Tribute to Jamie Weaver

Jamie Weaver

THE LANCET
Rheumatology

Articles

Opioid use, postoperative complications, and implant survival after unicompartmental versus total knee replacement: a population-based network study

Edward Burn, James Weaver*, Daniel Morales, Albert Prats-Uribe, Antonella Delmestri, Victoria Y Strauss, Ying He, Danielle E Robinson, Rafael Pinedo-Villanueva, Spyros Kolovos, Talita Duarte-Salles, William Sproviero, Dahai Yu, Michel Van Speybroeck, Ross Williams, Luis H John, Nigel Hughes, Anthony G Sena, Ruth Costello, Belay Birlie, David Culliford, Caroline O'Leary, Henry Morgan, Theresa Burkard, Daniel Prieto-Alhambra†, Patrick Ryan†*

Summary

Background There is uncertainty around whether to use unicompartmental knee replacement (UKR) or total knee replacement (TKR) for individuals with osteoarthritis confined to a single compartment of the knee. We aimed to emulate the design of the Total or Partial Knee Arthroplasty Trial (TOPKAT) using routinely collected data to assess whether the efficacy results reported in the trial translate into effectiveness in routine practice, and to assess comparative safety.

Methods We did a population-based network study using data from four US and one UK health-care database, part of the Observational Health Data Sciences and Informatics network. The inclusion criteria were the same as those for TOPKAT; briefly, we identified patients aged at least 40 years with osteoarthritis who had undergone UKR or TKR and who had available data for at least one year prior to surgery. Patients were excluded if they had evidence of previous knee arthroplasty, knee fracture, knee surgery (except diagnostic), rheumatoid arthritis, infammatory arthropathies, or septic arthritis. Opioid use from 91–365 days after surgery, as a proxy for persistent pain, was assessed for all participants in all databases. Postoperative complications (ie, venous thromboembolism, infection, readmission, and mortality) were assessed over the 60 days after surgery and implant survival (as measured by revision procedures) was assessed over the 5 years after surgery. Outcomes were assessed in all databases, except for readmission, which was assessed in three of the databases, and mortality, which was assessed in two of the databases. Propensity score matched Cox proportional hazards models were fitted for each outcome. Calibrated hazard ratios (cHRs) were generated for each database to account for observed differences in control outcomes, and cHRs were then combined using meta-analysis.

Findings 33 867 individuals who received UKR and 557 831 individuals who received TKR between Jan 1, 2005, and April 30, 2018, were eligible for matching. 32 379 with UKR and 250 377 with TKR were propensity score matched and informed the analyses. UKR was associated with a reduced risk of postoperative opioid use (cHR from meta-analysis 0·81, 95% CI 0·73–0·90) and a reduced risk of venous thromboembolism (0·62, 0·36–0·95), whereas no difference was seen for infection (0·85, 0·51–1·37) and readmission (0·79, 0·47–1·25). Evidence was insufficient to conclude whether there was a reduction in risk of mortality. UKR was also associated with an increased risk of revision (1·64, 1·40–1·94).

Interpretation UKR was associated with a reduced risk of postoperative opioid use compared with TKR, which might indicate a reduced risk of persistent pain after surgery. UKR was associated with a lower risk of venous thromboembolism but an increased risk of revision compared with TKR. These findings can help to inform shared decision making for individuals eligible for knee replacement surgery.

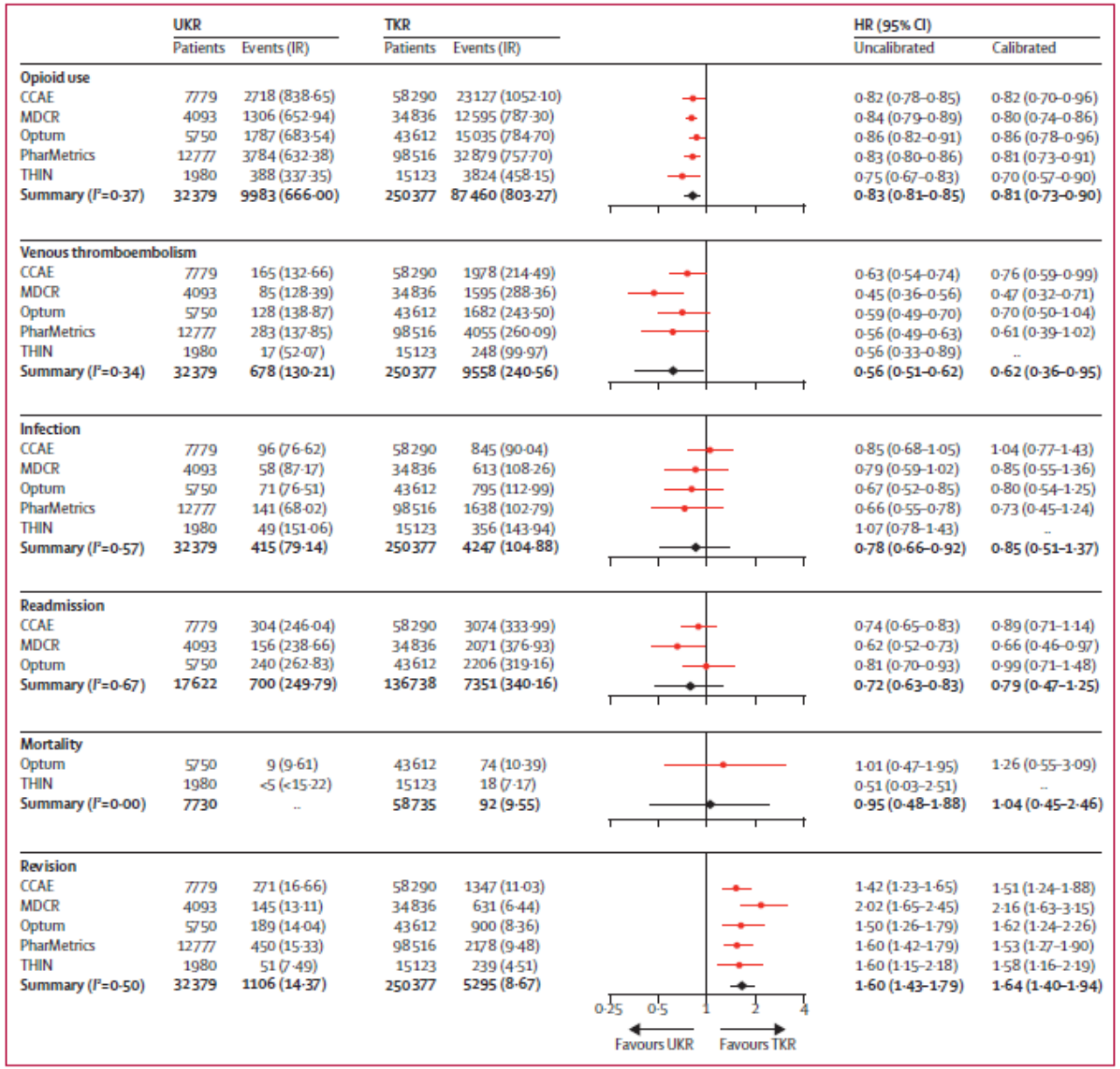

Figure: **Effect of procedure choice on opioid use, postoperative complications, and revision**

Numbers of propensity score matched individuals, observed events, HRs, and calibrated HRs for UKR relative TKR. Readmission data were not available in PharMetrics and THIN. Mortality data were only available in Optum and THIN. Calibration of HRs was infeasible for postoperative complications in THIN because there were too few negative control events observed during the 60-day time-at-risk. Adjusted HRs account for residual confounding identified by negative control outcomes analyses. Calibrated HRs were not estimated for 60-day outcomes in THIN due to too few control outcomes being observed. UKR=unicompartmental knee replacement. TKR=total knee replacement. HR=hazard ratio. IR=incidence rate. MDCR=Medicare Supplemental Database. CCAE=Commercial Database. Optum=Optum De-Identified Clinformatics Data Mart Database. PharMetrics=PharMetrics Plus. THIN=The Health Improvement Network.

7 Fredi M, Andreoli L, Bacco B, et al. First report of the Italian registry on immune-mediated congenital heart block (Lu.Ne registry). *Front Cardiovasc Med* 2019; **6**: 11.

Is there a need for review-a-thons?

