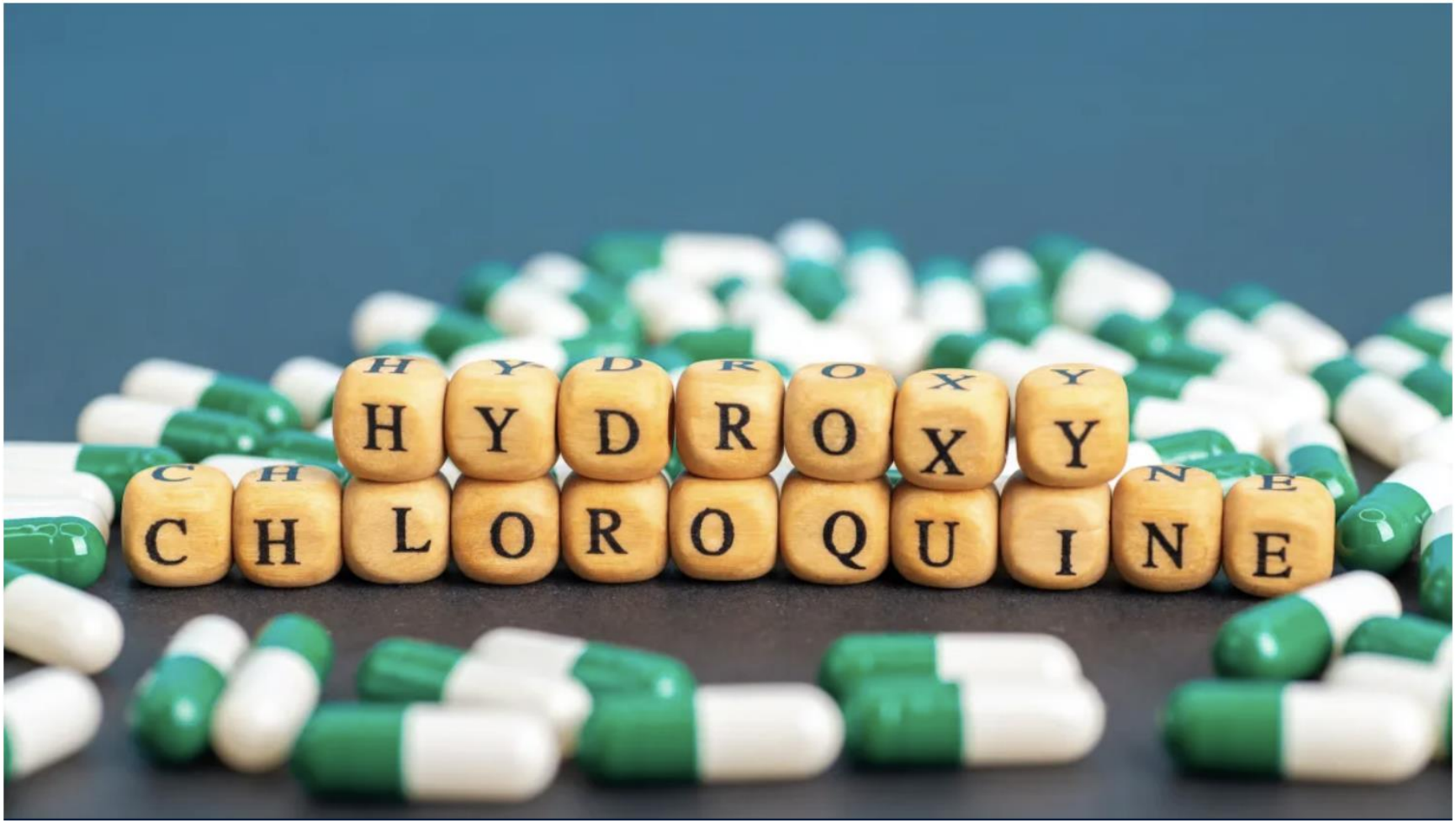

# Risk of HCQ alone and in combination with azithromycin in the treatment of RA: a multinational, retrospective study

Jennifer Lane & James Weaver

On behalf of COVID-19 Studyathon 2020

# (also known as Plaquenil)



# Where did the idea come from?

Traditionally Anti-malarial- unknown mechanism

Widely used Disease Modifying Anti-Rheumatic Drug (DMARD)

-> EULAR; ACR guidelines for Rheumatoid Arthritis- unknown mechanism

COVID studies in Asia

Raoult- France

Le professeur Didier Raoult, dans son bureau à Marseille, le 26 février 2020.

PHOTO - AFP/ARCHIVES - GERARD JULIEN

# Pandemic Media March 2020...

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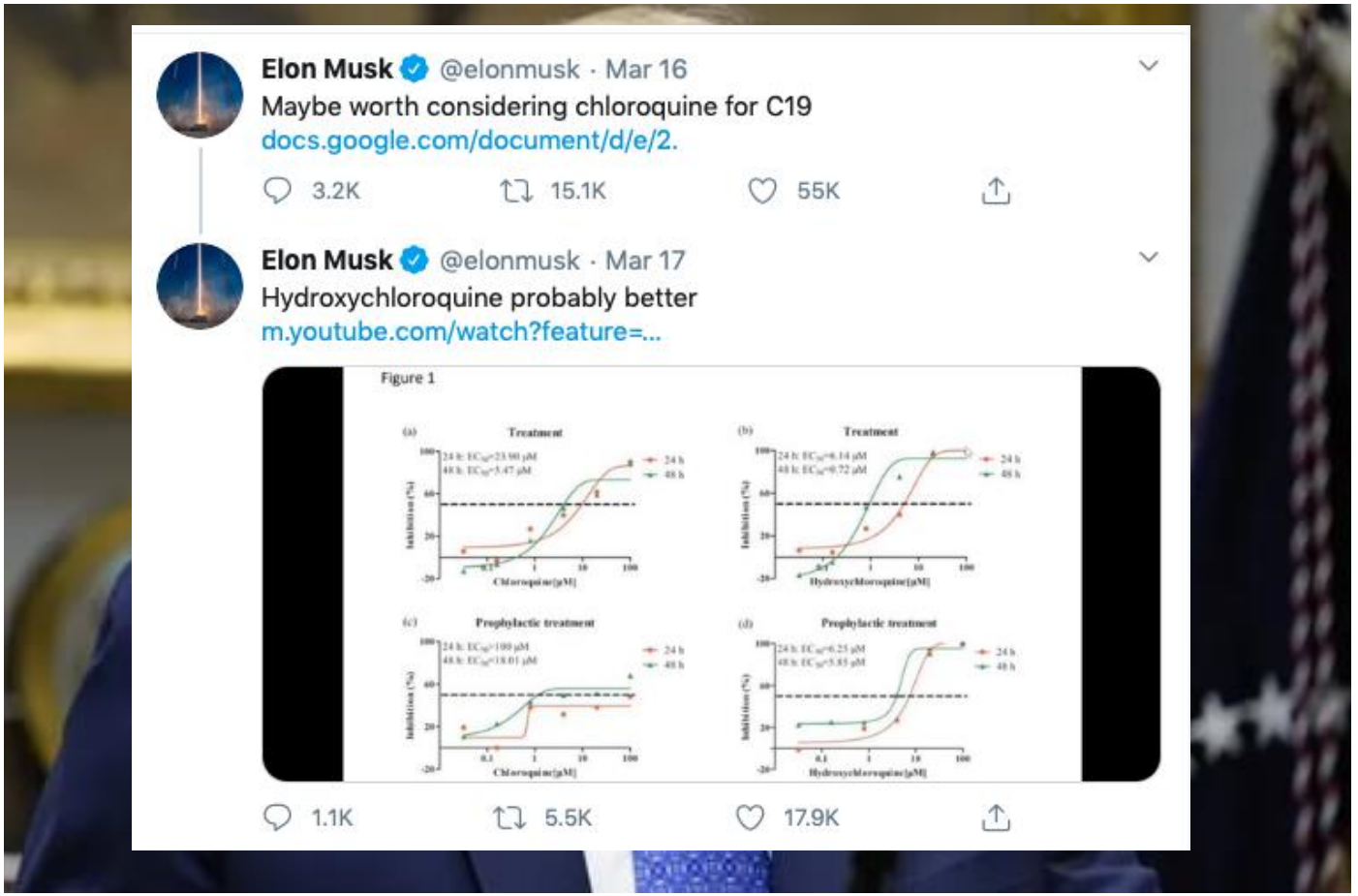

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Coronavirus outbreak

# Hydroxychloroquine: how an unproven drug became Trump's coronavirus 'miracle cure'


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## REVEALED: Hydroxychloroquine was prescribed to 300,000 more patients than usual in March after Trump claimed it was a 'game-changer' for coronavirus treatment

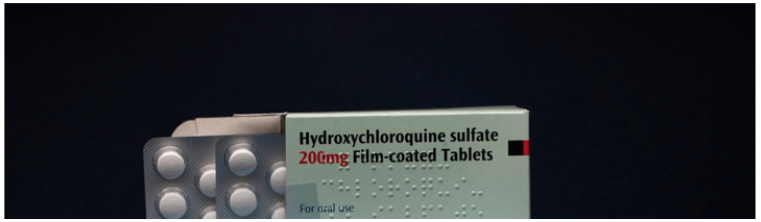
- Hydroxychloroquine is an anti-malaria drug that is most commonly used to treat lupus and rheumatoid arthritis
- Researchers looked at prescriptions of the drug between October 2019 and February 2020 and then from February 2020 to March 2020
- In March, President Trump hailed the drug as a 'game-changer' for treatment of coronavirus, after early results of a small-scale study were promising
- Between February and March, prescriptions for the drug increase by 86.2% from 367, 346 to 683,999

The New York Times

The Coronavirus Outbreak › | LIVE Latest Updates | Trump Tests Positive | Maps and Cases | Vaccine Tracker | Tips to Lower Indoor Risk

## *Malaria Drug Helps Virus Patients Improve, in Small Study*

A group of moderately ill people were given hydroxychloroquine, which appeared to ease their symptoms quickly, but more research is needed.



