TESIS DOCTORAL

Programa de Doctorado en Biomedicina y Farmacia

Datos de vida real para la mejora de la utilización y la efectividad de los medicamentos en el Sistema Nacional de Salud: contribuciones esenciales

Aníbal García Sempere

Memoria de investigación realizada por Aníbal García Sempere para la obtención del grado de Doctor en Biomedicina y Farmacia

Directores:

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Valencia, junio de 2020

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ANÍBAL GARCÍA SEMPERE

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Valencia, Junio de 2020

Índice

Certificado de los directores

VNIVERSITAT DE VALÈNCIA

María Pilar D'Ocon Navaza, Catedrática del Departamento de Farmacología de la Universitat de València, y **Gabriel Sanfélix Gimeno**, Doctor por la Universidad Miguel Hernández de Elx y Director del Área de Investigación de Servicios de Salud y Farmacoepidemiología de la Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO),

CERTIFICAN

Que la Tesis titulada "**Datos de vida real para la mejora de la utilización y la efectividad de los medicamentos en el Sistema Nacional de Salud: contribuciones esenciales**" presentada por D. **Aníbal García Sempere** ha sido realizada en la Fundación FISABIO y en la Universitat de València bajo nuestra dirección y asesoramiento, y en nuestro criterio reúne méritos suficientes para que su autor pueda obtener con ella el grado de Doctor por la Universitat de València,

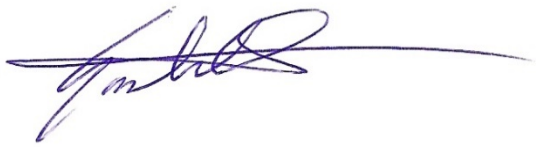
Concluido el trabajo de investigación, autorizamos la presentación de la Tesis para que sea juzgada por el tribunal correspondiente.

Lo que firmamos en Valencia, a 30 de Junio de 2020

La codirectora y tutora

Firmado: María Pilar D'Ocon Navaza

El codirector



Firmado: Gabriel Sanfélix Gimeno

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A mis directores, Dra. Pilar D'Ocon Navaza y Dr. Gabriel Sanfélix Gimeno por su confianza, su tiempo y su orientación para llevar a cabo el presente trabajo.

A los investigadores que figuran como coautores de las publicaciones presentadas en la presente tesis, que son fruto del esfuerzo multidisciplinar y del trabajo en equipo. Y a todos aquellos que de un modo u otro me han ayudado a llegar hasta aquí, muy especialmente a los Dres. Salvador Peiró i Moreno y Joan Josep Artells i Herrero por sus enseñanzas y apoyo incondicional.

Preámbulo

La presente memoria de tesis doctoral, presentada en la modalidad de compendio de artículos, tiene como objetivo principal avanzar en el conocimiento de la calidad de la prestación farmacoterapéutica en el Sistema Nacional de Salud mediante el uso de grandes bases de datos de práctica clínica. Los estudios que conforman la memoria aportan información nueva y esencial para el diseño de intervenciones de mejora de la calidad de la atención a los pacientes en patologías crónicas de elevada prevalencia, así como para la evaluación del impacto de dichas intervenciones sobre los procesos de manejo terapéutico de los pacientes y la obtención de resultados clínicos.

Dichas publicaciones, por orden de aparición a lo largo de la presente memoria, así como los índices de impacto de las revistas en que se encuentran publicados se detallan a continuación:

Artículo 1.

García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, Hurtado I, Peiró S, Sanfélix-Gimeno G, Diez-Domingo J. **Data resource profile: the Valencia Health System Integrated Database (VID).**

International Journal of Epidemiology, 2020.
doi:10.1093/ije/dyz266

Factor de impacto: 7,339
Ranking: D1 (97,04%; 6/186; Category: Public, Environmental and Occupational Health)

Artículo 2.

García-Sempere A, Hurtado I, Bejarano-Quisoboni D, Rodríguez-Bernal C, Santa-Ana Y, Peiró S, Sanfélix-Gimeno G. **Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study.**

PLoS One. 2019.
doi:10.1371/journal.pone.0211681.

Factor de impacto: 2,776
Ranking: Q1 (77,34%; 15/64; Category: Multidisciplinary Sciences)

Artículo 3.

García-Sempere A, Hurtado I, Bejarano D, Santa-Ana Y, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. **Group-based Trajectory Models to Assess Quality of INR Control and its Association with Clinical Outcomes.**

Medical Care, 2020.
doi:10.1097/MLR.0000000000001253

Factor de impacto: 3,795
Ranking: Q1 (85,22%; 28/186; Category: Public, Environmental & Occupational Health); Q1 (85,18%; 16/98; Category: Health Care Sciences & Services) ; D1 (92.07%; 7/82; Category: Health Policy & Services)

Artículo 4.

García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. **Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs.**

Current Medical Research and Opinion, 2019.
doi: 10.1080/03007995.2019.1601944.

Factor de impacto: 2,665
Ranking: Q1 (77,1%; 36/155; Category: Medicine, General & Internal)

Artículo 5.

Hurtado-Navarro I, García-Sempere A, Rodríguez-Bernal C, Sanfélix-Genovés J,Peiró S, Sanfélix-Gimeno G. **Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction But With the Persistence of Over and Underuse. Data From the ESOSVAL Cohort From 2009 to 2015.**

Frontiers in Pharmacology. 2019.
doi: 10.3389/fphar.2019.00768.

Factor de impacto: 3,831
Ranking: Q1 (81,80%; 48/261; Category: Pharmacology & Pharmacy)

Resumen

Los estudios de utilización de medicamentos con datos de vida real permiten informar una serie de cuestiones fundamentales en cuatro ámbitos principales de la gestión sanitaria y farmacoterapéutica: ¿cómo se utilizan los fármacos en el día a día?, ¿cuál es el grado de adecuación de dicho uso?, ¿cuáles son los resultados de dicha utilización en términos de beneficios clínicos, de utilización de servicios sanitarios y costes?, y finalmente, ¿cuál es el impacto de las medidas de gestión de la prestación farmacéutica sobre todo lo anterior?.

La presente tesis doctoral se presenta mediante un compendio de publicaciones que demuestran la contribución de los datos de vida real al conocimiento y mejora de la atención farmacoterapéutica en la Comunidad Valenciana. Concretamente, se abordan los siguientes aspectos:

García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, et al. Data resource profile: the Valencia health system integrated database (VID) [published online ahead of print, 2020 Jan 16]. Int J Epidemiol. 2020;dyz266. doi:10.1093/ije/dyz266

- Dado el papel esencial de las fuentes de datos de vida real en la presente tesis, se presenta en primer lugar el sistema de información sanitaria y poblacional disponible en la Comunidad Valenciana, detallando las características de las diferentes bases de datos que lo conforman, su alcance, ventajas y limitaciones. De este modo se establece el marco de interpretación de los resultados obtenidos en los diferentes estudios presentados a continuación.

García-Sempere A, Hurtado I, Bejarano-Quisoboni D, et al. Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study. PLoS One. 2019;14(2):e0211681

- A continuación, se analiza la calidad del control de la anticoagulación oral en pacientes con fibrilación atrial no valvular tratados con acenocumarol, así cómo los patrones de cambio a otras alternativas terapéuticas en el año 2015 en la Comunidad Valenciana. Se muestra que la calidad del control del índice internacional normalizado (INR) es subóptima, con alrededor de la mitad de los pacientes con valores de Tiempo en Rango Terapéutico (TRT) por debajo del 65%, indicando mal control. Sistemáticamente, las mujeres obtienen peores resultados de control del INR. Además, se hallan tasas muy

bajas de cambio a terapias anticoagulantes alternativas indicadas en pacientes con mal control de INR, lo que sugiere la existencia de un potencial problema de inercia terapéutica. Estos resultados señalan áreas prioritarias de actuación y contribuyen a un mejor diseño de intervenciones de mejora de la calidad de la atención en estos pacientes.

García-Sempere A, Hurtado I, Bejarano D, et al. Group-based Trajectory Models to Assess Quality of INR Control and Its Association With Clinical Outcomes. Med Care. 2020;58(4):e23-e30

- En el tercer artículo, se analiza la evolución dinámica del control de anticoagulación oral en pacientes con fibrilación atrial no valvular que inician tratamiento con acenocumarol en el período 2011 a 2015, utilizando el análisis de clases latentes que permite agrupar a los pacientes en diferentes trayectorias en función de su probabilidad de presentar valores de INR controlado (entre 2 y 3) a lo largo de su primer año de tratamiento. El análisis de trayectorias identifica cuatro trayectorias de control de INR (óptimo, al alza, a la baja, inadecuado) que resultan consistentes con las medidas tradicionales de TRT. Los pacientes clasificados en trayectorias de mal control o a la baja presentan mayor mortalidad que los pacientes clasificados en trayectorias de control óptimo o al alza. Esta técnica puede ser de utilidad en práctica clínica habitual complementando a las medidas tradicionales de control de INR.

García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. Curr Med Res Opin. 2019;35(9):1535-1544

- En el cuarto estudio, se demuestra la mayor precisión de los estimadores de adherencia a la medicación, calculados a partir de datos de vida real, cuando se utiliza información relacionada a nivel individual de prescripción y dispensación, en comparación con el diseño más comúnmente utilizado en los estudios de adherencia a la medicación, que se limita al uso de información de dispensación. Se analiza la adherencia a la medicación en una cohorte representativa de pacientes tratados (iniciadores y prevalentes) con medicación antiosteoporótica, comparando diferentes variantes metodológicas para el cálculo del Porcentaje de Días Cubiertos con medicación (PDC), y se establecen las

ventajas de utilizar información de prescripción y dispensación, tales como una mejor definición del inicio de terapia, la captura de períodos iniciales de no adherencia o de los pacientes menos adherentes, o una mayor precisión en la atribución de los períodos sin medicación al paciente o al prescriptor.

Hurtado-Navarro I, García-Sempere A, Rodríguez-Bernal C, Sanfélix-Genovés J, Peiró S, Sanfélix-Gimeno G. Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction But With the Persistence of Over and Underuse. Data From the ESOSVAL Cohort From 2009 to 2015. Front Pharmacol. 2019;10:768.

- Finalmente, se analiza la evolución de la utilización de la medicación antiosteoporótica en la misma cohorte que en el estudio previo, en el período 2009 a 2015, así como el impacto de tres intervenciones de política sanitaria sobre dicho uso (dos alertas de la Agencia Española del Medicamento y Productos Sanitarios sobre bifosfonatos y riesgo de osteonecrosis mandibular y fracturas atípicas, así como el cambio en el sistema de copago de 2012), empleando un diseño de series temporales interrumpidas. Se observa una reducción a la mitad en la utilización de dichos fármacos a lo largo del período, y se aprecia que tanto la segunda alerta como el cambio de copago tienen un papel importante en dicho declive, aunque no la primera alerta. Dicha reducción se produce tanto en pacientes de bajo como de alto riesgo, lo que plantea dudas sobre la selectividad de dichas medidas sobre la adecuación de los tratamientos. El presente trabajo evalúa la capacidad de este tipo de medidas de política farmacéutica sobre la prescripción y aporta información que orienta el diseño de intervenciones de mejoras en este ámbito.

En definitiva, la presente tesis ofrece una visión pormenorizada de las características de los datos de vida real y las bases de datos en que se registran, y aporta información inédita hasta la fecha en relación con el manejo farmacoterapéutico en práctica clínica real de patologías crónicas de alta prevalencia en la Comunidad Valenciana, empleando además aproximaciones metodológicas innovadoras. Los resultados presentados señalan potenciales áreas de mejora sobre las que actuar desde la gestión, y a su vez pueden contribuir a informar el diseño de intervenciones de mejora más efectivas.

Introducción

Interés de los estudios con datos de vida real

Los ensayos clínicos aleatorizados (ECA) están considerados como el *gold standard* para determinar la eficacia y seguridad de los tratamientos farmacéuticos. Los ECA son esenciales en epidemiología puesto que reproducen condiciones experimentales ideales y permiten la inferencia de causalidad entre intervención y resultado. Sin embargo, también se reconoce que los ECA no pueden aportar toda la información necesaria sobre el uso seguro y efectivo de los medicamentos una vez estos son puestos a disposición de médicos y pacientes. Los ECA adolecen de limitaciones inherentes a su propia naturaleza: son muy costosos, sus tamaños muestrales suelen ser reducidos y sus criterios de inclusión habitualmente muy estrictos; todo ello resulta en sesgos de representatividad, habitualmente en una infra-representación de los colectivos más vulnerables (pacientes ancianos, frágiles, embarazadas, polimedicados, y otros). Además, en los ECA convencionales los resultados de eficacia y seguridad se evalúan en el corto plazo y en entornos experimentales altamente controlados que distan mucho de la práctica clínica habitual. Por último, aquello que es considerado un "éxito" en el marco de un ECA (esto es, que el fármaco en estudio obtenga un resultado mejor que placebo en una variable subrogada), no ofrece sin embargo respuesta a las incertidumbres que afrontan médicos y pacientes en el día a día con respecto a la toma de decisiones farmacoterapéuticas: tratar o no tratar, qué fármaco elegir, tomarlo o no tomarlo, y cómo (Garrison LP Jr et al, 2007; Murdoch TB et al, 2013).

Debido a estas limitaciones, en las últimas décadas las agencias reguladoras han venido estableciendo la necesidad de llevar a cabo estudios post-comercialización para conocer la efectividad y seguridad de los tratamientos farmacológicos en la práctica clínica real. Adicionalmente, en los últimos años, ha habido un enorme crecimiento en el uso de bases de datos poblacionales para el desarrollo de estudios epidemiológicos, y se han acuñado los términos *Real World Data* (RWD) o datos de vida real, en referencia al origen no experimental de la información, y *Real World Evidence* (RWE) para referirse a la evidencia obtenida gracias al análisis del RWD (Association of British Pharmaceutical Industry, 2011). Dichas bases de datos comprenden, entre otras, las historias clínicas electrónicas, los registros de facturación, los datos de prescripción y dispensación de medicamentos, los registros de utilización de servicios y procedimientos, los registros diagnósticos, los registros de mortalidad, los sistemas de petición de pruebas diagnósticas y de recepción de sus resultados, etc. La posibilidad de disponer de grandes cantidades de datos individuales a lo largo del tiempo, y de relacionar a nivel de

paciente individual la información procedente de diferentes bases de datos ofrece nuevas y prometedoras posibilidades de análisis de la realidad. Sin embargo, es importante tener en cuenta que el uso de datos de vida real presenta una serie de desafíos específicos, en cuanto a la calidad y homogeneidad de los propios datos y de corte analítico y metodológico, que pueden limitar la validez de los estudios de RWE, así cómo saber aplicar adecuadamente las herramientas disponibles para superarlos.

Principales ámbitos de contribución de los estudios con datos de vida real a la mejora de la práctica clínica

La investigación basada en bases de datos de práctica clínica habitual tiene múltiples aplicaciones. Por ejemplo, al permitir grandes tamaños muestrales, habilita el estudio de eventos infrecuentes o de colectivos habitualmente excluidos de los ECA. También pueden ser representativos de la población y por tanto permiten estudiar patrones de uso de práctica habitual obteniendo resultados generalizables al conjunto de la población o a determinadas subpoblaciones; finalmente, pueden permitir evaluar los resultados de las diferentes estrategias farmacoterapéuticas utilizadas en el mundo real mediante estudios de efectividad y seguridad (y de efectividad y seguridad comparada). Además, tienen la gran ventaja de que se basan en fuentes de información de relativo fácil acceso al estar habitualmente disponibles en plazos y costes relativamente moderados.

Los estudios de RWE con medicamentos permiten informar una serie de cuestiones fundamentales en cuatro ámbitos principales: cómo se utilizan los fármacos en el día a día, cuál es el grado de adecuación de dicho uso, cuáles son los resultados de dicha utilización en términos de beneficios clínicos, de utilización de servicios sanitarios y costes, y finalmente, también para evaluar cuál es el impacto de las medidas de gestión de la prestación farmacéutica sobre todo lo anterior.

A. Patrones de utilización de medicamentos

La información descriptiva básica sobre prevalencia, incidencia, y duración de las terapias farmacológicas constituye información esencial para la planificación sanitaria y la evaluación de la calidad de la prescripción. Igualmente, tiene un gran interés conocer las características socio demográficas, clínicas (edad, sexo, comorbilidad, analíticas, etc) y de utilización de servicios sanitarios (ingresos, urgencias, visitas, fármacos) de los pacientes con determinados

diagnósticos, con y sin tratamiento, pacientes iniciadores de tratamientos, con cambios de tratamiento, etc. Aquí, suele tener interés identificar perfiles de pacientes más o menos propensos a recibir (o no) determinados tratamientos o intervenciones (Hallas J et al, 1997; Rodríguez-Bernal CL et al, 2017; Peterson AM et al, 2007). Por último, cabe mencionar que una de las dimensiones más importantes (y más estudiadas, aunque no siempre con bases de datos) en cuanto a patrones de uso de medicamentos en la vida real es la adherencia (y la persistencia) a las terapias prescritas. La adherencia (tomarse la mediación en el tiempo, dosis, y frecuencia prescritas) y la persistencia (la continuidad en el tiempo) a la medicación en terapias crónicas efectivas es esencial para lograr los beneficios de los tratamientos observados en los ensayos clínicos y obtener así mejores resultados para los pacientes. Aun así, e incluso en pacientes de alto riesgo y medicación esencial, se observa sistemáticamente que las tasas de adherencia en la vida real son subóptimas, suponiendo así un riesgo para los pacientes y un aumento de los costes sanitarios (Balkrishnan R et al, 2005; Ho PM et al, 2006; Benner JS et al, 2002; Ho PM et al, 2008; Fischer MA et al, 2010). Existe un importante volumen de estudios de adherencia a la medicación crónica en práctica clínica real, y una serie de medidas que se vienen empleando habitualmente para evaluar dicha adherencia (Andrade SE et al, 2006; Hess LM et al, 2006; Raebel MA et al, 2013). Por ejemplo, la Proporción de Días Cubiertos con medicación (PDC) o la *Medication Possession Ratio* (MPR) para medir la adherencia terapéutica, o medidas tales como el porcentaje de pacientes que discontinúan el tratamiento, en cuanto a la persistencia. Sin embargo, existe una notable variabilidad en la forma en que se calculan dichas medidas, así como ciertas deficiencias relativas a la disponibilidad de información (por ejemplo, en la gran mayoría de estudios, se calcula la adherencia en base a información de dispensación de recetas, pero no de la prescripción, lo que impide conocer el inicio real de los tratamientos así cómo los periodos de interrupción de los tratamientos por parte del médico) que invitan a interpretar con prudencia los resultados de gran parte de dichos estudios. Por otra parte, existe la posibilidad de innovar en el abordaje de la no adherencia, capturada habitualmente mediante medidas estáticas como promedios o porcentajes, con técnicas alternativas como los *Group-Based Trajectory Models* (GBTMs), que agrupan a los pacientes en grupos con características similares con respecto a la ocurrencia de un fenómeno en el tiempo, en este caso, los diferentes perfiles de adherencia en el tiempo (Franklin JM et al, 2013).