"IMI's EHDEN project dramatically demonstrated the power of using clinical data in research by replicating, during a five-day 'study-a-thon', the results of a systematic review covering 20 years of research, and a multi-year clinical trial."[1] In this quote the Innovative Medicine's Initiative (IMI) newsroom refers to the results of a recently published population-based network study, which reported on opioid use, postoperative complications, and implant survival after unicompartmental versus total knee replacement.[2] Is it possible that within 5 days, approximately 300 pages of study documentation (a study protocol comprised of 259 pages,[3] a published paper,[2] 30 pages of appendices,[2] and numerous of pages of R-syntaxes) were created?[3]

The project looks very transparent, but an adequate peer-review seems like a very time-consuming process. Personally, I spent at least 30 min comparing the methods section of the paper[2] with the study protocol.[3] Section 8.2 of the study protocol lists six different data sources;[3] however, the published paper only mentions five data sources. Why were the Medicaid patients not included in the published article?[2] There is also a seventh bullet-point listed to "add others" in section 8·2 of the study protocol.

Given the short time-window of follow-up to record events, how reliably was the actual date of surgery recorded in the published paper? I have some experience with a large UK primary care database in this area and as far as start of follow-up defined; as the actual date of surgery, the date of hospital admission, the date of discharge, or the date when the record was filed? Has this definition ever been validated? How was the end of the follow-up defined in each individual data source? Do any of the USA data sources overlap? If not, how do we know? Furthermore, how was the outcome "opioid use" being operationalised? Section 8.5.6 of the study protocol lists the following products "heroin, hydrocodone, and opioids"; however, does this list also include codeine, which is often used to reduce coughing rather than for pain relief? Some or maybe all these answers might be hidden somewhere in the 300 pages of documentation or in the R-syntaxes. Operational definitions and computer syntax are probably not materials that the readers of *The Lancet Rheumatology* would consider looking at, but they can substantially affect the associations and conclusion. Is there a need for review-a-thons to critically appraise study-a-thons?

I declare no competing interests.

Frank de Vries
frank.de.vries@mumc.nl

Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht 6229, Netherlands

1 Innovative Medicines Initiative. Can real world data replicate a clinical trial? EHDEN study suggests yes. https://www.imi.europa.eu/news-events/newsroom/can-real-world-data-replicate-clinical-trial-ehden-study-suggests-yes (accessed Nov 29, 2019).

2 Burn E, Weaver J, Morales D, et al. Opioid use, postoperative complications, and implant survival after unicompartmental versus total knee replacement: a population-based network study. *Lancet Rheumatol* 2019; **1**: e229–36.

3 Burn E, Weaver J. Morales D, et al. Prospective validation of a randomised trial of unicompartmental and total knee replacement: real word evidence from the OHDSI network. 2018. https://github.com/OHDSI/StudyProtocols/blob/master/UkaTkaSafetyEffectiveness/documents/OHDSI%20Oxford%20PLE%20Protocol%2030dec2018.docx (accessed March 1, 2020)

Author's reply:

"We would like to reassure the readers that the vast majority of the study[1] was indeed done within the 5 day study-a-thon, where we brought together individuals with knowledge of the data sources used, methodological approaches used, and the clinical area of interest. During this week the study was designed (with both the study protocol and the analytic code to implement it written), the analyses were run across the various data sources, and the results were then considered and interpreted. This time frame does of course leave aside the somewhat slower process of academic publishing (ie, editing the manuscript before submission, journal submission, and then responding to reviewer comments)."

*Daniel Prieto-Alhambra, Edward Burn, Patrick Ryan, James Weaver

Articles

THE LANCET
Rheumatology

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Juan M Banda, Edward Burn, Paula Casajust, Mitchell M Conover, Aedin C Culhane, Alexander Davydov, Scott L DuVall, Dmitry Dymshyts, Sergio Fernandez-Bertolin, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Benjamin Skov Kaas-Hansen, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G Lambert, Johan van der Lei, Kristine E Lynch, Rupa Makadia, Andrea V Margulis, Michael E Matheny, Paras Mehta, Daniel R Morales, Henry Morgan-Stewart, Mees Mosseveld, Danielle Newby, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Albert Prats-Uribe, Gowtham A Rao, Christian Reich, Jenna Reps, Peter Rijnbeek, Selva Muthu Kumaran Sathappan, Martijn Schuemie, Sarah Seager, Anthony G Sena, Azza Shoaibi, Matthew Spotnitz, Marc A Suchard, Carmen O Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Junqing Xie, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra, on behalf of the OHDSI-COVID-19 consortium*

Summary

Background Hydroxychloroquine, a drug commonly used in the treatment of rheumatoid arthritis, has received much negative publicity for adverse events associated with its authorisation for emergency use to treat patients with COVID-19 pneumonia. We studied the safety of hydroxychloroquine, alone and in combination with azithromycin, to determine the risk associated with its use in routine care in patients with rheumatoid arthritis.

Methods In this multinational, retrospective study, new user cohort studies in patients with rheumatoid arthritis aged 18 years or older and initiating hydroxychloroquine were compared with those initiating sulfasalazine and followed up over 30 days, with 16 severe adverse events studied. Self-controlled case series were done to further establish safety in wider populations, and included all users of hydroxychloroquine regardless of rheumatoid arthritis status or indication. Separately, severe adverse events associated with hydroxychloroquine plus azithromycin (compared with hydroxychloroquine plus amoxicillin) were studied. Data comprised 14 sources of claims data or electronic medical records from Germany, Japan, the Netherlands, Spain, the UK, and the USA. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate calibrated hazard ratios (HRs) according to drug use. Estimates were pooled where the I^2 value was less than 0·4.

Findings The study included 956 374 users of hydroxychloroquine, 310 350 users of sulfasalazine, 323 122 users of hydroxychloroquine plus azithromycin, and 351 956 users of hydroxychloroquine plus amoxicillin. No excess risk of severe adverse events was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. Self-controlled case series confirmed these findings. However, long-term use of hydroxychloroquine appeared to be associated with increased cardiovascular mortality (calibrated HR 1·65 [95% CI 1·12–2·44]). Addition of azithromycin appeared to be associated with an increased risk of 30-day cardiovascular mortality (calibrated HR 2·19 [95% CI 1·22–3·95]), chest pain or angina (1·15 [1·05–1·26]), and heart failure (1·22 [1·02–1·45]).

Interpretation Hydroxychloroquine treatment appears to have no increased risk in the short term among patients with rheumatoid arthritis, but in the long term it appears to be associated with excess cardiovascular mortality. The addition of azithromycin increases the risk of heart failure and cardiovascular mortality even in the short term. We call for careful consideration of the benefit–risk trade-off when counselling those on hydroxychloroquine treatment.