# COVID-19 studyathon

# Known Side effects: ‘first doing no harm’

## Hydroxychloroquine

- Retinal damage
- Cardiac conduction disorders (QT prolongation)
- Cardiomyopathy; ventricular hypertrophy
- Proximal myopathy
- Leucopenia,thrombocytopenia
- hypoglycaemia
- Bronchospasm
- Acute hepatic failure
- Psychosis, suicidality

## Macrolide antibiotics

- GI disorder
- pancreatitis
- Cardiac conduction disorders (QT prolongation)
- leucopenia
- Electrolyte disturbance
- Aggravation of myasthenia gravis
- Hallucinations
- Hearing impairment

# Before the studyathon... what was actually known?

Systematic review:

PubMed

EMBASE (1974- present)

ICTRP

ClinicalTrial.gov

Chinese Clinical Trial Registry

BioRxiv and MedRxiv

# Before the studyathon... what was actually known?

Systematic review: = 5458 original articles reviewed

PubMed

EMBASE (1974- present)

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# Aim: identifying historical safety

Identify the safety of: HCQ , and HCQ + azithromycin
In a historical population of RA users

Range of serious adverse events
Mortality

to run different methodologies simultaneously
(new user cohort design; self controlled case series)

# Protocol registration

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Home | Sitemap | Q & A | Notice Board | Links | Contact Us

Home > View Study

- News
- About Us
- ENCePP Documents
- Training in PhEpi and PV
- Code of Conduct
- Standards & Guidances
- ENCePP Study Seal
- Public Consultation
- Glossary of terms
- Resources Database
- Partners forum
- EU PAS Register
- About EU PAS Register

Administrative Details | Targets of the Study | Methodological Aspects | Documents

**Status:** Finalised

**First registered on:** 02/04/2020
**Last updated on:** 06/07/2020

## 1. Study identification

| | |
|---|---|
| **EU PAS Register Number** | EUPAS34497 |
| **Official title** | Hydroxychloroquine safety and potential efficacy as an antiviral prophylaxis in light of potential wide-spread use in COVID-19: a multinational, large-scale network cohort and self-controlled case series study |
| **Study title acronym** | |
| **Study type** | Observational study |
| **Brief description of the study** | The overarching objective is to investigate safety and potential efficacy as an antiviral prophylaxis in light of potential wide-spread use in COVID-19 |
| **Was this study requested by a regulator?** | No |
| **Is the study required by a Risk Management Plan (RMP)?** | Not applicable |

# Standardized, modular approach to fully specifying a comparative cohort study

Is **Target** exposure,

relative to **Comparator** exposure

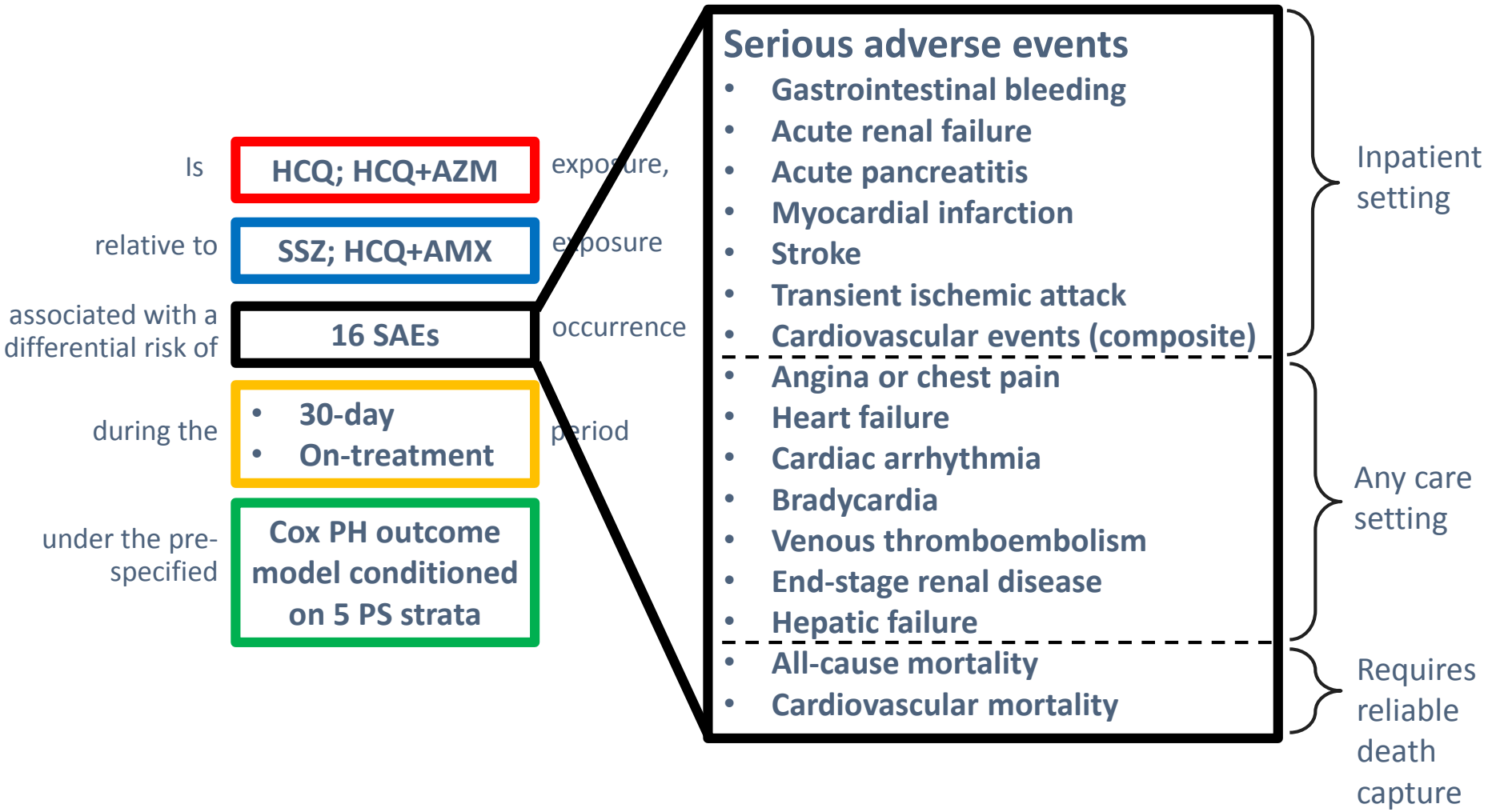
associated with a differential risk of **Outcome** occurrence

during the **Time-at-risk** period

under the pre-specified **Analysis specification**

Goal is to attribute causality to this association; only valid under certain assumptions

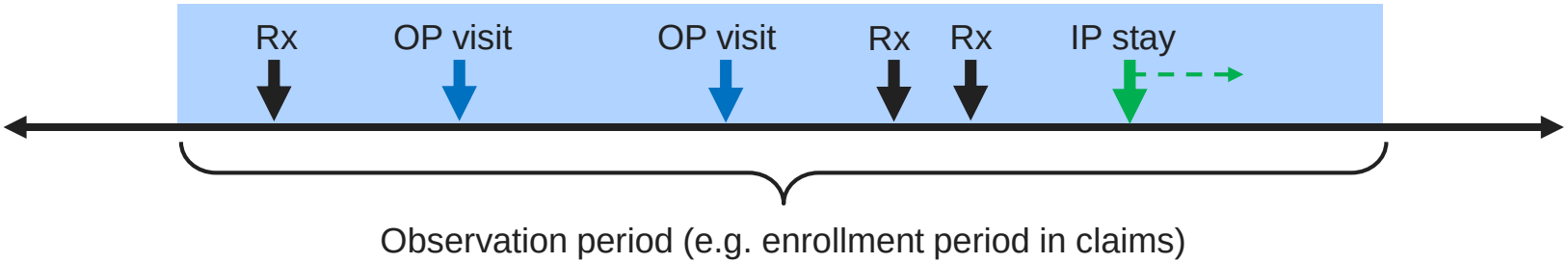
# Among patients with rheumatoid arthritis…




Outcome ascertainment cohort definitions and supporting references
https://www.thelancet.com/cms/10.1016/S2665-9913(20)30276-9/attachment/7e94f546-41b4-470a-958b-2351d1b63cc9/mmc1.pdf

# Observational data/RWD/routine care/…

- Longitudinal, time-stamped encounters, de-identified, patient-level data including diagnoses, procedures, prescriptions/dispensing, some lab measurements and results



# Distributed database network study

| Source | Population | Patients | Type |
|---|---|---|---|
| VA | US (Veterans) | 12M | Claims |
| DAGermany | Germany (general population) | 37M | EHR |
| IMRD | UK (general population) | 15M | EHR |
| AmbEMR | US (general population) | 49M | EHR |
| OpenClaims | US (general population) | 300M | Claims |
| CPRD | UK (general population) | 13M | EHR |
| CCAE | US (commercially insured, <65y) | 142M | Claims |
| MDCD | US (Medicaid enrollees) | 26M | Claims |
| MDCR | US (commercially insured, ≥65y) | 10M | Claims |
| IPCI | Netherlands (general population | 2.5M | EHR |
| JMDC | Japan (insured general population) | 5.5M | Claims |
| Clinformatics | US (commercially insured) | 85M | Claims |
| OptumEHR | US (general population) | 93M | EHR |
| SIDIAP | Catalonia (general population) | 7.7M | EHR |

# Distributed database network study

14 database

6 countries

7 administrative claims

7 electronic health records

**Real world heterogeneity of patient experience**

Data partners contributing to this study remain custodians of their individual patient-level health information and hold either exemption from institutional review boards or approval for participation

