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REVISIÓN BIBLIOGRÁFICA ABRIL Y MAYO 2023
Selección de artículos

REVISTAS GERIÁTRICAS

BMC Geriatrics

Prognostic significance of frailty in hospitalized elderly patients with community-acquired pneumonia: a retrospective cohort study

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Background

Frailty is associated with poor prognosis in a wide range of illnesses. However, its prognostic implications for older patients with community-acquired pneumonia (CAP) are not adequately addressed.

Methods

In this study, patients were classified into 3 groups according to the frailty index based on standard laboratory tests (FI-Lab) score: robust (FI-Lab < 0.2), pre-frail (FI-Lab 0.2–0.35), and frail (FI-Lab ≥ 0.35). The relationships between frailty and all-cause mortality and short-term clinical outcomes (length of stay, duration of antibiotic therapy, in-hospital mortality) were examined.

Results

Finally, 1164 patients were included, the median age was 75 years (interquartile range: 69, 82), and 438 patients (37.6%) were women. According to FI-Lab, 261(22.4%), 395(33.9%), and 508(43.6%) were robust, pre-frail, and frail. After adjustment for confounding variables, frailty was independently associated with prolonged antibiotic treatment ($p = 0.037$); pre-frailty and frailty were independently associated with longer inpatient days ($p < 0.05$ for both). The risk of in-hospital mortality was independently increased in frail patients (HR = 5.01, 95% CI = 1.51–16.57, $p = 0.008$) but not pre-frail patients (HR = 2.87, 95% CI = 0.86–9.63, $p = 0.088$) compared to robust patients. During a median follow-up of 33.9 months (interquartile range: 32.8 to 35.1 months), 408 (35.1%) patients died, of whom 29 (7.1%) were robust, 112 (27.5%) were pre-frail, and 267 (65.9%) were frail. Compared to robust patients, frail and pre-frail were significantly associated with increased risk for all-cause death (HR = 4.29, 95%CI: 1.78–10.35 and HR = 2.42 95%CI: 1.01–5.82, respectively).

Conclusions

Frailty is common among older patients with CAP and is strongly associated with increased mortality, longer length of stay, and duration of antibiotics. A routine frail assessment at the admission of elderly patients with CAP is necessary as the first step for appropriate multidisciplinary interventions.

Disponible en: https://doi.org/10.1186/s12877-023-04029-3

DRUGS AND AGING

Dosage Optimization of Digoxin in Older Patients with Heart Failure and Chronic Kidney Disease: A Population Pharmacokinetic Analysis

Zhong-Qiu Lin, Ling Guo, Li-Min Zhang, Jie-Jiu Lu & Xia Jiang

Background

Renal function is an important index for digoxin dose adjustment, especially in patients with chronic kidney disease (CKD). Decreased glomerular filtration rate is common in older patients with cardiovascular disease.

Objective

The aim of this study was to establish a digoxin population pharmacokinetic model in older patients with heart failure and CKD and to optimize the digoxin dose strategy.

Methods

Older patients with heart failure and CKD aged > 60 years from January 2020 to January 2021 and who had an estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m2 or urine protein production were enrolled in this retrospective study. Population pharmacokinetic analysis and Monte Carlo simulations (n = 1000) were performed using NONMEN software. The precision and stability of the final model were analyzed by graphical and statistical methods.

Results

Overall, 269 older patients with heart failure were enrolled. A total of 306 digoxin concentrations were collected, with a median value of 0.98 ng/mL (interquartile range [IQR] 0.62–1.61, range 0.04–4.24). The median age was 68 years (IQR 64–71, range 60–94) and eGFR was 53.6 mL/min/1.73 m2 (IQR 38.1–65.2, range 11.4–89.8). A one-compartment model with first-order elimination was developed to describe the digoxin pharmacokinetics. Typical values for clearance and volume of distribution were 2.67 L/h and 36.9 L, respectively. Dosage simulations were stratified by eGFR and metoprolol. Doses of 62.5 and 125 µg were recommended for older patients with eGFR < 60 mL/min/1.73 m2.

Conclusions

A population pharmacokinetic model of digoxin in older patients with heart failure and CKD was established in this study. A novel digoxin dosage strategy was recommended in this vulnerable population.

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Impact of a Comprehensive Intervention Bundle Including the Drug Burden Index on Deprescribing Anticholinergic and Sedative Drugs in Older Acute Inpatients: A Non-randomised Controlled Before-and-After Pilot Study

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Introduction

Implementation of the Drug Burden Index (DBI) as a risk assessment tool in clinical practice may facilitate deprescribing.

Objective

The purpose of this study is to evaluate how a comprehensive intervention bundle using the DBI impacts (i) the proportion of older inpatients with at least one DBI-contributing medication stopped or dose reduced on discharge, compared with admission; and (ii) the changes in deprescribing of different DBI-contributing medication classes during hospitalisation.

Methods

This before-and-after study was conducted in an Australian metropolitan tertiary referral hospital. Patients aged ≥ 75 years admitted to the acute aged care service for ≥ 48 h from December 2020 to October 2021 and prescribed DBI-contributing medication were included. During the control period, usual care was provided. During the intervention, access to the intervention bundle was added, including a clinician interface displaying DBI score in the electronic medical record. In a subsequent 'stewardship' period, a stewardship pharmacist used the bundle to provide clinicians with patient-specific recommendations on deprescribing of DBI-contributing medications.

