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REVISIÓN BIBLIOGRÁFICA SEPTIEMBRE 2020: Selección de artículos

REVISTAS GERIÁTRICAS

Archives of Gerontology and Geriatrics

Pharmacologic interventions for prevention of delirium in hospitalized older people: A meta-analysis

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Abstract

Introduction
To comprehensively assess the effects of pharmacologic interventions for prevention of delirium in hospitalized older people.

Materials and methods

A systematic review with meta-analysis following Preferred Reporting Items for Systematic reviews and Meta-Analyses methodology was performed. Hospitalized people aged 65 and older, recruited to randomized controlled clinical trials. The electronic databases MEDLINE, EMBASE, WOS and Cochrane Central Register of Controlled Trials were consulted (March 2019). Predefined criteria were used to determine inclusion of studies and to assess their methodologic quality.
Results
1855 records were identified in the database, and after removing the duplicates, the titles and abstracts evaluated were 1250 records. Finally, 25 randomized controlled trials contributed to meta-analysis (n = 5820): 1 anti-epileptics (n = 697), 2 anti-inflammatories (n = 615), 4 antipsychotics (n = 1193), 2 cholinesterase inhibitors (n = 87), 13 hypnotics/sedatives (n = 2909), 1 opioids (n = 52), 1 psychostimulants/nootropics (n = 81), 1 yokukansan (n = 186). Olanzapine (RR = 0.36; 95 %CI: 0.24, 0.52; k = 1; n = 400), rivastigmine (RR = 0.36; 95 %CI: 0.15, 0.87; k = 1; n = 62), dexmedetomidine (RR = 0.52; 95 %CI: 0.38, 0.71; I^2 = 55 %; k = 6; n = 2084), and ramelteon (RR = 0.09; 95 %CI: 0.01, 0.64; k = 1; n = 65) reduced the incidence of delirium compared to placebo/usual care. Only dexmedetomidine was also associated with a shorter duration of delirium (0.70 days reduction) and a lower consumption of psychotropic drugs (48 %). No effect was found in mortality, adverse events, urinary tract infections or post-operative complications.
Conclusions
This meta-analysis suggests that dexmedetomidine is effective in reducing the incidence and duration of delirium in hospitalized older patients. Individual studies reveal effects of ramelteon, olanzapine and rivastigmine on the incidence of delirium but the evidence is insufficient to draw a robust conclusion.

Disponible en: https://www.sciencedirect.com/science/article/abs/pii/S0167494320301655

Drugs and Aging

Safety and Tolerability Results from the PILLAR Study: A Phase IV, Double-Blind, Randomized, Placebo-Controlled Study of Mirabegron in Patients ≥ 65 years with Overactive Bladder-Wet

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Abstract
Background

In older patients with overactive bladder (OAB), mirabegron, a β3-adrenoreceptor agonist, represents an alternative treatment that may have a favorable risk–benefit profile.

Objectives

Our objective was to further examine the safety and tolerability of mirabegron versus placebo treatment in patients aged ≥ 65 years with OAB-wet.

Methods

We conducted a 12-week, double-blind, randomized, placebo-controlled phase IV study to compare mirabegron with placebo. Community-dwelling patients aged ≥ 65 years with OAB-wet (one or more incontinence episode and three or more urgency episodes, and an average of eight or more micturitions/24 h over a 3-day diary) were randomized to receive placebo or mirabegron 25 mg/day (optional dose escalation to 50 mg/day at week 4 or 8). Safety analyses were performed for adverse events (AEs) and vital signs on all randomized patients who received one or more dose of study drug.

Results

Treatment-emergent AEs (TEAEs), the majority mild or moderate in severity, were reported in 39.4% of placebo patients and 44.2 and 49.8% of those who received mirabegron 25 mg or 50 mg, respectively. The most common TEAEs in mirabegron-treated patients were urinary tract infection, headache, and diarrhea. The incidence of TEAEs was slightly higher in mirabegron patients aged ≥ 75 years than in those aged < 75 years. There were no clinically meaningful differences in changes in vital signs from baseline to end of treatment for any treatment group, and no differences were observed between mirabegron and placebo treatment groups. TEAEs tended to occur early post exposure and were not dose related.

Conclusions
Mirabegron treatment was well-tolerated in older adults with OAB-wet. Safety and tolerability were consistent with the known mirabegron safety profile.

