TITLE

Asymptomatic hyperuricemia: to treat or not to treat. A target trial emulation to assess major cardiorenal outcomes

PROMOTOR

The principal investigator acts as the sponsor of the study.

RESEARCH TEAM

Antonio Rodríguez-Miguel, PhD. Assistant Professor of Pharmacology. Department of Biomedical Sciences (Pharmacology). Universidad de Alcalá (IRYCIS), Madrid (Spain).

Francisco J. de Abajo, PhD, MPH. Full Professor of Pharmacology. Department of Biomedical Sciences (Pharmacology). Universidad de Alcalá (IRYCIS), Madrid (Spain).

Sara Rodríguez-Martín, PhD. Assistant Professor of Pharmacology. Department of Biomedical Sciences (Pharmacology). Universidad de Alcalá (IRYCIS), Madrid (Spain).

Encarnación Fernández Antón. Department of Biomedical Sciences (Pharmacology). Universidad de Alcalá (IRYCIS), Madrid (Spain).

PROTOCOL CODE, VERSION AND DATE

HYPER-TTE-HARV, v.2, June 21, 2024

The structure of the present study protocol is adapted from the format recommended by BIFAP. However, some changes have been introduced to tailor it to the special characteristics of the study design.

RESUMEN

Se define hiperuricemia como un estado en el que los niveles de ácido úrico sérico son superiores a 6.8 mg/dl, precisamente, el punto en el que se sitúa el límite de solubilidad del ácido úrico en condiciones fisiológicas. La mayor parte del ácido úrico total se produce endógenamente, mientras que el resto es consecuencia del metabolismo de purinas ingeridas en la dieta y de los azúcares, especialmente de la fructosa. El ácido úrico se elimina principalmente por vía renal, y en menor proporción por el intestino. Por tanto, los niveles totales de ácido úrico sérico son el resultado del equilibrio entre el metabolismo de dichos nutrientes y su excreción, siendo la hiperuricemia la consecuencia de una alteración de este equilibrio, ya sea por sobreproducción, reducción de la excreción, o una combinación de ambos.

Aunque el ácido úrico es bien conocido desde hace mucho tiempo, ciertos aspectos sobre su fisiopatología son aún desconocidos en parte. Concretamente, si la hiperuricemia desempeña un papel en el desarrollo de ciertos factores de riesgo cardiovascular, como son la diabetes o la hipertensión, o en el inicio y progresión de la enfermedad renal crónica, son aún objeto de debate.

En modelos animales, se ha observado que la hiperuricemia podría causar un engrosamiento de la arteriola aferente, lesión glomerular, fibrosis tubulointersticial, inflamación local tras el depósito de uratos en el tejido, y activación del sistema renina-angiotensina-aldosterona y, en consecuencia, hipertensión arterial, daño renal y proteinuria. Además, se cree que los niveles intracelulares elevados de ácido úrico en el hígado podrían inducir estrés

oxidativo mitocondrial y efectos metabólicos como la resistencia a la insulina, la acumulación de grasa visceral y la hipertensión arterial.

En humanos, esta relación es más difícil de desentrañar ya que la hiperuricemia está comúnmente asociada con la diabetes y es un marcador temprano de enfermedad renal crónica. Los estudios transversales publicados hasta la fecha han mostrado una asociación entre la hiperuricemia y la enfermedad renal crónica, aunque este diseño de estudio no es adecuado para establecer con claridad cuál es la dirección de la causalidad. Sin embargo, en estudios longitudinales, la hiperuricemia se ha asociado con una mayor incidencia de enfermedad renal crónica, aunque no tanto con un mayor riesgo de progresión a enfermedad renal terminal.

A pesar de que los niveles elevados de ácido úrico sérico podrían tener efectos perjudiciales en diferentes sistemas, las recomendaciones clínicas actuales abogan por no tratarla cuando es asintomática, ya que muchos pacientes no llegan a presentar ataques agudos de gota o cálculos a lo largo de sus vidas. Además, los medicamentos para reducir el ácido úrico no están exentos de riesgos graves, como las reacciones de hipersensibilidad.

En tres grandes ensayos clínicos aleatorizados no se ha observado que el uso de alopurinol (el medicamento hipouricemiante más empleado en la actualidad) ralentice la progresión de la enfermedad renal o prevenga los eventos cardiovasculares en sujetos sin antecedentes de gota. Sin embargo, en estos ensayos clínicos la mayoría de los pacientes tenían niveles normales de ácido úrico, un hecho que impidió probar la hipótesis de si tratar la hiperuricemia asintomática sería beneficioso o no en la prevención de dichos eventos.