Results

Overall, 457 hospitalisations were included. The proportion of patients with at least one DBI-contributing medication stopped/reduced on discharge increased from 29.9% (control period) to 37.5% [intervention; adjusted risk difference (aRD) 6.5%, 95% confidence intervals (CI) −3.2 to 17.5%] and 43.1% (stewardship; aRD 12.1%, 95% CI 1.0–24.0%). The proportion of opioid prescriptions stopped/reduced rose from 17.9% during control to 45.7% during stewardship (p = 0.04).

Conclusion

Integrating a comprehensive intervention bundle and accompanying stewardship program is a promising strategy to facilitate deprescribing of sedative and anticholinergic medications in older inpatients.

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Psychotropic Medication Prescribing to Patients with Dementia Admitted to Acute Hospitals in Ireland

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Background

Psychotropic medications are commonly prescribed to people with dementia (PwD) for non-cognitive symptoms of dementia (NCSD), but have significant risks. A national audit was performed in acute hospitals in the Republic of Ireland (ROI) to establish baseline practice prior to the launch and implementation of a National Clinical Guideline on the appropriate prescribing of psychotropic medications for NCSD. The objective of this study was to analyse psychotropic prescribing patterns and compare these with international data and with existing (limited) data from a previous audit round.

Methods

The pooled anonymous dataset from the second round of the Irish National Audit of Dementia Care (INAD-2) was analysed. The audit had collected retrospective data from 30 random healthcare records from each of 30 acute hospitals in 2019. Inclusion criteria were a clinical diagnosis of dementia of any type, hospital stay of 72 hours or more, and discharge or death within the audit period. Most hospitals (87%) self-audited their healthcare records, but a random sample of six healthcare records (20%) from each hospital were re-audited by a highly trained healthcare auditor. The audit tool was based on a tool used in the England and Wales National Audit of Dementia audit rounds (Royal College of Psychiatrists), adapted to the Irish healthcare setting and national priorities.

Results

In total, 893 cases were included, as one hospital could not retrieve 30 cases even within a more prolonged audit period. The sample comprised 55% females and 45% males; the median age was 84 years (interquartile range 79–88 years) and the majority (89.6%) were >75 years of age. Only 52% of healthcare records specified the type of dementia; within these, the most common diagnosis was Alzheimer's disease (45%). Most PwD (83%) were receiving psychotropic medication on admission; 40% were prescribed new or increased psychotropic medication during admission, mainly for medical indications, including end-of-life care and delirium. Anticonvulsants or cognitive enhancers were rarely prescribed for NCSD in hospital. However, new/increased antipsychotic medication was prescribed for NCSD in 11.8–17.6% of the total cohort, while 4.5–7.7% were prescribed a benzodiazepine for anxiety or NCSD. Overall, there was poor documentation of risk/benefit, or of discussion with the patient/family, and apparently inadequate review for efficacy and tolerability. Concurrently, acetylcholinesterase inhibitors appeared to be underused for cognitive impairment in the community.

Conclusion

This audit provides baseline data on psychotropic medication prescription for NCSD in Irish hospitals prior to a specific Irish guideline on this topic. Reflecting this, most PwD were receiving psychotropic medications on admission, and many were prescribed new/increased psychotropic medication in hospital, often without evidence of appropriate decision making and prescribing processes.

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A Motivational Interviewing Intervention to Improve Adherence to ACEIs/ARBs among Nonadherent Older Adults with Comorbid Hypertension and Diabetes

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Background

Hypertension and diabetes mellitus are independent risk factors for cardiovascular diseases. Due to the cardioprotective nature of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), they are recommended for patients with comorbid hypertension and diabetes. However, poor adherence to ACEIs/ARBs among older adults is a major public health concern. This study aimed to assess the effectiveness of a telephonic motivational interviewing (MI) intervention conducted by pharmacy students among a nonadherent older population (≥ 65 years old) with diabetes and hypertension.

Methods

Patients continuously enrolled in a Medicare Advantage Plan who received an ACEI/ARB prescription between July 2017 and December 2017 were identified. Group-based trajectory modeling (GBTM) was used to identify distinct patterns of ACEI/ARB adherence during the 1-year baseline period: adherent, gaps in adherence, gradual decline, and rapid decline in adherence. Patients from the three nonadherent trajectories were randomized into MI intervention or control group. The intervention consisted of an initial call and five follow-up calls administered by MI-trained pharmacy students and tailored to the baseline ACEI/ARB adherence trajectories. The primary outcome was adherence to ACEI/ARB during the 6- and 12-month periods post-MI implementation. The secondary outcome was discontinuation, defined as no refills for ACEI/ARB during the 6- and 12-month periods post-MI implementation. Multivariable regression analyses examined the impact of MI intervention on ACEI/ARB adherence and discontinuation while adjusting for baseline covariates.

Results

A total of 240 patients in the intervention group and 480 patients as randomly selected controls were included in this study. At 6 months, patients receiving the MI intervention had significantly better adherence (β = 0.06; p = 0.03) compared with the controls. Linear and logistic regression models also showed patients in the intervention group were more likely to be adherent than controls within 12 months of intervention implementation (β = 0.06; p = 0.02 and OR: 1.46; 95% CI 1.05–2.04, respectively). MI intervention did not have any significant impact on the ACEI/ARB discontinuation.

Conclusion

Patients who received the MI intervention were more likely to be adherent at 6 and 12 months following the intervention initiation, despite gaps in the follow-up calls due to COVID-19. Pharmacist-led MI intervention is an effective behavioral strategy to improve medication adherence among older adults and tailoring the intervention to past adherence patterns may enhance the intervention effectiveness.

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Optimising Medications in Older Vascular Surgery Patients Through Geriatric Co-management

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Background
Prescribing of potentially inappropriate medications and under-prescribing of guideline-recommended medications for cardiovascular risk modification have both been associated with negative outcomes in older adults. Hospitalisation represents an important opportunity to optimise medication use and may be achieved through geriatrician-led interventions.