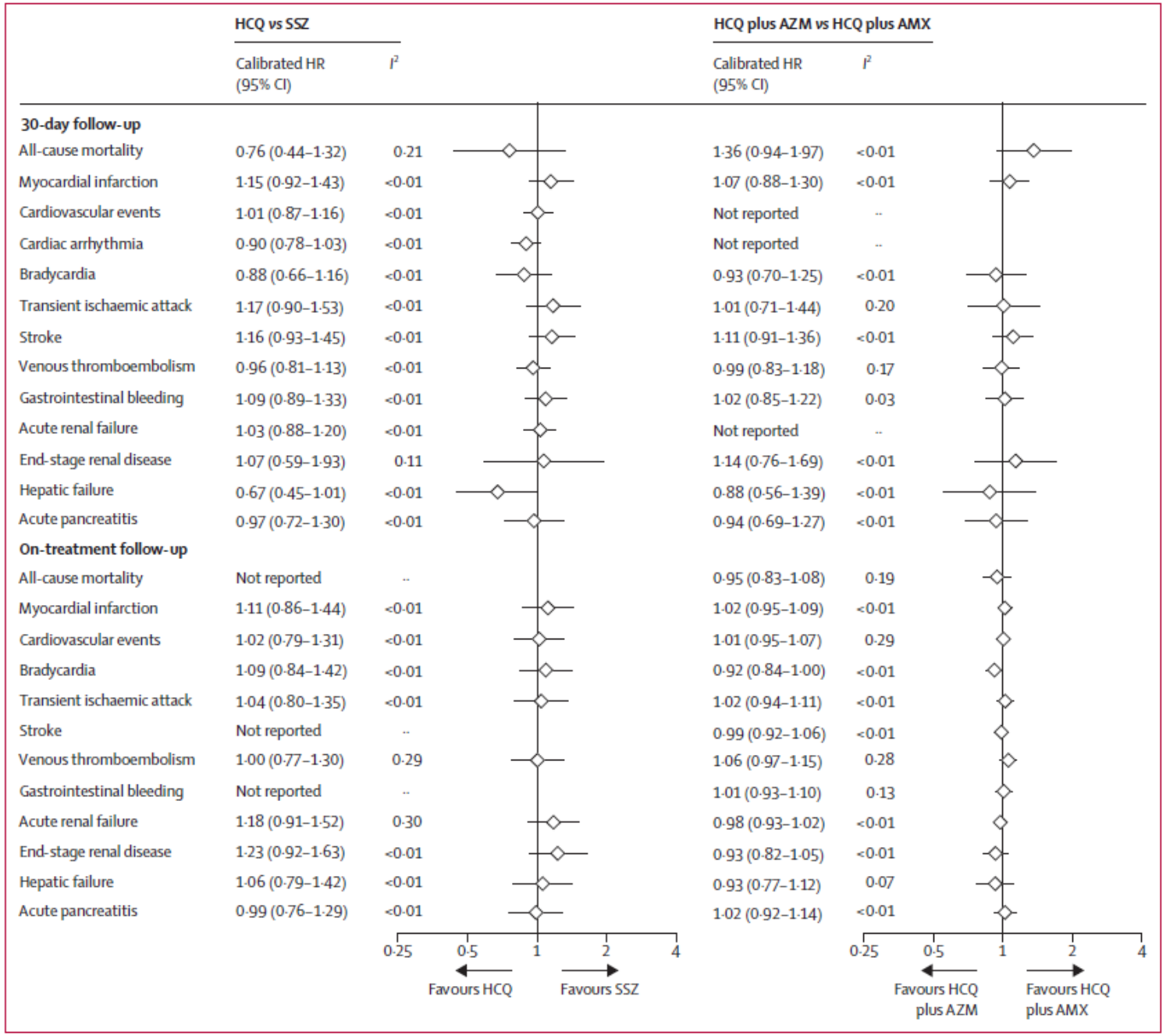

Figure 1: **Meta-analytic estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during 30-day (intention-to-treat) and long-term (on-treatment) follow-up**

AMX=amoxicillin. AZM=azithromycin. HCQ=hydroxychloroquine. HR=hazard ratio. SSZ=sulfasalazine.

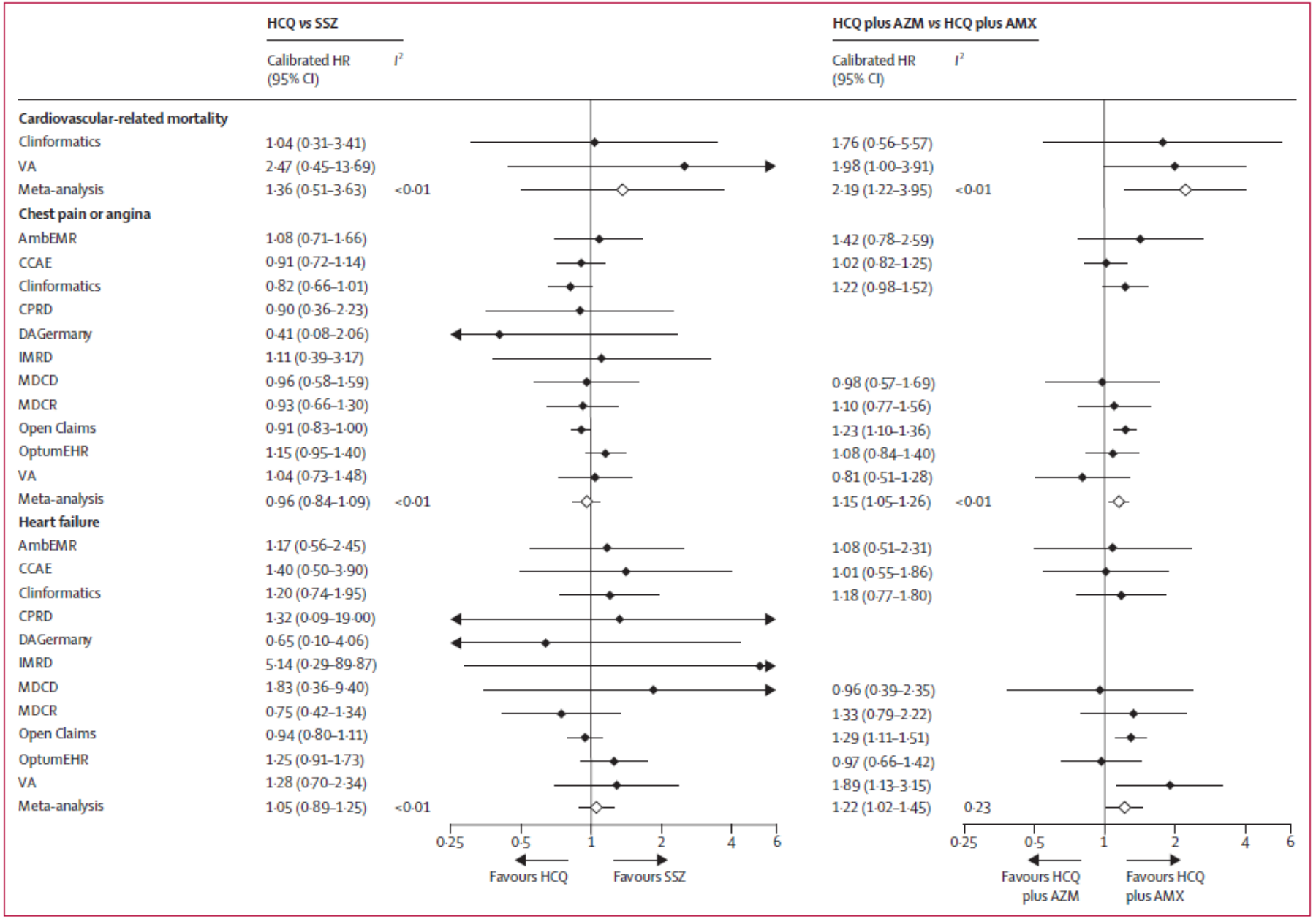

Figure 2: **Source-specific and meta-analytic-specific severe adverse event risk estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during 30-day (intention-to-treat) follow-up**

AmbEMR=IQVIA Ambulatory EMR. AMX=amoxicillin. AZM=azithromycin. CCAE=IBM Commercial Claims and Encounters. CPRD=Clinical Practice Research Datalink. DAGermany=IQVIA Disease Analyzer Germany. EMR=electronic medical record. HCQ=hydroxychloroquine. HR=hazard ratio. IMRD=IQVIA UK Integrated Medical Record Data. MDCD=IBM Multi-state Medicaid. MDCR=IBM Medicare Supplemental Database. OptumEHR=Optum de-identified Electronic Health Record. SSZ=sulfasalazine. VA=US Department of Veterans Affairs.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2020
EMA/202483/2020 Rev.[1]

COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are known to potentially cause heart rhythm problems, and these could be exacerbated if treatment is combined with other medicines, such as the antibiotic azithromycin, that have similar effects on the heart.

Recent studies[2,3] have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin.

Chloroquine and hydroxychloroquine are currently authorised for treating malaria and certain autoimmune diseases. In addition to side effects affecting the heart, they are known to potentially cause liver and kidney problems, nerve cell damage that can lead to seizures (fits) and low blood sugar (hypoglycaemia).

These medicines are being used in the context of the ongoing pandemic for treating patients with COVID-19 and investigated in clinical trials. However, clinical data are still very limited and inconclusive, and the beneficial effects of these medicines in COVID-19 have not been demonstrated. Results from large, well-designed studies are needed to make any conclusions.

Some clinical trials currently investigating the effectiveness of chloroquine or hydroxychloroquine in treating COVID-19 use higher doses than those recommended for the authorised indications. While serious side effects can occur with recommended doses, higher doses can increase the risk of these side effects, including abnormal electrical activity that affects the heart rhythm (QT-prolongation).

Healthcare professionals are recommended to closely monitor patients with COVID-19 receiving chloroquine or hydroxychloroquine and to take into account pre-existing heart problems that can make patients more prone to heart rhythm issues. They should carefully consider the possibility of side effects, particularly with higher doses, and exercise extra caution when combining treatment with other medicines such as azithromycin that may cause similar side effects on the heart.