Por otro lado, los médicos de primaria deben enfrentar diferentes problemas clínicos en su práctica diaria, y sus decisiones clínicas no siempre están alineadas con las recomendaciones actuales. En este sentido, cuando se trata de problemas de la vida real y según nuestra experiencia, no es raro encontrar médicos que deciden prescribir medicamentos hipouricemiantes a pacientes con hiperuricemia asintomática, mientras que otros no lo hacen, aparentemente siguiendo sus preferencias personales.

Los estudios observacionales desempeñan un papel importante para proporcionar evidencia sobre la efectividad de los tratamientos en la población diana cuando realizar un ensayo clínico aleatorizado no es posible por razones éticas o logísticas. No obstante, hacer inferencia causal con datos observacionales de la vida real es un desafío metodológico debido, precisamente, a la falta de aleatorización de los tratamientos, así como a una mala elección del diseño adecuado de estudio. En este sentido, para tratar de solventar estas limitaciones, la inferencia causal a través de la emulación de ensayos clínicos pragmáticos con datos observacionales proporciona el marco metodológico para evitar sesgos en el diseño y análisis de los estudios. A través del planteamiento de un protocolo de ensayo clínico aleatorizado hipotético y su cómo se trasladaría al ámbito observacional, esta metodología permite responder a la pregunta de investigación específica, evitando sesgos en el diseño y análisis.

El presente estudio se realizará tomando como fuente de información la base de datos BIFAP, la cual está compuesta por las historias clínicas pseudonimizadas de pacientes de 10 Comunidades Autónomas y, actualmente, contiene más de 20 millones de pacientes en seguimiento. A partir de ella, se predefinirá una

cohorte de sujetos que cumplan los criterios de elegibilidad. En ese momento, se seguirá a los sujetos, observando en cada momento del seguimiento, a través de la información registrada en las historias clínicas de los pacientes en BIFAP, si se cumplen los componentes principales para la emulación del ensayo, esto es, en resumen, la asignación de las estrategias de tratamiento y la adherencia a las mismas (es decir la evaluación de la compatibilidad de los datos y características individuales con la estrategia de tratamiento asignada, p. ej. los niveles de ácido úrico o síntomas relacionados con la hiperuricemia, entre otras), y la evaluación de los eventos de interés (o algún otro criterio de parada del seguimiento). Los sujetos en los que no se puedan asegurar estas condiciones, según lo protocolizado, serán censurados y analizados adecuadamente para evitar sesgos de selección.

La creación de la cohorte, así como el análisis de los datos, se realizará por el investigador principal en CAUSALab, adscrito a la *Harvard T.H. Chan School of Public Health* de la Universidad de Harvard, durante un periodo de estancia de investigación, bajo la supervisión del Prof. Miguel Hernán, Profesor de Bioestadística y Epidemiología en dicha escuela, y pionero en el desarrollo de la metodología de inferencia causal y emulación de ensayos clínicos, como la que se plantea en este protocolo.

El manejo de los datos de BIFAP y su traslado a la Universidad de Harvard para su análisis se adecuará a la legislación europea vigente sobre protección de datos de carácter personal. Se firmará un acuerdo de uso de datos entre las dos instituciones, la Universidad de Harvard y BIFAP. Los datasets entregados para la realización del estudio únicamente contendrán datos estructurados, sin texto libre y anonimizados. Por otro lado, los eventos de interés ya han sido

previamente validados por el equipo investigador en otros proyectos, por lo que no se plantean trabajos de validación adicionales. No obstante, si fueran necesarios, se realizarían por el resto del equipo investigador en las instalaciones de la AEMPS-BIFAP, de acuerdo con el Documento de Gobernanza de Acceso a BIFAP. El protocolo de estudio también será evaluado por el Comité de Ética de la Escuela de Salud Pública de Harvard.