Objective
We aimed to evaluate whether implementation of a novel model of care called Geriatric Comanagement of older Vascular (GeriCO-V) surgery patients is associated with improvements in medication prescribing.

Methods
We used a prospective pre-post study design. The intervention was a geriatric co-management model, where a geriatrician delivered comprehensive geriatric assessment-based interventions including a routine medication review. We included consecutively admitted patients to the vascular surgery unit at a tertiary academic centre aged ≥ 65 years with an expected length of stay of ≥ 2 days and who were discharged from hospital. Outcomes of interest were the prevalence of at least one potentially inappropriate medication as defined by the Beers Criteria at admission and discharge, and rates of cessation of at least one potentially inappropriate medication present on admission. In the subgroup of patients with peripheral arterial disease, the prevalence of guideline-recommended medications on discharge was determined.

Results
There were 137 patients in the pre-intervention group (median [interquartile range] age: 80.0 [74.0–85.0] years, 83 [60.6%] with peripheral arterial disease) and 132 patients in the post-intervention group (median [interquartile range] age: 79.0 (73.0–84.0) years, 75 [56.8%] with peripheral arterial disease). There was no change in the prevalence of potentially inappropriate medication use from admission to discharge in either group (pre-intervention: 74.5% on admission vs 75.2% on discharge; post-intervention: 72.0% vs 72.7%, p = 0.65). Forty-five percent of pre-intervention group patients had at least one potentially inappropriate medication present on admission ceased, compared with 36% of post-intervention group patients (p = 0.11). A higher number of patients with peripheral arterial disease in the post-intervention group were discharged on antiplatelet agent therapy (63 [84.0%] vs 53 [63.9%], p = 0.004) and lipid-lowering therapy (58 [77.3%] vs 55 [66.3%], p = 0.12).

Conclusions
Geriatric co-management was associated with an improvement in guideline-recommended antiplatelet agent prescribing aimed at cardiovascular risk modification for older vascular surgery patients. The prevalence of potentially inappropriate medications was high in this population, and was not reduced with geriatric co-management.

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Gerontology

Association of anticholinergic drug use with postoperative mortality among patients with hip fracture. A nationwide cohort study

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Purpose
Anticholinergic (AC) drugs are associated with various determinantal outcomes. Data regarding the effect of AC drugs on mortality among geriatric hip fracture patients are limited and inconsistent.

Methods
Using Danish health registries, we identified 31,443 patients aged ≥65 years undergoing hip fracture surgery. AC burden was assessed 90 days before surgery by the Anticholinergic Cognitive Burden (ACB) score and number of AC drugs. Logistic and Cox regression producing odds ratios (OR) and hazard ratios (HR) for 30- and 365- day mortality, adjusting for age, sex, and comorbidities were computed.

Results
AC drugs were redeemed by 42% of patients. The 30-day mortality increased from 7% for patients with ACB score of 0 to 16% for patients with ACB score of ≥5, corresponding to an adjusted OR 2.5 (CI: 2.0–3.1). The equivalent adjusted HR for 365-mortality was 1.9 (CI: 1.6–2.1). Using count of AC drugs as exposure we found a stepwise increase in ORs and HRs with increased number of AC drugs; Compared to non-users, adjusted ORs for 30-days mortality were 1.6 (CI: 1.4–1.7), 1.9 (CI: 1.7–2.1), and 2.3 (CI: 1.9–2.7) for users of 1, 2 and 3+ AC drugs. HRs for 365-day mortality were 1.4 (CI: 1.3–1.5), 1.6 (CI: 1.5–1.7) and 1.8 (CI: 1.7–2.0).

Conclusion
Use of AC drugs was associated with increased 30-day and 365-day mortality among older adults with hip fracture. Simply counting the number of AC drugs may be a clinically relevant and easy AC risk assessment tool. Continued effort to reduce AC drug-use is relevant.

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Journal of Clinical Interventions In Aging

An Exploratory Study of Sleep-Wake Differences of Autonomic Activity in Patients with Mild Cognitive Impairment: The Role of Melatonin as a Modulating Factor

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Purpose: The objective of the present study was to assess sleep-wake differences of autonomic activity in patients with mild cognitive impairment (MCI) compared to control subjects. As a post-hoc objective, we sought to evaluate the mediating effect of melatonin on this association.
Patients and Methods: A total of 22 MCI patients (13 under melatonin treatment) and 12 control subjects were included in this study. Sleep-wake periods were identified by actigraphy and 24hr-heart rate variability measures were obtained to study sleep-wake autonomic activity.
Results: MCI patients did not show any significant differences in sleep-wake autonomic activity when compared to control subjects. Post-hoc analyses revealed that MCI patients not taking melatonin displayed lower parasympathetic sleep-wake amplitude than controls not taking melatonin (RMSSD − 7 ± 1 vs 4 ± 4, p = 0.004). In addition, we observed that melatonin treatment was associated with greater parasympathetic activity during sleep (VLF 15.5 ± 0.1 vs 15.1 ± 0.1, p = 0.010) and in sleep-wake differences in MCI patients (VLF 0.5 ± 0.1 vs 0.2 ± 0.0, p = 0.004).
Conclusion: These preliminary findings hint at a possible sleep-related parasympathetic vulnerability in patients at prodromal stages of dementia as well as a potential protective effect of exogenous melatonin in this population.