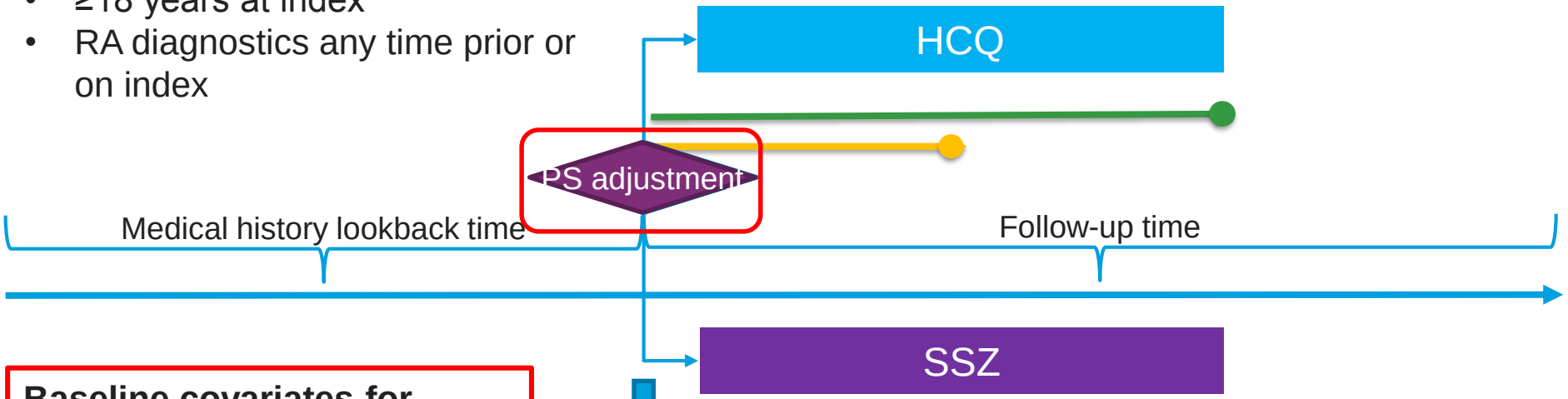
| | | | |
|---|---|---|---|
| SIDIAP | Catalonia (general population) | 7.7M | EHR |

# Comparative cohort study design

**Eligibility criteria:**
- First exposure after Sept 1, 2000
- ≥365 days prior observation
- ≥18 years at index
- RA diagnostics any time prior or on index

**Treatment strategies:**
1. HCQ vs SSZ
2. HCQ+AZM vs HCQ+AMX

**Causal contrasts:**
- On-treatment effect
- Fixed 30d effect




**Baseline covariates for confounding adjustment from observed sources:**
- Demographics
- Conditions, drugs, procedures, devices, measurements observed during the 365 and 30 days before and including index date
- Comorbidity and risk scores

**Index date: Day 0**

**TAR start: Day 1**

**Outcomes:**
- 16 severe adverse events
- No prior outcome (30d)

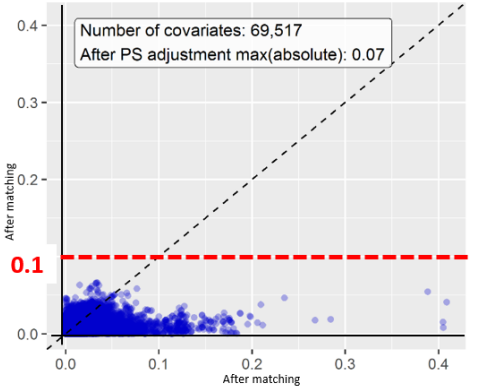
**Analysis plan:**
- Cox PH model
- Meta-analysis if $I^2$<40%

**Calibration outcomes for confounding adjustment from unobserved sources:**
65 negative controls

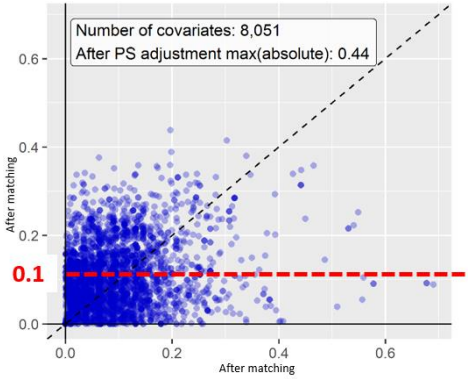
# Active comparators and propensity score stratification to control for observed confounding

- Active comparator, new user design nested within RA population
- Further balanced baseline covariates using propensity score[1] stratification
- Propensity-score: predicted probability of exposure, given observed baseline characteristics
  - Propensity scores created by large-scale regularized regression[2] (a data-adaptive, predictive model that reduces overfitting to optimize covariate balance on thousands of covariates)
  - Each patient has a propensity score and is characteristically similar to other patients with similar propensity scores
- Patients distributed across PS quintiles

Good example of covariate balance[3]




Bad example of covariate balance



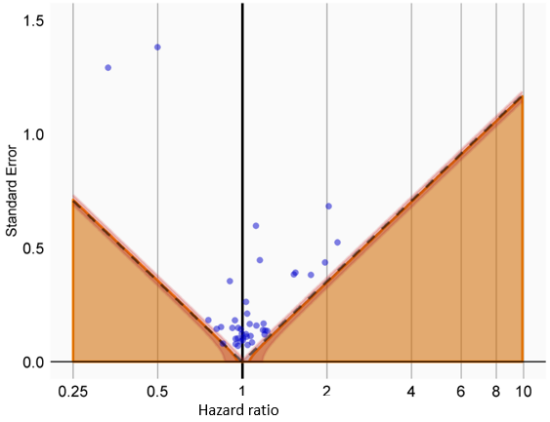


1. Rosenbaum PR, Rubin DB. Biometrika. 1983;70(1):41–55. doi.org/10.1093/biomet/70.1.41
2. Tian Y, Schuemie MJ, Suchard MA. Int J Epidemiol. 2018;47(6):2005-2014. doi:10.1093/ije/dyy120
3. Austin P. Stat Med. 2009 Nov 10;28(25):3083-107. doi: 10.1002/sim.3697.

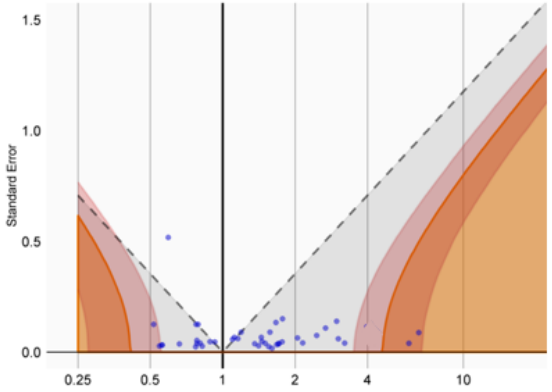
# Empirical calibration using negative control outcomes to control for unobserved confounding

- Negative control outcome experiments for each comparison where the null hypothesis of no effect is believed to be true
  - E.g. What is the risk of apnea between HCQ vs. SSZ?
- Estimated HRs for 65 negative control outcomes to generate an empirical null distribution
- Based on this error distribution, we calibrated the HRs and 95% CIs to reflect any observed, residual error[1,2]
- Control unmeasured confounding and other sources of systematic and random error
- PS and calibration methods demonstrate good operating characteristics across clinical questions and data sources[3]

Good example of calibration




Bad example of calibration





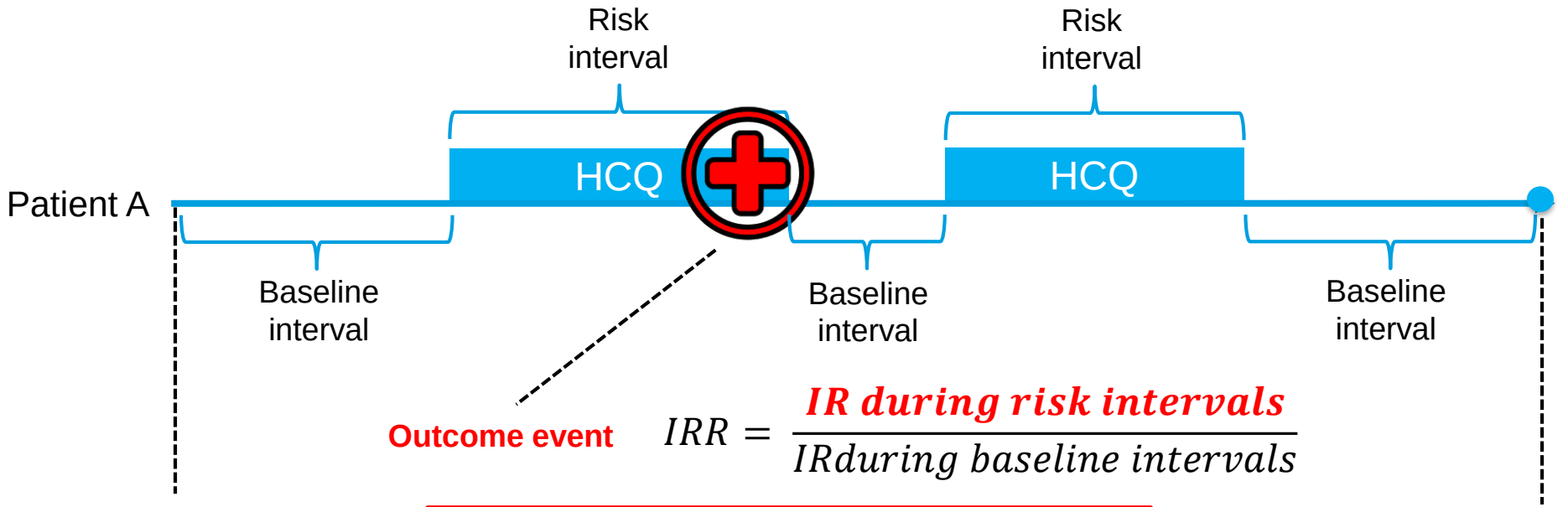
1. Schuemie MJ et al. Interpreting observational studies: why empirical calibration is needed to correct p-values. *Statistics in medicine* 2014; 33(2):209-18
2. Schuemie MJ et al. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proceedings of the National Academy of Sciences of the United States of America* 2018; 115(11): 2571-7
3. Schuemie MJ et al. How Confident Are We About Observational Findings in Health Care: A Benchmark Study. Harvard Data Science Review, 2(1). https://doi.org/10.1162/99608f92.147cc28e

# Self-controlled case series design

**Eligibility criteria:**
- Prevalent users of HCQ
- No RA or other restrictions
- Severe adverse event observed

**Treatment strategy:**
- Periods of HCQ exposure vs periods w/o HCQ exposure

**Time-varying confounding adjustment**
- Age-seasonality adjustment
- Pre-exposure window
- Event-dependent observation correction (sensitivity)




