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D²4H
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醫衞大數據深析實驗室 ®

Utilization of Real-world Evidence for Supporting Marketing Registration of Pharmaceutical Products: A Case Study

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Acknowledgement

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- I am partly funded by the Hong Kong Innovation and Technology Commission.
- Co-investigators: Prof E Lai, Dr TC Lin, Dr J L Lange, Dr L Chen, Dr CW Sing, Dr CL Cheung, Dr SC Shao, Prof YH Kao Yang from The University of Hong Kong, National Cheng Kung University, Amgen and The Keelung Chang Gung Memorial Hospital.

Declaration of interests (all opinion is my)

- Member of the Pharmacy and Poisons Board, Hong Kong Government (Medicine Regulatory Agency in Hong Kong)

Declaration of interests

- Received research and educational funding from
  - Hong Kong Government, European Commission, UK Government and Australian Government
  - Bayers, GSK, Janssen-Cilag, Novartis, Pfizer and Takeda (unrelated to current talk).
- Non-executive Director of Jacobson Pharma in Hong Kong
- Founder of Therakind Ltd (A spin-off company of UCL and Great Ormond Street Hospital) in the UK
  - Therakind received royalties from Neuraxpharm for Buccolam (a licensed medication developed by Therakind for prolonged seizure treatment previously marketed by Takeda)

Contents

- Background of regulatory use of real world evidence (RWE)
- Principles of using RWE
- Case study of using RWE in supporting registration in China
- New spin-off company “Advanced Data Analytics for Medical Science” (ADAMS) in support pharmaceutical industry

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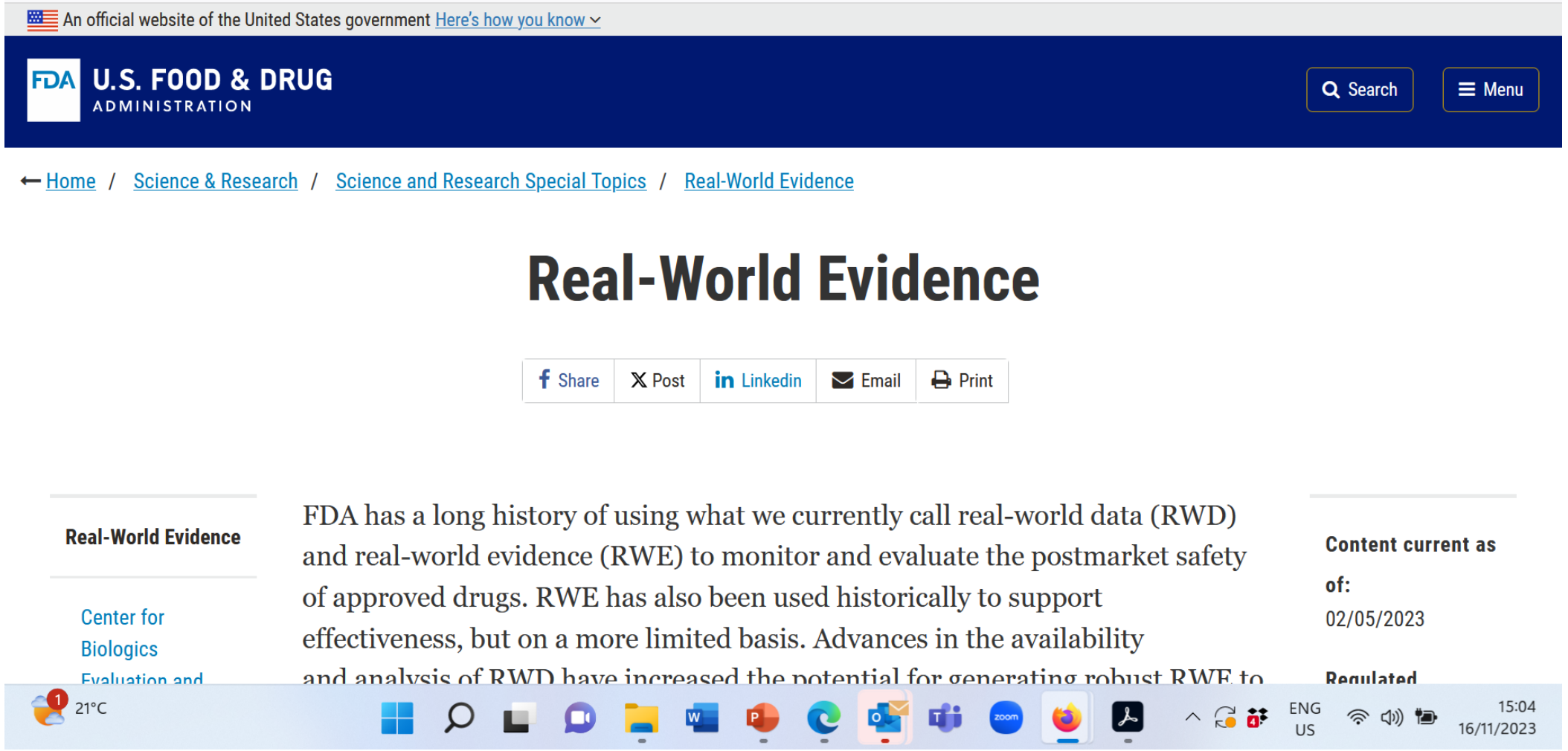
Background

HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

Real-world evidence framework to support EU regulatory decision-making

Background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FDA has a long history of using what we currently call real-world data (RWD) and real-world evidence (RWE) to monitor and evaluate the postmarket safety of approved drugs. RWE has also been used historically to support effectiveness, but on a more limited basis. Advances in the availability and analysis of RWD have increased the potential for generating robust RWE to
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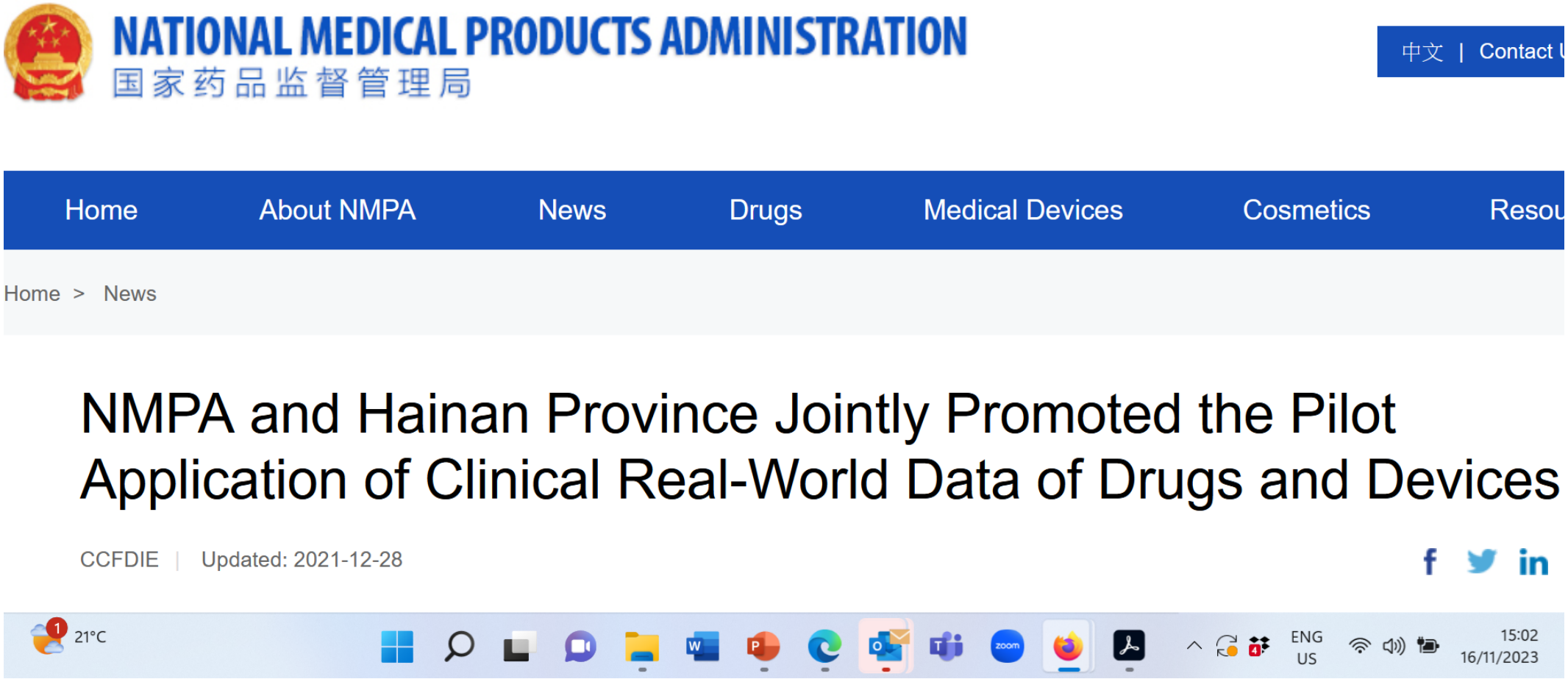
Background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Principles in conducting a non-interventional RWE study

What is the research question?	**Develop a specific hypothesis for a defined research question to bridge the evidence gaps**
Are available data fit-for-purpose?	**(1) representativeness (2) validity and (3) missing data**
Are methods of sufficient rigor?	**(1) Study design (2) Study analysis and (3) Sensitivity analysis**
Is the study credible?	**(1) Stakeholder engagement (2) Transparency (3) Reproducibility (4) Consistency with existing evidence**

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A case study of RWE in China for an indication within a new population for denosumab

Therapeutic Innovation & Regulatory Science (2022) 56:137–144
https://doi.org/10.1007/s43441-021-00342-4

DIA

ORIGINAL RESEARCH

A Novel Case Study of the Use of Real-World Evidence to Support the Registration of an Osteoporosis Product in China

Neal E. Storm, DRSc, MS, MBA, RAC[1,2] · Wen Chang, PhD[1] · Tzu-Chieh Lin, PhD[1] · Jeff L. Lange, PhD[1] · Brian Bradbury, DSc[1] · Cathy W. Critchlow, PhD[1] · Steven K. Galson, MD, MPH[1]

Received: 9 June 2021 / Accepted: 19 September 2021 / Published online: 11 October 2021

