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Review Article

The Association of Potentially Inappropriate Medication at Older Age With Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies

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A B S T R A C T

Objective: The aim of this systematic review was to identify, evaluate, and meta-analyze cohort studies reporting the association of potentially inappropriate medication (PIM) intake with mortality and cardiovascular events.
Design: A systematic review and meta-analysis of prospective and retrospective cohort studies were conducted. Study appraisal included a thorough risk of bias assessment. Data synthesis followed a random-effects model.
Data sources: The included studies were retrieved from the databases MEDLINE and ISI Web of Knowledge. Additionally, the authors checked the references of the included studies for further relevant literature.
Eligibility criteria for selecting studies: For inclusion in a study, the population needed to be older than 60 years of age and not restricted to having one specific disease. The outcome had to address all-cause mortality or cardiovascular events. Studies that examined polypharmacy or specific drugs were excluded.
Results: At first, 13 studies were included in a meta-analysis. The association of PIM with overall mortality was not statistically significant (risk ratio; 95% confidence interval, 1.13; 0.95–1.35). However, the majority of studies showed a high risk of specific forms of bias. These biases can be excluded by applying a new user design. It ascertains that adverse events occurring early in therapy are recorded. After restricting the meta-analysis to three studies with a new user design, the association of PIM use and mortality was statistically significant (risk ratio; 95% confidence interval, 1.59; 1.45–1.75). Only one study focused on cardiovascular events and found no statistically significant association. However, the study was not conducted with a new user design.
Conclusion: In studies with adequate methods (new user design), PIM use, defined by Beers criteria or the HEDIS-DAE list, was associated with a 1.6-fold increased mortality in older adults. Physicians should therefore avoid prescribing PIM for older adults whenever feasible. Further new user design studies are required for cardiovascular outcomes and to compare the predictive value of different PIM criteria for mortality.

Contributors: D.C.M., L.K.H., and B.S. were involved in the conception and design of the review, developed the search strategy, and performed the study selection. D.C.M. and L.K.H. extracted data from included studies. D.C.M., L.K.H., and B. S. were involved in the data analysis. All authors were involved in the interpretation and discussion of results. D.C.M. drafted the manuscript and BS revised it. L.K.H., J. W., and H.B. revised it critically for important intellectual content. All authors approved the final version of the article. All authors had access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. B.S. is the guarantor of this systematic review.

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Drugs play an important role in the care of older people, as the majority of chronic diseases occur at an advanced age. In developed countries, about 90% of individuals aged 65 years and older are taking at least one prescribed drug.[1,2] However, with older age, the constitution of the body changes, resulting in altered absorption, metabolism, and elimination of drugs, which consequently are less tolerated.[3] In addition, the elderly are often frail and have comorbidities. Although older adults take the highest share of all prescribed drugs, trials on drug safety and efficacy are normally conducted with highly selected, rather young individuals.[4] Hence, evidence of drug safety and efficacy for multimorbid or frail elderly people is often lacking.

Potentially inappropriate medication (PIM) includes drugs and drug combinations that should be avoided in older adults because they might cause more harm than benefit for the user, and safer alternatives are available.[5] There are two approaches to assess the inappropriate use of medication, namely implicit and explicit procedures.[6] Implicit measurements are based on the judgment of a clinician for an individual patient.[6] Often, they are neither reproducible nor generalizable, and the procedure is time-consuming.[6] In contrast, explicit measurements imply the utilization of definite criteria. Mark H. Beers and colleagues introduced their explicit PIM criteria in 1991.[5] They were the first to conduct an expert survey to identify PIM and reached a consensus that was published in list format. Since then, the Beers list was updated several times, and further explicit PIM criteria were published, such as the STOPP/START criteria,[7] the Healthcare Effectiveness Data and Information Set-Use of High-Risk Medications in the Elderly (HEDIS-DAE) list,[8] and many others.[9–15] These PIM criteria are all based on expert opinions, mainly synthesized by the Delphi method. Although decisions are guided by a literature search, high-quality evidence (as defined by GRADE system) is lacking because the elderly are rarely represented in clinical trials.[4,16] For this reason, the quality of evidence of PIM lists is usually on a moderate or low level.[17]

It is still unknown whether the intake of PIM is associated with clinically relevant outcomes. Therefore, the aim of this systematic review is to identify, appraise, and meta-analyze the available evidence on the association of PIM intake with mortality and cardiovascular events from cohort studies. We were particularly interested in cardiovascular events, as many PIM are assumed inappropriate for the elderly because they are supposed to increase the risk for heart failure, stroke, or arrhythmias.[17] In addition, we wanted to investigate whether the strength of the association varies according to the applied PIM criteria.