B. Adecuación y calidad de la prescripción

Los estudios de utilización de medicamentos permiten evaluar la adecuación de las decisiones terapéuticas. Conocer en qué medida los tratamientos se prescriben a aquellos candidatos que más se van beneficiar, y con la intensidad terapéutica adecuada (adecuación), y sobre todo en qué casos no se trata cuando se debería (infrautilización) o se trata a pacientes que no precisan del tratamiento (sobreutilización) es esencial para el diseño de políticas de mejora de la calidad de la prescripción. Aquí, las grandes bases de datos permiten establecer asociaciones entre características de los prescriptores y de las organizaciones (jugando aquí por ejemplo un papel importante la metodología de regresión multinivel, relevante en general a la hora de identificar patrones de utilización marcados por los niveles de la organización sanitaria) y los patrones de uso de los medicamentos (adecuado y no adecuado), así como conocer qué características de los pacientes se asocian a un peor o mejor manejo terapéutico (Merlo J et al, 2005; García-Sempere A et al, 2017; Sanfélix-Gimeno G et al, 2011). En definitiva, los datos de vida real pueden ser de gran utilidad en tareas de revisión de la adecuación de la prescripción en múltiples vertientes, comúnmente: la adecuación en la selección del fármaco, así como de su dosificación, frecuencia y ruta de administración prescrita, con respecto a la mejor evidencia disponible o los estándares regulatorios de aplicación (indicaciones recogidas en ficha técnica, recomendaciones de las Guías de Práctica Clínica (GPC), guías farmacoterapéuticas, Informes de Posicionamiento Terapéutico (IPT), alertas regulatorias, visados, etc.); la identificación de bolsas de prescripción inadecuada (infra o sobreuso, duplicidades terapéuticas, contraindicaciones, …); la identificación de variaciones en el uso debidas a factores no clínicos; o la evaluación de la calidad del manejo diferencial entre subgrupos poblacionales de mayor o menor riesgo o con diferentes características socio-económicas (tomando aquí especial importancia las consideraciones de inequidad por razones de edad, de género, socioculturales, etc.), entre otros.

C. Efectividad y seguridad en práctica clínica real

Los estudios basados en datos de vida real permiten responder la pregunta de cómo funcionan realmente los medicamentos en el día a día de la atención sanitaria. Se podría argumentar que esta es la piedra angular de los estudios basados en bases de datos clínico-administrativas. En definitiva, conocer cuál es la efectividad y seguridad de los medicamentos en el contexto de la práctica local, y en qué medida estas se corresponden con la eficacia y seguridad experimental observadas en los ensayos clínicos que de hecho permitieron su comercialización, ofrece una información esencial para la gestión asistencial (Sox HC et al, 2012).

Las bases de datos de vida real han devenido una herramienta útil para investigadores, reguladores y gestores para estudiar el perfil de seguridad y efectividad al poder incluir grandes números de pacientes a lo largo de largos períodos de tiempo, lo que permite poder estudiar en grandes cohortes la ocurrencia en el tiempo de eventos raros o de baja incidencia y su relación con las diferentes estrategias de tratamiento. Los medicamentos constituyen una partida muy importante en el conjunto del gasto sanitario público, y en general, si bien utilizados, aportan un gran potencial terapéutico, y por tanto su uso adecuado es un elemento esencial de sostenibilidad y efectividad de la actuación sanitaria. Los estudios de base poblacional con múltiples bases de datos aportan información esencial para priorizar la utilización y selección de medicamentos en el día a día.

En definitiva, los estudios de efectividad y seguridad, también conocidos como estudios de efectividad comparada en el caso de la evaluación de los resultados de diferentes comparadores activos en práctica clínica real, aportarían la evidencia última (¿qué resultados obtienen?), pero está fuertemente ligada a los patrones de utilización (¿a quién y con qué se trata?) y de adecuación y calidad de la prescripción (¿en qué medida se maximiza el balance riesgo/beneficio?) vistos anteriormente (Schneeweiss S et al, 2007; Schneeweiss S et al, 2011).

Cabe resaltar por último que los estudios basados en datos de vida real, para reflejar adecuadamente la realidad analizada, suelen conllevar una elevada complejidad en el apartado del diseño del estudio y del análisis estadístico, debido a la necesidad de implementar ajustes para compensar diferentes sesgos inherentes al análisis de cohortes observacionales, a la naturaleza de los propios datos, o a la toma de decisiones en práctica clínica. En los estudios observacionales existe una cadena de potenciales sesgos a considerar y corregir a la hora de tratar de establecer relaciones de causalidad entre la intervención (decisión de tratamiento o no, con un fármaco u otro, intervención de gestión, adherencia a un tratamiento) y efecto (impacto en variables clínicas de efectividad y seguridad, en utilización de servicios sanitarios, en costes), como por ejemplo el hecho de que los pacientes más enfermos sean más propensos a recibir tratamiento (*confounding by indication*).

En este sentido, recientemente se han puesto en marcha distintas iniciativas por parte de investigadores de referencia en el ámbito de la inferencia causal y las principales agencias regulatorias que tratan de establecer un marco metodológico que permita maximizar la capacidad de los estudios observacionales para establecer relaciones de causalidad, acercando dichos diseños a los ensayos clínicos. Básicamente, los estudios con bases de datos administrativas adolecen de los principales sesgos inherentes a los estudios observacionales,

sesgos de selección y de información. Existen diferentes estrategias, tanto en el diseño como en el análisis, para corregir estos elementos de confusión, a aplicar en función de si las potenciales variables de confusión son conocidas y medibles (esto es, están disponibles en las bases de datos) o no. En el caso en que las variables de confusión sean conocidas se pueden emplear técnicas de ajuste tradicionales cómo la estratificación, el *matching* (emparejamiento de muestras), la modelización multivariante o el uso de métodos de puntuación de propensión *(propensity scores)*. En el caso de variables de confusión no observadas, se puede recurrir a otras alternativas como el análisis de variables instrumentales o los diseños de casos cruzados (*case-crossover*), en que los pacientes del grupo expuesto (casos) serán sus propios controles (Schneeweiss S et al, 2005; Goodman SN et al, 2017; Agoritsas T et al, 2017).

D. Impacto de las intervenciones de gestión de la prestación farmacéutica

Un último elemento de gran interés para la gestión, dónde los estudios con grandes bases de datos de vida real pueden aportar información única, es la evaluación del impacto de las diferentes medidas de gestión de la prescripción sobre el uso, adecuación y resultados de las terapias farmacológicas. Entre dichas intervenciones destacan las políticas de copago farmacéutico; en este sentido, los estudios con datos de vida real permiten establecer el impacto diferencial de los copagos en función de diferentes características de los pacientes, como por ejemplo la renta, sobre cuestiones tales como la adherencia a la medicación y los resultados en salud (Schneeweiss S et al, 2007; Eaddy MT et al, 2012; González López-Valcárcel B et al, 2017). Aquí, los estudios de series temporales interrumpidas en cohortes longitudinales son uno de los diseños más apropiados para el análisis del impacto de dichas intervenciones (Jandoc R, 2015). Junto con los copagos, es relevante también conocer el impacto de otras intervenciones como la instauración de alertas o visados de inspección, la protocolización del uso de determinados fármacos, y otras intervenciones, sobre la utilización, la efectividad y la seguridad.

La presente tesis pretende aportar evidencia novedosa y relevante para la mejora de la gestión farmacoterapéutica y asistencial en nuestro entorno, aplicando métodos de análisis y técnicas de ajuste apropiadas, en las referidas dimensiones de potencial de contribución de los estudios con bases de datos. Concretamente se abordan cuestiones de capital relevancia para mejorar la calidad del manejo terapéutico de los pacientes en el SNS: patrones de utilización, análisis de la adherencia a la medicación y de la adecuación del uso de medicamentos en determinadas patologías crónicas prevalentes en el Sistema Nacional de Salud, así como a la efectividad y

seguridad de dichos fármacos en la práctica clínica diaria. Finalmente se abordará la evaluación del impacto de intervenciones de política sanitaria que afectan a dicha utilización.

Datos de vida real en nuestro ámbito: el Sistema Integrado de Información Sanitaria de la Comunidad Valenciana

En la Comunidad Valenciana, la *Conselleria de Sanitat* ha desarrollado un importante esfuerzo de informatización de sus servicios, de integración de estos y de trazabilidad de los usuarios a través de un identificador único de paciente. Los sistemas de información electrónicos de la Comunidad Valenciana, hacen factible la combinación de la información relativa a las altas hospitalarias, la historia clínica ambulatoria, los sistemas de gestión de la prestación farmacéutica (prescripción y dispensación) y otros, ofreciendo una gran oportunidad para tratar de dar respuesta a las cuestiones anteriormente apuntadas. Las principales bases de datos que conforman el Sistema Integrado de Información Sanitaria de la Comunidad Valenciana destacan:

1. Sistema de Información Poblacional (SIP): Proporciona el número de identificación para cada persona en la AVS, y registra algunas características demográficas y fechas de altas y bajas administrativas, incluyendo muerte.

2. Conjunto Mínimo Básico de Datos (CMBD): Es una base de información clínica y administrativa de los hospitales que incluyen información de ingresos, altas, diagnósticos y procedimientos utilizando la Clasificación Internacional de Enfermedades como sistema de clasificación.

3. Historia Médica Electrónica para la atención ambulatoria (ABUCASIS): Disponible en todos los centros de atención primarias y otros entornos ambulatorios, ofrece información sobre diagnósticos, historia médica personal y familiar, de laboratorio resultados, estilo de vida, etc., de los pacientes.

4. Módulo farmacéutico (GAIA): Parte de ABUCASIS, incluye información de las prescripciones de recetas por parte de los médicos e información de las dispensaciones en farmacia por parte de los pacientes.

5. Catálogo de Recursos Corporativa (CRC): Proporciona información proporciona información acerca de la organización geográfica y funcional de la AVS, sus centros de salud, servicios de salud y los profesionales de la asistencia sanitaria prestada.

Dada la importancia central de las fuentes de los datos de vida real en la elaboración de la presente tesis, se presenta en un artículo introductorio la descripción pormenorizada la red integrada de bases de datos de información sanitaria y poblacional de la Comunidad Valenciana (*García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, et al. Data resource profile: the Valencia health system integrated database (VID) [published online ahead of print, 2020 Jan 16]. Int J Epidemiol. 2020;dyz266. doi:10.1093/ije/dyz266*). En este primer artículo se da a conocer con el detalle necesario las bases de datos que se han empleado para llevar a cabo el resto de los artículos que conforman el presente trabajo, ofreciendo una visión de conjunto de dicha red de información, apuntando sus fortalezas y debilidades, y detallando para cada una de las bases la información y mediciones que estas contienen, sus aspectos destacables en términos relativos con otras fuentes de datos de vida real disponibles en el ámbito nacional e internacional, así como su alcance en términos de cobertura poblacional y temporal. De este modo se establece el marco necesario para la presentación del conjunto de resultados de la tesis.

Objetivos

Esta tesis doctoral se desarrolla mediante la modalidad de compendio de publicaciones, específicamente artículos científicos en revistas indexadas en el *Journal Citation Reports* (JCR). Los estudios que la conforman tienen la finalidad de aportar información original y relevante para el diseño de intervenciones de mejora de la calidad de la atención a los pacientes en patologías crónicas de elevada prevalencia, así como para la evaluación del impacto de dichas intervenciones sobre los procesos de manejo terapéutico de los pacientes y la obtención de resultados clínicos. El trabajo se ha planteado, por tanto, con los siguientes objetivos:

Objetivo general

Mostrar las posibilidades de contribución de los estudios con grandes bases de datos a la mejora de la gestión farmacoterapéutica, de la calidad de la prescripción y del manejo farmacoterapéutico de los pacientes.

Objetivos específicos

Este objetivo general se desglosa en cuatro objetivos específicos que se desarrollan en base a la presentación de casos concretos de estudios con grandes bases de datos, principalmente utilizando cohortes poblacionales de la Comunidad Valenciana o de otras Comunidades Autónomas del Sistema Nacional de Salud (SNS):

1. Descripción de las características de las fuentes de datos de vida real disponibles en la Comunidad Valenciana, su alcance y relevancia.

2. Evaluación de los patrones y la calidad del manejo farmacoterapéutico en pacientes crónicos y de la relación entre dichos patrones de manejo y resultados clínicos.

3. Análisis de las diferencias entre los estimadores de adherencia secundaria a la medicación construidos con información sobre prescripción y dispensación de medicamentos, y los elaborados con datos de dispensación únicamente.

4. Evaluación del impacto de una serie de intervenciones de política farmacéutica sobre la utilización de medicamentos.

El desarrollo del primer objetivo consistió en la descripción y análisis de las fuentes de datos de vida real disponibles, como base para los estudios focalizados en los restantes objetivos.

Para la consecución del segundo objetivo se ha analizado la calidad de manejo de la prevención del ictus isquémico de los pacientes con fibrilación atrial de la Comunidad Valenciana tratados con fármacos anti-vitamina K y los resultados obtenidos han dado lugar a dos artículos

- *García-Sempere A, Hurtado I, Bejarano-Quisoboni D, et al. Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study. PLoS One. 2019;14(2):e0211681*

- *García-Sempere A, Hurtado I, Bejarano D, et al. Group-based Trajectory Models to Assess Quality of INR Control and Its Association With Clinical Outcomes. Med Care. 2020;58(4):e23-e30*).

En el primer artículo se ofrece una visión transversal de la calidad del manejo de más de 22.000 pacientes tratados con VKA en el año 2015, incorporando la perspectiva de género, y aportando así información inédita a nivel local. En el segundo artículo se adopta una visión longitudinal, analizando la calidad de dicho manejo en el período 2010 a 2015 en 8.000 pacientes iniciadores de terapia durante su primer año de tratamiento utilizando una técnica de análisis de clases latentes.

La evaluación de la adherencia a los medicamentos mediante grandes bases de datos es una de las líneas de investigación más extensivas en el ámbito de la farmacoepidemiología. Sin embargo, una gran mayoría de estudios sobre adherencia a medicamentos en la vida real se basan en información de dispensación únicamente (49). El tercer objetivo de este trabajo ha consistido en el análisis comparativo de ambas estrategias y ha dado lugar a un artículo:

- *García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. Curr Med Res Opin. 2019;35(9):1535-1544*)

en el que se muestra la mayor precisión de los estimadores de adherencia construidos con información relacionada a nivel individual de prescripción y dispensación. Para ello se ha empleado una cohorte de más de 11.000 pacientes de más de 50 años, tratados con medicación antiosteoporótica

Para desarrollar el cuarto objetivo, se emplea la misma cohorte de pacientes tratados con medicación antiosteoporótica, y se describe la utilización de dichos fármacos en el período 2009 a 2015, analizando el impacto de las alertas de seguridad relativas a fármacos de la Agencia Española de Medicamentos y Productos Sanitarios, así como el impacto del cambio de sistema de copago farmacéutico que tuvo lugar en Julio de 2012. Se analiza el impacto de las citadas medidas sobre el conjunto de la cohorte, así como de forma estratificada, en pacientes con diferentes características y niveles de riesgo de fractura osteoporótica. Para llevar a cabo dicho análisis se emplean series temporales interrumpidas y modelos de regresión segmentada y los resultados obtenidos han dado lugar a un articulo:

- *Hurtado-Navarro I, García-Sempere A, Rodríguez-Bernal C, Sanfélix-Genovés J, Peiró S, Sanfélix-Gimeno G. Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction But With the Persistence of Over and Underuse. Data From the ESOSVAL Cohort From 2009 to 2015. Front Pharmacol. 2019;10:768*.

Métodos

Fuentes de datos

Se empleó la información disponible en el Sistema de Información Sanitaria de la Comunidad Valenciana. Las características de las bases de datos que conforman dicho sistema, su alcance, información y mediciones contenidas se explican con detallan en el primer artículo de la presente tesis.

Las ventanas temporales de los diferentes estudios de esta tesis se extienden desde 2008 hasta 2015 variando según el tipo de estudio, patología estudiada y pregunta planteada.

Variables

Las variables que se obtienen a partir de las diferentes bases, y que son empleadas tanto para la descripción de las características basales de las cohortes como en los análisis estadísticos son las siguientes:

1. Medicamentos: Nombre genérico, precio, esquema de dosificación, régimen, fecha de prescripción y dispensación, copago reducido.

2. Pacientes: Fecha de nacimiento, sexo, copago, comorbilidades (por ejemplo, accidente cerebrovascular, insuficiencia cardíaca, cardiopatía isquémica, enfermedad valvular cardíaca, arritmias, enfermedades de la tiroides, diabetes, apnea del sueño, enfermedad pulmonar obstructiva crónica, insuficiencia renal crónica, demencia, entre otros); estilo de vida y factores de riesgo (por ejemplo, obesidad, hipertensión, tabaquismo, ingesta de alcohol, sedentarismo); tratamientos y procedimientos anteriores o basales (realizados en los 12 meses anteriores a las fechas índices) y tratamientos concomitantes. Adicionalmente, se incluye información sobre la utilización de los servicios de salud, visitas, incluyendo especialidades médicas, hospitalizaciones, visitas a servicios de urgencias durante los períodos de seguimiento y en los 12 meses anteriores.

3. Sistema de salud: Variables de centros de atención primaria, zona básica de salud, departamento de salud, y/o hospital.

Aspectos éticos y legales

En todos los estudios que utilizaron datos de pacientes se siguieron los principios establecidos en la Declaración de Helsinki y fueron previamente clasificados por la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) y aprobados por un Comité Ético de Investigación (CEI) o un Comité Ético de Investigación con Medicamentos (CEIm). Los datos fueron cedidos para el respectivo proyecto de investigación por la Conselleria de Sanidad Universal y Salud Pública de la Generalitat Valenciana y se adoptaron las medidas necesarias para el cumplimiento de la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales.

