosphonates with different pharmacokinetics and pharmacodynamics and the actual possibility of replacing these drugs with compounds recently developed for the treatment of osteoporosis, with a more favorable safety profile and good tolerance.

On the other hand, our research underlines the potential harm linked to drugs that have been synthesized and are recommended for the treatment of cardiovascular diseases. This is the case of statins whose toxicity, according to a research published in 2013 by Patel et al,[40] may be exacerbated when co-prescripted with macrolides (especially clarithromycin and erythromycin). Considering the high frequency of use of both classes of drugs related to the prevalence of cardiovascular diseases in elders and the presence of macrolides in first-line therapy of community-acquired pneumonia – which is in turn a main cause of hospitalization in patients over 65 – it is very important to clarify the possible effect of such a co-prescription. In fact, the natural decline in renal function that accompanies aging may exaggerate the consequences of a rhabdomyolysis with a dramatic increase in the frequency of acute kidney failure and an excess of mortality.

As in the most recent 2015 version of Beers criteria, we took into account some drug–disease or drug–syndrome interactions. Some of them are well known and have been extensively explored in the literature, as is the case for antipsychotics and dementia, while others are completely new (ie., antidiabetics and stage renal disease or disability), thus opening the way to new and interesting knowledge acquisitions or future research areas.

To our knowledge, the present work is the first time a systematic review of studies has reported any kind of

association between drug use and ADRs in multimorbid older adults suffering from cardiovascular diseases. However, the results we report should be read keeping in mind some limitations. First, we did not include any study assessing under use of medications, and it is now clear that underprescribing appropriate medications can be as great a concern as is overprescribing. Prescribing strategies that seek to simply limit the overall number of drugs prescribed to older adults in the name of improving quality of care may be seriously misdirected. Second, considering the broad and complex spectrum of scenarios existing when it comes to multimorbid older adults, and the heterogeneity of studies present in the literature, our search strategy might have missed some relevant hits. However, bibliographies of the selected papers were scrutinized in an attempt to reduce such occurrence. Third, the heterogeneity of study methodologies and care settings precludes the direct translation of our findings in definitive criteria of IP. However, this was an a priori assumption that suggests the setting up and running of ad hoc studies aimed at validating the criteria suggested here. Finally, a judgment of appropriateness cannot be issued on the basis of an all-or-nothing principle, but we should consider dose-dependent appropriateness of every drug for every target population. In this regard, none of the possible indicators relates to drug dosage, and we know that drug doses can be a main determinant for adverse drug events. Moreover, older patients often present an increased volume of distribution and a decreased drug clearance, which can prolong drug half-lives and lead to increased plasma drug concentrations. In addition, a decline in hepatic function with advancing age may account for significant variability in drug metabolism among older adults.

Other limitations were the exclusion of studies published in languages other than English and a lack of risk-of-bias assessment while quality of reporting was assumed to be directly related to quality of information.

Conclusion

The correct clinical and pharmacological management of complex older adults requires the availability of reliable tools of risk stratification, outcome prediction, and appropriateness of care. According to the present systematic review, both cardiovascular and non-cardiovascular drugs increase the risk of ADRs in older adults with cardiovascular diseases. As part of the I-GrADE consortium, the authors of the present study propose a list of potential indicators of IP for application in the context of multimorbid older adults suffering from cardiovascular diseases. It is worth passing such potential indicators through a validation process carried out in the real-world older population and across different care settings. This is part of the commitment of I-GrADE, and such a process will eventually lead to the publication of a reliable list of indicators of IP tailored to the aforementioned population. This and other efforts by the scientific community are required in the near future in order to cope with the emergency that stems from the rapid aging of the world population and to eventually provide better and more sustainable care to older adults.

Acknowledgment

*I-GrADE members: Alessandra Bettiol, Niccolò Lombardi, Ersilia Lucenteforte, Alessandro Mugelli, Alfredo Vannacci (University of Florence, Florence), Alessandro Chinellato (ULSS 9 Treviso, Treviso), Stefano Bonassi, Massimo Fini, Cristiana Vitale (IRCCS San Raffaele Pisana, Rome), Roberto Bernabei, Graziano Onder, Davide Liborio Vetrano (Catholic University, Rome), Claudia Bartolini, Rosa Gini, Francesco Lapi, Giuseppe Roberto (ARS Toscana, Florence), Nera Agabiti, Silvia Cascini, Marina Davoli, Ursula Kirchmayer, Chiara Sorge (ASL 1 Rome), Giovanni Corrao, Federico Rea (University of Milano-Bicocca, Milano), Achille Patrizio Caputi, Francesco Giorgianni, Michele Tari, and Gianluca Trifirò (University of Messina, Messina).

Disclosure

EL received research support from the Italian Agency of Drug (AIFA), which is not related to this study. AM received research support from the AIFA, the Italian Ministry for University and Research (MIUR), Gilead, and Menarini. In the past 2 years he has received personal fees as speaker/consultant from Menarini Group, IBSA, Molteni, Angelini, and Pfizer Alliance, none of which are related to this study. GC received research support from the European Community (EC), the European Medicine Agency (EMA), the Italian Agency of Drug (AIFA), and the Italian Ministry of Health, and of University and Research (MIUR). He has taken part in a variety of projects that were funded by pharmaceutical companies (ie, Novartis, GSK, Roche, AMGEN, and BMS). He has also received honoraria as member of the Advisory Board from Roche. None of these is related to this study.

AV, in the past 2 years, has received personal fees as consultant from Molteni, which is not related to this study. The authors report no other conflicts of interest in this work.

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