Disponible en: https://link.springer.com/article/10.1007/s40266-020-00783-w

Platinum-Based Chemotherapy in Older Patients with Non-Small Cell Lung Cancer: What to Expect in the Real World

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Abstract

Background

The role of platinum-based chemotherapy (PBC) for the treatment of older patients with non-small cell lung cancer (NSCLC) is still a matter of debate, despite the advent of immunotherapy.

Objective

The aim of the study was to identify factors associated with first-line PBC prescription and, secondly, to evaluate the impact of first-line PBC on survival, treatment intensity, risk of hospitalization, and subsequent treatments.

Patients and Methods

We reviewed a consecutive series of 474 older patients (age ≥ 70 years) diagnosed with stage IIIB–IV NSCLC at the Department of Oncology, University Hospital of Udine, Italy from January 2009 to March 2017.

Results

Overall, 198 patients were deemed eligible, and 65.2% received a PBC. At multivariate analysis, older age was the only factor associated with PBC prescription. In the whole cohort, 46 patients (23.2%) were hospitalized for chemotherapy-related toxicity. Both PBC prescription (odds ratio [OR] 2.23, 95% confidence interval [CI] 1.02–4.87, p = 0.04) and tumor burden (OR 2.39, 95% CI 1.07–5.32, p = 0.03) emerged as independent risk factors for hospitalization. Moving to significant predictors of patterns of care, Eastern Cooperative Oncology Group (ECOG) performance status > 0 was associated with greater risk of first-line failure (OR 2.20, 95% CI 1.15–4.20, p = 0.02), while bone metastases (OR 0.29, 95% CI 0.12–0.69, p = 0.005) and a Charlson Comorbidity Index score ≥ 3 (OR 0.40, 95% CI 0.19–0.84, p = 0.016) independently predicted lower probability of receiving second-line therapy. Remarkably, PBC did not significantly impact overall survival (hazard ratio [HR] 0.83, 95% CI 0.61–1.14, p = 0.24) and progression-free survival (HR 0.95, 95% CI 0.70–1.28, p = 0.73) compared to single-agent chemotherapy (SAC). However, according to an exploratory landmark analysis, patients who received four cycles of treatment or maintenance therapy experienced prolonged overall survival, regardless of PBC use.

Conclusions

This study evaluated the real-world use of PBC in older patients with NSCLC, offering an insight into the determinants of its prescription and the pattern of care of these patients. Of note, PBC

use was associated with a higher likelihood of hospitalization for chemotherapy-related toxicity, with no benefit on survival compared to SAC.

Disponible en: https://link.springer.com/article/10.1007/s40266-020-00785-8

Journal of the American Geriatrics Society

DOACs Versus VKAs in Older Adults Treated for Acute Venous Thromboembolism: Systematic Review and Meta-Analysis

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Abstract

BACKGROUND/OBJECTVES

Four direct-acting oral anticoagulants (DOACs) are currently approved by the Food and Drug Administration for the treatment of venous thromboembolism (VTE). Limited efficacy and safety data are available for their use in older adults (aged ≥75 years).

METHODS

Medline, Cochrane Central Register of Controlled Trials, Embase, EBSCO, Web of Science, and CINAHL databases were searched for trials comparing DOACs with vitamin K antagonists (VKAs) for the treatment of VTE in older adults from inception through January 1, 2020. Meta-analysis was performed to assess the combined endpoint of recurrent VTE and related deaths and bleeding events (composite of major and clinically relevant nonmajor bleeding). The Mantel-Haenszel relative risk (RR) random effects model was used to pool results across studies.

RESULTS

Six randomized controlled trials at low risk of bias met criteria for inclusion with a total of 3,665 patients aged 75 years and older with follow-up of 24 weeks or longer. Data for bleeding events were not available for dabigatran. Overall, DOACs had an improved efficacy over VKAs (RR = .56; 95% confidence interval [CI] = .38-.82). There was no statistically significant difference in the safety outcomes (RR = .77; 95% CI = .56-1.05). No significant heterogeneity was observed for efficacy outcome, and only moderate heterogeneity was observed for safety outcome.

CONCLUSION

In older adults with VTE, DOACs appear to improve rates of recurrent VTE and VTE-related deaths compared with VKAs with similar bleeding outcomes.