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[1] The text was updated on 23 April 2020 to correct the scope of the cited studies

[2] Mayla Gabriela Silva Borba, Fernando Fonseca Almeida Val, Vanderson Sousa Sampaio et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxiv doi: 10.1101/2020.04.07.20056424

[3] Lane J.C.E., Weaver J., Kosta K. et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv doi: 10.1101/2020.04.08.20054551

RHEUMATOLOGY

Rheumatology 2021;60:3222–3234
doi:10.1093/rheumatology/keaa771
Advance Access publication 25 December 2020

Original article

Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multinational network cohort study

Jennifer C. E. Lane [1,*], James Weaver[2,*], Kristin Kostka[3], Talita Duarte-Salles[4], Maria Tereza F. Abrahao[5], Heba Alghoul[6], Osaid Alser[7], Thamir M. Alshammari[8], Carlos Areia[9], Patricia Biedermann[10], Juan M. Banda[11], Edward Burn [1,4], Paula Casajust[12], Kristina Fister[13], Jill Hardin[2], Laura Hester[2], George Hripcsak[14,15], Benjamin Skov Kaas-Hansen[16,17], Sajan Khosla[18], Spyros Kolovos[1], Kristine E. Lynch[19,20], Rupa Makadia[2], Paras P. Mehta[21], Daniel R. Morales[22], Henry Morgan-Stewart[3], Mees Mosseveld[23], Danielle Newby[24], Fredrik Nyberg[25], Anna Ostropolets[14], Rae Woong Park[26], Albert Prats-Uribe [1], Gowtham A. Rao[2], Christian Reich[3], Peter Rijnbeek[23], Anthony G. Sena[2,23], Azza Shoaibi[2], Matthew Spotnitz[14], Vignesh Subbian[27], Marc A. Suchard[28], David Vizcaya[29], Haini Wen[30], Marcel de Wilde[23], Junqing Xie[1], Seng Chan You[26], Lin Zhang[31,32], Simon Lovestone[33], Patrick Ryan[2,14] and Daniel Prieto-Alhambra[1], for the OHDSI-COVID-19 consortium

Abstract

Objectives. Concern has been raised in the rheumatology community regarding recent regulatory warnings that HCQ used in the coronavirus disease 2019 pandemic could cause acute psychiatric events. We aimed to study whether there is risk of incident depression, suicidal ideation or psychosis associated with HCQ as used for RA.

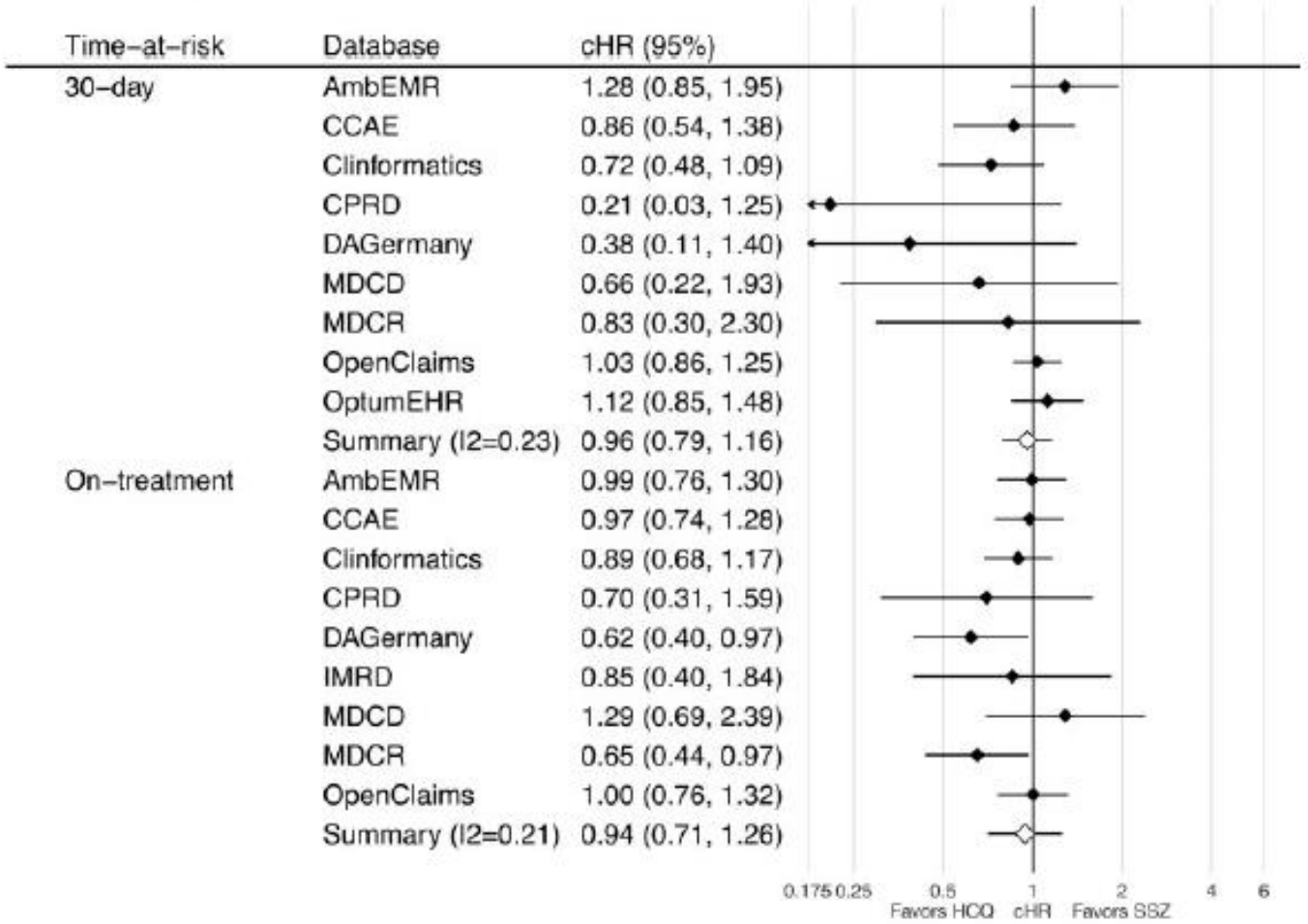
Methods. We performed a new-user cohort study using claims and electronic medical records from 10 sources and 3 countries (Germany, UK and USA). RA patients ≥18 years of age and initiating HCQ were compared with those initiating SSZ (active comparator) and followed up in the short (30 days) and long term (on treatment). Study outcomes included depression, suicide/suicidal ideation and hospitalization for psychosis. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate database-specific calibrated hazard ratios (HRs), with estimates pooled where $I^2 < 40\%$.

Results. A total of 918 144 and 290 383 users of HCQ and SSZ, respectively, were included. No consistent risk of psychiatric events was observed with short-term HCQ (compared with SSZ) use, with meta-analytic HRs of 0.96 (95% CI 0.79, 1.16) for depression, 0.94 (95% CI 0.49, 1.77) for suicide/suicidal ideation and 1.03 (95% CI 0.66, 1.60) for psychosis. No consistent long-term risk was seen, with meta-analytic HRs of 0.94 (95% CI 0.71, 1.26) for depression, 0.77 (95% CI 0.56, 1.07) for suicide/suicidal ideation and 0.99 (95% CI 0.72, 1.35) for psychosis.

Conclusion. HCQ as used to treat RA does not appear to increase the risk of depression, suicide/suicidal ideation or psychosis compared with SSZ. No effects were seen in the short or long term. Use at a higher dose or for different indications needs further investigation.

Trial registration. Registered with EU PAS (reference no. EUPAS34497; http://www.encepp.eu/encepp/viewResource.htm?id=34498). The full study protocol and analysis source code can be found at https://github.com/ohdsi-studies/Covid19EstimationHydroxychloroquine2.

FIG. 1 Forest plot of the association between short- (top) and long-term (bottom) use of HCQ (*vs* SSZ) and risk of depression, by database and in the meta-analysis



Drug Safety (2021) 44:479–497
https://doi.org/10.1007/s40264-021-01060-4

ORIGINAL RESEARCH ARTICLE

Comparative Risk Assessment of Severe Uterine Bleeding Following Exposure to Direct Oral Anticoagulants: A Network Study Across Four Observational Databases in the USA

James Weaver[1] · Azza Shoaibi[1] · Huy Q. Truong[2] · Leila Larbi[2] · Shujian Wu[3] · Peter Wildgoose[1] · Gowtham Rao[1] · Amy Freedman[1] · Lu Wang[1] · Zhong Yuan[1] · Elliot Barnathan[2]

Abstract

Background Antithrombotic therapies are associated with an increased bleeding risk. Abnormal uterine bleeding data have been reported in clinical trials of patients with venous thromboembolism (VTE), but data are limited for patients with atrial fibrillation (AF).

Objective Using real-world data from four US healthcare databases (October 2010 to December 2018), we compared the occurrence of severe uterine bleeding among women newly exposed to rivaroxaban, apixaban, dabigatran, and warfarin stratified by indication.

Methods To reduce potential confounding, patients in comparative cohorts were matched on propensity scores. Treatment effect estimates were generated using Cox proportional hazard models for each indication, in each database, and only for pairwise comparisons that met a priori study diagnostics. If estimates were homogeneous ($I^2 < 40\%$), a meta-analysis across databases was performed and pooled hazard ratios reported.

Results Data from 363,919 women newly exposed to a direct oral anticoagulant or warfarin with a prior diagnosis of AF (60.8%) or VTE (39.2%) were analyzed. Overall incidence of severe uterine bleeding was low in the populations exposed to direct oral anticoagulants, although relatively higher in the younger VTE population vs the AF population (unadjusted incidence rates: 2.8–33.7 vs 1.9–10.0 events/1000 person-years). In the propensity score-matched AF population, a suggestive, moderately increased risk of severe uterine bleeding was observed for rivaroxaban relative to warfarin [hazard ratios and 95% confidence intervals from 0.83 (0.27–2.48) to 2.84 (1.32–6.23) across databases with significant heterogeneity], apixaban [pooled hazard ratio 1.45 (0.91–2.28)], and dabigatran [2.12 (1.01–4.43)], which were sensitive to the time-at-risk period. In the propensity score-matched VTE population, a consistent increased risk of severe uterine bleeding was observed for rivaroxaban relative to warfarin [2.03 (1.19–3.27)] and apixaban [2.25 (1.45–3.41)], which were insensitive to the time-at-risk period.