Abstract

On June 23, 2020, Prolia® (denosumab) was approved by the National Medical Products Administration (NMPA) in the People's Republic of China as the first monoclonal antibody for the treatment of postmenopausal women with osteoporosis at high risk of fractures. Its brand name in Chinese is 普罗力, a transliteration from the English name "Prolia", which has an implied meaning of "to give strength to everyone"— a suitable name for a potent anti-resorptive therapy. The approval was supported by a novel marketing authorization application (MAA) that included data from Prolia's global clinical trial program establishing favorable efficacy and safety, augmented by results from a real-world evidence (RWE) study confirming the effectiveness and safety of Prolia in clinical practice within Taiwan and Hong Kong. Key constructs for this registration-quality RWE study included the fit-for-purpose assessment of data quality, methodology and quantitative assessment of potential biases, good practices of study conduct, and reproducibility of results. Using data from clinical practice in Taiwan and Hong Kong to evaluate the benefits versus risks of Prolia treatment in ethnic Chinese women with postmenopausal osteoporosis, the RWE study results for effectiveness were comparable to efficacy demonstrated in the global clinical trial program and results for safety were consistent with the incidence observed in global post-marketing safety studies. While RWE is often used to monitor postmarket safety of drug products, support health insurance coverage decisions, and inform clinicians on real-world use of medicines, it has not been widely used to support regulatory approval for new medicines in lieu of clinical bridging studies in countries where such studies are required. Well-conducted registrational RWE studies can play a pivotal role in complementing the totality of evidence presented in an MAA. The benefits of such an approach include avoiding the collection of additional placebo-controlled trial data in populations where adequate ethnic characterization of efficacy, effectiveness, and safety may already exist from postmarketing sources, and accelerate access for patients to innovative medicines in important regions. Here, we describe a regulatory case study of a novel MAA incorporating RWE that provided important evidence to confirm the benefit:risk of a new drug and facilitated a label expansion to a new patient population.

Osteoporosis International (2022) 33:1155–1164
https://doi.org/10.1007/s00198-021-06291-w

ORIGINAL ARTICLE

Effectiveness of denosumab for fracture prevention in real-world postmenopausal women with osteoporosis: a retrospective cohort study

E. C.-C. Lai[1] · T.-C. Lin[2] · J. L. Lange[2] · L. Chen[2] · I. C. K. Wong[3] · C.-W. Sing[3] · C.-L. Cheung[3] · S.-C. Shao[4] · Y.-H. Kao Yang[1]

Received: 10 September 2021 / Accepted: 27 December 2021 / Published online: 15 January 2022

Abstract

Summary To determine denosumab's effectiveness for fracture prevention among postmenopausal women with osteoporosis in East Asia, the risk of fracture was compared between patients continuing denosumab therapy versus patients discontinuing denosumab after one dose. The real-world effectiveness was observed to be consistent with the efficacy demonstrated in the phase III trial.

Introduction After therapeutic efficacy is demonstrated for subjects in global clinical trials, real-world evidence may provide complementary knowledge of therapeutic effectiveness in a heterogeneous mix of patients seen in clinical practice. This retrospective cohort study was conducted to compare the fracture risk in real-world clinical care received in Taiwan and Hong Kong between a treatment cohort (patients receiving denosumab 60 mg subcutaneously every 6 months) versus an off-treatment cohort (patients discontinuing after 1 dose of denosumab, which has no known clinical benefit) among real-world postmenopausal women.

Methods This study included 38,906 and 2,835 postmenopausal women receiving denosumab in Taiwan and Hong Kong, respectively. The primary endpoint was hip fracture, and secondary endpoints were clinical vertebral and nonvertebral fractures. Propensity-score-matched analysis, adjusting for known covariates, was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The robustness of findings was evaluated with a series of sensitivity and quantitative bias analyses.

Results In this study, 554 hip fractures were included in the primary Taiwan population analysis. The crude incidence rate was 0.9 per 100 person-years in the treatment cohort ($n = 25{,}059$) and 1.7 per 100 person-years in the off-treatment cohort ($n = 13{,}847$). After adjusting for prognostic differences between cohorts, denosumab reduced the risk of hip fractures by 38% (HR = 0.62, CI:0.52–0.75). Risk reductions of similar magnitude were observed for the secondary endpoints and for the analysis of the smaller Hong Kong population.

Conclusion The effectiveness of denosumab for fracture reduction among real-world postmenopausal women with osteoporosis was consistent with the efficacy demonstrated in a global clinical trial.

Registration: EnCePP registration number: EUPAS26372; registration date: 12/11/2018.

What is the research question?

- **Available evidence of denosumab:**

- **Evidence Gap: Data in Chinese population**

Research question: Is the safety and effectiveness of denosumab for fracture reduction in Chinese women with post-menopausal osteoporosis consistent with the global patient population?

Storm NE, et al. A Novel Case Study of the Use of Real-World Evidence to Support the Registration of an Osteoporosis Product in China. Ther Innov Regul Sci. 2022
National Academies of Sciences. 2019. Examining the impact of real-world evidence on medical product development: Proceedings of a workshop series. Washington, DC

Are available data fit-for-purpose?