El presente estudio forma parte de un proyecto más amplio cuyo objetivo es estudiar la epidemiología y los factores asociados al desarrollo de la enfermedad renal crónica en BIFAP, que fue previamente aprobado por el Comité Científico de BIFAP el 23 de septiembre de 2020 (ML-PRD-Epi) y por el Comité de Ética de Investigación con Medicamentos del Hospital Universitario "12 de Octubre" el 21 de septiembre de 2021, el cual otorgó una exención para el consentimiento informado, ya que los datos están pseudonimizados, en cumplimiento con las leyes españolas y europeas sobre protección de datos de carácter personal. Sin embargo, dado que en este proyecto se solicitan nuevos datos y el dataset final será analizado en la Universidad de Harvard, es necesaria una aprobación específica de un Comité de Ética de Investigación con Medicamentos (CEIm) y del Comité Científico de BIFAP.

El dataset final será construido y analizado en la Universidad de Harvard, no obstante, se aplicará la ley europea sobre protección de datos de carácter personal, así como las leyes locales en este sentido. Adicionalmente, como prueba de este compromiso, se firmará un acuerdo de uso de datos entre la *Harvard T.H. Chan School of Public Health* y BIFAP. El protocolo del presente proyecto de investigación también será sometido a evaluación por el Comité de Ética de la *Harvard T.H. Chan School of Public Health*.

El protocolo del presente proyecto no contempla la evaluación individual del balance beneficio-riego de los tratamientos en estudio, ni la obtención del consentimiento informado (por las cuestiones anteriormente descritas), ni tampoco plantea posibles interferencias con los hábitos de prescripción de los médicos de Atención Primaria.

INTRODUCTION

Hyperuricemia is defined as a serum uric acid level >6.8 mg/dl, where the limit of solubility at physiological conditions is placed.[1] Most of the total body uric acid is produced endogenously while the remaining accounts for the metabolism of dietary purines and sugar, especially fructose. Uric acid is mainly excreted by the kidneys and in a lower proportion by the intestines. Thus, serum uric acid results from the balance between nutrients metabolism and excretion, being hyperuricemia the consequence of an alteration of this balance, either by overproduction, underexcretion or a combination of both.[1,2]

Although discovered long time ago, certain aspects of the pathophysiology of uric acid are still not clearly understood. In particular, whether elevated uric acid plays a role in the development of cardiovascular risk factors, such as diabetes or hypertension, or the initiation and progression of chronic kidney disease, are still subjects of debate.[1-5]

In animal models, hyperuricemia causes afferent arteriole thickening, glomerular injury, tubulointerstitial fibrosis, local inflammation after tissue urate deposition, and activation of the renin-angiotensin system and, therefore, hypertension, proteinuria, and kidney damage. Also, increased intracellular levels of uric acid in

the liver is thought to induce mitochondrial oxidative stress and metabolic effects as insulin resistance, fat accumulation and hypertension.[2,3,5]

In humans, such relationship is more difficult to unravel since hyperuricemia is commonly associated with diabetes and is an early marker of chronic kidney disease. Cross-sectional studies showed an association between hyperuricemia and chronic kidney disease, but such study design fails to establish the direction of causality. In longitudinal studies, hyperuricemia was associated with an increased risk of incident chronic kidney disease rather than with a risk for progression to end-stage renal disease.[2-5]

Despite it is likely injurious, recent guidelines advocate for not to treat asymptomatic hyperuricemia as many patients do not present gout flares or stones throughout their lives, and urate-lowering drugs (ULDs) are not absent of serious risks.[4,6] At present, three large randomized clinical trials have found no benefit of allopurinol (the most widely used ULD) in slowing kidney disease progression or prevention of cardiovascular events among subjects without history of gout. However, these trials included patients with normal uric acid levels so that precluded to test the hypothesis of whether to treat asymptomatic hyperuricemia would be beneficial or not.[2]

Conversely, physicians must face different clinical issues in their daily practice, and their clinical decisions are not always aligned with updated guidelines. In this sense, when it comes to real-world, it is not uncommon to find physicians who decide to prescribe ULDs to patients with asymptomatic hyperuricemia while others do not, apparently following their personal preferences.[7]

Observational studies play an important role providing information on the effectiveness of treatments in the target population when randomized trials are not possible. However, making causal inferences are challenging due to lack of randomization and wrong decisions on the study design. To overcome this, the target trial emulation provides the framework to avoid bias by designing the hypothetical randomized experiment to answer the specific question of interest using real-world data and suitable methodology.[8-10]

OBJECTIVES

Main objective

To evaluate whether to treat asymptomatic hyperuricemia with ULDs would reduce the incidence of cardiorenal outcomes, in particular, chronic kidney disease, ischemic stroke, and acute myocardial infarction.