Conclusions For women who need antithrombotic therapy, personalized management strategies with careful evaluation of benefits and risks are required.

ClinicalTrials.gov Registration NCT04394234; registered in May 2020.

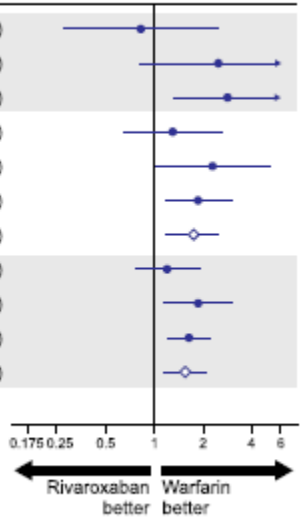
Table 1 Selected baseline characteristics. For the full set of baseline characteristics, visit the online application: https://data.ohdsi.org/DoacsWarfarinSub/. The online application is searchable for the baseline prevalence of any covariate by navigating to the "Population Characteristics" tab and selecting the "Raw" view and searching for a covariate of interest before and after 1:1 propensity score matching for the comparison of rivaroxaban vs warfarin in the atrial fibrillation population from the Optum database

Characteristic	Before matching			After matching		
	Rivaroxaban[a] (*n* = 21,858)	Warfarin[b] (*n* = 35,005)		Rivaroxaban (*n* = 13,891)	Warfarin (*n* = 13,891)	
	%	%	Std. diff	%	%	Std. diff
Age group, years						
25–29	0.0	0.0	0.01	0.0	0.0	0.01
30–34	0.1	0.1	0.01	0.1	0.0	0.02
35–39	0.2	0.1	0.01	0.2	0.1	0.02
40–44	0.4	0.2	0.02	0.3	0.2	0.03
45–49	0.8	0.4	0.04	0.5	0.4	0.02
50–54	1.9	1.1	0.06	1.4	1.3	0.00
55–59	3.9	2.5	0.08	2.6	2.5	0.01
60–64	6.6	4.7	0.08	5.1	4.9	0.01
65–69	14.8	11.7	0.09	12.8	12.9	0.00
70–74	18.8	17.1	0.04	18.5	18.5	0.00
75–79	18.7	19.5	− 0.02	19.5	19.4	0.00
80–84	18.2	27.6	− 0.22	21.3	22.0	− 0.02
85–89	15.7	14.9	0.02	17.6	17.7	0.00
Medical history: general						
Acute respiratory disease	24.5	27.0	− 0.06	24.8	25.1	− 0.01
Attention-deficit/hyperactivity disorder	0.2	0.1	0.01	0.1	0.2	− 0.01
Chronic liver disease	1.5	1.9	− 0.03	1.7	1.7	0.00
Chronic obstructive lung disease	18.7	21.7	− 0.07	20.1	20.0	0.00
Crohn's disease	0.3	0.4	− 0.01	0.3	0.5	− 0.02
Dementia	6.1	6.9	− 0.03	6.9	6.7	0.01
Depressive disorder	16.2	16.2	0.00	16.3	16.3	0.00
Diabetes mellitus	30.4	35.1	− 0.10	31.8	31.8	0.00
Gastroesophageal reflux disease	22.0	20.5	0.04	21.3	22.0	− 0.02
Gastrointestinal hemorrhage	2.5	3.8	− 0.07	2.9	2.8	0.00
Human immunodeficiency virus infection	0.1	0.0	0.01	0.1	0.0	0.01
Hyperlipidemia	64.2	64.1	0.00	64.2	64.3	0.00
Hypertensive disorder	82.0	83.6	− 0.04	83.2	83.1	0.00
Lesion of liver	1.0	1.2	− 0.02	1.1	1.0	0.01
Obesity	18.5	15.2	0.09	16.7	16.8	0.00
Osteoarthritis	32.7	30.9	0.04	32.3	32.4	0.00
Pneumonia	10.3	13.4	− 0.09	11.5	11.3	0.01
Psoriasis	1.2	0.8	0.04	1.0	0.9	0.01
Renal impairment	20.9	29.2	− 0.19	23.9	23.4	0.01
Rheumatoid arthritis	2.9	3.2	− 0.01	3.1	3.2	0.00

Fig. 2 Calibrated hazard ratios and calibrated 95% confidence intervals (CIs) for each pairwise comparison during primary and sensitivity observation periods in the atrial fibrillation (AF) population after 1:1 propensity score matching: (**a**) rivaroxaban vs warfarin; (**b**) apixaban vs warfarin; (**c**) dabigatran vs warfarin; (**d**) rivaroxaban vs apixaban; (**e**) rivaroxaban vs dabigatran; and (**f**) apixaban vs dabigatran. Estimates are reported for pairwise comparisons in databases where study diagnostic passed. Summary meta-analytic estimates are reported where $I^2 < 40\%$. *CCAE* IBM MarketScan® Commercial Database, *cHR* calibrated hazard ratio, *ITT* intent-to-treat, *MDCD* IBM MarketScan® Multi-state Medicaid, *MDCR* IBM MarketScan® Medicare Supplemental Beneficiaries

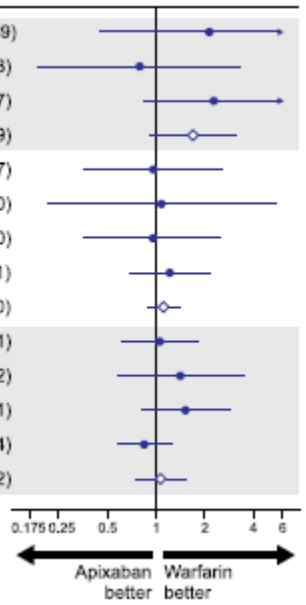
(a)

Time-at-risk	Database	Number of AF matched pairs	Number of events: Rivaroxaban	Number of events: Warfarin	cHR (95% CI)
On-treatment	CCAE	2909	6	9	0.83 (0.27–2.48)
	MDCR	9362	12	5	2.51 (0.83–7.87)
	Optum	13,891	22	11	2.84 (1.32–6.23)
On-treatment	CCAE	2909	25	17	1.30 (0.65–2.62)
(30-day gap)	MDCR	9362	28	9	2.31 (1.04–5.24)
	Optum	13,891	54	28	1.87 (1.17–2.98)
	Summary	26,162	107	54	1.74 (1.20–2.50)
ITT	CCAE	2909	53	45	1.21 (0.77–1.92)
	MDCR	9362	54	29	1.86 (1.16–3.03)
	Optum	13,891	119	76	1.64 (1.22–2.22)
	Summary	26,162	226	150	1.55 (1.16–2.07)



(b)

Time-at-risk	Database	Number of AF matched pairs	Number of events: Apixaban	Number of events: Warfarin	cHR (95% CI)
On-treatment	CCAE	1971	5	<5	2.12 (0.46–10.69)
	MDCR	6554	<5	5	0.80 (0.19–3.33)
	Optum	13,282	11	7	2.26 (0.84–6.07)
	Summary	21,807	<21	<17	1.69 (0.91–3.09)
On-treatment	CCAE	1971	11	9	0.97 (0.36–2.57)
(30-day gap)	MDCD	1518	<5	<5	1.08 (0.21–5.40)
	MDCR	6554	13	8	0.96 (0.36–2.50)
	Optum	13,282	32	23	1.21 (0.69–2.11)
	Summary	23,325	<61	<45	1.11 (0.88–1.40)
ITT	CCAE	1971	29	29	1.06 (0.62–1.81)
	MDCD	1518	12	9	1.42 (0.58–3.52)
	MDCR	6554	29	19	1.51 (0.82–2.81)
	Optum	13,282	52	63	0.85 (0.58–1.24)
	Summary	23,325	122	120	1.07 (0.75–1.52)



Weaver et al. BMC Medical Research Methodology (2023) 23:246
https://doi.org/10.1186/s12874-023-02073-6

BMC Medical Research Methodology

RESEARCH Open Access

Development and evaluation of an algorithm to link mothers and infants in two US commercial healthcare claims databases for pharmacoepidemiology research

James Weaver[1*], Jill H. Hardin[1], Clair Blacketer[1], Alexis A. Krumme[1], Melanie H. Jacobson[1] and Patrick B. Ryan[1]

Abstract

Background Administrative healthcare claims databases are used in drug safety research but are limited for investigating the impacts of prenatal exposures on neonatal and pediatric outcomes without mother-infant pair identification. Further, existing algorithms are not transportable across data sources. We developed a transportable mother-infant linkage algorithm and evaluated it in two, large US commercially insured populations.