Representative	Hong Kong electronic medical records (>80% of medical care) Taiwan claims data (>99% of population) Includes all types of patients often excluded from clinical trials
Large sample size	Includes ~ 40,000 Chinese women with real-world use of denosumab Enables identifying rare safety events
Complete follow-up	Single system for data collection enable complete follow-up for identifying safety and effectiveness endpoints Study includes patients with up to 5 years of denosumab use
Contains key endpoints of clinical interest	Enables the characterization of outcomes most important to patients Study includes clinical fractures

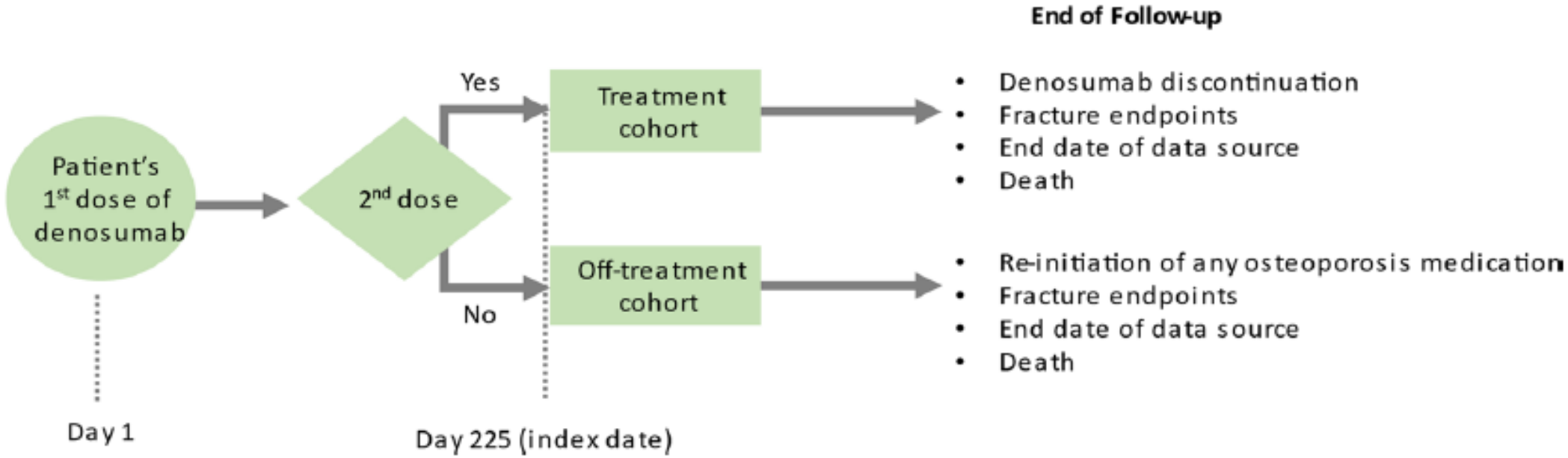
Are available data fit-for-purpose?

Validity of endpoint	**Endpoint of hospitalized hip fracture validated in both data sources by independent assessment of radiographs** **Hong Kong -- 100% of hip fractures coded as fracture, where verified to be fracture [(1)]** **Taiwan -- 98% of hip fractures coded as fracture, where verified to be fracture**
Validity of exposure	**Therapies administered by a health care provider provides clear record of use**
Validity of co-variates	**59 co-variates with a relationship to outcome were available in data source**

1) Sing CW et al. Validity of major osteoporotic fracture diagnosis codes in the Clinical Data Analysis and Reporting System in Hong Kong. Pharmacoepidemiol Drug Saf. 2017
2) Lai EC, Lin TC, Lange JL, Chen L, Wong ICK, Sing CW, Cheung CL, Shao SC, Yang YK. Effectiveness of denosumab for fracture prevention in real-world postmenopausal women with osteoporosis: a retrospective cohort study. Osteoporos Int. 2022

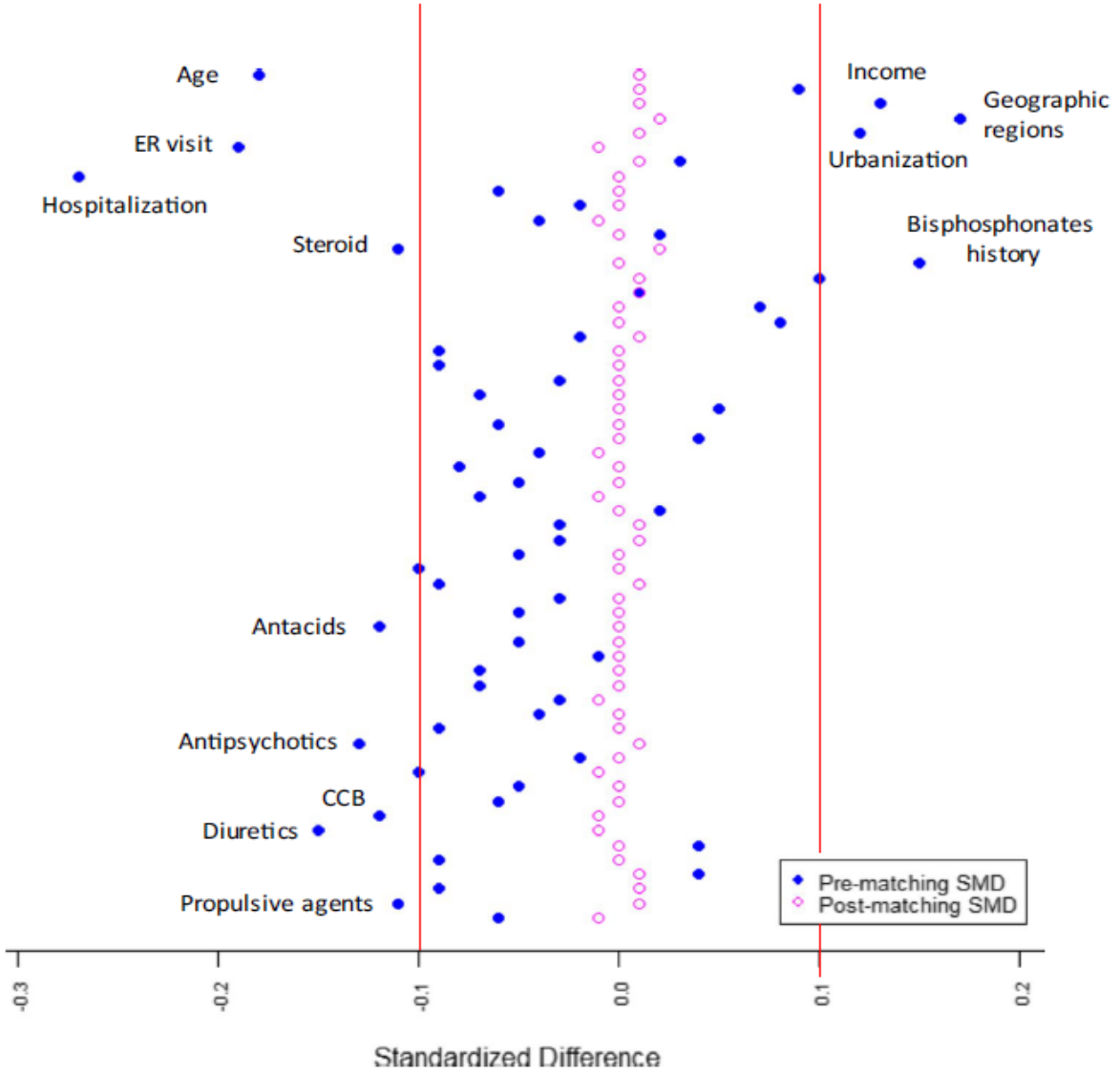
Study design: Are methods of sufficient rigor?