**Calibration outcomes for confounding adjustment from unobserved sources:**
65 negative controls

# Results preamble

**Overall counts**

| Exposure | N |
|---|---|
| HCQ | 956 374 |
| SSZ | 310 350 |
| HCQ+AZM | 323 122 |
| HCQ+AMX | 351 956 |

- On-treatment duration of HCQ therapy ranged from median of 43 days (IQR 43–193) in AmbEMR to 338 days (106–1507) in CPRD
- On-treatment during of HCQ+AZM therapy ranged from median of 16 days (IQR 16–1381) in DAGermany to 91 days (IQR 16–880) in CPRD

# Results preamble

## Outcome availability

| Source | Any setting | Inpatient | All-cause mortality | CV mortality |
|---|---|---|---|---|
| VA | ✓ | ✓ | ✓ | ✓ |
| DAGermany | ✓ | ✓ | | |
| IMRD | ✓ | | ✓ | ✓ |
| AmbEMR | ✓ | | | |
| OpenClaims | ✓ | ✓ | | |
| CPRD | ✓ | | ✓ | ✓ |
| CCAE | ✓ | ✓ | | |
| MDCD | ✓ | ✓ | | |
| MDCR | ✓ | ✓ | | |
| IPCI | ✓ | ✓ | ✓ | |
| JMDC | ✓ | ✓ | | |
| Clinformatics | ✓ | ✓ | ✓ | ✓ |
| OptumEHR | ✓ | ✓ | | |
| SIDIAP | ✓ | | ✓ | |

- Hospital-based events unavailable in primary care records:
  - CPRD, IMRD, SIDIAP
- All-cause mortality only available in:
  - CPRD, IMRD, IPCI, Clinformatics, SIDIAP, VA
- CV mortality only available in:
  - CPRD, IMRD, Clinformatics, VA

# Results preamble

## Diagnostics passed

| Source | HCQ vs SSZ | AZM vs AMX |
|---|---|---|
| VA | ✓ | ✓ |
| DAGermany | ✓ | |
| IMRD | ✓ | |
| AmbEMR | ✓ | ✓ |
| OpenClaims | ✓ | ✓ |
| CPRD | ✓ | |
| CCAE | ✓ | ✓ |
| MDCD | ✓ | ✓ |
| MDCR | ✓ | ✓ |
| IPCI | | |
| JMDC | | |
| Clinformatics | ✓ | ✓ |
| OptumEHR | ✓ | ✓ |
| SIDIAP | | |

- Estimates are reported only where diagnostics passed:
  - ASMD < 0.1
  - Non-zero counts in both treatment arms during TAR*
  - Any Residual error observed in empirical null distribution corrected through calibration

* On-treatment time-at-risk unavailable in Optum EHR

# Study population characteristics in CCAE

- Majority of patients between 50-65 years (~55-60%)

- **HCQ vs SSZ before PS stratification:**
  - ⇧ women (82.0 vs 74.3%)
  - ⇧ Systemic Lupus Erythematosus (1.5 vs 0.5%)
  - ⇩ Crohn's disease (0.6 vs 1.8%)
  - ⇩ Psoriasis (3.0 vs 8.0%)
  - ⇩ Ulcerative colitis (0.6 vs 1.9%)
  - ⇩ Immunosuppressants (39.6 vs 53.0%)
  - ⇩ Systemic corticosteroids (72.9 vs 76.9%)

- **HCQ+AZM vs HCQ+AMZ before PS stratification:**
  - ⇧ Acute respiratory disease (62.5 vs 50.7%)
  - ⇧ Pneumonia (6.8 vs 4.3%)
  - ⇧ Drugs for obstructive airway diseases (43.6 vs 37.0%)
  - ⇧ Systemic corticosteroids (42.5 vs 37.4%)
  - ⇩ Acute sinusitis (14.7 vs 18.5%)
  - ⇩ Analgesics (32.0 vs 37.7%)

- Achieved PS strata-weighted covariate balance for HCQ vs SSZ and HCQ+AZM vs HCQ vs AMX in many data sources; blinded results where covariate balance not achieved

# CV mortality, chest pain/angina, and heart failure during 30d time-at-risk

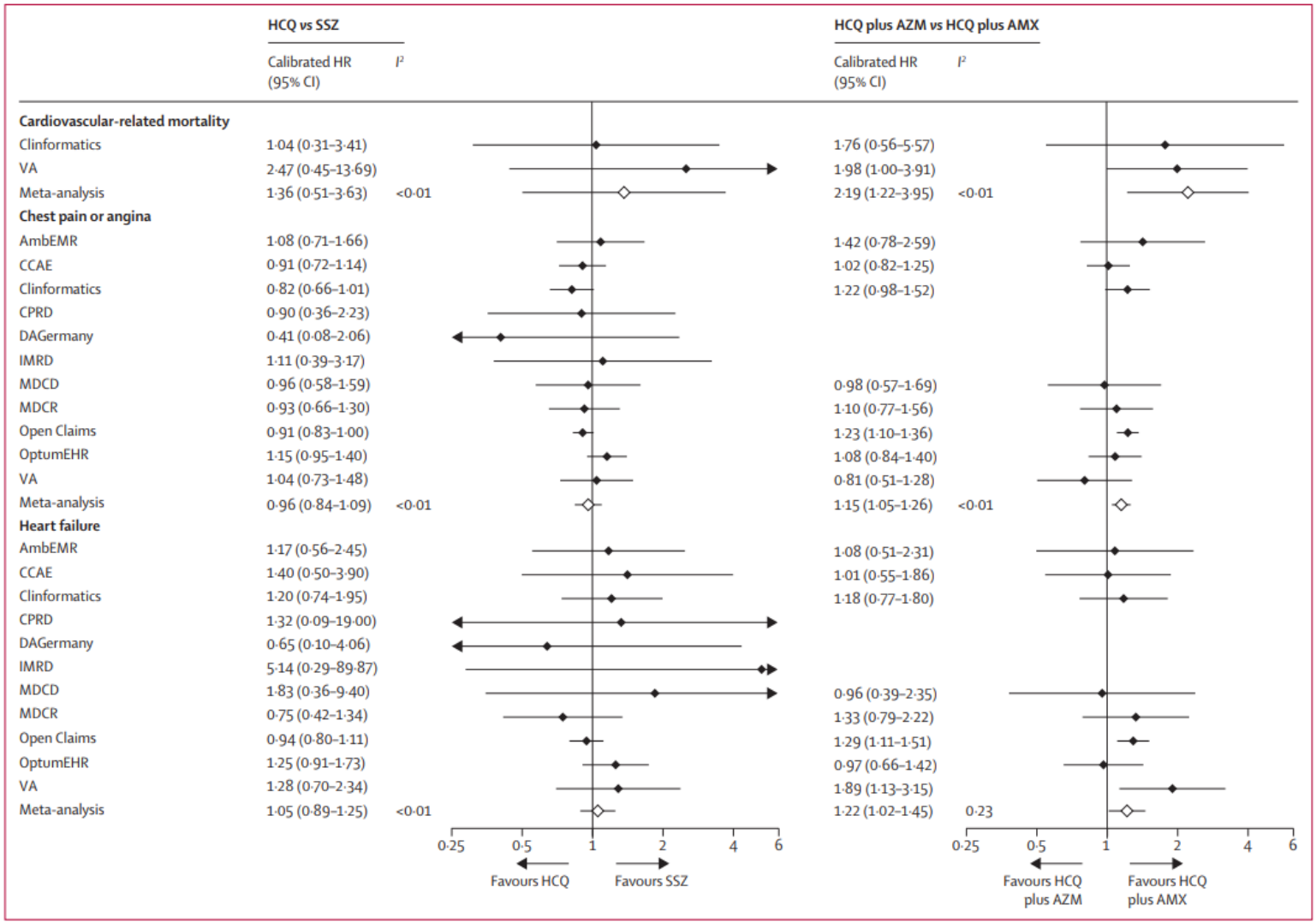



***Figure 2:*** **Source-specific and meta-analytic-specific severe adverse event risk estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during 30-day (intention-to-treat) follow-up**

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.

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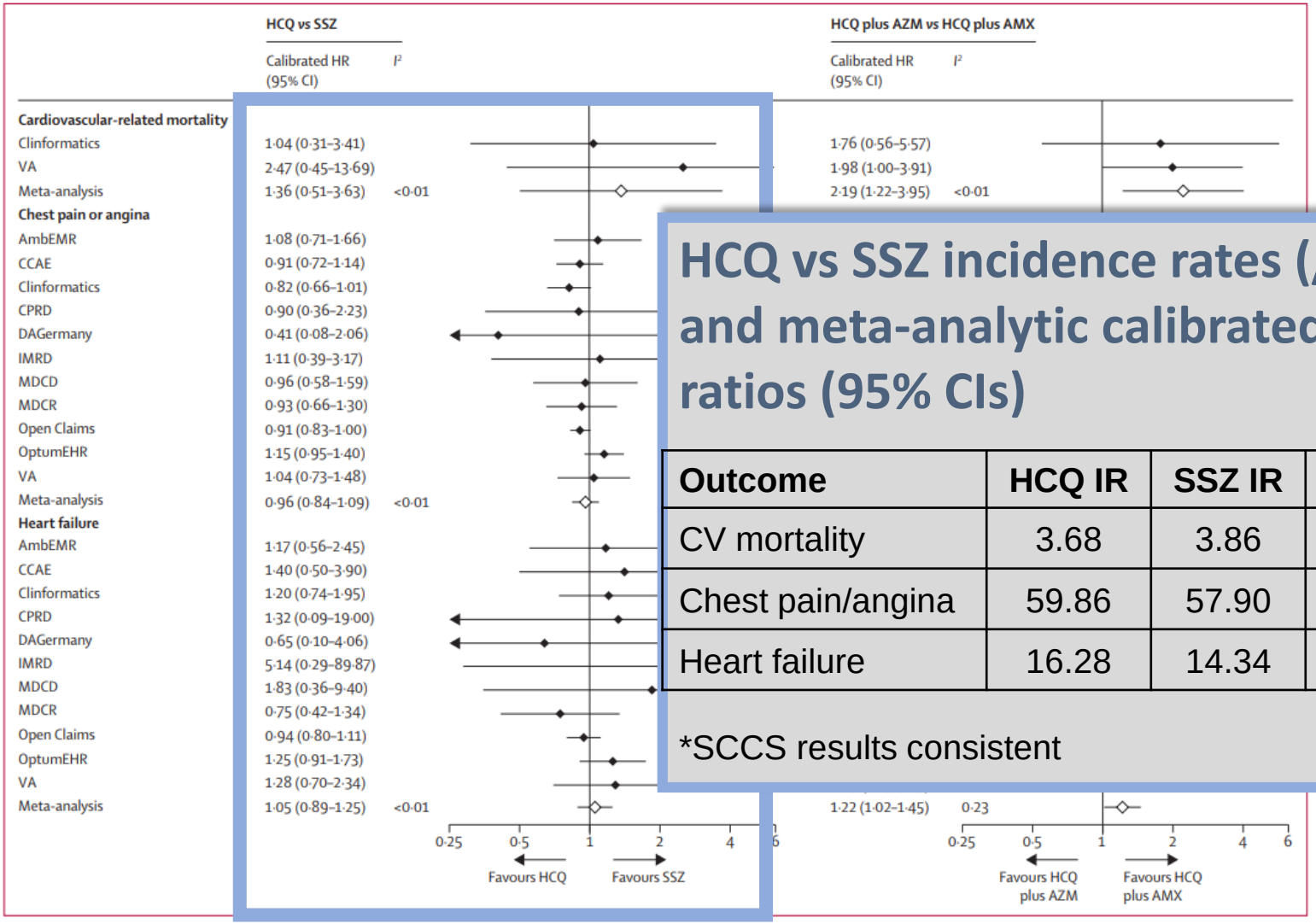