Specific objectives

1) To estimate the risk of cardiorenal outcomes as acute myocardial infarction, ischemic stroke, and chronic kidney disease among treated and untreated subjects.

2) To estimate and compare the risk curves among treated and untreated subjects with hyperuricemia.

3) To estimate the incidence of gout (first acute flare) over time, overall and among treated and untreated subjects.

METHODS

Study design

From 2003 to 2019, a retrospective cohort will be constructed following the components of the target trial that articulates the causal question, as specified below.

Specification of the target trial and its emulation using real-world data from BIFAP[11]

The key elements of the protocol and requirements for emulation should include the following:[9]

1. Eligibility criteria

Subjects must fulfill the following criteria:

- Subjects with age >18 (some ULDs are not indicated below this age), and of any sex.
- Incident asymptomatic hyperuricemia, defined as a first record of serum uric acid >6.8 mg/dl and without prior records of gout, gout flares, gout arthritis, colchicine use or a similar suggestive term.
- No previous history of: cancer (except non-melanoma skin cancer) within the last 3 years, acute myocardial infarction, ischemic stroke, and kidney disease (estimated glomerular filtration rate -eGFR-, albuminuria or proteinuria outside the normal range and/or a diagnosis of chronic or acute kidney disease, dialysis, or kidney transplantation).
- A minimum registry of 1-year with their primary care physician in the database with the standards of quality registration applied by the staff of BIFAP. The

assessment of the number of previous visits to primary care will help to relax the expectation that subjects will keep active in the health system throughout the study period.

1.1. Requirements for emulation:

Pre-baseline and baseline data to be retrieved from the database are:

- Age and sex
- Clinical characteristics including hyperuricemia, gout, gout-related conditions, and kidney diseases. These will be defined through laboratory parameters (eGFR, serum creatinine, proteinuria/albuminuria), and/or dictionary codes, and/or use of comedications.
- Acute myocardial infarction and ischemic stroke were previously validated by the research team for other projects. No other validation study is proposed as chronic kidney disease will be defined mainly based on laboratory parameters (eGFR, serum creatinine and albuminuria/proteinuria).

2. Treatment strategies

Eligible subjects will be assigned to one of the following:

-New use of a ULD (allopurinol or febuxostat) unless clinically contraindicated or the occurrence of symptoms related to hyperuricemia. New use will be defined as no prior record of a prescription of ULDs in the database. Contraindications include hypersensitivity reactions associated with allopurinol (Stevens-Johnson

syndrome, toxic epidermal necrolysis), and symptoms include use of colchicine, gout flares or other related entities.

-No pharmacological treatment (assumed as other medical care like changes in dietary or lifestyle habits) unless clinically indicated (e.g. due to symptoms related to hyperuricemia, as described above).

As an alternative, comparison of ULDs as active principles a could be also considered.

Under all strategies all variables related to adherence (e.g. serum uric acid, gout flares, among others) should be recorded at different time windows (depending on the data available adequate time windows should be studied).

2.1. Requirements for emulation:

Data to determine the new use and adherence to ULDs will include the start date of each prescription, and optionally dose. To determine the adherence to treatment strategies at baseline, data on start and end dates of prescriptions and duration will be needed, as well as serum uric acid records and other clinical characteristics to ensure adherence (eGFR, serum creatinine, use of colchicine, gout flares or hypersensitivity reactions, among others). The selection of the adequate time windows will depend on the data available.

The impossibility to assess the adherence to treatments at some timepoint will be considered as loss to follow-up and managed accordingly via inverse probability of censoring weights.

3. Assignment to treatment strategies

In an ideal target trial, treatments must be allocated at random, under either double or single blinding.

3.1. Requirements for emulation

Treatments are not randomly assigned under observational conditions, but clinical experience tells us that there is an important component of physician´s preference. To ensure exchangeability at baseline, pre-baseline predictors of initiation of each treatment must be measured and controlled for. These predictors will include age, sex, antecedents of cardiovascular risk factors and diseases or antecedents of kidney diseases, among others. Comedications related to these conditions will be ascertained as well.