Design principles to emulate a clinical trial [(1)]	**New users design -** a cohort of patients from the time of treatment initiation to facilitate assessing patients' pretreatment characteristics and to capture all events occurring anytime during follow-up. **Active comparison group** – Treatment cohort (patients receiving denosumab every 6 months) versus a off-treatment cohort that had discontinued therapy after 1 dose of denosumab - supports assumption that patients initiating a treatment have similar level of baseline disease severity - one dose of denosumab has no known clinical benefit (i.e., a proxy for placebo of randomized clinical trial)



Contributions of study design and use of propensity scores to balance cohorts on 59 risk factors for fracture outcome

Fig. 2 Balance of covariates ($N=59$) before and after propensity score matching—Taiwan. CCB = calcium channel blocker; ER = emergency room; SMD = standardized mean difference. SMD < 0.1 represents a difference between treatment and off-treatment cohorts that is not statistically significant. The covariates labeled in the figure are those with SMD > 0.1



Lai EC, Lin TC, Lange JL, Chen L, Wong ICK, Sing CW, Cheung CL, Shao SC, Yang YK. Effectiveness of denosumab for fracture prevention in real-world postmenopausal women with osteoporosis: a retrospective cohort study. Osteoporos Int. 2022

Are methods of sufficient rigor?

Approaches used to assess unmeasured confounding

High-Dimensional Propensity Score Analysis: Adjust for large numbers of covariates, as these variables may collectively be proxies for unmeasured confounding factors

- Results consistent with primary analysis

Quantitative Bias Analysis: Estimate the strength of unmeasured confounding needed to explain the results in context of likely prevalence of unmeasured confounding factors

- Smoking prevalence of < 5% in study population, hence not able to explain results

Negative Control Outcomes: An endpoint with no expectation of difference in incidence rates between cohorts

- Fracture events during the first dose of treatment)

Inspect the balance of unmeasured variables (bone mineral density and body mass index) within subset (7%) of study population having available data

- Balance in covariates suggested these variables were less likely to be significant confounders in study population

Is the study credible?

Regulatory interaction process before, during, and after study

June 2018

China Center for Drug Evaluation
Meeting #1

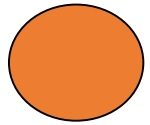
Initial discussion if RWE-based approach applicable to inform if benefit:risk of denosumab in Chinese women is consistent with global patient population

China Center for Drug Evaluation
Meeting #2

Feedback on technical components of protocol and analytical plan prior to study start; including local clinicians and RWE experts, study investigators

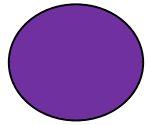
China Center for Drug Evaluation
Meeting #3

Discussion of RWE results; how to integrate into marketing application and process for regulatory review



Marketing authorization application

June 2020



Marketing approval

Denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fractures

Storm NE, Chang W, Lin TC, Lange JL, Bradbury B, Critchlow CW, Galson SK. A Novel Case Study of the Use of Real-World Evidence to Support the Registration of an Osteoporosis Product in China. Ther Innov Regul Sci. 2022

Is the study credible?

Reproducibility of study

1) **Conceptual replication** Research question is approached by different investigators using a different data source and similar methods to assess if same clinical interpretation

   - per protocol replication of analysis in Hong Kong and in Taiwan by individual investigators

2) **Direct replication** Research question is approached by using the same methods in the same data source to evaluate if the same results

   - Public posting of protocol (ENCePP) and statistical analysis plan
   - Extensive detail on data curation
   - SAS code used in analysis with detailed annotation

Is the study credible?