## HCQ vs SSZ incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

| Outcome | HCQ IR | SSZ IR | cHR (95% CI) |
|---|---|---|---|
| CV mortality | 3.68 | 3.86 | 1.36 (0.51-3.63) |
| Chest pain/angina | 59.86 | 57.90 | 0.96 (0.84-1.09)* |
| Heart failure | 16.28 | 14.34 | 1.05 (0.89-1.25)* |

*SCCS results consistent

***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**

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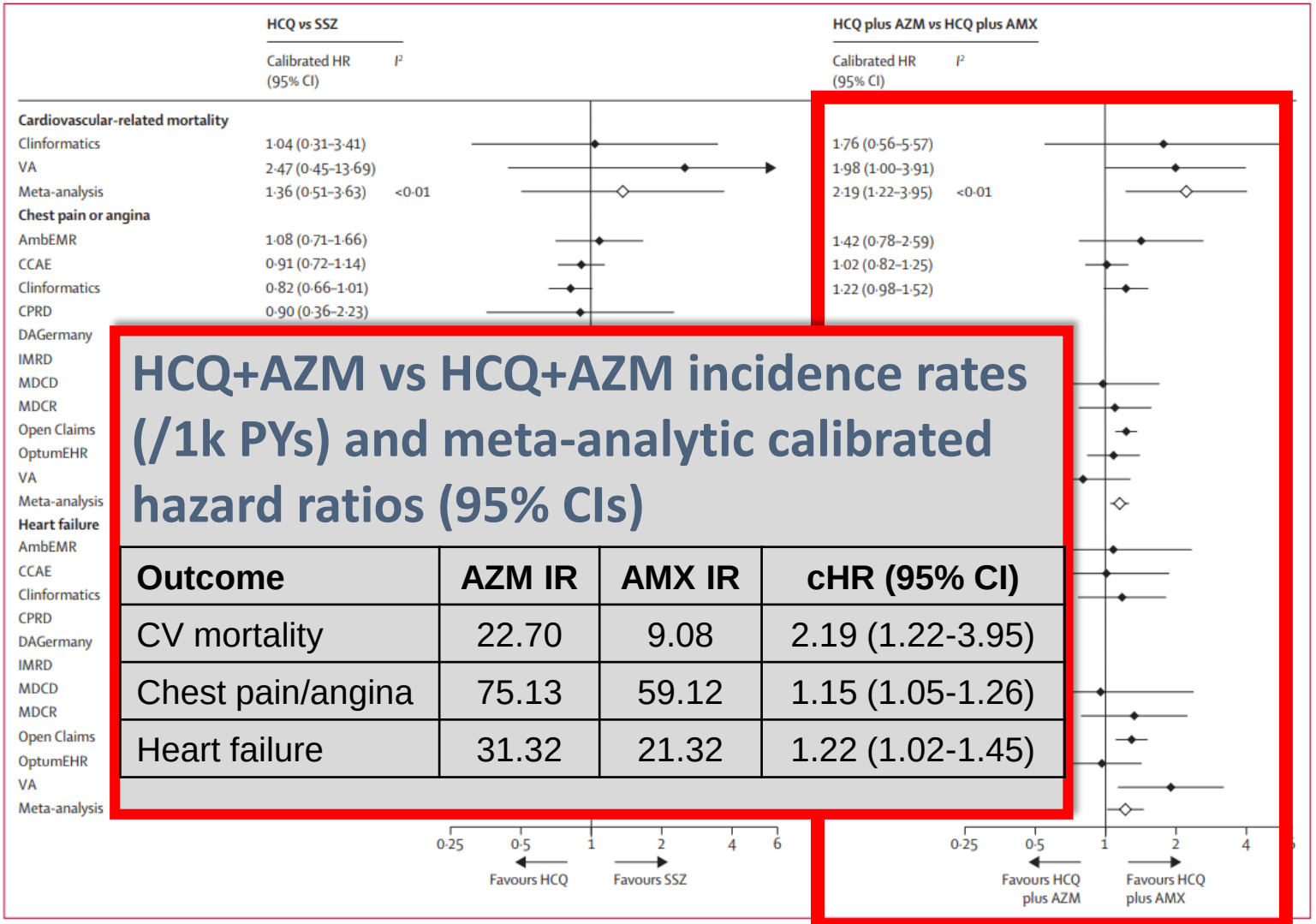


## HCQ+AZM vs HCQ+AZM incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

| Outcome | AZM IR | AMX IR | cHR (95% CI) |
|---|---|---|---|
| CV mortality | 22.70 | 9.08 | 2.19 (1.22-3.95) |
| Chest pain/angina | 75.13 | 59.12 | 1.15 (1.05-1.26) |
| Heart failure | 31.32 | 21.32 | 1.22 (1.02-1.45) |

***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**

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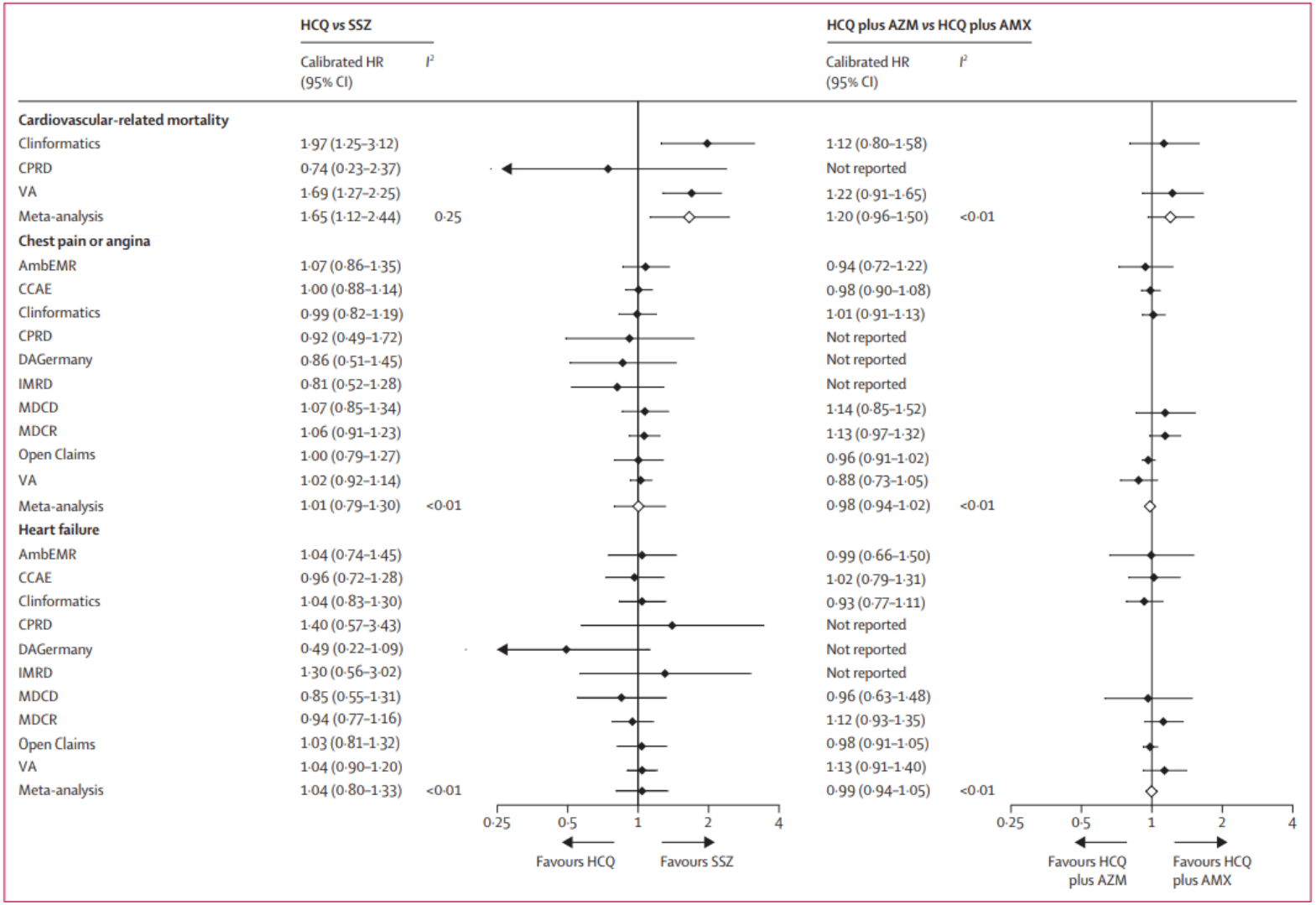


***Figure 3*: Source-specific and meta-analytic specific severe adverse event risk estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during long-term (on-treatment) follow-up**