Análisis

Se emplearon diferentes técnicas de análisis en los diferentes artículos, atendiendo a dar respuesta a las diferentes preguntas de investigación. En cada uno de los artículos se describió en primer lugar las características basales de las diferentes cohortes, utilizando los parámetros adecuados (medias o proporciones) para cada variable con sus respectivos intervalos de confianza del 95% (IC95%). A continuación, y en función de los objetivos y tipos de variables manejadas en cada artículo, se emplearon diferentes técnicas de regresión multivariante (logística, de riesgos proporcionales, o segmentada) para analizar diferentes tipos de asociaciones:

- En *García-Sempere A, Hurtado I, Bejarano-Quisoboni D, et al. Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study. PLoS One. 2019*, se analizó la calidad de la anticoagulación oral con fármacos anti-vitamina K (VKA) para la prevención de ictus en pacientes con fibrilación atrial en el año 2015, atendiendo a las diferencias por razón de género. Se emplearon las medidas habituales de evaluación del manejo de los fármacos anti-vitamina-K, como son los valores de INR (*International Normalized Ratio*; valor que refleja el grado de control de la anticoagulación; en fibrilación atrial no valvular el rango de INR que se considera buen control está entre 2 y 3), el tiempo en rango terapéutico o el porcentaje de determinaciones de INR en rango. A continuación, se llevó a cabo un análisis de regresión logística multivariante para identificar los factores asociados al mal control, estimando las correspondientes *Odds Ratio* con su respectivo IC95%. Por último, se analizó, estratificando

por género, las tasas de cambio terapéutico (fenómeno habitualmente descrito con el anglicismo *switching*) de VKA a terapias alternativas (anticoagulantes de acción directa) en pacientes bien y mal controlados.

- En *García-Sempere A, Hurtado I, Bejarano D, et al. Group-based Trajectory Models to Assess Quality of INR Control and Its Association With Clinical Outcomes. Med Care. 2020*, se empleó la técnica de análisis de clases *Group-based Trajectory Models* (GBTM) para clasificar a los pacientes en distintas trayectorias temporales en función de la evolución de su probabilidad de presentar un INR en rango en el tiempo. De forma simultánea a la obtención de las trayectorias se estimó la relación entre características individuales de los pacientes y la pertenencia a cada trayectoria (Nagin D et al, 2005), obteniendo las correspondientes *Odds Ratio* con sus respectivos IC95%. Por último, para analizar la asociación entre las trayectorias y una serie de medidas de resultados clínicos (mortalidad, ictus y sangrado) se utilizaron modelos de riesgos proporcionales de Cox ajustados y se presentan las correspondientes Hazard Ratio con sus respectivos IC95%.

- En *García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. Curr Med Res Opin. 2019*, se analizaron las diferencias de los estimadores de adherencia secundaria (utilizando para ello el indicador más utilizado en la literatura científica sobre adherencia farmacoterapéutica, como es la Proporción de Días Cubiertos o PDC) cuando estos se calculan con datos de dispensación de medicamentos o con datos combinados de prescripción y dispensación. Se detallaron los efectos sobre el estimador y se cuantificaron dichos efectos utilizando una cohorte poblacional de hombres y mujeres de 50 años o más tratados con fármacos antiosteoporóticos.

- Utilizando la misma cohorte de pacientes con osteoporosis, en *Hurtado-Navarro I, García-Sempere A, Rodríguez-Bernal C, Sanfélix-Genovés J, Peiró S, Sanfélix-Gimeno G. Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction But With the Persistence of Over and Underuse. Data From the ESOSVAL Cohort From 2009 to 2015. Front Pharmacol. 2019* se trabajó con series temporales interrumpidas y se emplearon regresiones lineales segmentadas para analizar el impacto de las intervenciones de política sanitaria (alertas de la AEMPS y cambio del copago farmacéutico) sobre la utilización de medicación osteoporótica. Los modelos pueden

detectar la ocurrencia de efectos inmediatos (cambios de nivel) y cambios de tendencia (cambios de pendiente).

Todos los análisis se realizaron usando los software estadísticos STATA (StataCorp, College Station, TX) y R (R Foundation for Statistical Computing, Vienna, Austria).

Resultados

Artículo 1

García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, et al. Data resource profile: the Valencia health system integrated database (VID) [published online ahead of print, 2020 Jan 16]. Int J Epidemiol. 2020;dyz266. doi:10.1093/ije/dyz266

Artículo 2

García-Sempere A, Hurtado I, Bejarano-Quisoboni D, et al. Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study. PLoS One. 2019;14(2):e0211681

Artículo 3

García-Sempere A, Hurtado I, Bejarano D, et al. Group-based Trajectory Models to Assess Quality of INR Control and Its Association With Clinical Outcomes. Med Care. 2020;58(4):e23-e30

Artículo 4

García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. Curr Med Res Opin. 2019;35(9):1535-1544

Artículo 5

Hurtado-Navarro I, García-Sempere A, Rodríguez-Bernal C, Sanfélix-Genovés J, Peiró S, Sanfélix-Gimeno G. Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction But With the Persistence of Over and Underuse. Data From the ESOSVAL Cohort From 2009 to 2015. Front Pharmacol. 2019;10:768.

Data resource profile: the Valencia Health System Integrated Database (VID).

García-Sempere A[1,2,], Orrico-Sánchez A[3], Muñoz-Quiles C[3], Hurtado I[1,2], Peiró S[1,2], Sanfélix-Gimeno G[1,2#], Diez-Domingo J[3].

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Data Resource Basics

The Valencia Health System Integrated Database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with approximately 5 million inhabitants and an annual birth cohort of 48,000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation) and healthcare utilization data from hospital care, emergency departments, specialised care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology and others, and also public health databases from the population screening programs. All the information in the VID databases can be linked at the individual level through a single personal identification code. The databases were initiated at different moments in time (see details in the Data Collected section), but all in all the VID has provided comprehensive individual-level data fed by all the databases from 2008 to date.

The VID in the context of the Spanish National Health System.

The Spanish National Health System (SNHS) is the result of a system consolidation process started in 1978 and leading to the nearly universal coverage of all citizens, providing care based on need and free at the point of delivery, except for a cost-sharing scheme for pharmaceuticals dispensed out of hospitals [1]. Care delivery is mainly undertaken through a network of publicly owned, staffed and operated inpatient and outpatient centres. In 2002 a process of devolution to the seventeen regions that comprise the Spanish state was completed. Each regional NHS is geographically organized into Primary Healthcare Districts (around 5,000-25,000 people served by one Primary Care Centre), which in turn are embedded into Healthcare Departments (about

150,000-250,000 people served by one public hospital). Each region develops and operates its own information systems and the development of real-world data (RWD) research capabilities is heterogeneous, the Valencia region being among the top in terms of data availability and the linkage capacity of databases at a population level.

Data Collected

Data are sourced from a variety of datasets owned by the Health Department of the Valencia Regional Government. All data included in the databases can be obtained at the individual level. The type of available data, measurements collected and update frequency is different for each dataset. The main characteristics of each dataset are described below and in Figure 1.

The **Population Information System** (*Sistema de información Poblacional*, SIP) is a region-wide database that provides basic information on VHS coverage (dates and causes of VHA entitlement or disentitlement, insurance modality, pharmaceutical copayment status, assigned Healthcare Department, Primary Healthcare District and primary care doctor, etc.) and also some sociodemographic data such as sex, date of birth, nationality, country of origin, previous year income strata, employment status, risk of social exclusion, geographic location, address, and other administrative data. Importantly, the SIP database includes the date of death captured from the Mortality Registry. The SIP database is paramount to the VID as it is the source of the individual, exclusive and permanent identifier number associated to each individual (the SIP number) that is then used throughout the rest of the databases, allowing data linkage across the multiple databases in the network (see Figure 1).

The **Ambulatory Medical Record** (ABUCASIS) was implemented in 2006 as the electronic medical record (EMR) for primary and specialised outpatient activity, reaching 96% population coverage from 2009. ABUCASIS is integrated by two main modules: the ***Ambulatory Information System*** (*Sistema de Información Ambulatoria*, SIA) and the ***Pharmaceutical Module*** (*Gestor Integral de*

la Prestación Farmacéutica, GAIA), including paediatric and adult primary care, mental health care, prenatal care and specialist outpatient services, as well as providing information about dates, visits, procedures, lab test results, diagnoses, clinical and lifestyle information. It also includes information on several health programs (healthy children, vaccines, pregnancy, notifiable diseases, etc.), the primary care nurse clinical record and the health-related social assistance record. The SIA module uses the International Classification of Diseases 9th revision Clinical Modification (CIE9CM) for coding diagnoses. The SIA also uses the Clinical Risk Groups (CRG) system (3M™) [2] to stratify the morbidity of the entire population.

The **GAIA Pharmaceutical module** stores data on all outpatient pharmaceutical prescriptions and dispensations using the Anatomical Therapeutic Chemical (ATC) Classification System and the National Pharmaceutical Catalogue which allow the identification of the exact content of each dispensation. In-hospital medication is not included. GAIA provides detailed information on prescriptions issued by physicians, such as the duration of treatment and dosage. GAIA includes a comprehensive e-prescription paper-free system connected to all community pharmacies in the region that permits the linkage of individual prescriptions and dispensations through a specific prescription identification number. This results in a competitive advantage with regard to other pharmaceutical databases that usually only have dispensation information from pharmacy claims and enables a refined estimation of common and relevant research features such as medication adherence.

The **Hospital Medical Record** (ORION) has been in implementation since 2008 and provides comprehensive information covering all areas of specialised care from admission, outpatient consultations, hospitalisation, emergencies, diagnostic services (labs, imaging, microbiology, pathology, etc.), pharmacy, surgical block including day surgery, critical care, prevention and safety, social work, at-home hospitalisation and day hospitalisation. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated

and available for all hospitals, including the ***Minimum Basic Data Set at Hospital Discharge*** (MBDS) and the ***Accident & Emergency Department*** clinical record.

The **MBDS** is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the VHS hospitals, including public-private partnership hospitals (around 450,000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographical area and zone of residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode and the Diagnosis Related Groups (DRG) assigned at discharge. The MBDS used the ICD9CM system for coding until December 2015 and the ICD10ES (a Spanish translation of the ICD10CM) afterwards. The MBDS was extended in 2015 to include the "present on admission" (POA) diagnosis marker, information on tumor morphology and the private hospitals.

The **Accident & Emergency Department** clinical record was launched in 2008 and collects triage data, diagnoses, tests and procedures performed in public emergency rooms. As with the MBDS, the coding system used was ICD9CM until December 2015 and ICD10ES afterwards. Diagnosis codification has been increasing from about 45% of all EDR visits between 2008 and 2014 up to around 75% in 2017, basically due to the progressive incorporation of hospital coding.

The **Corporate Resources Catalogue** (*Catálogo de Recursos Corporativos*, CRC) provides information on the geographical and functional organization of the provision of care in the region (distribution of hospitals, primary care centres, etc.) and health care professionals, (including age, gender and specialty).

The **Microbiological Surveillance Network** (*Red de Vigilancia Microbiológica de la Comunidad Valenciana*, RedMIVA) contains the results of the microbiological analyses performed in VHS. Data is transferred from the laboratories to the RedMIVA database on a daily basis, providing real-time detection of circulating microorganisms and resistance patterns, and enabling

microbiological surveillance. Importantly, RedMIVA gathers not only positive but also negative determinations. This database has been available since 2008.

The **Vaccine Information System** (*Sistema de Información Vacunal*, SIV) stores all the information on vaccination in the VHS since 2000, though data are only considered reliable after 2005. Available data include vaccine by type, manufacturer, batch number, number of doses, location and administration date, adverse reactions related to vaccines, rejected vaccinations and, if applicable, risk groups.

The **Cancer Information System** integrates three population-based information resources. The ***Childhood Cancer Registry*** provides information on cancer in the population under 20 years old; the ***Castellón Tumour Registry*** provides information on cancer in the province of Castellón; and the ***Oncologic Information System*** (NEOS) integrates medical information from all patients with malignant tumors in the region. The System was created in 1999 and delivers information on incidence, prevalence, tumor site and tumor type from 2004.

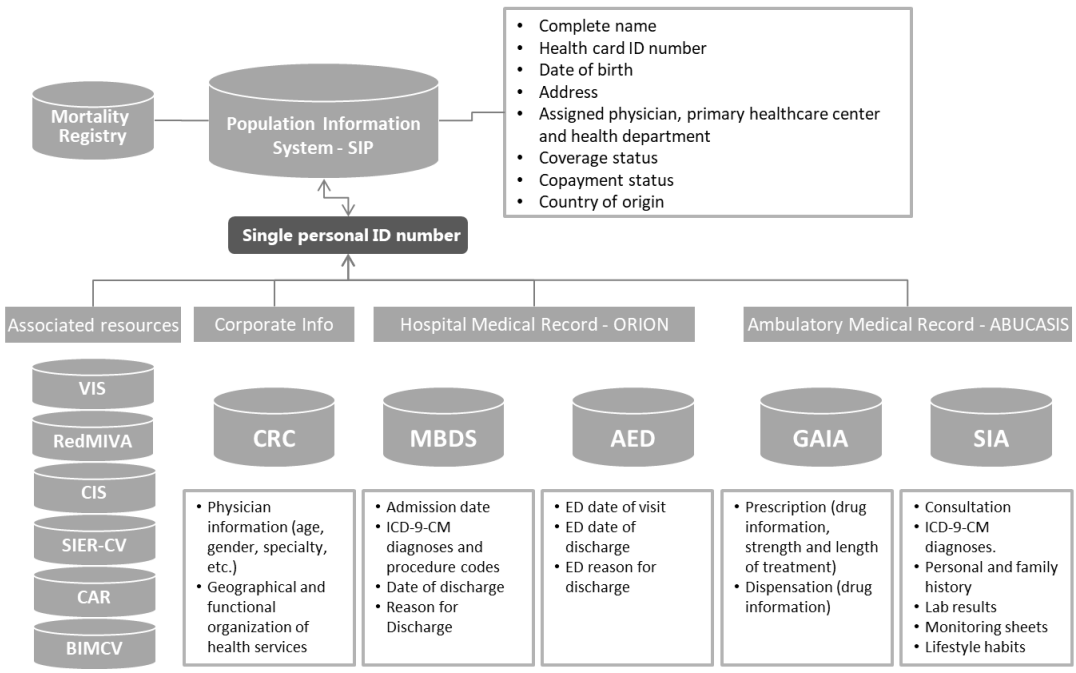
The **Rare Diseases Information System** *(Sistema de Información de Enfermedades Raras de la Comunidad Valenciana,* SIER-CV*)* was created in 2012 to provide population-wide epidemiological information on rare diseases in the region, allowing for the analysis of incidence, prevalence, patient characteristics, geographical distribution, etc. It includes the Congenital Anomalies Registry, which has provided information from 2007 on the prevalence of congenital anomalies in the region and the exposure to teratogen agents, and allows for research on the etiology of these diseases, including genetic and environmental risk factors and their interaction.

The **Medical Imaging Databank** ***(****Biobanco de Imagen Médica de la Comunidad Valenciana,* BIMCV) is a digital biobank of medical images that provides access to the images and associated clinical records of all imaging studies performed in the VHS, with an average of 5.3 million studies per year from 210 different imaging techniques. Access to these datasets is a breakthrough for research and population imaging studies. The BIMCV is part of the Spanish node of the European

Research Infrastructure for Imaging Technologies in Biological and Biomedical Sciences (Euro-BioImaging) and incorporates tools to anonymize radiological images.

In all databases in the VID, data are collected daily as a part of the routine clinical care provided to patients. Accordingly, data may be available for research until the data are extracted. Only in some cases, such as the MBDS and the AED records, are data subject to a consolidation and quality check process before data is available for research, so data from the last quarter before the data extraction may be missing or non-consolidated.

Figure 1. The Valencia Health System Integrated Database (VID)



VIS: Vaccine Information System; RedMIVA: Microbiological Surveillance System; CIS: Cancer Information System; SIER-CV: Rare Diseases Information System; CAR: Congenital Abnormalities Registry; BIMCV: Medical Image Bank; CRC: Catalogue of Corporate Resources; MBDS: Minimum Basic hospital Data Set; AED: Accident & Emergency Department record; GAIA: Pharmaceutical Module; SIA: Ambulatory Information System

Ethical clearance

Ethics approval by an accredited Ethical Research Committee is required to access the data for research purposes (see Data Resource Access section). The Valencia Government Health Department ensures the anonymization of data by providing only de-identified datasets, unless

researchers have the informed consent of patients to access their data. In the case of dynamic cohort studies, it maintains the pseudo-anonymization codes to allow the successive incorporation of information into the cohort.

Funding

The VID is funded by and is the property of the Valencia Government Health Department. Access to data for researchers has no financial cost but is covered by research ethics and authorization processes.

Data Resource Use

The VID is a unique and far-reaching research tool that enables real world data research to be conducted: in epidemiological surveillance [3,4], population risk and burden of disease [5-10], healthcare resource and drug utilization [11-15], quality and appropriateness of care [16-18], medication adherence [19-24], evaluation of safety [25-27] and effectiveness [28-32] of therapies in the real world, spatio-temporal analysis [33-35], economic analysis [36-38] or the analysis of the impact of policy interventions (such as copayments, warnings from regulatory agencies, etc.) on healthcare utilization and outcomes [39,40]. Also worth noting is the presence of several cross-national studies, participation in the Atlas of Variations in Medical Practice in the SNHS [41], and the potential of the VID to develop post-authorization studies based on RWD that are increasingly demanded by regulators, payers, providers and patients. Moreover, some research groups currently collaborate with the EMA and the FDA in regulatory projects using the VID data.

Strengths and Weaknesses

Strengths

VID has several strengths and some differential features with regard to other information resources. First, it links population-wide healthcare data with sociodemographic and administrative data, which allows the study of the determinants of health and the consequences of illness and treatments at an individual level in the population. This allows for the inclusion in studies of populations that are usually excluded from experimental designs, such as pregnant women, the elderly, people with multiple chronic diseases or paediatric populations. Second, it allows for the construction and follow-up of large cohorts of patients over time and the development of longitudinal studies, enabling research on the adoption of technologies and the monitoring of outcomes in the long term. Third, it is a population-based data network providing insight into a population of 5 million inhabitants. This large size allows for the analysis of small subgroups of population, or the identification of rare events that are not usually captured in clinical trials and other designs based on primary data. Fourth, data quality in some of the databases is high, such as the SIP, the Pharmaceutical Module or the CMBD (admissions data), RedMiva or the Vaccines registry. Fifth, the cost of developing research and the timing of access to the data is considerably lower than in experimental designs such as clinical trials. Finally, the possibility of linking prescription and dispensation data at the individual level allows for an accurate analysis of drug utilization, such as medication adherence studies.

Weaknesses

Some of the databases that comprise the VID are subject to the limitations inherent to routine clinical practice electronic databases. There may be information biases due to absent registration (data completeness) or differing data recording practices (data accuracy, misclassification, heterogeneity) in the electronic databases, although this is an intrinsic

problem of any repository using data from routine clinical practice. Data quality may be a strength in some databases, but also a weakness in other repositories or for certain data, such as incompleteness of early data from AED records or coding reliability of diagnostic information in the EMR. Also, we do not have information about people that are not in contact with the public healthcare service or who are attended to in the private sector. Finally, different datasets cover different periods and we lack data on specific mortality causes and inhospital pharmaceutical prescription (the latter will be available in forthcoming years as it is currently in the process of being integrated as part of the ORION information system).