Methods

The planning, execution, and reporting of the present systematic review occurred in adherence to the standards of reporting of meta-analyses of observational studies in epidemiology (MOOSE Statement) (Appendix, Table A1).[18]

Search Strategy and Data Extraction

We searched two medical databases for relevant cohort studies: MEDLINE via Pubmed and the ISI Web of Knowledge. We combined synonymous or related expressions for the terms “potentially inappropriate medication,” “mortality,” and “cardiovascular disease.” Keywords and a search string were developed after consulting a librarian and are shown in the Appendix, Table A2. No language restrictions were applied, and the time period was set from 1991 onward, as the first consensus-based PIM list was published in this year.[5]

The publications detected through the search strategy were imported into the literature management software Thomas Reuters EndNote™ (New York, NY), and evident duplicates were deleted. Case reports, comments, editorials, letters, randomized clinical trials, and reviews were excluded. The titles and abstracts of the remaining publications were screened, and those apparently not relevant to the review topic were excluded. The subsequent full-text selection and data extraction were performed independently by two reviewers (D.C.M., L.K.H.). They applied the following exclusion criteria: Authors did not conduct a cohort study, no data were reported, participants were younger than 60 years of age, population was defined by specific diseases or conditions (eg, hip fracture or neurological injuries), outcome was neither mortality nor cardiovascular events, mortality was not assessed as a separate endpoint (eg, combination of death, hospitalizations and emergency department visits), the study used the same cohort as another publication, only one specific PIM or PIM class (eg, anticholinergic drugs) or polypharmacy was defined as the exposure, or risk factors for PIM or interventions for PIM were examined. In the case of disagreement, consensus was reached by discussion. If no consensus could be found, a third researcher (B.S.) was consulted.

Risk of Bias/Confounding Assessment

We assessed the risk of bias within studies by using a modified Newcastle-Ottawa-Scale (NOS).[19] Points were ascribed for a low risk of bias in categories like representativeness of the exposed cohort, ascertainment of exposure, selection of the nonexposed cohort, outcome assessment, adjustment for potential confounders, and adequate length of follow-up. We assigned an additional point in the NOS if a study adjusted for the number of comorbidities or a comorbidity index. The rationale was that comorbidity plays an important role in the present research. It is associated with higher mortality (outcome) and supposedly increases the probability for the prescription of a PIM (exposure). Therefore, it may cause confounding, namely confounding by indication.[20] Uncontrolled confounding by indication can bias the results toward stronger risk effect measures. In this altered template of the NOS, a study is scored from 0 to 9 points. The more points a study receives, the lower its risk of bias.

In addition to the NOS, we assessed the risk for types of bias that frequently occur in pharmacoepidemiological studies, namely immortal time bias and healthy-user/sick-stopper bias.[21,22] Immortal time bias can occur when exposure is defined in a way that leads to a period of cohort follow-up during which the outcome under study cannot occur.[22] This span is called *immortal time*. It induces bias by making an exposure appear to be protective.[22]

Healthy-user/sick-stopper bias describes the phenomenon that patients with better health status are more likely to tolerate and thus adhere to a therapy, especially if it is preventive or for asymptomatic conditions, whereas sick and frail individuals tend to stop treatment.[23] The healthy-user/sick-stopper bias is closely related to healthy adherer effects.[21] Both can result in artificially protective associations between (preventive) treatments and mortality.[24] Although the healthy-user/sick-stopper bias is usually present in the context of preventive treatments, it also needs to be considered in the appraisal of observational studies about PIM, which do not only cover preventive drugs. Healthier patients may have a higher propensity of PIM exposure, as they adhere to therapy because they compensate adverse drug events better. Results might be biased toward weaker or even protective effects of PIM on mortality and cardiovascular events.

Data Analysis

Extracted data were pooled using the software Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ). We applied the DerSimonian and Laird random-effects model because we suspected different effects between the studies.[25] Heterogeneity was examined