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REVISTAS FARMACÉUTICAS

American Journal of Health System Pharmacist

Preventing medication history errors in high-risk patients: Impact of California Senate Bill 1254

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Abstract

Purpose

California Senate Bill (SB) 1254 (effective January 1, 2019) requires pharmacy staff at acute hospitals with more than 100 beds to obtain a medication profile for high-risk patients upon hospital admission. This multicenter study sought to evaluate the statewide impact of California SB 1254 by capturing the errors intercepted and harm prevented as a result of the passage of the bill.

Methods

This was a multicenter, prospective, observational study conducted at 11 hospitals in California for 6 consecutive weeks between January 2020 and March 2020. Participating sites captured medication history errors identified among high-risk patients using organization-specific criteria. Errors were categorized by type and ranked for severity of potential or actual harm based on the modified National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) categories.

Results

Study sites had an average daily census of 180 to 800 patients. Approximately 94% (n = 2,554) of medication histories conducted disclosed at least 1 error. Approximately 54% (n = 1,474) of histories disclosed at least 1 serious or potentially life-threatening error. Approximately 6 errors were identified and prevented per patient (95% CI, 5.62-6.01 errors per patient), and 1 in 4 errors (25%) was categorized as potentially serious or life-threatening.

Conclusion

Among high-risk patients, pharmacy-led medication histories significantly reduced medication errors. If not intercepted, these errors would have likely resulted in substantial morbidity and mortality. Future research should evaluate opportunities to standardize high-risk criteria to support patient prioritization and allocation of resources.

Disponible en: https://doi.org/10.1093/ajhp/zxad038

British Journal of Clinical Pharmacy

Added value of patient- and drug-related factors to stratify drug-drug interaction alerts for risk of QT prolongation: Development and validation of a risk prediction model

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Abstract

Aims

Many clinical decision support systems trigger warning alerts for drug-drug interactions potentially leading to QT prolongation and torsades de pointes (QT-DDIs). Unfortunately, there is overalerting and underalerting because stratification is only based on a fixed QT-DDI severity level. We aimed to improve QT-DDI alerting by developing and validating a risk prediction model considering patient- and drug-related factors.

Methods

We fitted 31 predictor candidates to a stepwise linear regression for 1000 bootstrap samples and selected the predictors present in 95% of the 1000 models. A final linear regression model with those variables was fitted on the original development sample (350 QT-DDIs). This model was validated on an external dataset (143 QT-DDIs). Both true QTc and predicted QTc were stratified into three risk levels (low, moderate and high). Stratification of QT-DDIs could be appropriate (predicted risk = true risk), acceptable (one risk level difference) or inappropriate (two risk levels difference).

Results

The final model included 11 predictors with the three most important being use of antiarrhythmics, age and baseline QTc. Comparing current practice to the prediction model, appropriate stratification increased significantly from 37% to 54% appropriate QT-DDIs (increase of 17.5% on average [95% CI +5.4% to +29.6%], padj = 0.006) and inappropriate stratification decreased significantly from 13% to 1% inappropriate QT-DDIs (decrease of 11.2% on average [95% CI −17.7% to −4.7%], padj ≤ 0.001).

Conclusion

The prediction model including patient- and drug-related factors outperformed QT alerting based on QT-DDI severity alone and therefore is a promising strategy to improve DDI alerting.

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Risk factors for and preventability of drug-related hospital revisits in older patients: A post-hoc analysis of a randomized clinical trial

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Abstract

Aim

The aims of this study were (1) to identify older patients' risk factors for drug-related readmissions and (2) to assess the preventability of older patients' drug-related revisits.

Methods

Post hoc analysis of a randomized clinical trial with patients aged ≥65 years at eight wards within four hospitals in Sweden. (1) The primary outcome was risk factors for drug-related readmission within 12 months post-discharge. A Cox proportional hazards model was made with sociodemographic and clinical baseline characteristics. (2) Four hundred trial participants were randomly selected and their revisits (admissions and emergency department visits) were assessed to identify potentially preventable drug-related revisits, related diseases and causes.

Results

Among 2637 patients (median age 81 years), 582 (22%) experienced a drug-related readmission within 12 months. Sixteen risk factors (hazard ratio >1, $P < 0.05$) related to age, previous hospital visits, medication use, multimorbidity and cardiovascular, liver, lung and peptic ulcer disease were identified. (2) The 400 patients experienced a total of 522 hospital revisits, of which 85 (16%) were potentially preventable drug-related revisits. The two most prevalent related diseases were heart failure (n = 24, 28%) and chronic obstructive pulmonary disease (n = 13, 15%). The two most prevalent causes were inadequate treatment (n = 23, 27%) and insufficient or no follow-up (n = 22, 26%).

Conclusion

Risk factors for drug-related readmissions in older hospitalized patients were age, previous hospital visits, medication use and multiple diseases. (2) Potentially preventable drug-related hospital revisits are common and might be prevented through adequate pharmacotherapy and continuity of care in older patients with cardiovascular or lung disease.

Disponible en: https://doi.org/10.1111/bcp.15621

European Journal of Clinical Pharmacology

Effect of digoxin on all-cause and cardiovascular mortality in patients with atrial fibrillation with and without heart failure: an umbrella review of systematic reviews and 12 meta-analyses

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Abstract

Purpose

To perform a systematic umbrella review with meta-analysis to evaluate the certainty of evidence on mortality risk associated with digoxin use in patients with atrial fibrillation (AF) with or without heart failure (HF).

Methods

We systematically searched MEDLINE, Embase, and Web of Science databases from inception to 19 October 2021. We included systematic reviews and meta-analyses of observational studies investigating digoxin effects on mortality of adult patients with AF and/or HF. The primary outcome was all-cause mortality; secondary outcome was cardiovascular mortality. Certainty of evidence was evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool and the quality of systematic reviews/meta-analyses by the A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR2) tool.