Consistency with prior evidence

Randomized clinical trial (2010)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., and Claus Christiansen, M.D., for the FREEDOM Trial*

Table 2. Effect of Denosumab on the Risk of Fracture at 36 Months.*

Outcome	Denosumab	Placebo	Difference in Rates (95% CI)	Relative Risk or Hazard Ratio (95% CI)†	P Value
	no. (%)				
Hip fracture	26 (0.7)	43 (1.2)	0.3 (−0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04

Real world evidence (2021)

Osteoporosis International
https://doi.org/10.1007/s00198-021-06291-w

ORIGINAL ARTICLE

Effectiveness of denosumab for fracture prevention in real-world postmenopausal women with osteoporosis: a retrospective cohort study

E. C.-C. Lai[1] · T.-C. Lin[2] · J. L. Lange[2] · L. Chen[2] · I. C. K. Wong[3] · C.-W. Sing[3] · C.-L. Cheung[3] · S.-C. Shao[4] · Y.-H. Kao Yang[1]

Table 1 Fracture risk in treatment and off-treatment cohorts—Taiwan population

Site	Treatment Cohort (*N* = 13, 419)			Off-Treatment Cohort (*N* = 13, 419)			Hazard ratio in propensity score-matched cohort (95% CI)
	Patients with a fracture	Person-years	Patients with a fracture per 100 Person-years	Patients with a fracture	Person-years	Patients with a fracture per 100 Person-years	
Hip	183	17,066	1.07	371	21,619	1.72	0.62 (0.52 to 0.75)

What is the research question?

- **Available evidence of denosumab:**

- ~~**Evidence Gap: Data in Chinese population**~~

New evidence:

Results of our studies have shown that denosumab in Chinese population is consistent with other populations

It was licensed by the NMPA in 2020 based on the totality of the existing data including RWE from HK & Taiwan

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Why choose our team?

Track record in investigating fractures

JAMA

Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation

Wallis C. Y. Lau, BSc; Esther W. Chan, PhD; Ching-Lung Cheung, PhD; Chor Wing Sing, BSc; Kenneth K. C. Man, MPH; Gregory Y. H. Lip, MD; Chung-Wah Siu, MD; Joanne K. Y. Lam, FHKAM; Alan C. H. Lee, FHKAM; Ian C. K. Wong, PhD

IMPORTANCE The risk of osteoporotic fracture with dabigatran use in patients with nonvalvular atrial fibrillation (NVAF) is unknown.

OBJECTIVE To investigate the risk of osteoporotic fracture with dabigatran vs warfarin in patients with NVAF.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with NVAF from 2010 through 2014 and prescribed dabigatran or warfarin were matched by propensity score at a 1:2 ratio with follow-up until July 31, 2016.

EXPOSURES Dabigatran or warfarin use during the study period.

MAIN OUTCOMES AND MEASURES Risk of osteoporotic hip fracture and vertebral fracture was compared between dabigatran and warfarin users using Poisson regression. The corresponding incidence rate ratio (IRR) and absolute risk difference (ARD) with 95% CIs were calculated.

RESULTS Among 51 496 patients newly diagnosed with NVAF, 8152 new users of dabigatran (n = 3268) and warfarin (n = 4884) were matched by propensity score (50% women; mean [SD] age, 74 [11] years). Osteoporotic fracture developed in 104 (1.3%) patients during follow-up (32 dabigatran users [1.0%]; 72 warfarin users [1.5%]). Results of Poisson regression analysis showed that dabigatran use was associated with a significantly lower risk of osteoporotic fracture compared with warfarin (0.7 vs 1.1 per 100 person-years; ARD per 100 person-years, −0.68 [95% CI, −0.38 to −0.86]; IRR, 0.38 [95% CI, 0.22 to 0.66]). The association with lower risk was statistically significant in patients with a history of falls, fractures, or both (dabigatran vs warfarin, 1.6 vs 3.6 per 100 person-years; ARD per 100 person-years, −3.15 [95% CI, −2.40 to −3.45]; IRR, 0.12 [95% CI, 0.04 to 0.33]), but not in those without a history (0.6 vs 0.7 per 100 person-years; ARD per 100 person-years, −0.04 [95% CI, 0.67 to −0.39]; IRR, 0.95 [95% CI, 0.45 to 1.96]) (*P* value for interaction, <.001).

Supplemental content

CME Quiz at jamanetworkcme.com and CME Questions page 1172

Annals of Internal Medicine ORIGINAL RESEARCH

Association Between Treatment With Apixaban, Dabigatran, Rivaroxaban, or Warfarin and Risk for Osteoporotic Fractures Among Patients With Atrial Fibrillation

A Population-Based Cohort Study

Wallis C.Y. Lau, PhD; Ching-Lung Cheung, PhD; Kenneth K.C. Man, PhD; Esther W. Chan, PhD; Chor Wing Sing, PhD; Gregory Y.H. Lip, MD; Chung-Wah Siu, MD; Joanne K.Y. Lam, MBBS; Alan C.H. Lee, MBBS; and Ian C.K. Wong, PhD

Background: It is unclear whether anticoagulant type is associated with the risk for osteoporotic fracture, a deleterious complication of anticoagulants among patients with atrial fibrillation (AF).

Objective: To compare the risk for osteoporotic fracture between anticoagulants.

Design: Population-based cohort study.

Setting: Territory-wide electronic health record database of the Hong Kong Hospital Authority.