Disponible en: https://onlinelibrary.wiley.com/doi/10.1111/jgs.16549

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Journal of Geriatric Oncology

Opioid Use and the Risk of Falls, Fall Injuries and Fractures among Older Adults: A Systematic Review and Meta-Analysis

Abstract

Background

There is increasing concern about opioid use as a pain treatment option among older adults. Existing literature implies an association between opioid use and fracture, increasing the risk of death and disabilities; yet, this relationship with other fall-related outcomes has not been fully explored. We performed a meta-analysis to evaluate the associations between opioid use and adverse health outcomes of falls, fall injuries, and fractures among older adults.

Methods

A systematic literature search was conducted using nine databases: Medline, Embase, CINAHL, PsycInfo, Global Health, Northern Light Sciences Conference Abstracts, Cochrane CENTRAL, WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov. We log-transformed effect sizes (relative risk [RR], odds ratio [OR], and hazard ratio [HR]) to compute pooled risk estimates comparable across the studies. The random-effects model was applied to calculate the pooled risk estimates due to heterogeneity. Meta-regressions explored differences in risk estimates by analysis method, study design, setting, and study quality.

Results

Thirty studies, providing 34 relevant effect sizes, met the inclusion criteria for this meta-analysis. Overall, opioid use was significantly associated with falls, fall injuries, and fractures, with effect sizes ranging from 0.15 to 0.71. In meta-regressions, no selected factors explained heterogeneity.

Conclusion

While heterogeneity is present, results suggest an increased risk of falls, fall injuries, and fractures among older adults who used opioids. Findings highlight the need for opioid education and nonopioid-related pain management interventions among older adults to decrease fall-related risk.

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REVISTAS FARMACÉUTICAS

European Journal of Clinical Pharmacology

Pattern of treatment of behavioural and psychological symptoms of dementia and pain: evidence on pharmacoutilization from a large real-world sample and from a centre for cognitive disturbances and dementia

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Abstract

Purpose

Data concerning the number of diagnoses and of the drugs prescribed to patients affected by dementia are still scarce. Here we test whether or not (1) prescription of symptomatic drugs against Alzheimer's disease (AD) may approximate the number of patients affected by dementia in Italy and (2) adherence to this treatment affects the pattern of prescription of drugs (i.e. antipsychotics and antidepressants) for behavioural and psychological symptoms of dementia (BPSD) and the previously reported limited prescription of analgesics.

Methods

This retrospective observational study concerns 84,235 subjects older than 60 years and registered in the provincial prescription database of the health district of Cosenza accounting for a population of 298,000 inhabitants. The prescribing pattern of antipsychotics, antidepressants, and analgesics has been investigated in patients receiving concurrent prescriptions of acetylcholinesterase inhibitors (AChEI) and/or memantine. Data from a single centre for cognitive disturbances and dementia (CDCD) in the same health district were used to explore at which stage dementia was diagnosed. The study was approved by Calabria Region Ethical Committee no. 31/2017 and registered on October 31, 2017.

Results

The data show that 859 patients are treated with AChEI and/or memantine; 420 patients (48.89%) receive at least 80% of the recommended medications. CDCD data indicate a delay in dementia diagnosis, which often was made when the patients were moderately to severely demented (Mini Mental State Examination, MMSE ≤ 20). Adherence did not influence prescription of most of the drugs explored, but use of non-steroidal anti-inflammatory drugs was higher in non-adherent patients. Antipsychotics and antidepressants are frequently used (20.61–20.71% and 42.37–51.43%, respectively), and this, at least in part, might stem from the observed under-treatment of chronic pain (opioids are prescribed in the 4.76% and 12.46% of adherent and non-adherent patients and gabapentin and pregabalin are used in the 4.29% and 4.07% of adherent and non-adherent patients respectively), resulting in more frequent BPSD. 16.43% of patients receive antipsychotics for longer than 6–12 weeks.

Conclusion

This 2-year period study, including a wide cohort of community demented patients, shows that dementia is diagnosed late and that prevalence of BPSD prescriptions is high and not impacted by adherence to anti-dementia drugs. The rate of prescription of potentially harmful antipsychotics and antidepressants appears to be high though whether the concomitantly observed limited prescription of analgesics might be a contributing factor needs to be further investigated. Our data support the development of strategies to improve the management of BPSD.