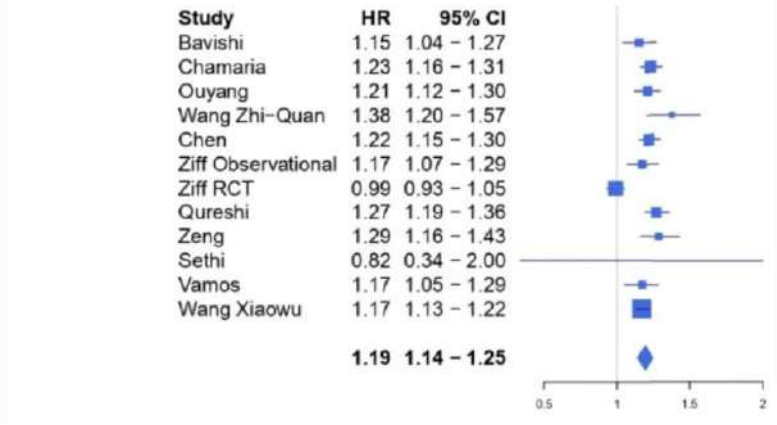
Results

Eleven studies accounting for 12 meta-analyses were included with a total of 4,586,515 patients. AMSTAR2 analysis showed a high quality in 1, moderate in 5, low in 2, and critically low in 3 studies. Digoxin was associated with an increased all-cause mortality (hazard ratio [HR] 1.19, 95% confidence interval [95%CI] 1.14–1.25) with moderate certainty of evidence and with an increased cardiovascular mortality (HR 1.19, 95%CI 1.06–1.33) with moderate certainty of evidence. Subgroup analysis showed that digoxin was associated with all-cause mortality both in patients with AF alone (HR 1.23, 95%CI 1.19–1.28) and in those with AF and HF (HR 1.14, 95%CI 1.12–1.16).

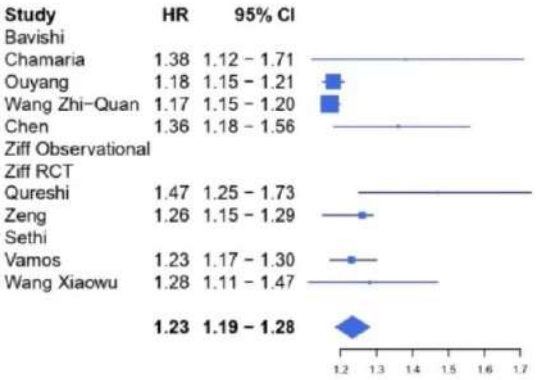
Conclusion

Data from this umbrella review suggests that digoxin use is associated with a moderate increased risk of all-cause and cardiovascular mortality in AF patients regardless of the presence of HF.

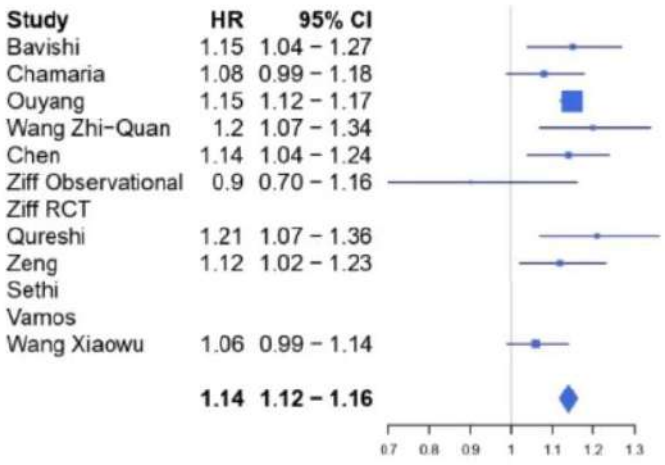
*Panel **A**: All-cause mortality in the whole population.*



*Panel **B**. All-cause mortality in patients with AF only.*



*Panel **C**. All-cause mortality in patients with both AF and HF.*



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Annals of Pharmacotherapy

Co-prescribing of Central Nervous System–Active Medications for COPD Patients: Impact on Emergency Room Visits and Hospitalization

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Abstract

Background

Anxiety and chronic pain are common comorbidities in patients with chronic obstructive pulmonary disease (COPD), which are frequently managed with benzodiazepines (BZDs) and opioids, respectively.

Objective

The purpose of this study was to determine whether different combinations of opioids, BZD, and their substitutes—gabapentinoids (GABA) and selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs)—are associated with lower risk of acute respiratory events in COPD patients with co-occurring chronic pain and anxiety.

Methods

This retrospective cohort study used a nationally representative sample of Medicare beneficiaries with COPD, chronic pain, and anxiety. Patients were grouped based on drug combination (opioid + BZD/Z-hypnotics, opioid + GABA, opioid + SSRI/SNRI, BZD/Z-hypnotics + GABA, BZD/Z-hypnotics + SSRI/SNRI, GABA + SSRI/SNRI, or ≥3 drugs). The primary outcome was emergency room (ER) visit or hospitalization due to acute respiratory events assessed up to 180 days following initiation of drug combination. Overdose secondary to central nervous system (CNS)–related drugs was also assessed up to 180 days following initiation of drug combination.

Results

The drug combination opioid + GABA was associated with decreased risk for ER visit (hazard ratio [HR] = 0.73; 95% CI = 0.61-0.87) and hospitalization (HR = 0.69; 95% CI = 0.55-0.85). Opioid + SSRI/SNRI also showed decreased risk for ER visit (HR = 0.84; 95% CI = 0.71-0.99). There was no significant difference in risk for CNS-related drug overdose among different drug combinations compared with opioid + BZD/Z-hypnotics.