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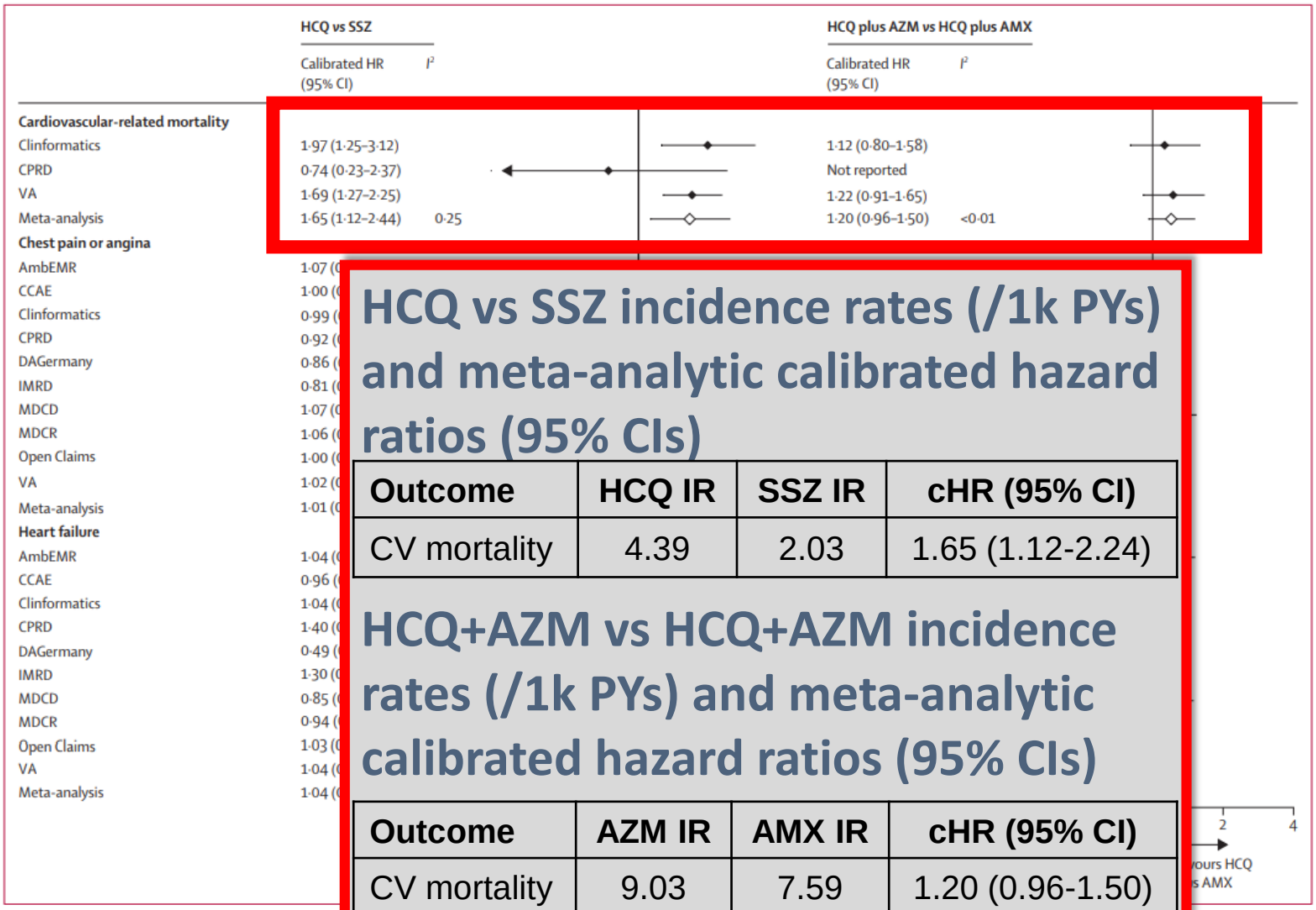


## HCQ vs SSZ incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

| Outcome | HCQ IR | SSZ IR | cHR (95% CI) |
|---|---|---|---|
| CV mortality | 4.39 | 2.03 | 1.65 (1.12-2.24) |

## HCQ+AZM vs HCQ+AZM incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

| Outcome | AZM IR | AMX IR | cHR (95% CI) |
|---|---|---|---|
| CV mortality | 9.03 | 7.59 | 1.20 (0.96-1.50) |

*Figure 3*: Source-specific and meta-analytic specif… rm
(on-treatment) follow-up

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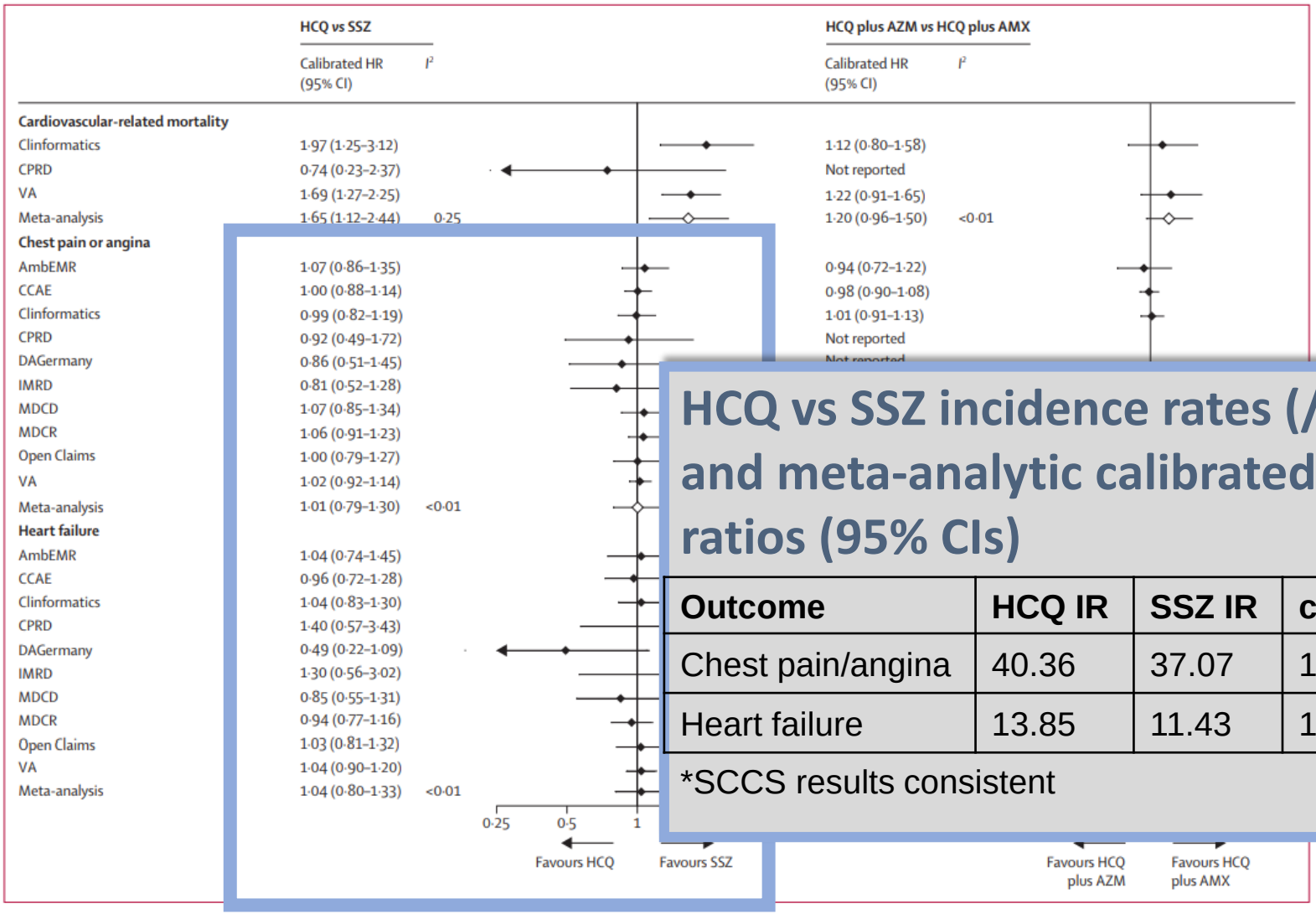


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| Outcome | HCQ IR | SSZ IR | cHR (95% CI) |
|---|---|---|---|
| Chest pain/angina | 40.36 | 37.07 | 1.01 (0.79-1.30)* |
| Heart failure | 13.85 | 11.43 | 1.04 (0.80-1.33)* |