Data Resource Access

Any researcher may request anonymized data from the VHS. The transfer of this type of data (anonymized, but with some risk of re-identification, in accordance with European regulations) by the VHS requires that the request be accompanied by: 1) a complete study protocol that explains the planned use of data, 2) the approval of the project by an ethics committee and, if it includes pharmaceutical data, 3) the classification of the study by the Spanish Agency of Medicines (some classifications may warrant additional authorizations). The VHS Data Commission reviews these requests, and approves or otherwise each specific data transfer for research purposes. Authorization to access the data under these requirements should be requested electronically from the Management Office of the VHS Data Commission (http://www.san.gva.es/web/dgfps/acceso-a-la-aplicacion)

Following authorization, researchers are required to commit to keeping the data in a secure environment, to not attempting to re-identify or to cross with other databases, to not using the data for purposes or projects other than those specified in the project protocol (although a new authorization may be requested for these purposes) and to not transferring the data to third parties. These latter commitments limit the possibility of storing data in open data repositories or including data as supplementary material in published articles.

Profile in a Nutshell

- The Valencia Health System Integrated Database (VID) is the result of the linkage, by means of a single personal identification number, of a set of publicly-owned population-wide healthcare, clinical and administrative electronic databases in the region of Valencia, Spain, which has provided comprehensive information for about 5 million inhabitants since 2008.
- The VID is a powerful resource for conducting real-world research in healthcare and has some unique features when compared to other relevant data sources at a local and a European level, such as its population-wide coverage, the richness of linkable information at individual level, and the inclusion of information not usually linkable at an individual level such as imaging, microbiological data, public health data or the ability to link prescription and dispensation data.
- The VID includes sociodemographic and administrative information (sex, age, nationality, etc.) and healthcare information such as diagnoses, procedures, lab data, pharmaceutical prescriptions and dispensations, hospitalizations, mortality, healthcare utilization and public health data. It also includes a set of specific associated databases with population-wide information on significant care areas such as cancer, rare disease, vaccines or imaging data.
- Access to the VID data may be requested by any researcher (providing the corresponding documentation required) from the Valencia Health System Data Commission (http://www.san.gva.es/web/dgfps/acceso-a-la-aplicacion).

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Artículo 1

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Artículo 2

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Artículo 3

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Artículo 4

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Artículo 5

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Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study.

Sex, quality of INR control and switching

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Abstract

Background Worldwide, there is growing evidence that quality of international normalized ratio (INR) control in atrial fibrillation patients treated with Vitamin K Antagonists (VKA) is suboptimal. However, sex disparities in population-based real-world settings have been scarcely studied, as well as patterns of switching to second-line Non-VKA oral anticoagulants (NOAC). We aimed to assess the quality of INR control in atrial fibrillation patients treated with VKA in the region of Valencia, Spain, for the whole population and differencing by sex, and to identify factors associated with poor control. We also quantified switching to Non-VKA oral anticoagulants (NOAC) and we identified factors associated to switching.

Methods This is a cross-sectional, population-based study. Information was obtained through linking different regional electronic databases. Outcome measures were Time in Therapeutic Range (TTR) and percentage of INR determinations in range (PINRR) in 2015, and percentage of switching to NOAC in 2016, for the whole population and stratified by sex.

Results We included 22,629 patients, 50.4% were women. Mean TTR was 62.3% for women and 63.7% for men, and PINNR was 58.3% for women and 60.1% for men ($p<0.001$). Considering the TTR<65% threshold, 53% of women and 49.3% of men had poor anticoagulation control ($p<0.001$). Women, long-term users antiplatelet users, and patients with comorbidities, visits to Emergency Department and use of alcohol were more likely to present poor INR control. 5.4% of poorly controlled patients during 2015 switched to a NOAC throughout 2016, with no sex differences. .

Conclusion The quality of INR control of all AF patients treated with VKA in 2015 in our Southern European region was suboptimal, and women were at a higher risk of poor INR control. This reflects sex disparities in care, and programs for improving the quality of oral anticoagulation

should incorporate the gender perspective. Clinical inertia may be lying behind the observed low rates of switching in patient with poor INR control.

Introduction

Patients with atrial fibrillation (AF) are at an increased risk of stroke and thus require anticoagulant prophylaxis. For decades, treatment with vitamin K antagonists (VKA) has been the gold standard for stroke prevention in AF [(1)]. The use of oral anticoagulants such as warfarin has been shown in clinical trials to reduce the risk of stroke by two thirds [(2)]. However, the efficacy and safety of VKA are closely associated with the quality of anticoagulation control. Use of VKA can be challenging due to their narrow therapeutic range, as therapy must be tightly controlled and maintained within a therapeutic index of international normalized ratio (INR) values of between 2 and 3. Additionally, the need for periodic INR monitoring, high inter-patient variability in treatment response, numerous drug and food interactions and medication non-adherence are well-documented barriers to optimal INR control [(3-9)].

There is a growing body of evidence showing that INR control in routine clinical practice, and even in clinical trials, is usually far from ideal, close to poor and even patient-endangering. Many registry-based studies, real-world studies and systematic reviews have consistently reported that INR control in routine clinical practice is largely suboptimal [(10-18)]. Time in Therapeutic Range (TTR), the more commonly used measure of anticoagulation control expressing the percentage of time a patient is correctly anticoagulated with INR values of between 2 and 3, shows wide variations depending on settings, organizations and patients [(19)]. Also differing calculation methods for TTR and thresholds for the definition of “good control” are used, varying within organisations and over time. For instance, TTR≥70% is defined as optimal care by the European Society of Cardiology (ESC), whether a TTR<65% is defined as suboptimal care by the National Institute of Clinical Excellence (NICE) [(8)], and recent evidence suggests the threshold of good control should be elevated to >80% to minimize risks [(20)]. All in all, evidence worldwide shows

that a large proportion of VKA treated patients, ranging from one third to three quarters, do not achieve adequate INR control and are thus at an increased risk of stroke (when INR<2) or bleeding (when INR>3). Furthermore, sex (being a woman) has been identified as an independent predictor of poor TTR [21], but the extent of differences between women and men has not to date been quantified in a real-world setting.

In the Spanish NHS with universal healthcare coverage, evidence on INR control quality is in line with that observed abroad, showing that poor INR control may be affecting between one and two thirds of patients using VKA. However, studies addressing this issue are sparse and based on collaborative research registries or in local healthcare centres with reduced populations [22-30], with absence of studies based on information routinely collected from the entire population served, and thus the generalizability of their results may be limited or they may not accurately reflect average ordinary clinical practice. Additionally, these studies systematically ignore the sex perspective. Also, patterns of switching from VKA to Non-VKA Oral Anticoagulants (NOAC) are unknown, although NOAC are relegated to a second line of treatment after VKA in Spain. NOAC use in Spain is subject to conditions such as poor INR control, ineffectiveness of or contraindication to VKA, increased risk of intracranial hemorrhage or inability to access INR facilities. This study aims to assess the quality of INR control per sex in 2015 in the whole population of patients treated with acenocoumarol for AF in the region of Valencia, and to identify factors associated with poor INR control. We further aimed to describe patterns of switching from VKA to NOAC during 2016 and to identify factors associated to switching patterns. Main analyses are performed for the whole population and stratified by sex.

Methods

Design and setting

This cross-sectional population-based study was conducted in the Valencia Health Agency (VHA), the public health system of the region of Valencia in Spain, covering about 97% of the 5 million

inhabitants region's population. We selected all patients diagnosed AF or flutter [diagnosis code of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 427.31 and 427.32] treated with acenocoumarol in 2015 (marginal use of warfarin, phenprocoumon or fluindione, mainly by non-residents, was not included).

We defined patients treated with acenocoumarol in 2015 by those having at least one dispensation of the drug in the last quarter of 2015, by having initiated acenocoumarol before December 2014 and by not having any prescription for any other oral anticoagulants in 2015. Additionally, we only selected patients with at least 4 INR determinations in 2015. People without pharmaceutical/health coverage by the VHA, mainly some government employees whose prescriptions are reimbursed by civil service insurers and thus not included in the pharmacy databases of the VHA, and patients not registered in the municipal census (non-residents or temporary residents), or those who left the region or were disenrolled from VHA coverage for other causes, were excluded because of limitations on follow-up. Additionally, availability of information about INR determinations in the EMR was not homogeneous for each of the 24 Health Areas (HAs, the administrative and territorial management units in the region) that make up the public health care provision network in the region. INR data is linked to the EMR from local, HA-based INR records, and this process has been implemented in a disparate manner by HAs. We only include patients belonging to HAs with INR information for at least 70% of their patients (8 HAs were excluded, representing only 23 % of patients; see Figure 1 and Supplementary File 1).

Data sources

Information was obtained from the VHA electronic information systems. The Population Information System (SIP) provides information on the population under VHA coverage and registers certain demographic characteristics, including the geographical location and contextual situation of each person and dates and causes of VHA discharge, including death. The

Minimum Basic Dataset (MBDS) at hospital discharge is a synopsis of clinical and administrative information on all hospital discharges, including diagnoses and procedures (ICD codes). The electronic medical record for ambulatory care (EMR), available in all primary healthcare centers and walk-in facilities, has information about diagnoses, personal, and family medical history, laboratory results and lifestyle as well as information about both physician prescriptions and dispensations from pharmacy claims. Pharmaceutical prescription and dispensation data, including concomitant medication, is highly reliable as it used for reimbursement purposes. INR information in the EMR is retrieved from HA-based INR records registered by hematologists and primary care doctors who manage oral anticoagulation in each HA. All the information in these systems is linked at an individual level through a unique identifier.

Outcome measures

Main outcome measures were the Time in Therapeutic Range (TTR) using the Rosendaal linear interpolation method and the percentage of INR determinations in range (PINRR). We calculated TTR and PINRR using all INR determinations available throughout the whole year 2015. We also calculated the percentage of switching from acenocoumarol to direct oral anticoagulants (NOACs: apixaban, dabigatran or rivaroxaban) in 2016.

Covariates

Variables potentially related to the risk of atrial fibrillation and to the use of oral anticoagulants in the study population over the study period were considered. These included socio-demographic characteristics, comorbidities and healthcare resource utilisation in the preceding 12 months. Based on comorbidity information, we calculated and added relevant patient-level risk predictor scores—CHADS2, CHA2DS2-VASC, and HAS-BLED scores– to the dataset.

Analysis

First, we described patient characteristics. Second, we assessed the quality of INR control by calculating TTR (time in therapeutic range) using Rosendaal and PINRR, and we obtained the

percentage of patients with poor control, using two updated and relevant definitions of poor control: the commonly used threshold of TTR<65% (and recommended by the UK's NICE) and the threshold proposed by the ESC of TTR<70%. Third, to identify factors associated with poor INR control we used multivariable regression analysis. Fourth, we described the patterns of switching from acenocoumarol to NOAC in the following year, 2016. Fifth, we again used logistic regression analysis, including a dichotomous variable of INR control, to identify factors associated with switching to NOAC (estimates were calculated using the Rosendaal method and the NICE threshold). We used stepwise regression models with entry and exit significance levels of 0.05 and 0.1, respectively. We carried out additional sensitivity analyses with regard to acceptable INR ranges of [1.8-3.2] instead of [2-3], as some studies employ this measure justified the potential margin of error of the coagulometer and real-world reluctance to modify treatment in face of slight INR deviations [24,31,32] (± 0.2). C-Statistics was used to assess model discrimination and Hosmer-Lemeshow test for calibration. Finally, we compared our selected population to the whole number of AF patients treated with acenocoumarol in the region in 2015 to check for the generalizability of our results. All calculations and statistical analyses were conducted using STATA 14® (StataCorp, College Station, TX).

Ethics

The study protocol was approved by the regional Ethics Committee for Clinical Research of the General Directorate of Public Health and the Centre for Public Health Research. Informed patient consent was waived because, according to European rules and the Spanish laws on data privacy, the Valencia Government Health Department transferred to researchers only non-identifiable data.

Results

Patient characteristics

A total of 22,629 AF patients treated with acenocoumarol with at least 4 INR determinations in the year 2015 and meeting inclusion and exclusion criteria were included in the study (Figure 1). Mean age was 77 years old, 50.4% were women, 81.5% had hypertension, 14.8% had had a previous stroke or TIA and 45.2% were long-term acenocoumarol users (patients using acenocoumarol for more than 6 years). Mean number of INR determinations during 2015 was 14 (median: 13; p25: 10; p75: 17), and 95.3% of patients had a CHA2DS2-VASC score ≥2 and 87.1% a HAS-BLED score ≥3.

Figure 1. Flowchart

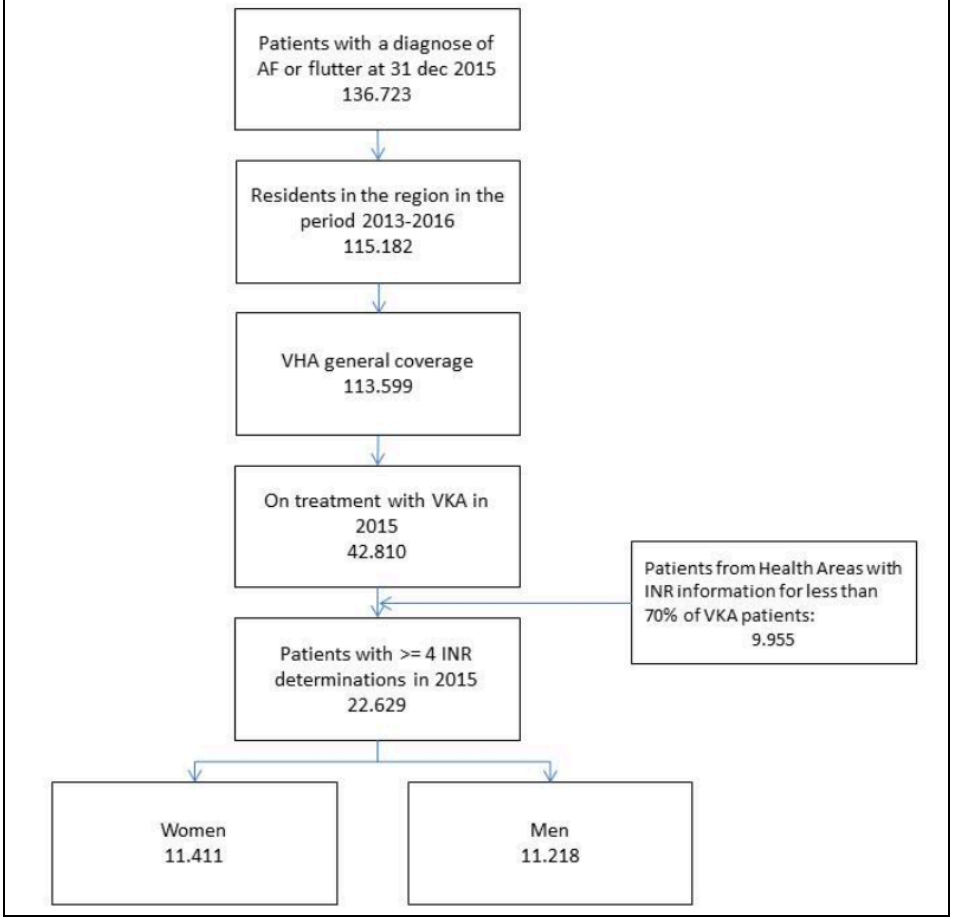


Table 1. Patient characteristics, by sex and for the whole cohort				
	Total	**Female**	**Male**	**p-value**
N	22,629	11,411 (50.43%)	11,218 (49.57%)	
Age				<0.001
< 65	2,132 (9.42%)	799 (7.00%)	1,333 (11.88%)	
65 – 74	5,589 (24.70%)	2,421 (21.22%)	3,168 (28.24%)	
≥75	14,908 (65.88%)	8,191 (71.78%)	6,717 (59.88%)	
Country				<0.001
ESP	21,163 (93.52%)	10,766 (94.35%)	10,397 (92.68%)	
EUR	686 (3.03%)	260 (2.28%)	426 (3.80%)	
NON-EUR	272 (1.20%)	136 (1.19%)	136 (1.21%)	
DES	508 (2.24%)	249 (2.18%)	259 (2.31%)	
Income				<0.001
0 – 18.000	19,181 (84.76%)	10,182 (89.23%)	8,999 (80.22%)	
> 18.000	3,448 (15.24%)	1,229 (10.77%)	2,219 (19.78%)	
Risk of social exclusion	1,035 (4.57%)	724 (6.34%)	311 (2.77%)	<0.001
Diagnosis				*<0.001*
Atrial fibrillation	21,624 (95.56%)	11,030 (96.66%)	10,594 (94.44%)	
Flutter	1,005 (4.44%)	381 (3.34%)	624 (5.56%)	
Time since Therapy Initiation				0.703
1 – 3 Years	5,411 (23.91%)	2,739 (24.00%)	2,672 (23.82%)	
3 – 6 Years	6,611 (29.21%)	3,305 (28.96%)	3,306 (29.47%)	
> 6 Years	10,607 (46.87%)	5,367 (47.03%)	5,240 (46.71%)	
Comorbidities				
Congestive heart failure	4,759 (21.03%)	2,693 (23.60%)	2,066 (18.42%)	<0.001
Hypertension	18,817 (83.15%)	9,677 (84.80%)	9,140 (81.48%)	<0.001
Diabetes	8,905 (39.35%)	4,342 (38.05%)	4,563 (40.68%)	<0.001
Liver disease	2,095 (9.26%)	1,017 (8.91%)	1,078 (9.61%)	0.070
Renal disease	3,684 (16.28%)	1,879 (16.47%)	1,805 (16.09%)	0.443
Previous ischemic stroke or TIA	3,241 (14.32%)	1,664 (14.58%)	1,577 (14.06%)	0.260
Thromboembolism	1,609 (7.11%)	974 (8.54%)	635 (5.66%)	<0.001
Hemorrhagic stroke	160 (0.71%)	77 (0.67%)	83 (0.74%)	0.559
Gastrointestinal bleeding	1,644 (7.27%)	767 (6.72%)	877 (7.82%)	0.001
Other bleeding	7,596 (33.57%)	4,009 (35.13%)	3,587 (31.98%)	<0.001
Vascular disease	4,191 (18.52%)	1,636 (14.34%)	2,555 (22.78%)	<0.001
Dementia	1,916 (8.47%)	1,156 (10.13%)	760 (6.77%)	<0.001
Depression	3,403 (15.04%)	2,460 (21.56%)	943 (8.41%)	<0.001
Cancer	3,878 (17.14%)	1,570 (13.76%)	2,308 (20.57%)	<0.001
Alcohol	189 (0.84%)	12 (0.11%)	177 (1.58%)	<0.001
Healthcare utilisation (mean, SD)				
Hospitalizations	0.54 (1.16)	0.50 (1.14)	0.56 (1.18)	<0.001
ED visits	1.00 (2.00)	1.06 (2.08)	0.94 (1.91)	<0.001
Outpatients visits	12.13 (7.66)	12.84 (7.86)	11.40 (7.38)	<0.001
Specialist visits	3.22 (4.64)	3.09 (4.57)	3.34 (4.71)	<0.001
Cardiology visits	0.83 (1.18)	0.79 (1.13)	0.88 (1.23)	<0.001
Neurologic visits	0.17 (0.60)	0.17 (0.60)	0.16 (0.59)	0.367
Mental Health visits	0.11 (0.89)	0.14 (0.93)	0.08 (0.86)	<0.001
Social care visits	0.11 (0.74)	0.12 (0.80)	0.09 (0.67)	0.004
Medication use				
NSAID	2,328 (10.29%)	1,202 (10.53%)	1,126 (10.04%)	0.219
Antiplatelet	1,903 (8.41%)	593 (5.20%)	1,310 (11.68%)	<0.001
Scores				
CHADS2 score ≥2	17,495 (77.31%)	9,155 (80.23%)	8,340 (74.34%)	<0.001
CHA2DS2-VASC score ≥ 2	21,567 (95.31%)	11,231 (98.42%)	10,336 (92.14%)	<0.001
HAS-BLED ≥2	22,238 (98.27%)	11,244 (98.54%)	10,994 (98.00%)	0.002
HAS-BLED ≥3	19,707 (87.09%)	10,170 (89.12%)	9,537 (85.02%)	<0.001

ESP: Spain; EUR: European; NON-EUR: Non-european; DES: Unknown; TIA: transient ischemic attack; ED: emergency department; NSAID: nonsteroidal anti-inflammatory drug.