Conclusion and Relevance

Opioids in combination with GABA and SSRI/SNRI demonstrate relatively lower risk for acute respiratory events among patients with COPD and comorbid chronic pain and anxiety. The findings emphasize the need for multimodal management in this vulnerable population.

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Pharmacoepidemiology & Drug Safety

Effect of tramadol and DOACs with special attention to dabigatran on concomitant use, on the risk of mayor bleeding using BIFAP database in Spain

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Abstract

Background

Tramadol, a weak opioid, inhibits the reuptake of serotonin, a key feature on vascular homeostasis. A suspected interaction exists between dabigatran and tramadol, which might trigger an excess on risk of bleeding however, there is a gap in knowledge on this topic.

Purpose

To estimate the effects of tramadol, dabigatran and concomitant use on the risk of hospitalized major bleeds (Gastrointestinal bleeding and intra-extracranial bleeds).

Methods

Among a validated established cohort of new users of oral anticoagulants for non-valvular atrial fibrillation (NVAF) aged 18 years or older, we identified all hospitalized bleed episodes (GIB and extra/intracranial bleeds) within 2008–2015. A nested case–control analysis was conducted using conditional logistic regression. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated for dabigatran, tramadol, and concomitant use. Several sensitivity analyses were carried out.

Results

aORs (95%CIs) for current use of only dabigatran, only tramadol and concomitant users were 1.73 (1.37–2.18) and 1.38 (1.13–1.67) and 2.04 (0.74–5.67) compared with non-users of both drugs (>365 days). aORs for current continuers and non-continuer users of dabigatran were 1.36 (1.00–1.86) and 2.19 (1.61–2.98), respectively. For the latter, non-continuer users with a short duration of dabigatran cumulated the highest risk (3.36 [1.88–5.99]). There also was an increased risk with concomitant use of tramadol and rivaroxaban (2.24 [1.19–4.21]), or antagonist of vitamin K (1.30 [1.00–1.69]).

Conclusion

There was a trend towards and increased risk of excess bleeds when using concomitantly with dabigatran. The effect decreases with a narrower definition of current use.

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Prevalence of Potentially Inappropriate Medications in Patients With Multimorbidity According to LESS-CHRON and STOPPFrail Criteria

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Abstract

Objective

LESS-CHRON (List of Evidence-Based Deprescribing for Chronic Patients) and STOPPFrail (Screening Tool of Older Persons' Prescriptions in Frail adults with limited life expectancy) are criterion-based deprescribing tools. This study aimed to identify the prevalence of potentially inappropriate medications (PIMs) with these tools in an outpatient, polymedicated, older population with multimorbidity.

Design

Single-center cross-sectional observational study. PIMs and criteria subject to deprescribing identified by each tool were collected in patients who were being followed up on outpatient internal medicine consultation.

Methods

PIMs were identified by STOPPFrail and LESS-CHRON criteria reviewing medical histories and pharmacologic treatments of the patients in the electronic health card system. Sociodemographic, clinical, and pharmacologic variables were recorded. A correlation analysis between treatment tools and clinical values was performed using the nonparametric Spearman rho correlation.

Results

Eighty-three patients with a median of 14.4 (interquartile range 12-17) prescribed drugs were included. The total number of PIMs identified with LESS-CHRON was 158 vs 127 with STOPPFrail. Eight of the 27 criteria (29.6%) for LESS-CHRON and 15 of the 25 for STOPPFrail were found to be not applicable. A significant correlation was obtained for both tools with the number of prescribed drugs at the time of inclusion. The Profund, Barthel, and Frail-VIG index only showed a significant correlation with LESS-CHRON.

Conclusion and Implications

Both tools have shown the capacity to identify PIMs that can be deprescribed in the population studied. However, LESS-CHRON appears to have a greater detection potential in the subgroup of patients analyzed. STOPPFrail brings a certain complementarity in other areas of therapy not covered by LESS-CHRON.

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Annals of Internal Medicine

Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial

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Abstract

Background

For patients with heart failure, reduced left ventricular ejection fraction and iron deficiency, intravenous ferric carboxymaltose administration improves quality of life and exercise capacity in the short-term and reduces hospital admissions for heart failure up to 1 year. We aimed to evaluate the longer-term effects of intravenous ferric derisomaltose on cardiovascular events in patients with heart failure.

Methods

IRONMAN was a prospective, randomised, open-label, blinded-endpoint trial done at 70 hospitals in the UK. Patients aged 18 years or older with heart failure (left ventricular ejection fraction ≤45%) and transferrin saturation less than 20% or serum ferritin less than 100 µg/L were eligible. Participants were randomly assigned (1:1) using a web-based system to intravenous ferric derisomaltose or usual care, stratified by recruitment context and trial site. The trial was open label, with masked adjudication of the outcomes. Intravenous ferric derisomaltose dose was determined by patient bodyweight and haemoglobin concentration. The primary outcome was recurrent hospital admissions for heart failure and cardiovascular death, assessed in all validly randomly assigned patients. Safety was assessed in all patients assigned to ferric derisomaltose who received at least one infusion and all patients assigned to usual care. A COVID-19 sensitivity analysis censoring follow-up on Sept 30, 2020, was prespecified. IRONMAN is registered with ClinicalTrials.gov, NCT02642562.