*SCCS results consistent

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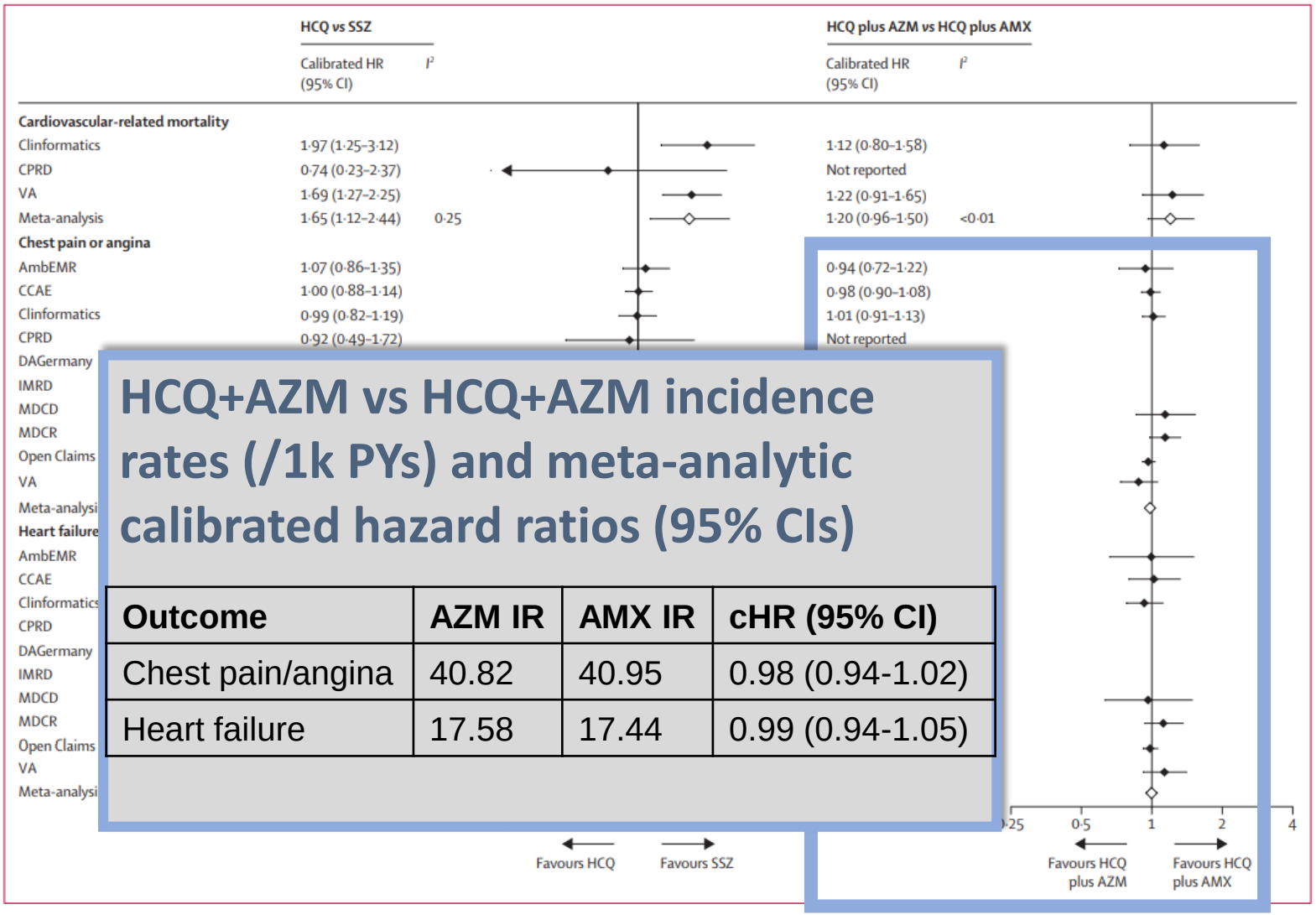
# CV mortality, chest pain/angina, and heart failure during on-treatment time-at-risk




## HCQ+AZM vs HCQ+AZM incidence rates (/1k PYs) and meta-analytic calibrated hazard ratios (95% CIs)

| Outcome | AZM IR | AMX IR | cHR (95% CI) |
|---|---|---|---|
| Chest pain/angina | 40.82 | 40.95 | 0.98 (0.94-1.02) |
| Heart failure | 17.58 | 17.44 | 0.99 (0.94-1.05) |

***Figure 3*: 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 long-term (on-treatment) 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.

# All-cause mortality, MI, CV events, cardiac arrhythmia, bradycardia, TIA, stroke, VTE, GI bleeding, acute renal failure, ESRD, hepatic failure, and acute pancreatitis during 30d and on-treatment time-at-risk

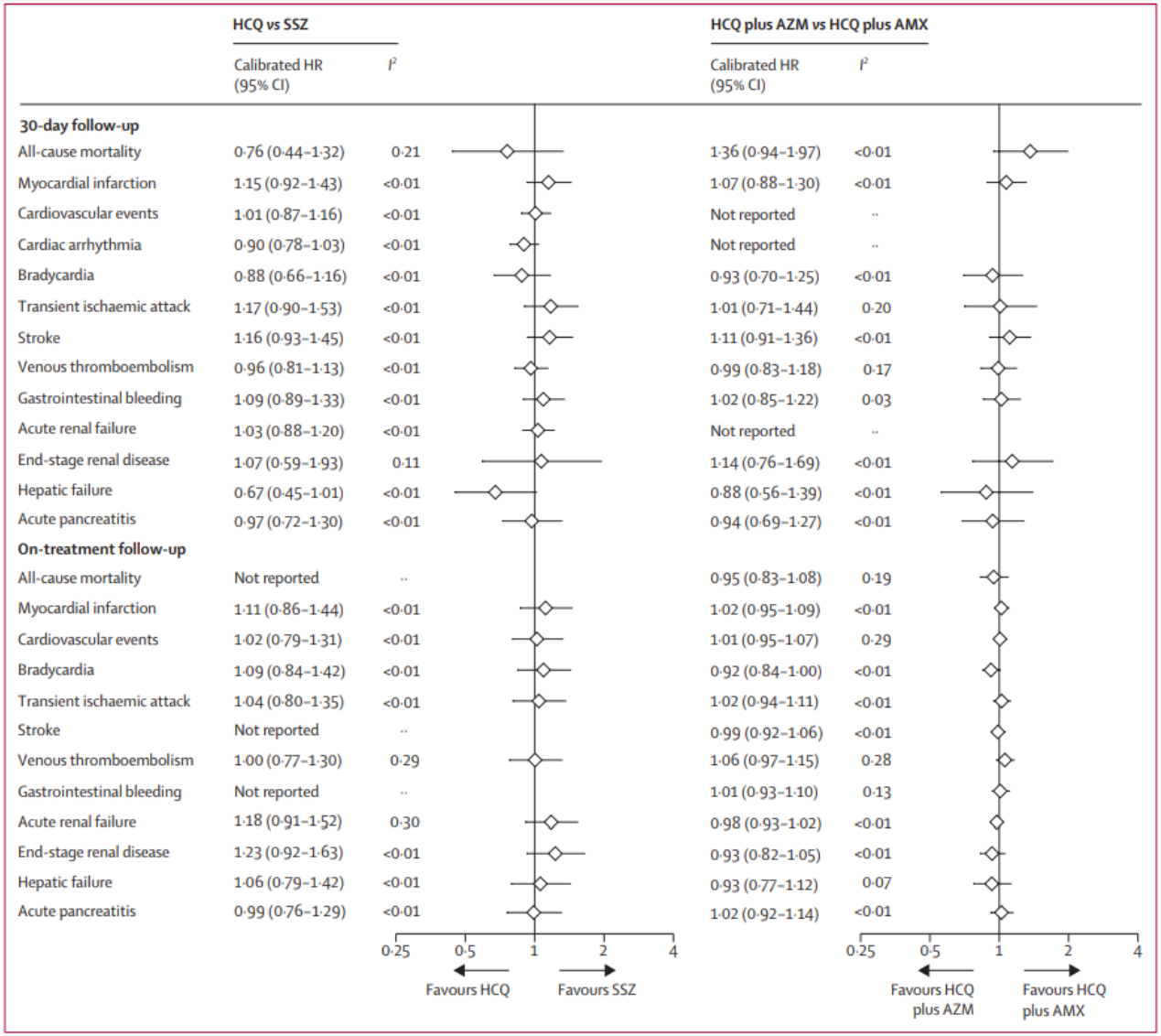
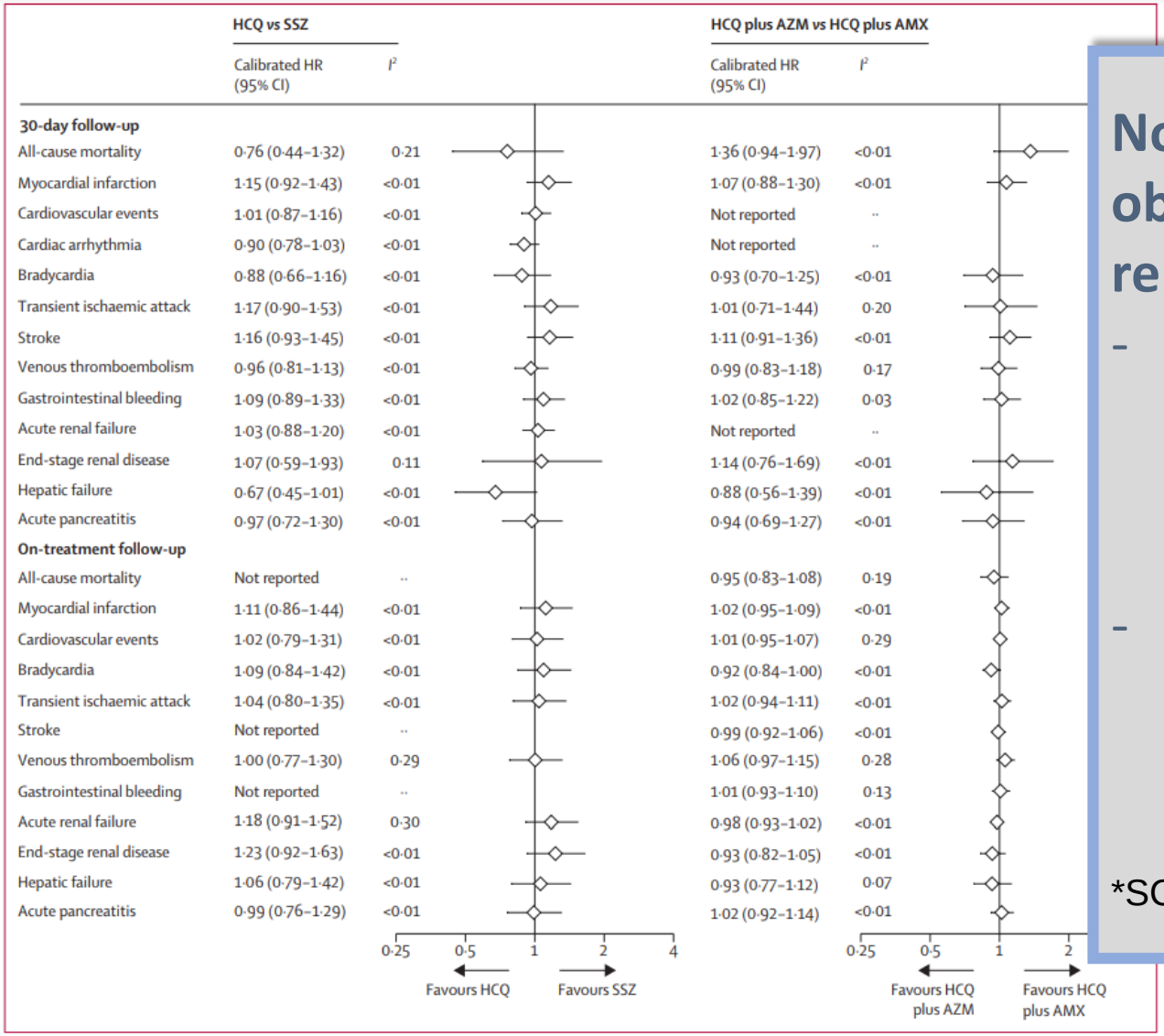