Disponible en: https://link.springer.com/article/10.1007/s00228-020-02995-w

The Annals of Pharmacotherapy

Effect of Dexmedetomidine on Delirium in Elderly Surgical Patients: A Meta-analysis of Randomized Controlled Trials

Chunmei Lin, MD, MS, Hankun Tu, MD, Zhixuan Jie, MD, MS,

Xinkai Zhou, MD, Chaoyang Li, MD

Abstract

Objective:

The purpose of this meta-analysis is to assess the effect of dexmedetomidine on delirium in elderly surgical patients.

Study Selection and Data Extraction:

RCTs without language restrictions were included if delirium incidence was assessed in elderly surgical patients receiving dexmedetomidine. Intervention and basic information were extracted.

Data Synthesis:

21 studies were included. Dexmedetomidine reduced delirium occurrence (risk ratio [RR] = 0.55; 95% CI = 0.45 to 0.67) in elderly surgical patients with sufficient evidence from trial sequential analysis. Dexmedetomidine did not prevent delirium incidence for cardiac surgery (RR = 0.71; 95% CI = 0.44 to 1.15) with insufficient evidence. Dexmedetomidine decreased mortality incidence (RR = 0.47; 95% CI = 0.25 to 0.89), shortened the length of intensive care unit (ICU; standard mean difference [SMD] = −0.46) and hospital stays (SMD = −0.41), and increased bradycardia incidence (RR = 1.60).

Relevance to Patient Care and Clinical Practice:

This review revealed that dexmedetomidine could reduce delirium incidence for elderly noncardiac surgical patients, and the effect of dexmedetomidine on delirium for elderly cardiac surgical patients needs further studies to guide clinicians.

Conclusion:

Dexmedetomidine reduced delirium incidence in elderly surgical patients. The efficacy of dexmedetomidine on delirium for elderly cardiac surgical patients warrants further studies. Furthermore, dexmedetomidine was associated with an increased bradycardia incidence, shorter length of ICU/hospital stays, and a lower incidence of mortality.

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Pharmacoepidemiology and Drug Safety

Alzheimer's disease and related dementias risk: Comparing users of non-selective and M3-selective bladder antimuscarinic drugs

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Abstract

Purpose

Bladder antimuscarinic (BAM) drug use is associated with increased risk of Alzheimer's disease and related dementias (ADRD). It is hypothesized that BAMs with non-selective receptor binding may increase ADRD risk more than M3-selective BAMs. This study compared ADRD risk for users of non-selective and M3-selective BAMs and examines ADRD risk associated with overall BAM use.

Methods

Retrospective cohort study of Medicare claims for 71 688 individuals who used BAM drugs during 2007-2009 without an ADRD diagnosis. We compared ADRD incidence (2011-2016) between non-selective BAM users (fesoterodine, flavoxate, oxybutynin, tolterodine, trospium) and M3-selective BAM users (darifenacin, solifenacin). Logistic regressions compared individuals using target drugs in the same category of total standardized daily doses (TSDD) as a standardized measure of drug exposure, and adjusted for age, sex, race/ethnicity, healthcare utilization, other medication use, socioeconomic status, and comorbidities. Secondary analyses compared ADRD risk associated with different doses of BAMs overall.

Results

Non-selective BAM use (compared to M3-selective) was not significantly associated with ADRD incidence. Odds ratios for non-selective use were 0.97 (CI: 0.89-1.04) for 1-364 TSDD, 0.94 (CI: 0.83-1.06) for 365-729, 1.00 (CI: 0.87-1.16) for 730-1094, and 1.03 (CI: 0.88-1.20) for >1094. Higher TSDD of BAMs overall (combining both non-selective and M3-selective BAMs), when compared to 1-364 TSDD, were associated with increased ADRD incidence (OR = 1.05 (CI: 0.99-1.10) for 365-729, OR = 1.11 (CI: 1.05-1.17) for 730-1094, and OR = 1.10 (CI: 1.04-1.15) for >1094).

Conclusions

Non-selective and M3-selective BAM users had similar odds of ADRD incidence, and BAM use overall was significantly associated with ADRD incidence.