Findings

Between Aug 25, 2016, and Oct 15, 2021, 1869 patients were screened for eligibility, of whom 1137 were randomly assigned to receive intravenous ferric derisomaltose (n=569) or usual care (n=568). Median follow-up was 2·7 years (IQR 1·8-3·6). 336 primary endpoints (22·4 per 100 patient-years) occurred in the ferric derisomaltose group and 411 (27·5 per 100 patient-years) occurred in the usual care group (rate ratio [RR] 0·82 [95% CI 0·66 to 1·02]; p=0·070). In the COVID-19 analysis, 210 primary endpoints (22·3 per 100 patient-years) occurred in the ferric derisomaltose group compared with 280 (29·3 per 100 patient-years) in the usual care group (RR 0·76 [95% CI 0·58 to 1·00]; p=0·047). No between-group differences in deaths or hospitalisations due to infections were observed. Fewer patients in the ferric derisomaltose group had cardiac serious adverse events (200 [36%]) than in the usual care group (243 [43%]; difference -7·00% [95% CI -12·69 to -1·32]; p=0·016).

Interpretation

For a broad range of patients with heart failure, reduced left ventricular ejection fraction and iron deficiency, intravenous ferric derisomaltose administration was associated with a lower risk of hospital admissions for heart failure and cardiovascular death, further supporting the benefit of iron repletion in this population.

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British Medical Journal

Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials

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Abstract

Objective

To review the comparative effectiveness of osteoporosis treatments, including the bone anabolic agents, abaloparatide and romosozumab, on reducing the risk of fractures in postmenopausal women, and to characterise the effect of antiosteoporosis drug treatments on the risk of fractures according to baseline risk factors.

Design

Systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials.

Data sources

Medline, Embase, and Cochrane Library to identify randomised controlled trials published between 1 January 1996 and 24 November 2021 that examined the effect of bisphosphonates, denosumab, selective oestrogen receptor modulators, parathyroid hormone receptor agonists, and romosozumab compared with placebo or active comparator.

Eligibility criteria for selecting studies

Randomised controlled trials that included non-Asian postmenopausal women with no restriction on age, when interventions looked at bone quality in a broad perspective. The primary outcome was clinical fractures. Secondary outcomes were vertebral, non-vertebral, hip, and major osteoporotic fractures, all cause mortality, adverse events, and serious cardiovascular adverse events.

Results

The results were based on 69 trials (>80 000 patients). For clinical fractures, synthesis of the results showed a protective effect of bisphosphonates, parathyroid hormone receptor agonists, and romosozumab compared with placebo. Compared with parathyroid hormone receptor agonists, bisphosphonates were less effective in reducing clinical fractures (odds ratio 1.49, 95% confidence interval 1.12 to 2.00). Compared with parathyroid hormone receptor agonists and romosozumab, denosumab was less effective in reducing clinical fractures (odds ratio 1.85, 1.18 to 2.92 for denosumab *v* parathyroid hormone receptor agonists and 1.56, 1.02 to 2.39 for denosumab *v* romosozumab). An effect of all treatments on vertebral fractures compared with placebo was found. In the active treatment comparisons, denosumab, parathyroid hormone receptor agonists, and romosozumab were more effective than oral bisphosphonates in preventing vertebral fractures. The effect of all treatments was unaffected by baseline risk indicators, except for antiresorptive treatments that showed a greater reduction of clinical fractures compared with placebo with increasing mean age (number of studies=17; β=0.98, 95% confidence interval 0.96 to 0.99). No harm outcomes were seen. The certainty in the effect estimates was moderate to low for all individual outcomes, mainly because of limitations in reporting, nominally indicating a serious risk of bias and imprecision.

Conclusions

The evidence indicated a benefit of a range of treatments for osteoporosis in postmenopausal women for clinical and vertebral fractures. Bone anabolic treatments were more effective than bisphosphonates in the prevention of clinical and vertebral fractures, irrespective of baseline risk indicators. Hence this analysis provided no clinical evidence for restricting the use of anabolic treatment to patients with a very high risk of fractures.

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Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials

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Abstract

Objective

To compare the benefits and harms of drug treatments for adults with type 2 diabetes, adding non-steroidal mineralocorticoid receptor antagonists (including finerenone) and tirzepatide (a dual glucose dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist) to previously existing treatment options.

Design

Systematic review and network meta-analysis. Eligible randomised controlled trials compared drugs of interest in adults with type 2 diabetes. Eligible trials had a follow-up of 24 weeks or longer. Trials systematically comparing combinations of more than one drug treatment class with no drug, subgroup analyses of randomised controlled trials, and non-English language studies were deemed ineligible. Certainty of evidence was assessed following the GRADE (grading of recommendations, assessment, development and evaluation) approach.

Results

The analysis identified 816 trials with 471 038 patients, together evaluating 13 different drug classes; all subsequent estimates refer to the comparison with standard treatments. Sodium glucose cotransporter-2 (SGLT-2) inhibitors (odds ratio 0.88, 95% confidence interval 0.83 to 0.94; high certainty) and GLP-1 receptor agonists (0.88, 0.82 to 0.93; high certainty) reduce all cause death; non-steroidal mineralocorticoid receptor antagonists, so far tested only with finerenone in patients with chronic kidney disease, probably reduce mortality (0.89, 0.79 to 1.00; moderate certainty); other drugs may not. The study confirmed the benefits of SGLT-2 inhibitors and GLP-1 receptor agonists in reducing cardiovascular death, non-fatal myocardial infarction, admission to hospital for heart failure, and end stage kidney disease. Finerenone probably reduces admissions to hospital for heart failure and end stage kidney disease, and possibly cardiovascular death. Only GLP-1 receptor agonists reduce non-fatal stroke; SGLT-2 inhibitors are superior to other drugs in reducing end stage kidney disease. GLP-1 receptor agonists and probably SGLT-2 inhibitors and tirzepatide improve quality of life. Reported harms were largely specific to drug class (eg, genital infections with SGLT-2 inhibitors, severe gastrointestinal adverse events with tirzepatide and GLP-1 receptor agonists, hyperkalaemia leading to admission

to hospital with finerenone). Tirzepatide probably results in the largest reduction in body weight (mean difference −8.57 kg; moderate certainty). Basal insulin (mean difference 2.15 kg; moderate certainty) and thiazolidinediones (mean difference 2.81 kg; moderate certainty) probably result in the largest increases in body weight. Absolute benefits of SGLT-2 inhibitors, GLP-1 receptor agonists, and finerenone vary in people with type 2 diabetes, depending on baseline risks for cardiovascular and kidney outcomes