Methods We used two US commercial health insurance claims databases during the years 2000 to 2021. Mother-infant links were constructed where persons of female sex 12–55 years of age with a pregnancy episode ending in live birth were associated with a person who was 0 years of age at database entry, who shared a common insurance plan ID, had overlapping insurance coverage time, and whose date of birth was within ±60-days of the mother's pregnancy episode live birth date. We compared the characteristics of linked vs. non-linked mothers and infants to assess similarity.

Results The algorithm linked 3,477,960 mothers to 4,160,284 infants in the two databases. Linked mothers and linked infants comprised 73.6% of all mothers and 49.1% of all infants, respectively. 94.9% of linked infants' dates of birth were within ±30-days of the associated mother's pregnancy episode end dates. Characteristics were largely similar in linked vs. non-linked mothers and infants. Differences included that linked mothers were older, had longer pregnancy episodes, and had greater post-pregnancy observation time than mothers with live births who were not linked. Linked infants had less observation time and greater healthcare utilization than non-linked infants.

Conclusions We developed a mother-infant linkage algorithm and applied it to two US commercial healthcare claims databases that achieved a high linkage proportion and demonstrated that linked and non-linked mother and infant cohorts were similar. Transparent, reusable algorithms applied to large databases enable large-scale research on exposures during pregnancy and pediatric outcomes with relevance to drug safety. These features suggest studies using this algorithm can produce valid and generalizable evidence to inform clinical, policy, and regulatory decisions.

Keywords Data linkage, Pharmacoepidemiology, Drug safety, Perinatal research, Real-world databases

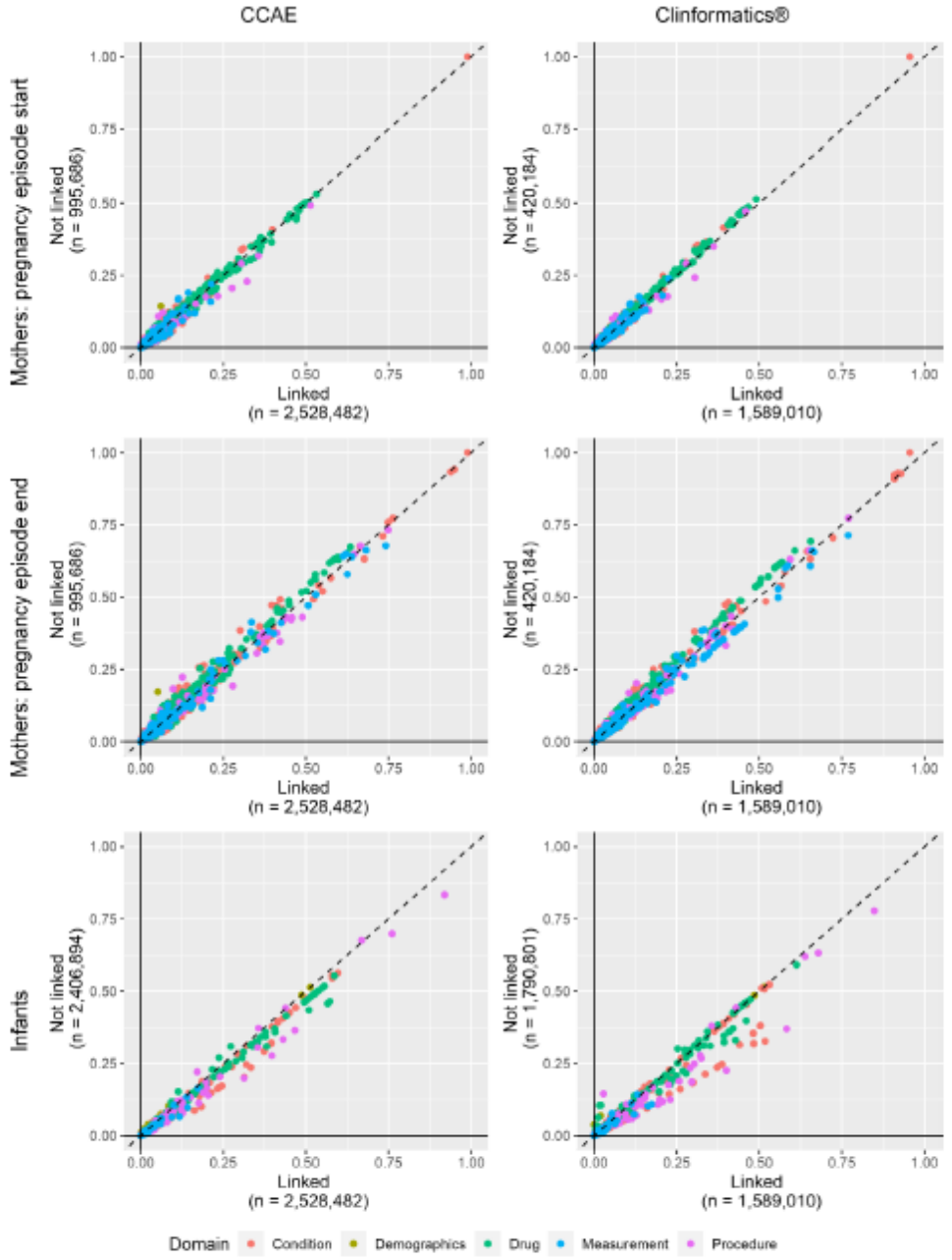


Fig. 2 Demographic, drug exposure, condition, procedure, measurement, and visit occurrence prevalence
Footnote: The x-axes display the prevalence of each covariate in the linked populations and the y-axes display the prevalence of each covariate in the non-linked populations. Data points that lay on the diagonal represent covariates that are equally prevalent in the linked and non-linked populations. Data points to the right the diagonal represent covariates that are more prevalent in the linked populations and those to the left are more prevalent in the non-linked populations

Results

All source code and an interactive web application for viewing full results is available at https://data.ohdsi.org/MotherInfantLinkEval/. A reader can navigate to this web-based application to review the full characterization results set for each linked vs. non-linked comparison. By default, the table reports characteristic prevalence results for linked vs. non-linked cohorts sorted by largest to smallest standardized mean difference between charac-

Development and evaluation of an algorithm to link mothers and infants in two US commercial healthcare claims databases for pharmacoepidemiology research

About | Mothers: pregnancy start | Mothers: pregnancy end | Infants

This research developed and evaluated an algorithm to link mothers and infants in two US commercial healthcare databases to facilitate observational maternal-infant research.

Abstract:

Background: Administrative healthcare claims databases are used in drug safety research but are limited for investigating the impacts of prenatal exposures on neonatal and pediatric outcomes without mother-infant pair identification. Further, existing algorithms are not transportable across data sources. We developed a transportable mother-infant linkage algorithm and evaluated it in two, large US commercially insured populations.

Methods: We used two US commercial health insurance claims databases during the years 2000 to 2021. Mother-infant links were constructed where persons of female sex 12-55 years of age with a pregnancy episode ending in live birth were associated with a person who was 0 years of age at databas entry, who shared a common insurance plan ID, had overlapping insurance coverage time, and whose date of birth was within ±60-days of the mother's pregnancy episode live birth date. We compared the characteristics of linked vs non-linked mothers and infants to assess similarity.

Results: The algorithm linked 3,477,960 mothers to 4,160,284 infants in the two databases. Linked mothers and linked infants comprised 73.6% of all mothers and 49.1% of all infants, respectively. 94.9% of linked infants' dates of birth were within ±30-days of the associated mother's pregnancy episode end dates. Characteristics were largely similar in linked vs. non-linked mothers and infants. Differences included that linked mothers were older, had longer pregnancy episodes, and had greater post-pregnancy observation time than mothers with live births who were not linked. Linked infants had less observation time and greater healthcare utilization than non-linked infants.

Conclusions: We developed a mother-infant linkage algorithm and applied it to two US commercial healthcare claims databases that achieved a high linkage proportion and demonstrated that linked and non-linked mother and infant cohorts were similar. Transparent, reusable algorithms applied to large databases enable large-scale research on exposures during pregnancy and pediatric outcomes with relevance to drug safety. These features suggest studies using this algorithm can produce valid and generalizable evidence to inform clinical, policy, and regulatory decisions.