Participants: Patients newly diagnosed with AF between 2010 and 2017 who received a new prescription for warfarin or a direct oral anticoagulant (DOAC) (apixaban, dabigatran, or rivaroxaban). Follow-up ended on 31 December 2018.

Measurements: Osteoporotic hip and vertebral fractures in anticoagulant users were compared using propensity score–weighted cumulative incidence differences (CIDs).

Results: There were 23 515 patients identified (3241 apixaban users, 6867 dabigatran users, 3866 rivaroxaban users, and 9541 warfarin users). Overall mean age was 74.4 years (SD, 10.8), ranging from 73.1 years (warfarin) to 77.9 years (apixaban). Over a median follow-up of 423 days, 401 fractures were identified (crude event number [weighted rate per 100 patient-years]: apixaban, 53 [0.82]; dabigatran, 95 [0.76]; rivaroxaban, 57 [0.67]; and warfarin, 196 [1.11]). After 24-month follow-up, DOAC use was associated with a lower risk for fracture than warfarin use (apixaban CID, −0.88% [95% CI, −1.66% to −0.21%]; dabigatran CID, −0.81% [CI, −1.34% to −0.23%]; and rivaroxaban CID, −1.13% [CI, −1.67% to −0.53%]). No differences were seen in all head-to-head comparisons between DOACs at 24 months (apixaban vs. dabigatran CID, −0.06% [CI, −0.69% to 0.49%]; rivaroxaban vs. dabigatran CID, −0.32% [CI, −0.84% to 0.18%]; and rivaroxaban vs. apixaban CID, −0.25% [CI, −0.86% to 0.40%]).

Limitation: Residual confounding is possible.

Conclusion: Among patients with AF, DOAC use may result in a lower risk for osteoporotic fracture compared with warfarin use. Fracture risk does not seem to be altered by the choice of DOAC. These findings may help inform the benefit-risk assessment when choosing between anticoagulants.

Primary Funding Source: The University of Hong Kong and University College London Strategic Partnership Fund.

Ann Intern Med. doi:10.7326/M19-3671 **Annals.org**
For author affiliations, see end of text.
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Track record in conducting multinational studies

Lancet Psychiatry

Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases

Sudha R Raman*, Kenneth K C Man*, Shahram Bahmanyar, Anick Berard, Scott Bilder, Takoua Boukhris, Greta Bushnell, Stephen Crystal, Kari Furu, Yea-Huei Kao Yang, Øystein Karlstad, Helle Kieler, Kiyoshi Kubota, Edward Chia-Cheng Lai, Jaana E Martikainen, Gèric Moura, Nicholas Moore, Dolores Montero, Hidefumi Nakamura, Anke Neumann, Virginia Pate, Anton Pottegård, Nicole L. Pratt, Elizabeth E Roughead, Diego Macias Saint-Gerons, Til Stürmer, Chien-Chou Su, Helga Zoega, Miriam C J M Sturkenboom, Esther W Chan, David Coghill, Patrick Ip, Ian C K Wong

Summary

Background The use of medications to treat attention deficit hyperactivity disorder (ADHD) has increased, but the prevalence of ADHD medication use across different world regions is not known. Our objective was to determine regional and national prevalences of ADHD medication use in children and adults, with a specific focus on time trends in ADHD medication prevalence.

Methods We did a retrospective, observational study using population-based databases from 13 countries and one Special Administrative Region (SAR): four in Asia and Australia, two in North America, five in northern Europe, and three in western Europe. We used a common protocol approach to define study populations and parameters similarly across countries and the SAR. Study populations consisted of all individuals aged 3 years or older between Jan 1, 2001, and Dec 31, 2015 (dependent on data availability). We estimated annual prevalence of ADHD medication use with 95% CI during the study period, by country and region and stratified by age and sex. We reported annual absolute and relative percentage changes to describe time trends.

Findings 154·5 million individuals were included in the study. ADHD medication use prevalence in 2010 (in children aged 3–18 years) varied between 0·27% and 6·69% in the countries and SAR assessed (0·95% in Asia and Australia, 4·48% in North America, 1·95% in northern Europe, and 0·70% in western Europe). The prevalence of ADHD medication use among children increased over time in all countries and regions, and the absolute increase per year ranged from 0·02% to 0·26%. Among adults aged 19 years or older, the prevalence of any ADHD medication use in 2010 varied between 0·003% and 1·48% (0·05% in Asia and Australia, 1·42% in North America, 0·47% in northern Europe, and 0·03% in western Europe). The absolute increase in ADHD medication use prevalence per year ranged from 0·0006% to 0·12%. Methylphenidate was the most commonly used ADHD medication in most countries.

Interpretation Using a common protocol and data from 13 countries and one SAR, these results show increases over time but large variations in ADHD medication use in multiple regions. The recommendations of evidence-based guidelines need to be followed consistently in clinical practice. Further research is warranted to describe the safety and effectiveness of ADHD medication in the short and long term, and to inform evidence-based guidelines, particularly in adults.

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See Online/Comment
http://dx.doi.org/10.1016/S2215-0366(18)30317-1

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Lancet Public Health

Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study

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Summary

Background Previous studies have reported an extremely unbalanced global access to opioid analgesics. We aimed to determine contemporary trends and patterns of opioid analgesic consumption at the global, regional, and national levels.