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Clinical Pharmacology & Therapeutics

Are Seniors Dependent on Benzodiazepines? A National Clinical Survey of Substance Use Disorder

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Abstract
Benzodiazepines and Z-drugs, zolpidem and zopiclone, (BZD/Z) are used longer than recommended in the elderly population. However, to date, very few attempts have been made to evaluate dependence on BDZ/Z among the elderly population. We conducted a national multicentric observational prospective study aimed at evaluating the prevalence of and risk factors for dependence among elderly adults. Patients aged 65 or older who were treated with BZD/Z for at least 3 months were evaluated through clinical interviews that conformed to official Diagnostic and Statistical Manual of Mental Disorders (DSM) dependence criteria. Among the 1,024 patients included in the survey, 442 of 976 (45.3%) met the dependence criteria. In the multivariate logistic regression model, dependent patients were categorized as follows: younger (odds ratio (OR) = 0.97), living mostly alone (OR = 1.45), showing psychiatric problems (OR = 2.22), having additional treatments (other than BZD/Z; OR = 1.37), having long-lasting treatment (OR = 1.04), exhibiting significant relationship difficulties (OR = 1.96), committing transgressional behaviors to procure BZD/Z (OR = 2.70), and wanting to stop their consumption of BZD/Z (OR = 7.60). A latent class analysis, which was applied to sort out subgroups within dependent patients, identified two profiles according to the prevalence of dependence items: profile 1 (73%), "withdrawal syndrome when BZD/Z is stopped" (100%) and "previous unsuccessful attempts to stop consumption" (82%); and profile 2 (27%), "tolerance" (76%) and "intake in larger amounts or over a longer period than intended" (86%). BZD/Z dependence is frequent in the elderly population, and among dependent patients, we found two profiles corresponding to positive and negative conditioning of the psychoactive effects of BZD/Z. This study is registered as NCT01920581.

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REVISTAS DE MEDICINA GENERAL

European Journal of Internal Medicine

JAMA Internal Medicine

The Exclusion of Older Persons From Vaccine and Treatment Trials for Coronavirus Disease 2019—Missing the Target

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Methods
Details of our approach, methods, and description of included clinical trials are shown in the eMethods in the Supplement.

Each of the 847 clinical trials was abstracted by at least 1 trained research associate, with reliability checks of all ratings. Age exclusions were identified by viewing all of the eligibility and exclusionary criteria. Specific age exclusions were classified into 5-year categories from ages 55 to

80 years; our focus was on exclusion of the 65 to 80 years age group most affected by COVID-19. Informed consent was waived because all data were deidentified and came from previously published studies.

Results

Table 1 identifies clinical trials by treatment with an exclusion by age. We found large variability in the age exclusions. Among the 847 trials, 195 (23%) included an age cut-off.

Table 2 displays indirect age-related exclusions preferentially affecting older adults; each trial could have multiple exclusions. The most common age-related exclusion was compliance concerns (213 trials), and 129 of these were related to consent. Next, were broad nonspecified exclusions, specific comorbidities, requirement of technology, and other reasons. A total of 366 (43%) trials had any exclusions, of which 252 (30%) did not have an age-based exclusion. Combining the results of age-based exclusions (Table 1) and exclusions preferentially affecting older adults (Table 2), 447 (53%) trials were considered high risk for excluding older adults.

In 232 phase 3 clinical trials, 38 (16%) included age cut-offs and 77 (33%) had exclusions preferentially affecting older adults; thus, 115 (50%) were considered high risk for excluding older adults. Of 18 vaccine trials, 11 (61%) included age cut-offs, and the remaining 7 had broad nonspecified exclusions; thus, 100% were considered high risk for excluding older adults.

Discussion

Our findings indicate that older adults are likely to be excluded from more than 50% of COVID-19 clinical trials and 100% of vaccine trials. Such exclusion will limit the ability to evaluate the efficacy, dosage, and adverse effects of the intended treatments. We acknowledge that some exclusions for severe or uncontrolled comorbidities will be essential to protect the health and safety of older adults. However, caution must be taken to avoid excluding otherwise eligible participants for reasons that are not well-justified. A limitation of this study is that we did not conduct detailed review of every study protocol; thus, we were unable to fully evaluate the appropriateness of all comorbidity exclusions.

Our concern is more than theoretical. Even without stated age-based exclusions, several recently published clinical trials of COVID-19 treatments had young age ranges, such as 1 recent study4 with a median age of only 40 years, meaning there would be no or few participants over age 75.

If the older age group is excluded from vaccine trials, efforts to ensure effectiveness, titrate dosage or frequency, and assess adverse effects in the group most vulnerable to COVID-19 will not be possible. Antibody responses to vaccines may decrease with age, and can improve with increasing antigen levels, adjuvants, or repeated dosing.5 Some have argued that only vaccination of younger populations is needed to achieve herd immunity (67% level of immunity),6 and therefore, vaccination of older adults is not essential; however, the high level of immunity required, coupled with the fact that many settings (eg, nursing homes) are comprised nearly exclusively of older adults, highlights the imperative for their inclusion in COVID-19 vaccine trials.