Key findings:

- This study was conducted to establish mother-infant links in US healthcare databases to facilitate research on prenatal exposures and infant health outcomes
- We found that linked mothers with live births comprise 73.6% of all mothers with live births and linked infants comprise 49.1% of all infants
- We also found that linked vs. non-linked mothers and infants have similar demographic and clinical profiles
- Substantial linked coverage and linked vs non-linked characteristic similarity suggests prenatal exposure causal risk assessment using linked cohorts will produce valid and generalizable evidence
- This mother-infant linkage algorithm is publicly available and easily implemented in databases converted to a common data model

Below are links for study-related artifacts that have been made available as part of this study:

- The full manuscript is available at: https://doi.org/10.1186/s12874-023-02073-6
- The full source code for the study is available at: https://github.com/ohdsi-studies/MotherInfantLinkEval

Weaver et al. BMC Medical Research Methodology (2024) 24:322
https://doi.org/10.1186/s12874-024-02428-7

BMC Medical Research Methodology

RESEARCH Open Access

The necessity of validity diagnostics when drawing causal inferences from observational data: lessons from a multi-database evaluation of the risk of non-infectious uveitis among patients exposed to Remicade®

James Weaver[1*], Erica A. Voss[1], Guy Cafri[2], Kathleen Beyrau[3], Michelle Nashleanas[3] and Robert Suruki[1]

Abstract

Background Autoimmune disorders have primary manifestations such as joint pain and bowel inflammation but can also have secondary manifestations such as non-infectious uveitis (NIU). A regulatory health authority raised concerns after receiving spontaneous reports for NIU following exposure to Remicade®, a biologic therapy with multiple indications for which alternative therapies are available. In assessment of this clinical question, we applied validity diagnostics to support observational data causal inferences.

Methods We assessed the risk of NIU among patients exposed to Remicade® compared to alternative biologics. Five databases, four study populations, and four analysis methodologies were used to estimate 80 potential treatment effects, with 20 pre-specified as primary. The study populations included inflammatory bowel conditions Crohn's disease or ulcerative colitis (IBD), ankylosing spondylitis (AS), psoriatic conditions plaque psoriasis or psoriatic arthritis (PsO/PsA), and rheumatoid arthritis (RA). We conducted four analysis strategies intended to address limitations of causal estimation using observational data and applied four diagnostics with pre-specified quantitative rules to evaluate threats to validity from observed and unobserved confounding. We also qualitatively assessed post-propensity score matching representativeness, and bias susceptibility from outcome misclassification. We fit Cox proportional-hazards models, conditioned on propensity score-matched sets, to estimate the on-treatment risk of NIU among Remicade® initiators versus alternatives. Estimates from analyses that passed four validity tests were assessed.

Results Of the 80 total analyses and the 20 analyses pre-specified as primary, 24% and 20% passed diagnostics, respectively. Among patients with IBD, we observed no evidence of increased risk for NIU relative to other similarly indicated biologics (pooled hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.38–1.40). For patients with RA, we observed no increased risk relative to similarly indicated biologics, although results were imprecise (HR: 1.23, 95% CI 0.14–10.47).

Table 3 Confusion matrix contingency cell counts and misclassification errors for the primary non-infectious uveitis outcome definition across databases

Database	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV
Amb EMR	496	1,412,594	241	465	0.516129	0.999829	0.672999	0.99967
Pharmetrics	2249	1,967,965	1244	6378	0.260577	0.999368	0.643573	0.996769
Optum® EHR	1369	1,946,703	317	3271	0.295043	0.999838	0.811981	0.998323
Clinformatics®	6007	1,658,007	1673	6725	0.471762	0.998992	0.782031	0.99596
CCAE	4044	1,912,446	949	6283	0.391595	0.999504	0.809934	0.996725

Key –Amb EMR: IQVIA Ambulatory Electronic Medical Records, Pharmetrics: IQVIA Adjudicated Health Plan Claims Data, Optum® EHR: Optum® De-Identified Electronic Health Record, Clinformatics®: Optum® De-Identified Clinformatics® Data Mart Database, CCAE: Merative™ MarketScan® Commercial Database, TP: true positives, TN: true negatives, FP: false positives, FN: false negatives, Sensitivity=TP/(TP+FN), Specificity=TN/(TN+FP), PPV=positive predictive value=TP/(TP+FP), NPV=negative predictive value=TN/(TN+FN), Primary outcome definition: [first occurrence of a NIU code with a second NIU code occurrence between 31 days and 365 days relative to first occurrence] OR [first occurrence of a NIU code during an ophthalmology visit]

Table 4 Diagnostic results for primary analyses, rows bolded passed four validity diagnostics

Study pop.	Database	Target	Comparator	T events	C events	0 event Pass	Max ASD	ASD Pass	Equipoise	Equipoise Pass	EASE	EASE Pass	Total Passed
AS	Amb EMR	Remicade®	AS comparator	0	0	0	0.302	0	0.531	1	0.976	0	1
AS	Pharmetrics	Remicade®	AS comparator	6	9	1	0.157	0	0.405	1	0.044	1	3
AS	Optum® EHR	Remicade®	AS comparator	< 5	6	1	0.218	0	0.638	1	0.233	1	3
AS	Clinformatics®	Remicade®	AS comparator	< 5	< 5	1	0.272	0	0.417	1	0.172	1	3
AS	CCAE	Remicade®	AS comparator	< 5	6	1	0.239	0	0.434	1	0.180	1	3
IBD	Amb EMR	Remicade®	IBD comparator	< 5	< 5	1	0.09	1	0.422	1	0.284	0	3
IBD	**Pharmetrics**	**Remicade®**	**IBD comparator**	**12**	**42**	**1**	**0.047**	**1**	**0.431**	**1**	**0.074**	**1**	**4**
IBD	**Optum® EHR**	**Remicade®**	**IBD comparator**	**< 5**	**7**	**1**	**0.055**	**1**	**0.480**	**1**	**0.087**	**1**	**4**
IBD	Clinformatics®	Remicade®	IBD comparator	6	15	1	0.105	0	0.412	1	0.040	1	3
IBD	**CCAE**	**Remicade®**	**IBD comparator**	**10**	**18**	**1**	**0.071**	**1**	**0.387**	**1**	**0.107**	**1**	**4**
PsO/PsA	Amb EMR	Remicade®	PsO/PsA comparator	0	0	0	0.145	0	0.254	0	0.344	0	0
PsO/PsA	Pharmetrics	Remicade®	PsO/PsA comparator	< 5	10	1	0.132	0	0.155	0	0.178	1	2
PsO/PsA	Optum® EHR	Remicade®	PsO/PsA comparator	6	< 5	1	0.099	1	0.306	0	0.246	1	3
PsO/PsA	Clinformatics®	Remicade®	PsO/PsA comparator	0	7	0	0.199	0	0.171	0	0.110	1	1
PsO/PsA	CCAE	Remicade®	PsO/PsA comparator	< 5	9	1	0.167	0	0.147	0	0.010	1	2
RA	Amb EMR	Remicade®(m)	RA comparator	< 5	0	0	0.127	0	0.445	1	0.307	0	1
RA	Pharmetrics	Remicade®(m)	RA comparator	< 5	6	1	0.179	0	0.352	1	0.158	1	3
RA	**Optum® EHR**	**Remicade®(m)**	**RA comparator**	**5**	**< 5**	**1**	**0.097**	**1**	**0.558**	**1**	**0.141**	**1**	**4**
RA	Clinformatics®	Remicade®(m)	RA comparator	< 5	8	1	0.252	0	0.363	1	0.034	1	3
RA	CCAE	Remicade®(m)	RA comparator	< 5	8	1	0.151	0	0.508	1	0.070	1	3

Key: <5=a censored value between 1 and 4; Amb EMR=IQVIA Ambulatory Electronic Medical Records; AS comparator=certolizumab pegol, golimumab, ixekizumab, or secukinumab; AS=ankylosing spondylitis; ASD=absolute standardized difference; CCAE=Merative™ MarketScan® Commercial Database; Clinformatics® = Optum® De-Identified Clinformatics® Data Mart Database; EASE=expected absolute systematic error; IBD comparator=golimumab, certolizumab pegol, ustekinumab, or vedolizumab; IBD=irritable bowel diseases (Crohn's disease or ulcerative colitis); Optum® EHR=Optum® De-Identified Electronic Health Record; Pharmetrics=IQVIA Adjudicated Health Plan Claims Data; PsO/PsA comparator=golimumab, certolizumab pegol, guselkumab, risankizumab, tildrakizumab, brodalumab, ixekizumab, secukinumab, or ustekinumab; PsO/PsA=psoriatic conditions plaque psoriasis or psoriatic arthritis; RA comparator=certolizumab pegol or tocilizumab; RA=rheumatoid arthritis; Remicade®(m)=Remicade® exposure with concurrent methotrexate; Study pop.=study population