Women were older (mean age was 78.1 vs 75.6 in men, p<0.001, and 71.8% aged 75 and over vs 59.9% for men), more deprived (89.2% earning less than 18.000 euros/year vs 80.2%; and 6.3% were at risk of social exclusion, compared to 2.8% of men), had more comorbidities such as prior congestive heart failure, hypertension, thromboembolism, dementia or depression, and presented higher stroke and bleeding risks scores. Men had more prior vascular disease and gastrointestinal bleeding (22.8% vs 14.3% in women and 7.8% vs 6.7% in women, respectively), malignancy and alcohol use, and also used more antiplatelet medication (20.7% vs 13.8% in women). No sex differences were found with regard to time in treatment with AVK, renal disease, hemorrhagic stroke or use of NSAIDs (Table 1).

Table 2. Mean TTR, PINRR and % of patients poorly controlled considering NICE (TTR≥65%) and ESC (TTR≥70%) thresholds and different acceptable INR range definitions

	Total	Women	Men	p-value
Mean TTR and PINNR (Mean, SD)				
INR range 2 - 3				
TTR	63.0 (19.75)	62.3 (19.71)	63.7 (19.78)	<0.001
PINRR	59.2 (18.87)	58.3 (18.81)	60.1 (18.89)	<0.001
INR 1.8 - 3.2				
TTR	76.2 (17.94)	75.5 (17.96)	76.8 (17.90)	<0.001
PINRR	72.8 (17.45)	72.0 (17.51)	73.6 (17.34)	<0.001
% patients poorly controlled (INR range 2-3)				
TTR<65%				
TTR	11,579 (51.2%)	6,044 (53%)	5,535 (49.3%)	<0.001
PINRR	14,058 (62.1%)	7,338 (64.3%)	6,720 (59.9%)	<0.001
TTR< 70%				
TTR	13,950 (61.7%)	7,211 (63.2%)	6,739 (60.1%)	<0.001
PINRR	15,950 (70.5%)	8,252 (72.3%)	7,698 (68.6%)	<0.001
% patients poorly controlled (INR range 1.8-3.2)				
TTR< 65%				
TTR	5,096 (22.5%)	2,675 (23.4%)	2,421 (21.6%)	0.001
PINRR	6,928 (30.6%)	3,716 (32.6%)	3,212 (28.6%)	<0.001
TTR< 70%				
TTR	6,965 (30.8%)	3,655 (32.0%)	3,310 (29.5%)	<0.001
PINRR	8,951 (39.6%)	4,736 (41.5%)	4,215 (37.6%)	<0.001

TTR: Time in Therapeutic Range; PINNR: Percentage of INR determinations in Range; INR: International Normalized Ratio; INR: International Normalized Ratio.

Quality of INR control

Mean TTR was 63% (62.3% for women and 63.7% for men, p<0.001), and PINNR was 59.2% (58.3% for women and 60.1% for men, p<0.001). Considering the TTR<65% threshold, 53% of women and 49.3% of men had poor anticoagulation control (p<0.001), rising to 63.2% and 60% respectively (p<0.001), when using the TTR<70% threshold. In sensitivity analysis, when using [1.8-3.2] as acceptable INR ranges and TTR<65% threshold for poor control, TTR rose to 75.5% for women and 76.8% for men (p<0.001), and PINNR was 72% and 73.6% for women and men (p<0.001), respectively; poor control affected from 22.5% to 30.8% of patients, depending on the threshold considered (Table 2).

Tabla 3. Factors associated with poor INR control.

	Odds Ratio	95%CI	p-value
Socio-demographics			
Female	1.13	1.07; 1.20	<0.001
Age 65-75 (ref: age<65)	0.88	0.80; 0.97	0.010
Age 75 and over (ref: age<65)	0.87	0.80; 0.95	0.004
Europe (country) (ref: Spain)	1.23	1.05; 1.44	0.007
Income >18.000e (ref: income ≤18.000)	0.89	0.82; 0.96	0.002
Comorbidities			
Congestive heart failure	1.19	1.12; 1.29	<0.001
Diabetes	1.14	1.08; 1.20	<0.001
Other bleeding	1.08	1.02; 1.14	0.011
Vascular disease	1.08	1.00; 1.16	0.036
Dementia	1.21	1.10; 1.35	<0.001
Depression	1.12	1.03; 1.20	0.005
Alcohol	1.70	1.25; 2.33	0.001
Healthcare utilisation			
Time since Therapy Initiation >6 years	1.05	1.00; 1.11	0.047
ED visits	1.04	1.03; 1.06	<0.001
Outpatient visits	1.01	1.00; 1.01	<0.001
Specialist visits	1.02	1.01; 1.03	<0.001
Cardiology visits	0.96	0.93; 0.99	0.012
Neurologic visits	0.91	0.86; 0.95	<0.001
Social care visits	1.04	1.00; 1.09	0.017
Antiplatelet	1.11	1.00; 1.23	0.045

n=22629; LL: -15461.213; p: <0.001; r^2: 0.014; C Statistic: 0.579; p (X2 Hosmer-Lemeshow): 0.807.Age (<65, 65-75, >75) and Country (Spain, Europe, Non-Europe, Unknown) are categorical variables. Sex, income, comorbidity variables and Time since Therapy Initiation >6 years are dichotomous variables. Visits are quantitative variables (the variable is number of visits), and accordingly the Odds ratios refer to the odds of presenting a poor INR control with every additional visit.

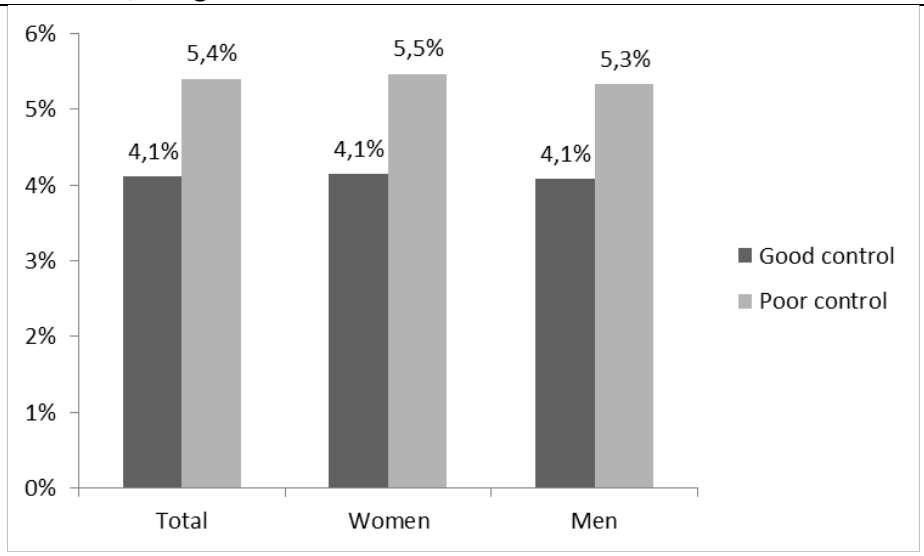
Women, long-term acenocoumarol users, antiplatelet users and “high risk” patients (defined as patients with comorbidities such as heart failure, diabetes, depression, dementia, vascular disease, use of alcohol and ED visits) were more likely to present poor INR control. Higher income, age (being 65 years old and over), and visiting a neurologist or a cardiologist were associated with achieving good INR control (Table 3), but the predictive capacity of the model was low (C Statistics: 0.579).

Switching to NOAC

Using Rosendaal’s TTR and the ≥65% threshold, 5.4% of poorly controlled patients during 2015 (5.5% women; 5.3% men) switched to a NOAC throughout 2016, as did 4.1% of patients with good INR control (similar for women and men), with similar figures when using the ≥70% threshold. From total switchers, and when considering the TTR≥65% threshold, 54.2% of poorly controlled and 51.1% of adequately controlled switched to apixaban in 2016, 25.4% and 26.4% to rivaroxaban, and 20.3% and 22.5% to dabigatran. No differences in terms of switching between women and men were found. Adequate INR control, presence of renal disease, and long-term use of acenocoumarol were associated with less likelihood of switching. Being non-European, having a higher income, more cardiology and primary care visits, and presence of vascular disease were positively associated with switching (Figure 2, Table 4). Predictive capacity of the model was also low (C-Statistics= 0.584).

Figure 2a. Percentage of switching to NOAC in 2016 by sex and quality of INR control, using Rosendaal's TTR and TTR≥65% threshold

Figure 2b. Percentage of switching to the different NOACS in 2016 by sex and quality of INR control, using Rosendaal's TTR and TTR≥65% threshold



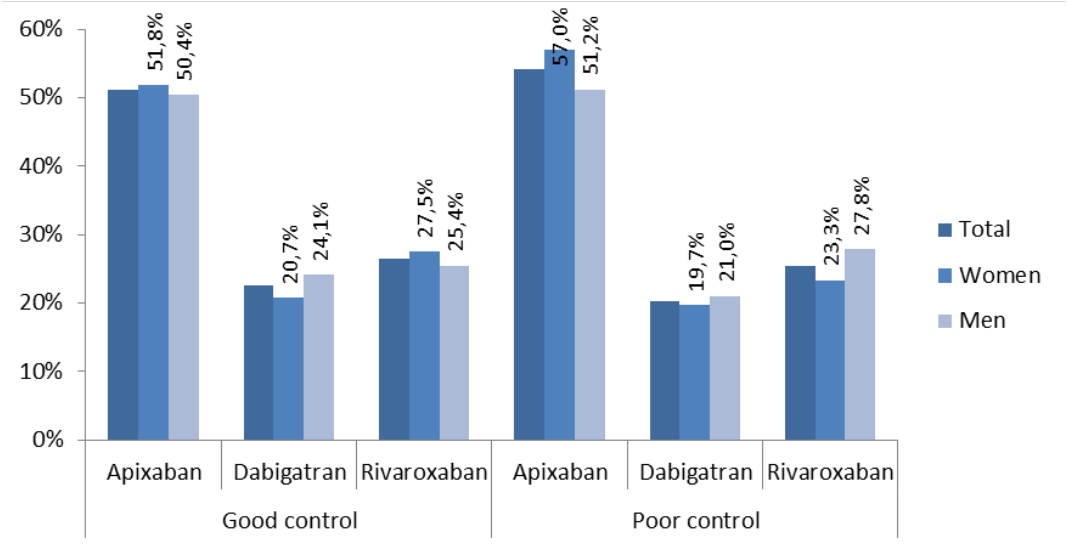


Table 4. Factors associated with switching to NOAC.			
	Odds Ratio	95%CI	p-value
Socio-demographics			
Non-Europe (country) (ref: Spain)	1,70	1.08;2.67	0.021
Income >18.000e (ref: income ≤18.000)	1,27	1.08;1.49	0.003
Adequate INR control	0.76	0.67;0.86	0.001
Comorbidities			
Renal disease	0.69	0.57; 0.83	0.001
Vascular disease	1.34	1.15;1.55	0.001
Healthcare utilisation			
Primary Care visits	1.01	1.00; 1.02	0.037
Cardiology visits	1.06	1.01; 1.11	0.018
Time since Therapy initiation>6 years	0.79	0.70; 0.89	0.001
n=22629; LL: -4282.49; p: <0.0001; r2: 0.012; C Statistic: 0.59; p (X2 Hosmer Lemeshow): 0.573. Adequate INR control: TTR≥65% (ref: TTR<65%). Country (Spain, Europe, Non-Europe, Unknown) is a categorical variable. Income, comorbidity variables and Time since Therapy Initiation >6 years are dichotomous variables. Visits are quantitative variables (the variable is number of visits), and accordingly the Odds ratios refer to the odds of presenting a poor INR control with every additional visit.			

Discussion

In this real-world, population-based study, we show that the quality of INR control in AF patients treated with VKA in 2015 in the region of Valencia is suboptimal, and that women are at a higher risk of uncontrolled INR. Depending on the definition used for acceptable INR ranges and TTR threshold, a quarter to two-thirds of patients had inadequate INR control during 2015. We also found that switching to NOAC in the following year was as low as 5.4% for patients with inadequate control and 4.1% for patients with adequate INR control. Importantly, women had a worse mean TTR, PINRR and poorer INR control than men, irrespective of definitions. In fact, being a woman, using VKA for more than 6 years and being at high risk were factors associated with poor INR control, while wealthier, older patients and those visiting a cardiologist or neurologist were more prone to good INR control. These figures are especially noticeable as VKA involve around two thirds of OAC treatments for AF patients and around 50% of new treatments [(9)].

Figures on poor INR controlled patients switching to NOAC seem to be low, especially when poor INR control is established by national guidelines as a principal driver to switching to NOAC therapy. This may be revealing a problem of clinical inertia, but this finding should be interpreted with caution, as our design excludes patients who had switched to NOAC before 2016. This would also come to explain the finding that long-term use of VKA is associated with less likelihood of switching (as we are analyzing patients that somehow may be resistant to switching). No sex differences were found with regard to switching. Considering that women have worse INR control, a relative worst care and a stronger clinical inertia for women versus men could be inferred.

The proportion of patients with poor INR control change depending on the threshold for good INR control used. The threshold suggested by the ESC is more restrictive than the NICE threshold, which is in fact the one considered by the Spanish national rules. Roughly 10% of patients comprise between 65% and 70% of TTR, so in a context where NOACs are placed as second-line therapies and where poor INR control is a major reason for switching to NOAC [8], the decision to adopt one or another threshold could theoretically have a significant impact on practice. However, in the light of our results with regard to switching and additional past findings about initiation with NOAC [9], factors other than TTR thresholds seem to be driving NOAC prescription.

Sensitivity analyses with regard acceptable INR ranges result in significant variations in our estimates of the quality of INR control. The rationale used by other authors to employ INR ranges of [1,8-3,2] to estimate TTR is to account for potential coagulometer error and to avoid problems inherent to overcorrection [24,31,32]. However, these arguments are debatable, and the widely accepted and evidence-based INR range of [2-3] [33-40], which in fact is a simplification of the original threshold of [1,45-2,8] on which current anticoagulation clinical guidelines are still based [41-43], seems more appropriate for the purposes of assessment and comparison.

To the best of our knowledge, this is the first real-world data study that quantifies the differences in the quality of anticoagulation between women and men. Studies in experimental settings, registries or based on small populations (44-47) have also shown sex differences with female patients being more vulnerable overall than male patients, being older and more deprived, and results in terms of TTR and percentage of patients with good TTR being worse in every scenario. This calls for a redefinition of strategies for improving the management of VKA patients, where the gender gradient should be explicitly addressed at every stage as an essential driver for action. We further identified factors associated with INR control and switching. This information may be valuable to identify priority interventions for most vulnerable patients, and also to tackle the issue of therapeutic inertia in the case of inadequately controlled VKA patients. Finally, we confirm that our results in real-life patients from a Southern European region are similar to those of other real-world patients from very distinct settings, registry-based studies or clinical trials, and that operational definitions such as acceptable INR ranges or thresholds of good INR control may have a significant impact on the direction of results.

Limitations

Our study is subject to some limitations. First, we included patients with at least 4 INR informed determinations in 2015. This excluded from analysis 47% of the total number patients treated with VKA in the region this year, raising a potential concern about the representativeness of our sample. However, we compared both populations (total VKA patients versus patients analyzed) and we found barely any differences (see Figure 1 and Supplementary File 1).

Second, our study is cross-sectional in design. This allows for an accurate description of the "state of the art" of the quality of INR control in all patients treated with VKA in one moment of time (December 2015), but the interpretation of some of our results, especially with regard to patterns of switching, should be interpreted with caution. Our population may be somehow "resistant" to switching because include long-term users that remain under treatment after

many years (and sometimes irrespective of their INR control). This may be lying behind the association identified between long-term use of VKA and poor INR control and less likelihood of switching [48], and also would explain the counterintuitive association of long-term VKA use with poor INR control. This would also explain, to some extent at least, the low rates of switching to NOAC observed in patients with uncontrolled INR. However, this information is still valuable because studies on INR control (commonly based on naïve users, as longitudinal follow-up of new users is a better design for inferring associations between exposure and outcomes) do not offer a view of the management of all the VKA patients in a moment of time, which is our goal in this study, and also because we bring the first population-based piece of evidence with regard to switching from VKA to NOAC in Spain. In a forthcoming study, we will evaluate a cohort of new VKA users and we will re-analyze the quality of INR control and switching, and we will check for consistency of our present estimates.

Third, despite including many relevant individual variables in our analysis, we cannot rule out the existence of omitted relative access to INR control facilities, or regarding the presence of a contraindication to NOAC, as these data are not routinely recorded in linkable clinical databases. These factors could be affecting some of our estimates, and further research should examine their influence on the quality of care, though their absence does not affect the relevance of our results. Fourth, information biases due to absent registration or differing data recording practices in the electronic databases might exist, although this is an inherent problem of any study using data from routine clinical practice. Moreover, misclassification (on exposure and covariates) is expected to be non-differential across groups of study subjects.