4. Follow-up

In the target trial the follow-up starts at treatment allocation (baseline) and ends at first occurrence of the outcomes of interest, death, or loss to follow-up. Regarding the latter, that will be any event that precludes to measure the outcomes of interest, or to measure the adherence to treatment strategies, or to measure post-baseline prognostic factors.

The start of recruitment will start on January 1, 2003. The study will end on December 31, 2019.

4.1. Requirements for emulation

Time zero (the timepoint where follow-up starts), eligibility criteria and treatment initiation must be aligned to avoid immortal time and selection bias.[12] Then, all subjects will be followed up to the occurrence of any of the outcomes of interest, or any of the following censorship criteria: death from all causes, loss to follow-up, turn 90 years old, or end of the study period (December 31, 2019). Loss to follow-up will be considered as the conditions explained above as well as when administrative exit from the database occurs.

When the comparison strategy is the non-use of a treatment, time zero is not easily ascertained, then immortal time bias emerges. In this case, a sequence of trials following the cloning-censoring-weighting approach will be applied to eliminate this bias.

All dates to determine loss to follow-up will be needed from the database.

5. Outcomes

Cardiorenal outcomes under study are:

-Incident acute myocardial infarction

-Incident ischemic stroke

-Incident chronic kidney disease

5.1. Requirements for emulation

To identify the outcomes of interest, search algorithms will be constructed including diagnostic codes and text-mining strategies in free-text from electronic medical records. Laboratory results (serum uric acid, serum creatinine, eGFR, glycosylated hemoglobin, among others) are routinely recorded in a specific place within the electronic medical records, however, free-text searches will be also explored to increase the retrieval of these parameters. Combinations of diagnostic codes and laboratory results could be used to define some of the outcomes of interest.

To avoid misclassification of cardiorenal outcomes, data validation studies were previously performed by the research team in other studies, specifically acute myocardial infarction, ischemic stroke, and chronic kidney disease.

In a previous study about chronic kidney disease, cases were identified as those with a record of eGFR <60 ml/min/1.73m^2 based on the 2009 creatinine-based CKD-EPI formula in a race agnostic manner and/or positive albuminuria (>30 mg/24h, >30 mg/g urinary creatinine) or positive proteinuria, which was confirmed in, at least, a second record of either. Stage of chronic kidney disease will be classified according to the following KDIGO categories: G1-G2, G3a, G3b, G4 and G5. By contrast, isolated pathological records will not qualify as chronic kidney disease.

Incident acute gout flare will be identified by a specific diagnostic record plus the initiation of colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids.

All dates and diagnostic codes are available.

6. Causal contrasts

Intention-to-treat and per-protocol effects will be estimated. As intention-to-treat measures the effect of being assigned to a treatment strategy, regardless the treatment actually received from randomization on, it could be interpreted a as biased estimate of per-protocol effect.

6.1. Requirements for emulation

The analogs of intention-to-treat and per-protocol analyses under observational conditions. In this case, intention-to-treat analysis measures the effect of being prescribed vs. non-prescribed at baseline, provided that assignment and prescription co-occurs, regardless of what happens henceforth. Per-protocol analysis measures the effect of receiving the treatment strategy at each timepoint throughout the follow-up, that is, considering exposure as a time-dependent variable.

7. Statistical analysis plan

Intention-to-treat and per-protocol analyses (as widely explained below).

Data curation and analysis will be performed in collaboration with the team of CAUSALab at Harvard T.H.Chan School of Public Health, under the supervision of Prof. Miguel Hernán, Kolokotrones Professor of Biostatistics and Epidemiology at University of Harvard.

7.1. Requirements for emulation

The dataset may be cloned into two separate sets, each one to estimate the observational analogs of the intention-to-treat and per-protocol effects.

Intention-to-treat analyze subjects regardless the adherence to treatments assigned. This method needs to adjust for baseline confounders, that is, imbalanced prognostic factors at baseline. The adjustment may be performed either propensity score matching or weighting (inverse probability weighting), or standardization, among others. In the present study, due to the characteristics of the database, factors to adjust are those predictors of prescription.

Per-protocol analysis needs to adjust for pre- and post-baseline non-adherence to treatments, in addition to those adjustments of intention-to-treat analysis. In per-protocol analysis, the deviation from the initial strategy assigned will result in censorship. As this may introduce post-baseline selection bias, adjustment for predictors of adherence must be performed, for example, via inverse probability of censoring weighting.