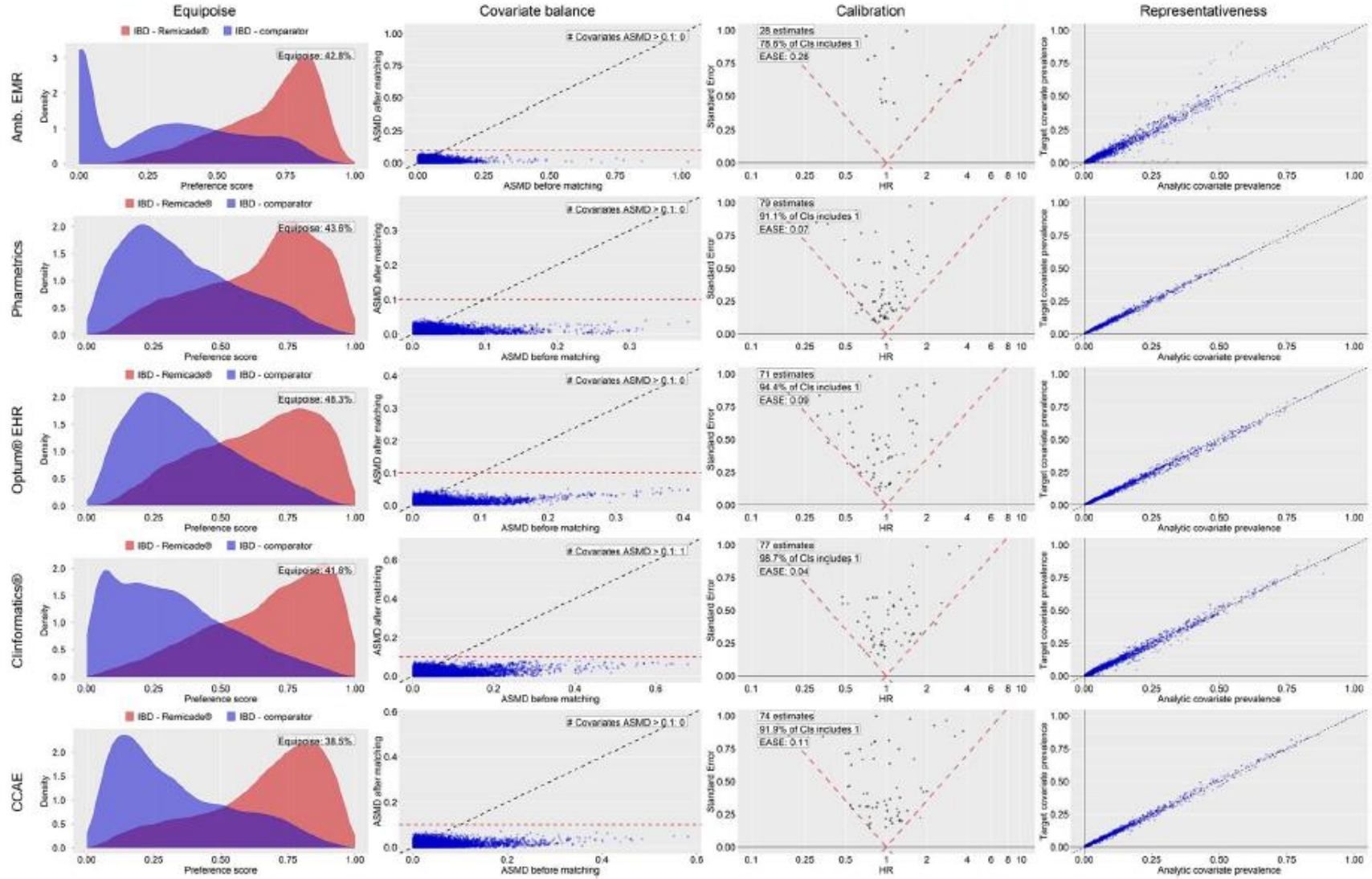


Fig. 1 Empirical equipoise, covariate balance, empirical calibration validity diagnostics and representativeness for IBD primary analysis

Key: Amb EMR = IQVIA Ambulatory Electronic Medical Records; ASMD = absolute standardized mean difference; CCAE = Merative™ MarketScan® Commercial Database; CI = Confidence Interval; Clinformatics® = Optum® De-Identified Clinformatics® Data Mart Database; EASE = expected absolute systematic error; HR = Hazard ratio; IBD = irritable bowel diseases (Crohn's disease or ulcerative colitis); IBD comparator = golimumab, certolizumab pegol, ustekinumab, or vedolizumab; Optum® EHR = Optum® De-Identified Electronic Health Record; Pharmetrics = IQVIA Adjudicated Health Plan Claims Data; Remicade®(m) = Remicade® exposure; Target covariate prevalence = prevalence of baseline covariates in the initial Remicade® exposure cohort before study design restrictions were applied; Analytic covariate prevalence = prevalence of baseline covariates in Remicade® exposure cohort after study design restrictions were applied (i.e., PS matching)

Analysis	Database	T events/patients	T IR/1,000 PYs	C events/patients	C IR/1,000 PYs	cHR (CI 95%)
1:10 PS matched, OT	Pharmetrics	12/10,169	1.00	42/16,836	2.33	0.69 (0.30, 1.58)
	Optum® EHR	4/8,697	0.70	7/13,613	0.92	0.48 (0.08, 2.73)
	CCAE	10/4,515	1.89	18/6,927	2.51	1.00 (0.27, 3.73)
	Summary (I2<0.01)	26/23,381	1.13	67/37,376	2.04	0.73 (0.38, 1.40)
1:10 PS matched, ITT	Amb EMR	2/3,263	0.20	4/4,597	0.33	0.25 (0.02, 2.90)
	Pharmetrics	27/10,169	1.23	68/16,836	2.12	0.63 (0.35, 1.16)
	Optum® EHR	18/8,727	0.63	26/13,633	0.75	0.81 (0.37, 1.75)
	CCAE	23/4,512	2.24	41/6,925	3.04	0.67 (0.29, 1.55)
	Summary (I2<0.01)	70/26,671	0.99	139/41,991	1.50	0.67 (0.43, 1.04)
1:1 PS matched, OT	Pharmetrics	12/10,169	1.00	30/10,169	2.50	0.62 (0.25, 1.52)
	Optum® EHR	4/8,697	0.70	5/8,697	1.02	0.59 (0.10, 3.56)
	CCAE	10/4,515	1.89	11/4,515	2.21	0.70 (0.19, 2.63)
	Summary (I2<0.01)	26/23,381	1.13	46/23,381	2.10	0.64 (0.32, 1.31)
1:1 PS matched, ITT	Amb EMR	2/3,263	0.20	4/3,263	0.40	0.25 (0.02, 2.86)
	Pharmetrics	27/10,169	1.23	50/10,169	2.24	0.62 (0.31, 1.21)
	Optum® EHR	18/8,727	0.63	23/8,727	0.86	0.80 (0.36, 1.76)
	CCAE	23/4,512	2.24	30/4,512	2.93	0.65 (0.27, 1.59)
	Summary (I2<0.01)	70/26,671	0.99	107/26,671	1.55	0.66 (0.41, 1.06)

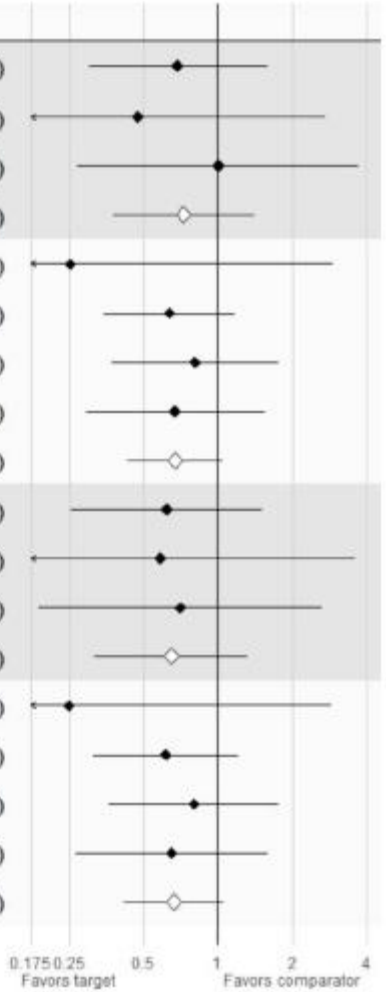


Fig. 4 Risk of non-infectious uveitis (NIU) among patients with inflammatory bowel diseases (IBD)
Key – PS: propensity score, OT: on-treatment, ITT: intention-to-treat, T: Remicade® new users with IBD, C: golimumab, certolizumab pegol, ustekinumab, or vedolizumab new users with IBD, IR: incidence rate, PYs: person-years, CCAE: Merative™ MarketScan® Commercial Database, Optum® EHR: Optum® De-Identified Electronic Health Record, Pharmetrics: IQVIA Adjudicated Health Plan Claims Data