Methods We analysed the global pharmaceutical sales data of 66 countries or regions from the IQVIA-Multinational Integrated Data Analysis System database on opioid analgesics between 2015 and 2019. Opioid analgesic consumption was measured in milligram morphine equivalent per 1000 inhabitants per day (MME per 1000/day). The global, regional, and national trend changes were estimated using linear regressions. Factors associated with consumption patterns and trend changes were explored in multivariable linear regression analyses.

Findings Overall opioid analgesic sales in the 66 countries or regions increased from 27·52 MME per 1000/day (16·63–45·54) in 2015 to 29·51 MME per 1000/day (17·85–48·79) in 2019 (difference per year 3·96%, 95% CI 0·26 to 7·80). Sales reduced yearly in North America (–12·84%; 95% CI –15·34 to –10·27) and Oceania (–2·96%; –4·20 to –1·70); increased in South America (28·69%; 7·18 to 54·53), eastern Europe (7·68%; 3·99 to 11·49), Asia (5·74%; 0·61 to 11·14), and western and central Europe (1·64%; 0·52 to 2·78); and did not differ in Africa or central America and the Caribbean. The global opioid consumption patterns were associated with country-level Human Development Index (p=0·040), cancer death rate excluding leukaemia (p=0·0072), and geographical location (p<0·0001). In 2019, opioid analgesic consumption ranged from 0·01 MME per 1000/day to 5·40 MME per 1000/day in the 17 countries and regions in the lowest consumption quartile, despite high income levels and cancer death rates in some of them.

Interpretation Global opioid analgesic consumption increased from 2015 to 2019. The trend changes were distinctive across regions, which could reflect the different actions in response to known issues of opioid use and misuse. Disparities in opioid analgesic consumption remained, indicating potential inadequate access to essential pain relief in countries with low consumption.

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Profile

"Father of the health-care big data research in Hong Kong"

The University of Hong Kong

way of thinking: first, meeting [illegible] wife Lisa, after which he converted to Christianity, and second, his move to the UK, where he studied pharmacy in Sunderland, northeast England, and his love of the mechanisms of drug action began to flourish. "Why Sunderland, you might ask?" Wong tells *The Lancet Psychiatry*. "My family did not have much money and back then, it was the cheapest place to study pharmacy in the UK!"

Today, Wong is an endowed Professor in Pharmacy at Hong Kong University, where he leads a team of 60 in health-care big data research. His students and colleagues call him "father of the health-care big data research in Hong Kong" because of his pioneering work and the large

as director of the Centre for Paediatric Pharmacy Research at the London School of Pharmacy, University College London Institute of Child Health, and Great Ormond Street Hospital. He was given a National Institute for Health and Care Research Public Health Career Scientist Award to analyse psychotropic drug use in children, for conditions such as ADHD, depression, schizophrenia, and epilepsy.

Following his father's death, Wong returned to Hong Kong in 2011 fearing that time remaining with his mother might be short. Since then, he has spent most of his time in Hong Kong, sadly losing his mother in the middle of the COVID-19 pandemic. The main focus of

For more on **lamotrigine-related skin rash** see *Annals of Pharmacotherapy* 1999; 33: 1037–42

For more on **RESPECT trial** see *BR J Gen Pract* 2010; 60: e10–19

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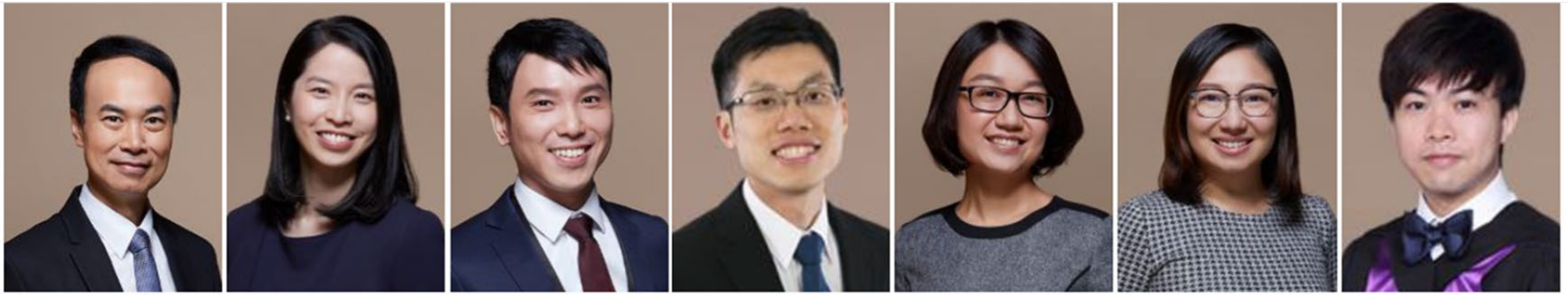

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Advanced Data Analytics for Medical Science (ADAMS)

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- Experts in using Hospital Authority data
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  - Japan, Korea, Taiwan, NZ, UK, US and Scandinavian countries
- Protocol design and study execution
  - Disease prevalence
  - Unmet medical need analysis
  - Risk Management Plan
  - Medication effectiveness and safety evaluation using Real World Data (RWD)
- Support 1+ application in Hong Kong

Conclusions

- **Regulatory guidance and use cases are supporting an emerging framework for RWE use to support regulatory decision-making**

- **Appropriateness of RWE use and implementation is guided by:**

What is the research question?

Are available data fit-for-purpose?

Are methods of sufficient rigor?

Is the study credible?


thank you
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