Conclusions

This network meta-analysis extends knowledge beyond confirming the substantial benefits with the use of SGLT-2 inhibitors and GLP-1 receptor agonists in reducing adverse cardiovascular and kidney outcomes and death by adding information on finerenone and tirzepatide. These findings highlight the need for continuous assessment of scientific progress to introduce cutting edge updates in clinical practice guidelines for people with type 2 diabetes.

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Denosumab and incidence of type 2 diabetes among adults with osteoporosis: population based cohort study

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Abstract

Objective

To estimate the effect of denosumab compared with oral bisphosphonates on reducing the risk of type 2 diabetes in adults with osteoporosis.

Design

Population based study involving emulation of a randomized target trial using electronic health records.

Setting

IQVIA Medical Research Data primary care database in the United Kingdom, 1995-2021.

Participants

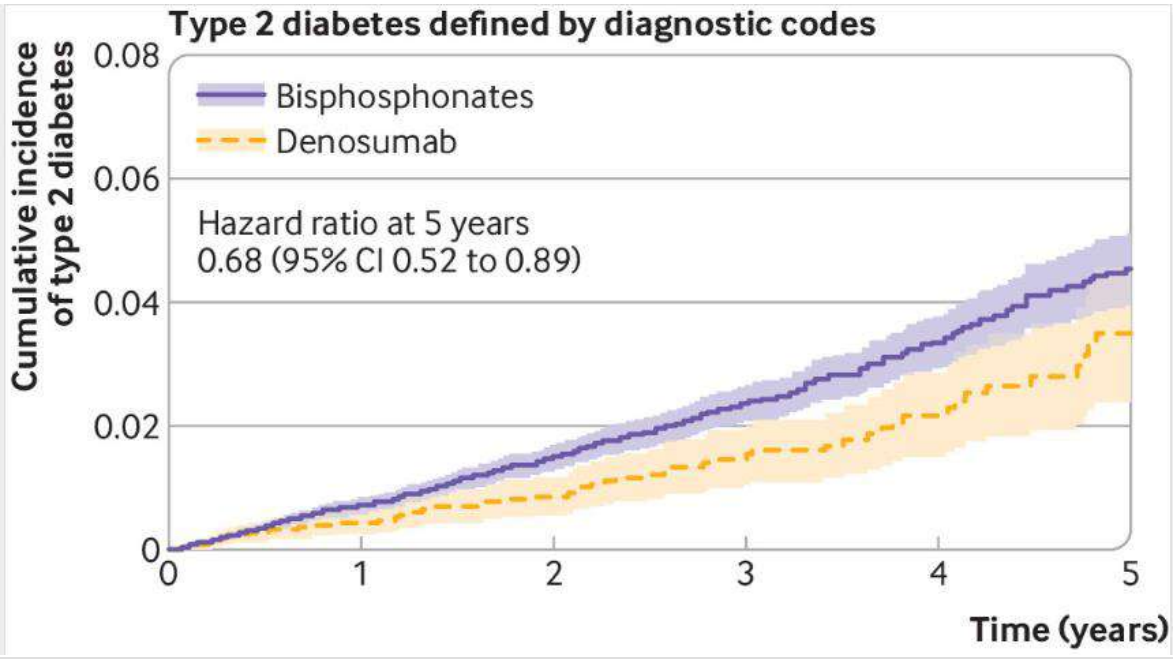
Adults aged 45 years or older who used denosumab or an oral bisphosphonate for osteoporosis. The primary outcome was incident type 2 diabetes, as defined by diagnostic codes. Cox proportional hazards models were used to estimate adjusted hazard ratios and 95% confidence intervals, comparing denosumab with oral bisphosphonates using an as treated approach.

Results

4301 new users of denosumab were matched on propensity score to 21 038 users of an oral bisphosphonate and followed for a mean of 2.2 years. The incidence rate of type 2 diabetes in denosumab users was 5.7 (95% confidence interval 4.3 to 7.3) per 1000 person years and in oral bisphosphonate users was 8.3 (7.4 to 9.2) per 1000 person years. Initiation of denosumab was associated with a reduced risk of type 2 diabetes (hazard ratio 0.68, 95% confidence interval 0.52 to 0.89). Participants with prediabetes appeared to benefit more from denosumab compared with an oral bisphosphonate (hazard ratio 0.54, 0.35 to 0.82), as did those with a body mass index ≥30 (0.65, 0.40 to 1.06).

Conclusions

In this population based study, denosumab use was associated with a lower risk of incident type 2 diabetes compared with oral bisphosphonate use in adults with osteoporosis. This study provides evidence at a population level that denosumab may have added benefits for glucose metabolism compared with oral bisphosphonates.



Cumulative incidence of type 2 diabetes as defined by diagnostic codes and by an alternative definition combining diagnostic codes, antidiabetes drugs, and laboratory test results among users of denosumab and matched users of bisphosphonates in IQVIA Medical Research Data. Shaded areas represent 95% confidence intervals (CIs)

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