With advanced preparation, staff training, and aging expertise, enrollment of older adults is feasible, allowing COVID-19 clinical trials to be as relevant and inclusive as possible.

Disponible: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2771091

New England Journal of Medicine

Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment

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Abstract

BACKGROUND

It is thought that a reduction in the frequency of basal insulin injections might facilitate treatment acceptance and adherence among patients with type 2 diabetes. Insulin icodec is a basal insulin analogue designed for once-weekly administration that is in development for the treatment of diabetes.

METHODS

We conducted a 26-week, randomized, double-blind, double-dummy, phase 2 trial to investigate the efficacy and safety of once-weekly insulin icodec as compared with once-daily insulin glargine U100 in patients who had not previously received long-term insulin treatment and whose type 2 diabetes was inadequately controlled (glycated hemoglobin level, 7.0 to 9.5%) while taking metformin with or without a dipeptidyl peptidase 4 inhibitor. The primary end point was the change in glycated hemoglobin level from baseline to week 26. Safety end points, including episodes of hypoglycemia and insulin-related adverse events, were also evaluated**RESULTS**A total of 247 participants were randomly assigned (1:1) to receive icodec or glargine. Baseline characteristics were similar in the two groups; the mean baseline glycated hemoglobin level was 8.09% in the icodec group and 7.96% in the glargine group. The estimated mean change from baseline in the glycated hemoglobin level was −1.33 percentage points in the icodec group and −1.15 percentage points in the glargine group, to estimated means of 6.69% and 6.87%, respectively, at week 26; the estimated between-group difference in the change from baseline was −0.18 percentage points (95% CI, –0.38 to 0.02, P=0.08). The observed rates of hypoglycemia with severity of level 2 (blood glucose level, <54 mg per deciliter) or level 3 (severe cognitive impairment) were low (icodec group, 0.53 events per patient-year; glargine group, 0.46 events per patient-year; estimated rate ratio, 1.09; 95% CI, 0.45 to 2.65). There was no between-group difference in insulin-related key adverse events, and rates of hypersensitivity and injection-site reactions were low. Most adverse events were mild, and no serious events were deemed to be related to the trial medications.

CONCLUSIONS

Once-weekly treatment with insulin icodec had glucose-lowering efficacy and a safety profile similar to those of once-daily insulin glargine U100 in patients with type 2 diabetes.
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Disponible: https://www.nejm.org/doi/full/10.1056/NEJMoa2022474

Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation

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Abstract

BACKGROUND

Implementation of appropriate oral anticoagulant treatment for the prevention of stroke in very elderly patients with atrial fibrillation is challenging because of concerns regarding bleeding.

METHODS

We conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven trial to compare a once-daily 15-mg dose of edoxaban with placebo in elderly Japanese patients (≥80 years of age) with nonvalvular atrial fibrillation who were not considered to be appropriate candidates for oral anticoagulant therapy at doses approved for stroke prevention. The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was major bleeding according to the definition of the International Society on Thrombosis and Haemostasis.

RESULTS

A total of 984 patients were randomly assigned in a 1:1 ratio to receive a daily dose of 15 mg of edoxaban (492 patients) or placebo (492 patients). A total of 681 patients completed the trial, and 303 discontinued (158 withdrew, 135 died, and 10 had other reasons); the numbers of patients who discontinued the trial were similar in the two groups. The annualized rate of stroke or systemic embolism was 2.3% in the edoxaban group and 6.7% in the placebo group (hazard ratio, 0.34; 95% confidence interval [CI], 0.19 to 0.61; P<0.001), and the annualized rate of major bleeding was 3.3% in the edoxaban group and 1.8% in the placebo group (hazard ratio, 1.87; 95% CI, 0.90 to 3.89; P=0.09). There were substantially more events of gastrointestinal bleeding in the edoxaban group than in the placebo group. There was no substantial between-group difference in death from any cause (9.9% in the edoxaban group and 10.2% in the placebo group; hazard ratio, 0.97; 95% CI, 0.69 to 1.36).

CONCLUSIONS

In very elderly Japanese patients with nonvalvular atrial fibrillation who were not appropriate candidates for standard doses of oral anticoagulants, a once-daily 15-mg dose of edoxaban was

superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding than placebo.

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