Fifth, although relevant predictors of poor INR control and clinical inertia have been identified, the discriminatory capacity of the regression model is low in both, suggesting that other non-identified factors are driving these phenomena. Sixth, we did not assess clinical outcomes, typically the occurrence of ischemic stroke, intracranial bleeding and other bleedings (including

gastrointestinal bleedings) related to the quality of INR control, and we could now answer the question of to what extent differences in INR control among women and men translate into worse outcomes. We will perform this analysis in a cohort of new VKA users as this design is more suitable for inferring causal relationships between treatment and outcomes.

Conclusion

This is the first study in our context to assess the quality of oral anticoagulation with VKA and switching to NOAC in AF patients on a population-basis using real-world data. The quality of INR control of all AF patients treated with VKA for stroke prevention in 2015 in our region was suboptimal, and women were at a higher risk of poor INR control. This reflects sex disparities in care, and programs for improving the quality of oral anticoagulation should incorporate the gender perspective at every step. In this sense, the approach used in our study with data from routine care could be incorporated into the EMR to improve patient follow-up. Observed low rates of switching in poor controlled patients is worrying, suggesting strong clinical inertia. Further studies should confirm our results, especially with regard to switching in new VKA users, and evaluate clinical outcomes associated with keeping patients with poor INR control on acenocoumarol.

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Supporting Information

S1 Table. Comparison of our population for analysis (VKA patients with at least 4 INR determinations in 2015) versus the whole population of VKA treated patients in 2015.

	Total	Analysis population	VKA patients in 2015	p
N		22,629	42,810	
Female	32,765 (50.07%)	11,411 (50.43%)	21,354 (49.88%)	0.184
Age				0.128
< 65	6,336 (9.68%)	2,132 (9.42%)	4,204 (9.82%)	
65 – 74	16,294 (24.90%)	5,589 (24.70%)	10,705 (25.01%)	
>75	42,809 (65.42%)	14,908 (65.88%)	27,901 (65.17%)	
Country				0.000
ESP	61,216 (93.55%)	21,163 (93.52%)	40,053 (93.56%)	
EUR	2,209 (3.38%)	686 (3.03%)	1,523 (3.56%)	
OTR	734 (1.12%)	272 (1.20%)	462 (1.08%)	
DES	1,280 (1.96%)	508 (2.24%)	772 (1.80%)	
Income				0.016
0 – 18.000	55,769 (85.22%)	19,181 (84.76%)	36,588 (85.47%)	
> 18.000	9,670 (14.78%)	3,448 (15.24%)	6,222 (14.53%)	
Risk of social exclusion	3,123 (4.77%)	1,035 (4.57%)	2,088 (4.88%)	0.083
Diagnosis				0.016
Atrial fibrillation	62,702 (95.82%)	21,624 (95.56%)	41,078 (95.95%)	
Flutter	2,737 (4.18%)	1,005 (4.44%)	1,732 (4.05%)	
Time since Therapy Initiation				0.627
1 – 3 Years	15,596 (23.83%)	5,411 (23.91%)	10,185 (23.79%)	
3 – 6 Years	19,003 (29.04%)	6,611 (29.21%)	12,392 (28.95%)	
> 6 Years	30,840 (47.13%)	10,607 (46.87%)	20,233 (47.26%)	
Comorbidities				
Congestive heart failure	13,673 (20.89%)	4,759 (21.03%)	8,914 (20.82%)	0.533
Hypertension	54,370 (83.09%)	18,817 (83.15%)	35,553 (83.05%)	0.731
Diabetes	25,662 (39.22%)	8,905 (39.35%)	16,757 (39.14%)	0.602
Liver disease	5,890 (9.00%)	2,095 (9.26%)	3,795 (8.86%)	0.095
Renal disease	10,558 (16.13%)	3,684 (16.28%)	6,874 (16.06%)	0.461
Previous ischemic stroke or TIA	9,358 (14.30%)	3,241 (14.32%)	6,117 (14.29%)	0.907
Thromboembolism	4,577 (6.99%)	1,609 (7.11%)	2,968 (6.93%)	0.397
Hemorrhagic stroke	446 (0.68%)	160 (0.71%)	286 (0.67%)	0.564
Gastrointestinal bleeding	4,659 (7.12%)	1,644 (7.27%)	3,015 (7.04%)	0.293
Other bleeding	21,738 (33.22%)	7,596 (33.57%)	14,142 (33.03%)	0.168
Vascular disease	12,176 (18.61%)	4,191 (18.52%)	7,985 (18.65%)	0.681
Dementia	5,547 (8.48%)	1,916 (8.47%)	3,631 (8.48%)	0.949
Depression	9,808 (14.99%)	3,403 (15.04%)	6,405 (14.96%)	0.794
Cancer	11,051 (16.89%)	3,878 (17.14%)	7,173 (16.76%)	0.215
Alcohol	590 (0.90%)	189 (0.84%)	401 (0.94%)	0.191
Healthcare utilization				
Hospitalizations	0.54 (1.18)	0.54 (1.16)	0.55 (1.19)	0.108
ED visits	1.03 (2.01)	1.00 (2.00)	1.04 (2.01)	0.021
Outpatients visits	11.89 (7.65)	12.13 (7.66)	11.76 (7.64)	0.000
Specialist visits	3.36 (4.84)	3.22 (4.64)	3.44 (4.95)	0.000
Cardiology visits	0.84 (1.20)	0.83 (1.18)	0.84 (1.21)	0.323
Neurologic visits	0.17 (0.61)	0.17 (0.60)	0.17 (0.61)	0.297
Mental Health visits	0.11 (0.86)	0.11 (0.89)	0.10 (0.84)	0.531
Social care visits	0.10 (0.74)	0.11 (0.74)	0.10 (0.74)	0.920

Medication use				
NSAID	6,598 (10.08%)	2,328 (10.29%)	4,270 (9.97%)	0.205
Antiplatelet	5,651 (8.64%)	1,903 (8.41%)	3,748 (8.75%)	0.135
Scores				
CHADS2 score >= 2	50,418 (77.05%)	17,495 (77.31%)	32,923 (76.90%)	0.239
CHA2DS2-VASC score >= 2	62,257 (95.14%)	21,567 (95.31%)	40,690 (95.05%)	0.143
HAS BLED >=2	64,259 (98.20%)	22,238 (98.27%)	42,021 (98.16%)	0.292
HAS BLED >=3	56,856 (86.88%)	19,707 (87.09%)	37,149 (86.78%)	0.262

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Group-based Trajectory Models to Assess Quality of INR Control and its Association with Clinical Outcomes.

INR control and outcomes using GBTM

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Abstract

Background The Time in Therapeutic Range (TTR) is the gold-standard measure used to assess the quality of oral anticoagulation with vitamin K antagonists (VKA). However, TTR is a static measure and International Normalized Ratio (INR) control is a dynamic process. Group Based Trajectory Models (GBTM) can address this dynamic nature by classifying patients into different trajectories of INR control over time.

Objectives To assess the quality of INR control in a population-based cohort of new users of VKA with a diagnosis of atrial fibrillation using GBTM.

Methods We classified patients into different trajectories according to their propensity for being adequately anticoagulated over their first year of treatment using GBTM, and we evaluated the association between trajectories and relevant clinical outcomes over the following year.

Results We included 8,024 patients in the cohort who fulfilled the inclusion criteria; mean number of INR determinations over the first year of treatment was 13.9. We identified four differential trajectories of INR control: Optimal (9.7% of patients, TTR: 83.8%), Improving (27.4% of patients, TTR: 61.2%), Worsening (28%; TTR: 69.1%) and Poor control (34.9%; TTR: 41.5%). In adjusted analysis, Poor and Worsening control patients had a higher risk of death than Optimal control patients (HR: 1.79, IC95%:1.36-2.36 and HR: 1.36, IC95%:1.02-1.81, respectively). Differences in other outcomes did not achieve statistical significance except for a reduced risk of TIA in the Improving Control group.

Conclusions GBTM may contribute to a better understanding and assessment of the quality of oral anticoagulation and may be used in addition to traditional, well-established measures such as TTR.

Introduction

Vitamin K antagonists (VKAs) such as warfarin or acenocoumarol, widely used in countries such as the Netherlands and Spain, among others, has been shown in clinical trials to reduce the risk of a stroke by two thirds [1], and for decades has been the gold standard for stroke prevention in patients with atrial fibrillation (AF)[2]. Nowadays, although new non-VKA oral anticoagulants (NOAC) are available, VKAs remain a viable oral anticoagulant for many patients because of their availability and cost [3]. However, the effectiveness and safety of VKAs in routine clinical practice are closely associated with the quality of anticoagulation control. Use of VKAs can be challenging due to their narrow therapeutic range, the need for periodic INR monitoring, high inter-patient variability in treatment response, numerous drug and food interactions and medication non-adherence [4]. Evidence worldwide shows that a large proportion of VKA treated patients, ranging from one third to three quarters, do not achieve adequate INR control and are thus at an increased risk of stroke or bleeding [5-9].

The therapeutic range for VKA therapy is defined in terms of the International Normalized Ratio (INR). In atrial fibrillation patients, a tight INR range between 2 and 3 is widely taken as providing an adequate anticoagulation control. The Time in Therapeutic Range (TTR) is the gold standard metric used in the literature to measure the quality of INR control. TTR estimates the percentage of time a patient's INR is within the desired treatment range or goal and is widely used as an indicator of anticoagulation control. TTR is commonly used to evaluate the quality of VKA therapy and is an important tool for the risk-benefit assessment of the therapy [10]. However, while TTR is a static measure, INR control is a dynamic process, where obtaining consistent INR levels in range over time maximizes the desired benefits and safety of VKA [11]. In this way, two patients with a similar TTR in a given period of time could in fact behave very differently throughout that period.

Group-based Trajectory Models (GBTM) [12], a type of latent class analysis, can be used as an alternative or complementary method to traditional measures for summarizing INR control. GBTM can address the dynamic nature of the process of maintaining an adequate control of anticoagulation by providing a classification of patients into different trajectories of INR control over time, described through graphics with high face validity. GBTM have become now widely used in healthcare research such as in the study of medication adherence [13] or control of cardiovascular risk factors[14] but to the best of our knowledge this approach has never been used to characterize the quality of oral anticoagulation over time.

We aimed to assess the quality of INR control in a population-based cohort of new users of VKA with a diagnosis of atrial fibrillation, by using GBTM to classify the patients into different trajectories according to their propensity for being adequately anticoagulated over their first year of treatment. We further examined the association between the trajectories of INR control identified and the occurrence of relevant clinical outcomes over the following year.

Methods

Design and setting

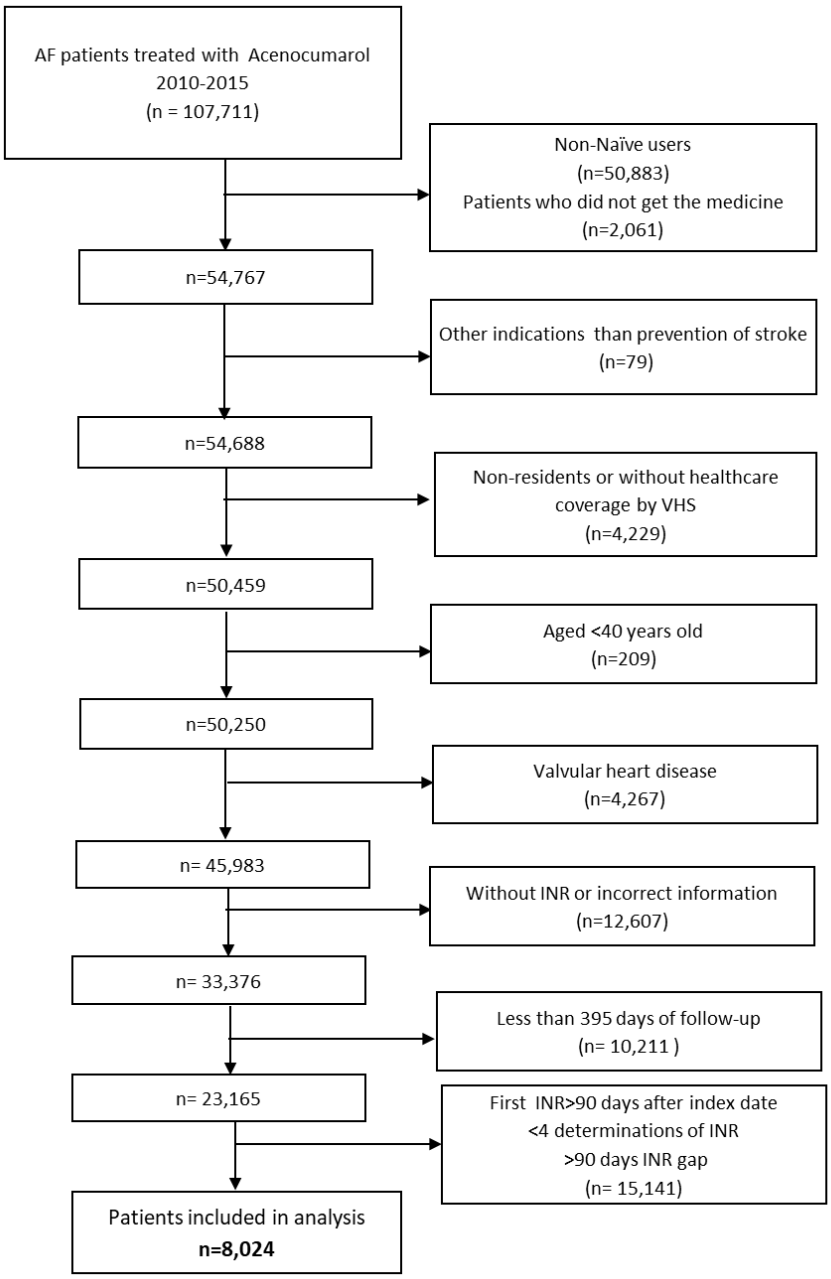
This real-world, population-based cohort study was conducted in the Valencia Health System (VHS), the public health system for the region of Valencia in Spain, covering about 97% of the region's population of 5 million inhabitants. We selected all patients diagnosed AF or atrial flutter [diagnosis code of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9CM) 427.31 and 427.32] initiating treatment with acenocoumarol in the period 2010-2015 and remaining under treatment for the whole year following the initiation of treatment (in fact, we required 13 months of follow-up, as we censored the first month after the initiation of therapy as this is considered a period of dose adjustment [14] for calculations). We

did not include a small fraction of patients, mainly foreigners, treated with other VKA such as warfarin, phenprocoumon or fluindione due to limitations of follow-up for non-residents.

We defined new users of acenocoumarol as those patients with no prescription of any oral anticoagulant the year before the first prescription (index date) in the period of inclusion. We defined patients under treatment for the whole of the first year by selecting patients: 1) that remained alive throughout the year, 2) with at least 4 determinations of INR between months 2 and 13 after the index date (with fewer than 90 days between the index date and the first INR determination available), and 3) with gaps between determinations of less than 90 days between months 2 and 13 (or between the last INR determination available and the end of the assessment period).

We excluded from the cohort: 1) non-naïve users (patients with a prescription of VKA in the year before the index date), 2) patients who did not refill their first prescription (primary non-adherent), 3) patients treated for other conditions other than stroke prevention in AF, 4) patients younger than 40 years old, 5) patients with valvular heart disease, 6) patients without INR or incorrect INR information and 7) patients with less than 395 days of follow-up. Due to limitations on follow-up, we further excluded: 8) people without health coverage by the VHS, mainly some government employees whose prescriptions are reimbursed by civil service insurers and are thus not included in the pharmacy databases of the VHS, 9) patients not registered in the census (non-residents or temporary residents), and 10) those who left the region or were disenrolled from VHS coverage for other causes (see Figure 1.). Justification for inclusion and exclusion criteria is reported in Supplementary Material Table S1.

Figure 1. Flowchart



Data sources

Information was obtained from the VHS electronic information systems. The Population Information System (SIP) provides information on the population under VHS coverage and registers certain demographic characteristics, including the geographical location and

contextual situation of each person and the dates and causes of VHS discharge, including death. The Minimum Basic Dataset (MBDS) at hospital discharge is a synopsis of clinical and administrative information on all hospital discharges, including diagnoses and procedures. The electronic medical record for ambulatory care (EMR), available in all primary healthcare and speciality centers, has information about diagnoses, personal and family medical history, laboratory results and lifestyle as well as information about both physician prescriptions and dispensations from pharmacy claims. All the information in these systems is linked at an individual level through a unique identifier.

Outcome measures

We used two measures of quality of INR control: a) the trajectories grouping patients according to their probability of being adequately anticoagulated (i.e. presenting biweekly INR values of between 2 and 3) over the first year of VKA treatment, using GBTM, and b) TTR (mean value and percentage of patients with TTR>=65%) for each trajectory. We calculated TTR using Rosendaal's linear interpolation method[15] .

The pre-specified clinical outcomes were: mortality, hospitalization for ischaemic stroke, for transient ischemic attack (TIA), for gastrointestinal bleeding, for major gastrointestinal bleeding (defined as a GI bleeding hospitalization needing a blood or blood components transfusion) and for intracranial haemorrhage. Only principal discharge diagnoses based on ICD9CM (see Supplementary Material S2) were used to define endpoints. Additionally, composite outcomes of effectiveness (ischaemic stroke or TIA) and safety (major bleeding-major GI bleeding or intracranial haemorrhage) were also analysed. All outcomes were analysed separately and only the first event was considered for analysis. Patients were followed up from month 14 after their first prescription and up to the relevant event, health system disenrollment, death, or end of follow-up (month 25), whichever came first.

Covariates

Variables potentially related to the risk of stroke and bleeding were considered. These included socio-demographic characteristics, comorbidities and healthcare resource utilisation in the preceding 12 months.

Analysis

First, we used GBTM to identify trajectories of the likelihood of being correctly anticoagulated (i.e. presenting an INR of between 2 and 3) over time. We created a biweekly series of INR values for each patient. We assigned to each fortnightly INR value the value of the closer INR determination available. GBTM was modeled with linear polynomial functions of time. Model selection was based on higher Bayesian information criterion (BIC), moderated by a preference for a useful parsimonious model which fitted the data well, the correspondence between each group's estimated probability and the proportion of study members classified to that group according to the maximum posterior probability rule, an average posterior probability value of <0.7 for each group, the odds of correct classification based on the posterior probabilities of group membership >5 for each group, and a minimum group size in the range of 10% of the study population to facilitate the analysis of association of group membership with outcomes. Second, we described patient characteristics. Third, we jointly estimated with the trajectories themselves the relationship of individual-level characteristics to trajectory group membership[16]. Fourth, we calculated the TTR using Rosendaal's method, and calculated mean TTR and the percentage of patients with TTR>=65% for each trajectory. Additionally, we constructed TTR density plots for each trajectory, highlighting the TTR: 65% reference which is commonly used as a threshold for adequate INR control [17]. Fifth, we used Cox proportional hazard models (crude and adjusted for sociodemographic, clinical and healthcare utilization information) to evaluate the occurrence of effectiveness and safety outcomes associated with each trajectory. All analyses were performed using Stata v14.