Risk curves under each treatment strategy will be constructed. Risks ratios and risk differences at different timepoints (i.e. 1-year, 5-year or 10-years risks) will be also performed and compared under different treatment strategies. A Cox proportional hazards model may be also fitted to estimate averaged hazard ratios approached through a pooled logistic regression with robust estimation of standard errors including discrete time of follow-up as an smooth function.

Subgroup analysis will be also performed by age, gender, or cardiovascular risk factors.

Longitudinal data will be needed and the measurement of pre- and post-baseline predictors of loss to follow-up (for intention-to-treat) and adherence (time-fixed and time-varying for per-protocol. -i.e- serum uric acid, serum creatinine, eGFR, or cardiovascular risk factors). The set of potential confounders will be selected

by expert criteria and after the construction and analysis of directed acyclic graphs.

The sequence of trials with the cloning-censoring-weighting approach will be applied when non-use of treatment is compared and grace periods or duration of the exposure is assessed, so that includes the emulation of one target trial by each day of follow-up by calendar time. If computational constraints occur, a random sample of non-exposed subjects will be selected.

Additional sensitivity analyses: the success of the target trial emulation relies on the assumption of no unmeasured and uncontrolled confounding. Indirect approaches to stress that assumption should be carried out as benchmarking with other published results, reversed treatment strategies, or negative or positive controls. These examples should be explored.

VARIABLES

Specific variables were drafted earlier within each of the components for emulation, but, briefly, the following variables will be needed:

Sociodemographic and lifestyle: age, sex, number of visits to primary care in the year before entry, smoking, alcohol abuse, body mass index.

Pre- and baseline (at entry) data to assess eligibility criteria and predictors of the exposure to ULDs: antecedents of hyperuricemia (as a diagnosis or as serum uric acid > 6.8 mg/dl, with dates), antecedents of symptomatic hyperuricemia (gout, gout flares, gout arthritis, colchicine use or a suggestive term, with dates), antecedents of kidney diseases (chronic kidney disease, acute kidney injury,

dialysis, kidney transplantation, eGFR, serum creatinine, proteinuria/albuminuria, with dates), antecedents of any cancer (except non-melanoma), antecedents of cardiovascular risk factors and diseases (hypertension, diabetes, heart failure, angina pectoris, peripheral artery disease, dyslipidemia and acute myocardial infarction, with dates) and ischemic stroke (with dates).

Data to assess the exposure to ULDs, follow-up, adherence to treatments and outcomes: start and end dates, dose, and duration of all prescriptions of ULDs (allopurinol and febuxostat), all dates and values of laboratory parameters (serum uric acid, eGFR, proteinuria/albuminuria, glycosylated hemoglobin), hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis, with dates), kidney diseases (as described above), symptomatic hyperuricemia (as described above), first occurrence of the outcomes of interest (as defined above).

Comedications: start and end dates, dose and duration of prescriptions will be requested for the following: ULDs (allopurinol, febuxostat), colchicine, glucose-lowering drugs, insulin, antihypertensive drugs, diuretics, NSAIDs, metamizole, paracetamol, SYADOAs, glucocorticoids, lipid-lowering drugs, antiplatelet drugs, oral anticoagulants, IBPs, and anti-H_2. Some pharmacological groups will be requested as those and by active principle.

The methods for construction of the covariates for adjustment or assessment of adherence will be those applied routinely for the staff of BIFAP so far.

A more detailed list of covariables could be created upon the approval of this project from BIFAP, and after agreement with the staff from BIFAP and CAUSALab. Once created, a “full download” will be requested to BIFAP.

The period for extraction of data will be the same as the period of study, except for those subjects whose time zero fall in the 2003. In this case, data for assessing the eligibility before that date will be needed.

LIMITATIONS

The target trial emulation framework relies on high quality and quantity of data records. In this sense, the adjustment of the requirements for emulation, especially those affecting to the definition of the treatment strategies and the evaluation of adherence, is an iterative process depending on the final data available in BIFAP. Once the emulation was possible, all subjects whose frequency of data recording or data quality preclude the assessment of any of the components of the emulation described above will be censored and managed accordingly.

The outcomes of interest have been previously defined and validated for other studies of the group with different purposes, so for the present study, will be used in the same conditions.