*Figure 1:* **Meta-analytic estimates for HCQ versus SSZ and HCQ plus AZM versus HCQ plus AMX new users during 30-day (intention-to-treat) and long-term (on-treatment) follow-up**

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

# All-cause mortality, MI, CV events, cardiac arrhythmia, bradycardia, TIA, stroke, VTE, GI bleeding, acute renal failure, ESRD, hepatic failure, and acute pancreatitis during 30d and on-treatment time-at-risk



| | HCQ vs SSZ | | HCQ plus AZM vs HCQ plus AMX | |
|---|---|---|---|---|
| | Calibrated HR (95% CI) | $I^2$ | Calibrated HR (95% CI) | $I^2$ |
| **30-day follow-up** | | | | |
| All-cause mortality | 0·76 (0·44–1·32) | 0·21 | 1·36 (0·94–1·97) | <0·01 |
| Myocardial infarction | 1·15 (0·92–1·43) | <0·01 | 1·07 (0·88–1·30) | <0·01 |
| Cardiovascular events | 1·01 (0·87–1·16) | <0·01 | Not reported | .. |
| Cardiac arrhythmia | 0·90 (0·78–1·03) | <0·01 | Not reported | .. |
| Bradycardia | 0·88 (0·66–1·16) | <0·01 | 0·93 (0·70–1·25) | <0·01 |
| Transient ischaemic attack | 1·17 (0·90–1·53) | <0·01 | 1·01 (0·71–1·44) | 0·20 |
| Stroke | 1·16 (0·93–1·45) | <0·01 | 1·11 (0·91–1·36) | <0·01 |
| Venous thromboembolism | 0·96 (0·81–1·13) | <0·01 | 0·99 (0·83–1·18) | 0·17 |
| Gastrointestinal bleeding | 1·09 (0·89–1·33) | <0·01 | 1·02 (0·85–1·22) | 0·03 |
| Acute renal failure | 1·03 (0·88–1·20) | <0·01 | Not reported | .. |
| End-stage renal disease | 1·07 (0·59–1·93) | 0·11 | 1·14 (0·76–1·69) | <0·01 |
| Hepatic failure | 0·67 (0·45–1·01) | <0·01 | 0·88 (0·56–1·39) | <0·01 |
| Acute pancreatitis | 0·97 (0·72–1·30) | <0·01 | 0·94 (0·69–1·27) | <0·01 |
| **On-treatment follow-up** | | | | |
| All-cause mortality | Not reported | .. | 0·95 (0·83–1·08) | 0·19 |
| Myocardial infarction | 1·11 (0·86–1·44) | <0·01 | 1·02 (0·95–1·09) | <0·01 |
| Cardiovascular events | 1·02 (0·79–1·31) | <0·01 | 1·01 (0·95–1·07) | 0·29 |
| Bradycardia | 1·09 (0·84–1·42) | <0·01 | 0·92 (0·84–1·00) | <0·01 |
| Transient ischaemic attack | 1·04 (0·80–1·35) | <0·01 | 1·02 (0·94–1·11) | <0·01 |
| Stroke | Not reported | .. | 0·99 (0·92–1·06) | <0·01 |
| Venous thromboembolism | 1·00 (0·77–1·30) | 0·29 | 1·06 (0·97–1·15) | 0·28 |
| Gastrointestinal bleeding | Not reported | .. | 1·01 (0·93–1·10) | 0·13 |
| Acute renal failure | 1·18 (0·91–1·52) | 0·30 | 0·98 (0·93–1·02) | <0·01 |
| End-stage renal disease | 1·23 (0·92–1·63) | <0·01 | 0·93 (0·82–1·05) | <0·01 |
| Hepatic failure | 1·06 (0·79–1·42) | <0·01 | 0·93 (0·77–1·12) | 0·07 |
| Acute pancreatitis | 0·99 (0·76–1·29) | <0·01 | 1·02 (0·92–1·14) | <0·01 |



*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.

**No increased risk observed across most remaining outcomes***

- HCQ potential reduced 30d risk of hepatic failure (0.67 [0.45-1.01])*
- HCQ+AZM potential increased 30d risk of all-cause mortality (1.36 [0.94-1.97])

*SCCS results consistent

# Discussion for RA, (and for covid)

**Rheumatoid Arthritis**

Increased cardiovascular short term risks HCQ + AZM vs HCQ + AMX

Long term risks HCQ vs SSZ

*Limitations*

*Misclassification; non concordance; incomplete recording SAEs*

*Relative risk*

**Extrapolation to COVID-19?**

- Short term use
- Higher doses
- Different population

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**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**

Jennifer C.E Lane, James Weaver, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F. Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Edward Burn, Paula Casajust, Mitch Conover, Aedin C. Culhane, Alexander Davydov, Scott L. DuVall, Dmitry Dymshyts, Sergio Fernández Bertolín, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G. Lambert, Johan ver 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 Sena, Azza Shoaibi, Matthew Spotnitz, Marc A. Suchard, Joel Swerdel, Carmen Olga Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra

**doi:** https://doi.org/10.1101/2020.04.08.20054551

**This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.**

Forbes

36,377 views | Apr 10, 2020, 05:59pm EDT

## Hydroxychloroquine And Azithromycin For COVID-19: Benefits TBD, Risks Clear

Harlan Krumholz Former Contributor

Healthcare

# Impact on Regulatory Bodies

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

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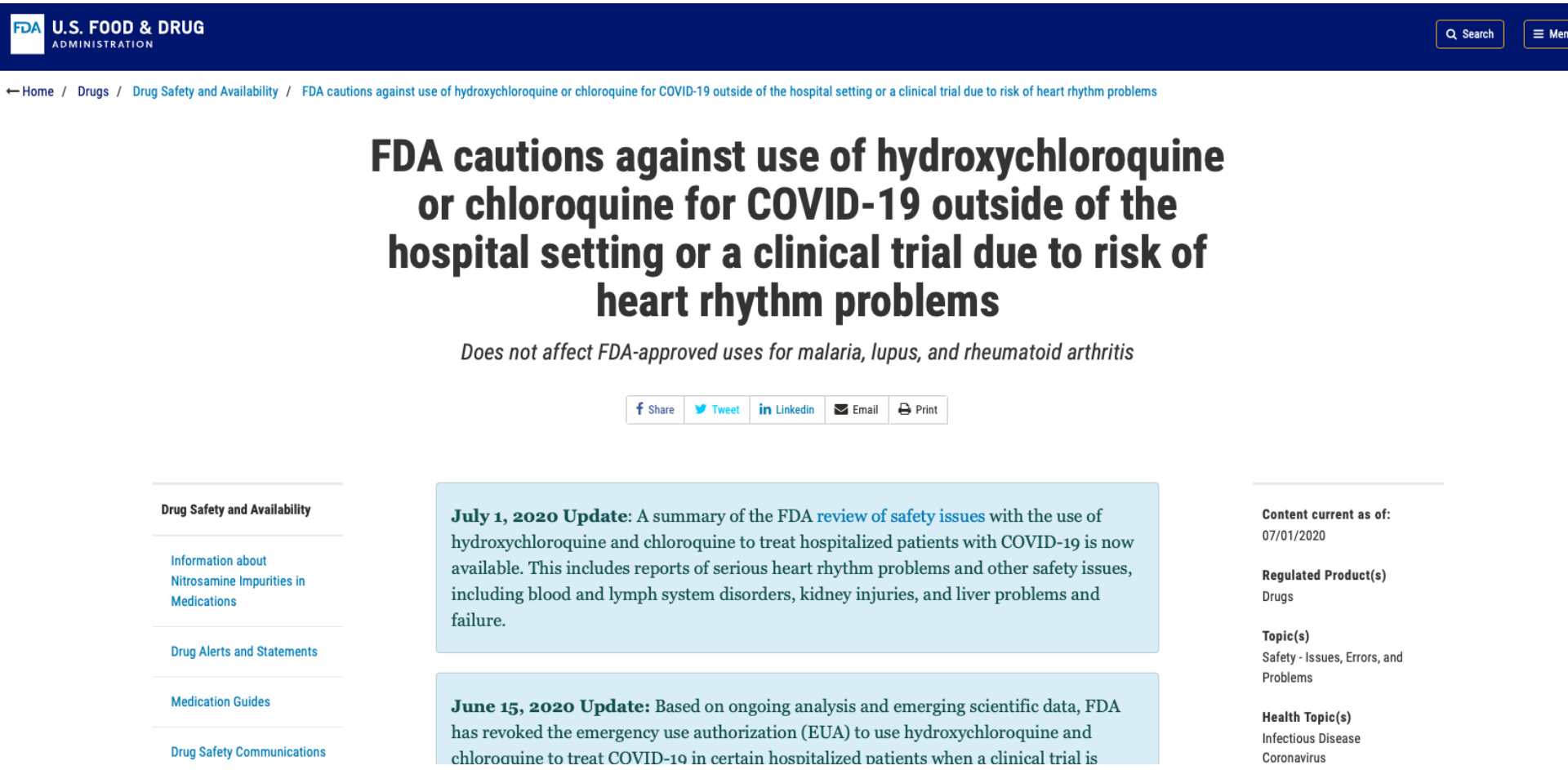
News 23/04/2020

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[1,2] 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).

# Impact on Regulatory Bodies



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## FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems

*Does not affect FDA-approved uses for malaria, lupus, and rheumatoid arthritis*

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**July 1, 2020 Update**: A summary of the FDA review of safety issues with the use of hydroxychloroquine and chloroquine to treat hospitalized patients with COVID-19 is now available. This includes reports of serious heart rhythm problems and other safety issues, including blood and lymph system disorders, kidney injuries, and liver problems and failure.

**June 15, 2020 Update:** Based on ongoing analysis and emerging scientific data, FDA has revoked the emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when a clinical trial is

**Content current as of:**
07/01/2020

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# Thank you to all the studyathon