Results

Characteristics of the cohort and trajectories of INR control

We included 8,024 patients in the cohort who fulfilled the inclusion criteria. The mean age was 75 years old and 50.3% were women. The most frequent comorbidities were hypertension (79.2%), and diabetes (34.2%) and 36.2% of patients used acetylsalicylic acid concomitantly (Table 1). The mean number of INR determinations over the first year of treatment was 13.9.

Table 1. Patient characteristics, for the total cohort and for each trajectory of INR control.

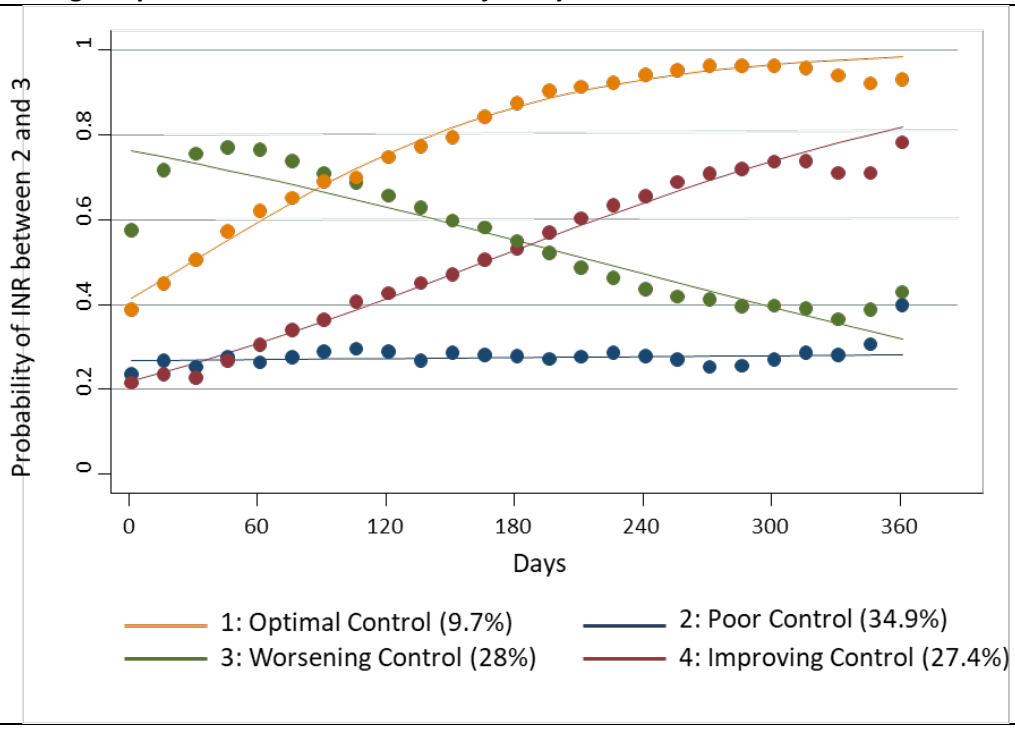
	Total		Optimal		Poor		Worsening		Improving	
N	8,024		780	(9.7%)	2,799	(34.9%)	2,249	(28.0%)	2196	(27.4%)
Sociodemographics										
Female	4,034	(50.3%)	384	(49.2)	1,465	(52.3)	1,063	(47.3)	1,122	(51.1)
Age (Mean, SD %)	74.89	(9.01)	73.8	(9.5)	74.9	(9.2)	75.1	(8.9)	75,0	(8,6)
<65	1,065	(13.3%)	125	(16.0)	395	(14.1)	284	(12.6)	261	(11.9)
65-74	2,271	(28.3%)	250	(32.1)	718	(25.7)	663	(29.5)	640	(29.1)
>75	4,688	(58.4%)	405	(51.9)	1,686	(60.2)	1,302	(57.9)	1,295	(59.0)
Country										
Spain	7,497	(93.4%)	737	(94.5)	2,565	(91.6)	2,118	(94.2)	2,077	(94.6)
Europe (other tan Spain)	264	(3.3%)	20	(2.4)	116	(4.1)	63	(2.8)	65	(2.7)
Other	263	(3.3%)	23	(2.9)	118	(4.2)	68	(3.0)	54	(2.4)
Income										
0-18.000	4,899	(61.0%)	515	(66.0)	1,606	(57.4)	1,450	(64.5)	1,328	(60.5)
>18.000	3,125	(39.0%)	265	(34.0)	1,193	(42.6)	799	(35.5)	868	(39.5)
Diagnosis										
Atrial Fibrilation	7,595	(94.7%)	739	(94.7)	2,659	(95.0)	2,127	(94.6)	2,070	(94.3)
Atrial Flutter	429	(5.3%)	41	(5.3)	140	(5.0)	122	(5.4)	126	(5.7)
Comorbidities										
Congestive heart failure	1,322	(16.5%)	85	(10.9)	577	(20.61)	344	(15.30)	316	(14.39)
Hypertension	6,353	(79.2%)	594	(76.1)	2,250	(80.4)	1,781	(79.2)	1,728	(78.7)
Diabetes	2,746	(34.2%)	249	(31.9)	1,045	(37.3)	707	(31.4)	745	(33.9)
Liver disease	499	(6.2%)	64	(8.2)	181	(6.5)	131	(5.8)	123	(5.6)
Renal disease	893	(11.1%)	60	(7.7)	381	(13.6)	229	(10.2)	223	(10.1)
Previous ischemic stroke or TIA	1,115	(13.9%)	111	(14.2)	416	(14.86)	302	(13.4)	286	(13.0)
Thromboembolism	540	(6.7%)	49	(6.3)	230	(8.2)	130	(5.8)	131	(6.0)
Haemorrhagic stroke	50	(0.6%)	6	(0.8)	15	(0.5)	14	(0.6)	15	(0.7)
Gastrointestinal bleeding	281	(3.5%)	30	(3.8)	115	(4.1)	82	(3.6)	54	(2.5)

Other bleeding	1,609	(20.1%)	118	(15.1)	631	(22.5)	443	(19.7)	417	(19.0)
Vascular disease	1,193	(14.9%)	90	(11.5)	473	(16.9)	321	(14.3)	309	(14.1)
Dementia	415	(5.2%)	28	(3.6)	167	(6.0)	96	(4.3)	124	(5.6)
Depression	1,009	(12.6%)	77	(9.9)	392	(14.0)	284	(12.6)	256	(11.7)
Cancer	969	(12.1%)	96	(12.3)	348	(12.4)	257	(11.4)	268	(12.2)
Alcohol	138	(1.7%)	10	(1.3)	62	(2.2)	34	(1.5)	32	(1.4)
Events during the first year of treatment (13 months)										
Ischaemic stroke	72	(0.9%)	4	(0.5)	25	(0.9)	19	(0.8)	24	(1.1)
TIA	17	(0.2%)	3	(0.4)	5	(0.2)	4	(0.2)	5	(0.2)
Gastrointestinal bleeding	55	(0.7%)	2	(0.3)	28	(1.0)	11	(0.5)	1	(0.6)
Haemorrhagic stroke	9	(0.1%)	0	(0.0)	3	(0.1)	4	(0.2)	2	(0.1)
Healthcare utilization										
Hospitalizations	0.7	(1.2)	0.58	(1.0)	0.89	(1.3)	0.68	(1.1)	0.69	(1.1)
ED visits	1.4	(1.8)	1.32	(1.7)	1.56	(2.1)	1.28	(1.7)	1.26	(1.7)
Outpatients visits	11.4	(7.2)	11.02	(7.5)	11.70	(7.6)	11.31	(7.0)	11.16	(6.8)
Specialist visits	0.5	(2.0)	0.34	(1.3)	0.66	(2.3)	0.49	(2.0)	0.47	(1.7)
Cardiology visits	0.2	(0.8)	0.13	(0.7)	0.22	(0.9)	0.18	(0.8)	0.17	(0.7)
Neurologic visits	0.1	(0.5)	0.09	(0.4)	0.14	(0.5)	0.99	(0.4)	0.11	(0.5)
Mental Health visits	0.01	(0.2)	0.00	(0.0)	0.01	(0.2)	0.01	(0.2)	0.01	(0.2)
Social care visits	0.1	(0.8)	0.08	(0.5)	0.12	(0.9)	0.09	(0.5)	0.10	(0.8)
Medication use										
NSAID	1,681	(21.0%)	157	(20.1)	595	(21.3)	445	(19.8)	484	(22.0)
ASA	2,901	(36.2%)	273	(35.0)	1,004	(35.9)	835	(37.1)	789	(35.9)
Clopidogrel	378	(4.7%)	33	(4.2)	133	(4.7)	98	(4.4)	114	(5.2)
ASS and clopidogrel	323	(4.0%)	27	(3.5)	141	(5.0)	76	(3.4)	79	(3.6)
Other antiagre.	370	(4.6%)	28	(3.6)	145	(5.2)	91	(4.0)	106	(4.8)
coxibs	522	(6.5%)	43	(5.5)	212	(7.6)	138	(6.1)	129	(5.9)

A four-group model with linear specifications for all groups was chosen based on specified selection criteria (Supplementary Material Table S3). The diagnostics of accuracy for the 4-group model are reported in Supplementary Material Table S4. The characteristics of the groups are shown in Table 1. Figure 2 illustrates the estimated biweekly probability of presenting an INR of between 2 and 3 for patients in each trajectory. 9.7% of the patients in the cohort were classified into trajectory 1, designated as “Optimal Control”, and were likely to be in range most of the time throughout the year, with a mean TTR of 83.8% (see Figure 3). 34.9% of the patients were classified into trajectory 2, designated as “Poor Control”, where patients were most of the time out of range throughout the year (mean TTR: 41.5%). Trajectory 4 showed a positive trend of

improving INR control (designated as “Improving Control”) and comprised 27.4% of the patients, while trajectory 3 showed the opposite trend (designated as “Worsening Control”) and grouped 28% of the patients. The mean TTR for patients classified into the group of Improving Control was 61.2% and 69.1% in the case of patients in the Worsening Control group (see Figure 3).

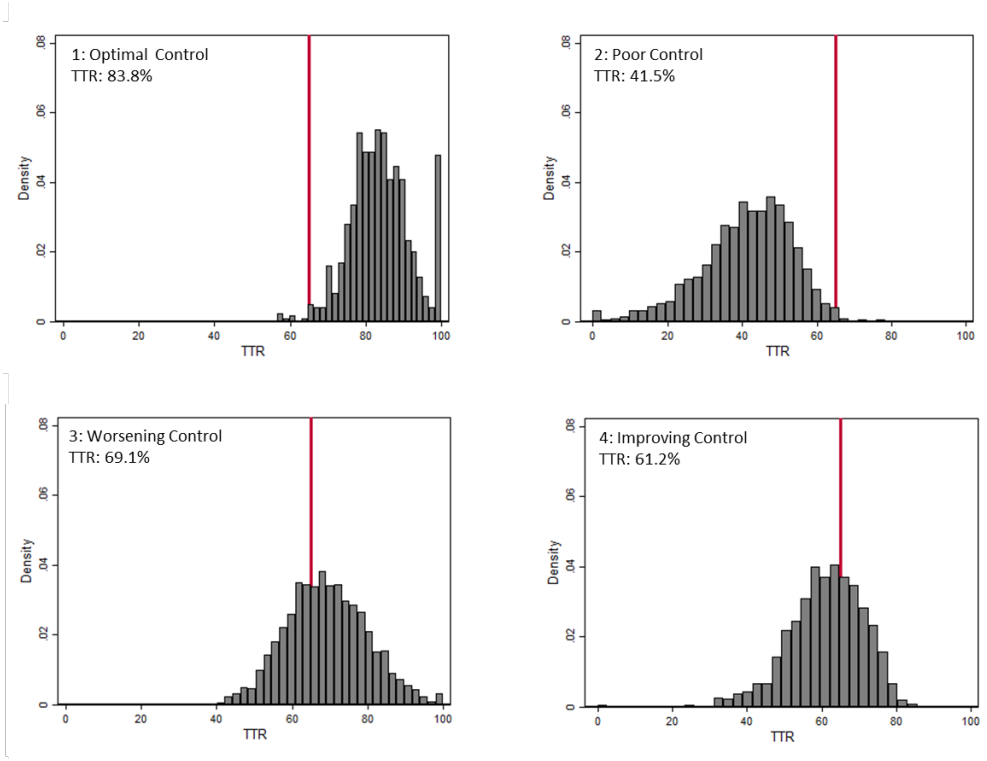
Figure 2. Trajectories of INR control in the first year of treatment (n=8,024) and the percentage of patients included in each trajectory.



Factors associated with suboptimal control

Poor Control patients were more likely to be other European (ref: Spain, OR: 1.76), to have heart failure (OR: 1.72), vascular disease (OR: 1.40), diabetes (OR: 1.25), renal disease (OR: 1.41), depression (OR: 1.43) and a higher income (OR: 1.50) than Optimal Control patients. Worsening Control patients were more likely to be older and have depression than optimally treated patients. Improving Control patients were more prone to have a higher income than Optimal Control patients (see Supplementary Material Table S5).

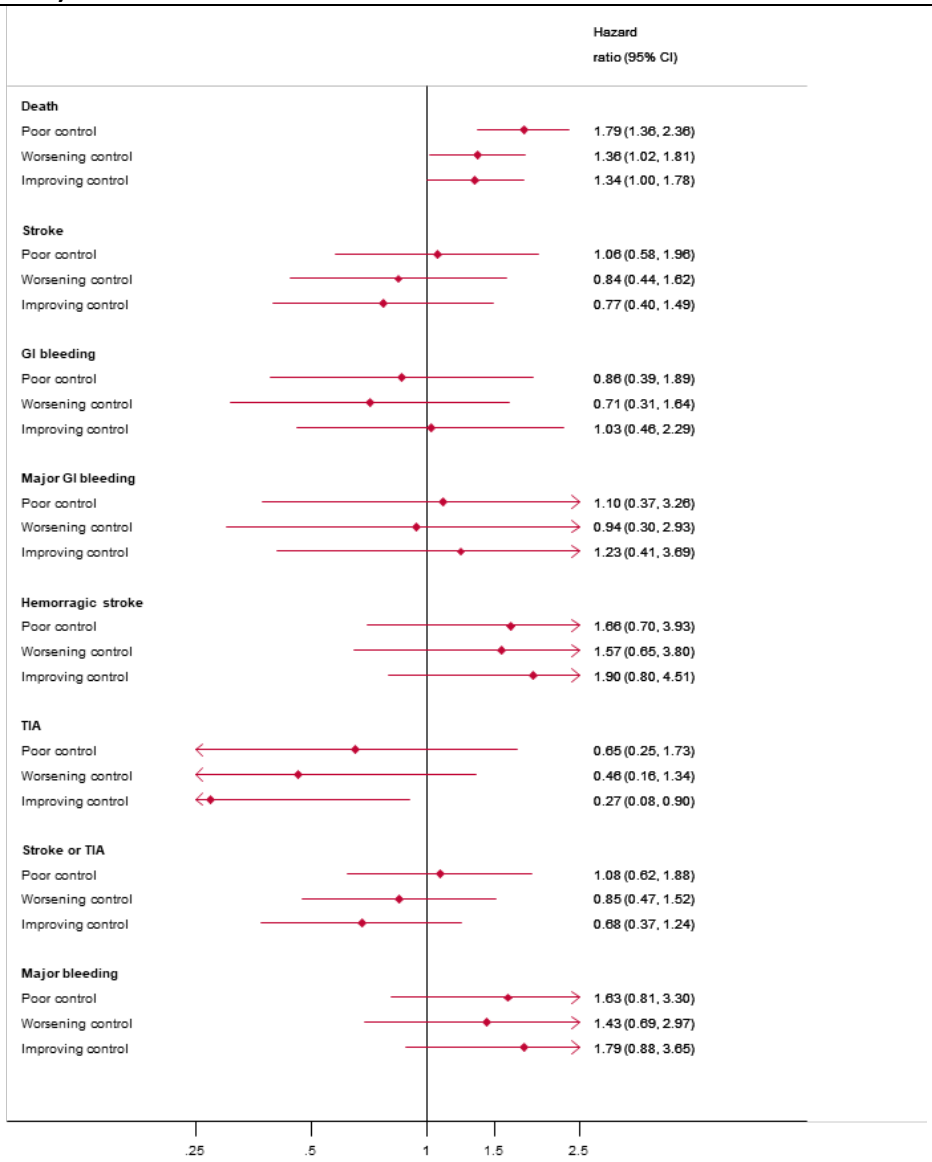
Figure 3. Density plots of the distribution of individual TTRs under each trajectory, and the mean TTR for each trajectory. TTR: 65% is marked with a line as a reference of adequate quality of INR control.



Association of trajectories and outcomes

In adjusted analyses, Poor Control patients had a significantly higher risk of death than Optimal Control patients (HR: 1.79, IC95%:1.36-2.36), as did patients in a trajectory of Worsening Control (HR:1.36, IC95%:1.02-1.81). The difference was non-significant for Improving Control patients (HR: 1.34, IC95%: 1.00-1.78). Improving control patients showed a reduced risk of TIA (OR: 0.27, IC95%: 0.08-0.90). No additional significant differences were found with respect to stroke, any bleeding or TIA. A trend towards a higher risk of hemorrhagic stroke and major bleeding could be observed in all groups with respect to the Optimal Control group (Figure 4).

Figure 4. Association of clinical outcomes and trajectories of INR control. Hazard ratios (and 95% CI interval) are shown.



Discussion

In the population of patients initiating treatment with acenocoumarol, we identified four distinct trajectories of anticoagulation control over the first year of treatment. Patients that maintained optimal INR control throughout their first year of VKA therapy had a lower risk of mortality with respect to patients with inadequate or unsustained INR control over time. The mortality risk was higher for patients in the trajectory systematically out of range and the

worsening trajectory than for patients classified in the trajectories of improving or optimal control. Importantly, only 10% of the patients achieved a sustained level of INR determinations in range, while more than a third were systematically out of control, and the remaining had periods of good control combined with periods of inadequate INR. These findings should cause concern with regard to the overall quality of care we deliver to these patients.

GBTM proved to be a useful tool for characterizing the dynamic process of INR control over time, and for identifying distinct subgroups of patients with regard **to** their propensity to be adequately anticoagulated. For instance, patients with improving and worsening control over the year had similar mean yearly TTR values but behave in opposite directions. In the light of our results, improvement interventions may be tailored differently for these two groups of patients that could be considered as similar if the assessment was based solely in average, cross-sectional measures such as TTR.