ETHICS AND LEGAL FRAMEWORK

This study is part of a bigger project to study chronic kidney disease in BIFAP that was previously approved by the BIFAP Scientific Committee on September 23, 2020 (ML-PRD-Epi) and by the Ethics Committee of the University Hospital “12 de Octubre” on September 21, 2021, that also granted a waiver for the informed consent as all data were pseudonymized, in compliance with the

Spanish and European laws on protection of personal data. However, as new data are requested and the final dataset will be analyzed at the University of Harvard, a specific approval from a Research Ethics Committee for medicines (CEIm) and the BIFAP Scientific Committee is needed.

The final dataset will be curated and analyzed at the University of Harvard, but. the European law on personal data protection will be applied, as well as local laws. The final dataset will be merely made of structured data, without free-text variables and completely anonymized.

A Data User Agreement will be signed by the Harvard T.H. Chan School of Public Health and BIFAP as a prove of this commitment. This project will be also submitted for approval to the Ethics Committee of the Harvard T.H. Chan School of Public Health.

No additional validation studies of the outcomes are planned, however, if necessary, those will be carried out by the rest of the research team in the facilities of the AMEPS-BIFAP, as stated in the Document for Data Access of BIFAP.

The final dataset will be released upon approval of the Scientific Committee and the Advisory Committee of BIFAP.

PROTECTION OF SUBJECTS UNDER STUDY

a) Benefit-risk balance assessment: not applicable.

b) Informed consent: not applicable.

c) Personal data protection: see details above in “Ethics and legal framework”.

d) Interference with drug prescriptions: not applicable

WORKING PLAN

2024	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Ethics Committee and BIFAP Scientific Committee approval												
Data User Agreement approval												
Data extraction												
2025 (at University of Harvard)												
Data curation												
Data analysis												
Publications												

PUBLICATION AND DIFUSION PLAN

All results will be published in high impact journals as well as to presented to national and international congresses.

REFERENCES

1. Lohr JW, Batuman V. Hyperuricemia. MedScape. 2022. Available at: https://emedicine.medscape.com/article/241767-overview?form=fpf. Accessed November 10, 2023.

2. Johnson RJ, Sanchez Lozada LG, Lanaspa MA, Piani F, Borghi C. Uric Acid and Chronic Kidney Disease: Still More to Do. *Kidney Int Rep*. 2022;8(2):229-239. doi: 10.1016/j.ekir.2022.11.016

3. Nashar K, Fried LF. Hyperuricemia and the progression of chronic kidney disease: is uric acid a marker or an independent risk factor? *Adv Chronic Kidney Dis*. 2012;19(6):386-91. doi: 10.1053/j.ackd.2012.05.004.

4. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359(17):1811-21. doi: 10.1056/NEJMra0800885. Erratum in: *N Engl J Med*. 2010;362(23):2235.

5. Johnson RJ, Nakagawa T, Jalal D, Sánchez-Lozada LG, Kang DH, Ritz E. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant*. 2013;28(9):2221-8. doi: 10.1093/ndt/gft029

6. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S76-99. doi: 10.1161/01.cir.0000437740.48606.d1. Erratum in: *Circulation*. 2014;129(25 Suppl 2):S100-1. Erratum in: *Circulation*. 2015;131(4):e326.

7. Rodríguez-Martín S, de Abajo FJ, Gil M, González-Bermejo D, Rodríguez-Miguel A, Barreira-Hernández D, et al. Risk of Acute Myocardial Infarction Among New Users of Allopurinol According to Serum Urate Level: A Nested Case-Control Study. *J. Clin. Med*. 2019; 8(12):2150. doi:10.3390/jcm8122150

8. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to

postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;19(6):766-79. doi: 10.1097/EDE.0b013e3181875e61

9. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol*. 2016;183(8):758-64. doi: 10.1093/aje/kwv254

10. Dickerman BA, García-Albéniz X, Logan RW, Denaxas S, Hernán MA. Avoidable flaws in observational analyses: an application to statins and cancer. *Nat Med*. 2019;25(10):1601-1606. doi: 10.1038/s41591-019-0597-x.

11. Maciá-Martínez MA, Gil M, Huerta C, Martín-Merino E, Álvarez A, Bryant V, et al.; BIFAP Team. Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP): A data resource for pharmacoepidemiology in Spain. *Pharmacoepidemiol Drug Saf*. 2020;29(10):1236-1245. doi: 10.1002/pds.5006

12. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70-75. doi: 10.1016/j.jclinepi.2016.04.014