The threshold of TTR>65% is a commonly used indicator of optimal VKA control. Using this criterion, most patients classified in the group of improving control (mean TTR: 61.**2**%; TTR>=65%: 3**8**.0%) would be considered as inadequately treated, whereas the majority of patients in the group of worsening control (mean TTR=69%; TTR>=65%: 63.**4**%) would be considered as optimally treated. However, at the end of the year, patients in the latter group, for whom control is worsening, may be at a higher risk than patients for whom the likelihood of being in range is increasing with time (importantly, mortality in the following year was higher in the worsening control group than in the improving control group). The opposite would apply if facing the issue prospectively (at the moment of treatment initiation, patients in the Improving Control group are at a higher risk that patients in the Worsening Control group). In this sense, the longitudinal characterization of the process of INR control provides additional information to assess patient risk that can be useful for targeting priority groups for intervention at different moments of time. Also, with regard to our results relative to the association of suboptimal

control trajectories with higher mortality risk, and consistent with other findings in the literature, consideration should be given to revising the TTR threshold for good INR control upwards to values in the range of 80% [18,19].

Characterizing anticoagulation control trajectories over time may provide a better understanding of the mechanisms, their associated factors and their associated outcomes underlying suboptimal anticoagulation control than static, average/cross-sectional measures such as TTR. And at the same time they have also been shown to work in a consistent way with regard to traditional metrics of INR control. For instance, we observed that the distribution of patients' individual TTR under each trajectory and the mean TTR associated with each trajectory reflected an adequate summary measure of what could be observed over time with the trajectories. In this sense, TTR and trajectories coincide in the overall directionality of results and seem to work well together to provide a more complete vision of the quality of INR control.

Limitations

Our study is subject to some limitations. First of all, the construction of trajectories requires certain inclusion criteria that exclude a large proportion of patients, and probably produces a population which is different from the general one of patients with AF under OAC treatment (but with less severity, since they have not died in the first year, with greater adherence since they have a minimum of INR controls, etc.). This restriction, largely inherent to GBTM methodology, is an important limitation for the generalizability of our results. Second, despite including many relevant individual variables in our analysis, we cannot rule out the existence of unmeasured confounding. These factors could be affecting the construction of the trajectories and the analysis of association to outcomes. Third, information biases due to absent registration or differing data recording practices in the electronic databases might exist, although this is an inherent problem of any study using data from routine clinical practice. Moreover, misclassification (on exposure and covariates) is expected to be non-differential across the

groups of study subjects. Fourth, a healthy adherer effect may be lying behind the differences between groups with respect to outcomes.

Conclusion

To the best of our knowledge, there are no previous studies using GBTM to represent the evolution of INR control in patients with atrial fibrillation treated with VKA. Four distinct trajectories of anticoagulation control over the first year of treatment (optimal control, improving control, worsening control and poor control) were identified. Patients in trajectories of improving and maintained optimal INR control over their first year of VKA treatment had a lower risk of mortality than patients in trajectories of unsustained control. This highlights the interest in and relevance of analyzing the phenomenon of INR control in a longitudinal way. GBTM can contribute to a better understanding and assessment of the quality of oral anticoagulation with VKA and may be used in addition to with traditional, well-established measures such as TTR.

Supplementary Material

Table S1. Rationale for inclusion and exclusion criteria

Inclusion criterion	Rationale
1) Patients that remained alive throughout the year	To ensure at least one year of follow-up for every patient (in fact, we required one month for initial dose adjustment + one year of follow-up)
2) Patients with at least 4 determinations of INR between months 2 and 13 after the index date (with fewer than 90 days between the index date and the first INR determination available),	To ensure a minimum level of INR monitoring throughout the year.
3) Patients with gaps between determinations of less than 90 days between months 2 and 13 (or between the last INR determination available and the end of the assessment period).	To ensure a minimum level of INR monitoring throughout the year.

Exclusion criterion	Rationale
1) Non-naïve users	Adequate design to assess outcomes.[1]
2) Patients who did not refill their prescription	To conform a homogeneous risk cohort.
3) Patients treated for other conditions	To conform a homogeneous risk cohort.
4) Patients younger than 40 years old	To conform a homogeneous risk cohort.
5) Patients with valvular heart disease	To conform a homogeneous risk cohort.
6) Patients without INR or incorrect INR information	Adequate INR information was not retrievable from some of the 24 Health Departments (HDs) of the VHS. We selected only HDs with INR information for at least 70% of patients in treatment.
7) Patients with less than 395 days of follow-up	Minimum follow-up time required for analysis (one month for dose adjustment + one year for follow-up)
8) People without health coverage by the VHS, mainly some government employees whose prescriptions are reimbursed by civil service insurers and are thus not included in the pharmacy databases of the VHS	Follow-up is limited or not possible.
9) People not registered in the census (non-residents or temporary residents)	Follow-up is limited or not possible.
10) People who left the region or were disenrolled from VHS coverage for other causes	Follow-up is limited or not possible.

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Table S2. International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) codes used to define study clinical outcomes.

Clinical Outcomes	
Isquemic stroke	433.x1, 434.x1, 436.xx
TIA	435.xx
GI bleeding	455.2, 455.5, 455.8, 456.0, 456.20, 459.0,530.7, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9
Major GI bleeding	GI bleeding + ICD-9 procedure code of blood or blood components transfusion (99.03, 99.04, 99.05, 99.06, 99.07, 99.09)
Intracranial haemorrhage	430.xx, 431.xx, 432.xx, 852.0x, 852.2x, 852.4x, 853.0x

Table S3. Model fit statistics

Model	BIC	AIC	Entropy	Minimum size
2 groups	-115687.56	-115582.71	0.90	0.40
3 groups	-113422.63	-113219.91	0.86	0.26
4 groups	**-112734.45**	**-112433.87**	**0.80**	**0.10**
5 groups	-112353.32	-111954.87	0.80	0.06
6 groups	-111765.83	-111706.41	0.74	0.05
7 groups	-111612.05	-111542.14	0.73	0.02

AIC: akaike information criterion; BIC: bayesian information criteria; In bold the models selected after fulfilling all criteria. The criteria for rejecting k class models (and, thus, selecting k-1 class models) was the presence of some of the following criteria: BIC score higher; entropy (minimum membership probability) <0.7; and minimum sample size in the range of 10%.

Table S4. Diagnostics of assignment accuracy for the 4-group model

Trajectory	n	AvPP	OCC	p	P
1	780	0.85	51.71	0.10	0.10
2	2799	0.85	10.37	0.35	0.34
3	2249	0.86	15.51	0.28	0.28
4	2196	0.80	10.63	0.27	0.28

AvPP: average posterior probability; OCC: odds of correct classification; p: proportion of study members classified in each group; P: estimated probability of classification

Table S5. Factors Associated with Suboptimal Control

	Uncontrolled		Improving Control		Worsening Control	
Characteristics	OR	p-value	OR	p-value	OR	p-value
Age 64-75 (ref:<65)	0.81	0.153	1.17	0.305	1.08	0.641
Age>75 (ref:<65)	1.06	0.660	**1.38**	**0.033**	1.35	0.060
Female	1.07	0.469	0.86	0.134	1.03	0.756
Europe (ref: Spain)	**1.76**	**0.038**	0.97	0.926	1.21	0.535
Other country (ref: Spain)	1.52	0.102	1.04	0.879	0.88	0.676
Income>18.000/year	**1.50**	**0.000**	1.10	0.339	**1.29**	**0.019**
Atrial fibrillation	0.96	0.834	0.94	0.785	0.91	0.667
Congestive Heart Failure	**1.72**	**0.000**	1.32	0.068	1.25	0.161
Hypertension	1.09	0.455	1.09	0.460	1.02	0.894
Diabetes	**1.25**	**0.028**	1.00	0.964	1.14	0.230
Liver disease	0.77	0.126	0.71	0.065	0.71	0.077
Renal disease	**1.41**	**0.041**	1.15	0.423	1.16	0.419
Previous ischemic stroke or TIA	0.96	0.787	0.88	0.356	0.87	0.329
Thromboembolism	1.09	0.654	0.79	0.250	0.87	0.510
Hemorragic stroke	0.78	0.674	0.91	0.874	1.07	0.916
GI bleeding	1.01	0.976	0.86	0.540	0.70	0.185
Other bleeding	**1.42**	**0.006**	1.26	0.086	1.20	0.203
Vascular disease	**1.40**	**0.017**	1.18	0.269	1.19	0.259
Dementia	1.61	0.060	1.19	0.511	1.58	0.092
Depression	**1.43**	**0.020**	**1.38**	**0.044**	1.21	0.272
Cancer	1.02	0.896	0.89	0.435	1.00	0.976
Events during first year of treatment (13 months)						
GI bleeding	3,18	0,158	1,44	0,684	2,33	0,340
Hemorragic stroke	2,90	0,760	3,58	0,738	2,12	0,829
Ischemic stroke	1,88	0,400	1,84	0,430	2,36	0,291
TIA	0,30	0,165	0,46	0,334	0,49	0,408

OR: Odds Ratio; GI: Gastrointestinal; TIA: Transient Ischemic Attack

Reference category is "Optimal Control"

Statistically significant categories are marked in bold

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Artículo 1

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Artículo 3

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Artículo 4

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Artículo 5

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Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs.

Linked prescription and dispensation data to improve medication adherence estimates

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Abstract

Objective We compare estimates of Proportion of Days Covered (PDC) based on dispensation-only data versus linked prescription and dispensation information, and we analyse their differences in a real-world cohort of patients with osteoporosis.

Methods Prospective cohort study. We compared four alternative measures of PDC, using dispensation-only data: a) with a fixed assessment interval and b) censoring the assessment interval at the moment of the last refill, and using linked prescription and dispensation data: c) considering a minimum prescription gap of three months to interpret interruption by the physician and d) considering any prescription gap.

Results The mean PDC at 12 months for new users was 63.1% using dispensation-only data and a fixed interval, 86.0% using dispensation-only data and a last-refill interval, 81% using linked dispensation and prescription data and censoring any period without prescription, and 78.3% when using linked prescription and dispensation data and censoring periods of at least 3 months. For experienced users, the figures were 80.0%, 88.9%, 83% and 81%, respectively. Overall, dispensation-based measures presented issues of patient misclassification.

Conclusion Linked prescription and dispensation data allows for more precise PDC estimates than dispensation-only data, as both primary non-adherence and early non-adherence periods, and fully non-adherent patients, are all identified and accounted for.

Introduction

Medication non-adherence is one of the most important barriers to getting the best benefit from pharmaceutical treatments in the real world, and to the same extent as demonstrated in clinical trials. For instance, osteoporosis medications have shown efficacy for the prevention of fragility fractures[1] but medication adherence in patients with osteoporosis has been found to be suboptimal in several studies[2-5]. Poor adherence has been documented across the spectrum of chronic disease[6-16] and is associated with adverse health outcomes and higher health care costs. Worldwide, the improvements in chronic medication initiation and adherence are at the cornerstone of policy interventions orientated towards maximizing the value of modern healthcare even if, at least to date, such interventions have usually shown mixed results.[11]

In routine clinical practice, many factors may contribute to poor medication adherence including those related to patients, to physicians and to health care systems [17,18]. The common belief that patients are solely responsible for taking their treatment is misleading and most often reflects a misunderstanding of how other factors affect people's behaviour and their capacity to adhere to their treatment. A better understanding of the relative contribution of patient and physician predictors of initiation, adherence, and interruption of treatment can be useful for a better understanding of the complex phenomenon of non-adherence and for designing more effective interventions.

Real world evidence on medication non-adherence is mainly based on information available in refill databases. Studies based on data which is routinely collected in the provision of care have been extremely useful for assessing adherence to and persistence with medication in patients with chronic diseases, and the impact of non-adherence and treatment interruption on clinical outcomes. However, one common feature of those studies is that they lack information about physician prescription, and adherence estimates are calculated by using dispensation data captured from pharmacy claims. When it is not possible to link prescription and dispensation

data at the individual level, it is difficult to ascertain the exact moment of initiation of therapy (essential for analysing primary non-adherence) and it is also impossible to discern whether a gap in adherence may be due to patient non-adherence or to an interruption (even if temporary) of prescription as decided by a doctor. In this sense, traditional adherence estimates based on refill claims data that are not linked to prescription data, which in fact are the most prevalent in the literature, should be interpreted with caution as therapy initiation and the attribution of adherence gaps will not be reliably addressed.

In the region of Valencia in Spain, the electronic health information systems include an advanced electronic prescription manager that allows a link to be made between every patient treated in the region, prescriptions issued by doctors and the refills dispensed at the pharmacy. In this way, it is possible to overcome the aforementioned limitations of dispensation-based estimators and to calculate more refined adherence measures. To what extent the adjusting adherence estimates based solely on dispensations with prescription information impacts on adherence estimates has, to the best of our knowledge, never been explored.

In this paper we compare traditional, dispensation-based estimates with estimates using linked prescription and dispensation information, and we illustrate and quantify their differences by estimating real-world, long-term medication secondary adherence in a cohort of patients aged 50 years and over in the region of Valencia.

Methods

Design

Prospective cohort comprising the patients of the ESOSVAL cohort (fully described elsewhere [19]) with at least one physician prescription (to estimate secondary adherence with linked prescription and dispensation data) or one dispensation (to estimate secondary adherence with claims-only data) of an osteoporotic medication issued between June 2009 and June 2011.

Study setting

The study was conducted in the Valencia Health System (VHS), an extensive public hospital and primary healthcare centre network, which covers about 97% of the 5 million inhabitants of the Valencia region, located on the Mediterranean coast of Spain.

Population

Patients from the ESOSVAL cohort with at least one osteoporotic medication prescribed between June 2009 and June 2011 were included. The ESOSVAL cohort consists of 11,035 women and men aged 50 years and over attending 272 primary healthcare centres in the VHS for any health condition between November 2009 and September 2010. Subjects were recruited by opportunity sampling by around 600 general practitioners and primary care nurses collaborating in the ESOSVAL study following prospectively defined criteria.

We categorized patients into two groups: new users of osteoporotic treatments (when no previous dispensations or prescriptions for an osteoporotic drug were registered in the 6 months previous to the index date), and experienced users (all the rest).

Data sources

We combined data from the outpatient electronic medical record and the pharmaceutical management module of the electronic information systems of the VHS and a specific osteoporosis risk-monitoring sheet employed for the follow-up of the ESOSVAL cohort to create a database with sociodemographic and clinical characteristics and information on all physician prescriptions written and all prescriptions filled at the pharmacy for all patients studied. In the VHS, prescriptions and dispensations are linked at the individual level; treatments can be short or long term (maximum one year for chronic therapies which, for instance, would include 12 monthly prescriptions, with a window for refilling of 10 days for each prescription) and there is no monthly reimbursement limitation.

Covariates

Sociodemographic and clinical characteristics included age; sex; educational level; history of hip fracture in parents or siblings; personal history of any previous osteoporotic fracture; body mass index (BMI); falls in the last year (≥1 fall); 10-year risk of hip fracture estimated with the Fracture Risk Assessment Tool (FRAX)[20] and categorized into <3% and ≥3%; other secondary causes of osteoporosis; use of glucocorticoids; using the World Health Organization (WHO) osteoporosis classification criteria based on T-scores, Bone Mineral Density results were classified as normal, osteopenia or osteoporosis[21]; sedentarism; use of calcium and vitamin D supplementation; polypharmacy (defined as having 6 or more dispensations concomitantly) and pharmaceutical copayment (categorized as no copayment for pensioners and people without resources or a copayment of 40% for the active population).

Main outcome measures

The main outcome measure was the Proportion of Days Covered (PDC) at 12 and 24 months. PDC is generically defined as the total number of days covered with medication on hand during a specified follow-up period divided by the number of days in the patient's follow-up period[22].

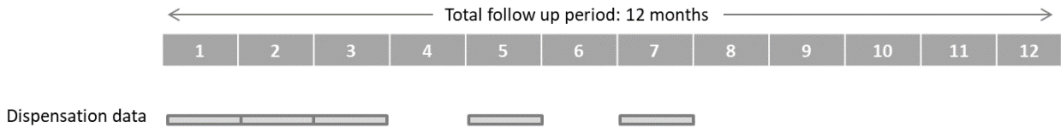
We provided four alternative PDC measures. We calculated PDC with dispensation-only data in two ways, as found predominantly in the literature: a) censoring patients only in the case of death or loss to follow-up due to disenrollment, where the assessment period (almost) coincides with the follow-up period (called the "fixed interval" specification in the present study) and b) censoring the assessment periods also at the moment of the last dispensation within the follow-up period (called the "last-refill interval" in the present study). We further calculated PDC by linking prescription and dispensation data. We calculated the prescription-adjusted PDC with two different operational definitions to consider treatment interruption periods decided by the physician: c) considering a minimum prescription gap of three months to adjust PDC (meaning that, when there is a gap of three months or longer in prescription, this period is censored and is not accounted for as patient non-adherence), and d) considering any prescription gap as

physician interruption (meaning that, when there is any gap in prescription, this period is censored and excluded from the calculation of the estimator). Table 1 lists the main definitions and acronyms used in this study, and Figure 1 provides illustrative examples of the calculation of PDC using the four alternative measures.

Table 1. Definitions used in this study

Concept	*Definitions*	*Acronym*
Primary non-adherence	Failure to have a new prescription filled (discrete event).	None
Early non-adherence	Failure to have the initial prescriptions (typically the two first prescriptions) filled (discrete event).	None
Secondary adherence	Ongoing process that measures whether or not the patient fills dispensations as prescribed during a period of follow-up and assessment.	None
Follow-up period	Total length of the period in which PDC is formally calculated, f.i., 6 months, 12 months, etc. This is the formal definition of the period in which adherence is measured, normally stated in the Title and the Methods section of the studies.	None
Assessment period	Effective period in which PDC is estimated within the follow-up period. For instance, when censoring patient time during the follow-up for any reason, the assessment period is shorter than the follow-up. If no patients are censored during the follow-up period, both follow-up and assessment periods coincide.	None
Concept	*Definitions*	*Acronym*
PDC (Proportion of Days Covered)	Total number of days covered with medication during a specified assessment period divided by the number of days in patient's assessment period.	PDC
PDC using dispensation-only data and fixed interval	PDC calculated with information on dispensations-only, where the assessment period is equivalent to the follow-up period (except for reasonable censoring due to death, exclusion from insurance or other losses to follow-up unrelated to medication use).	PDC-DFI
PDC using dispensation-only data and a last-refill interval	PDC calculated with information on dispensations-only, where the assessment period is censored at the time of the last dispensation within the follow-up period.	PDC-DLR
PDC using prescription and dispensation data and censoring any prescription gap	PDC calculated using linked prescription and dispensation data. Any gap in days' supply coinciding with gaps in prescription (days not covered with prescription) is censored from the calculation of PDC.	PDC-PD
PDC using prescription and dispensation data and censoring when prescription gaps are 3 months or longer	PDC calculated using linked prescription and dispensation data. Periods equal to or longer than 3 months without prescriptions are censored and thus not included either in the numerator or in the denominator for the calculation of PDC.	PDC-PD3

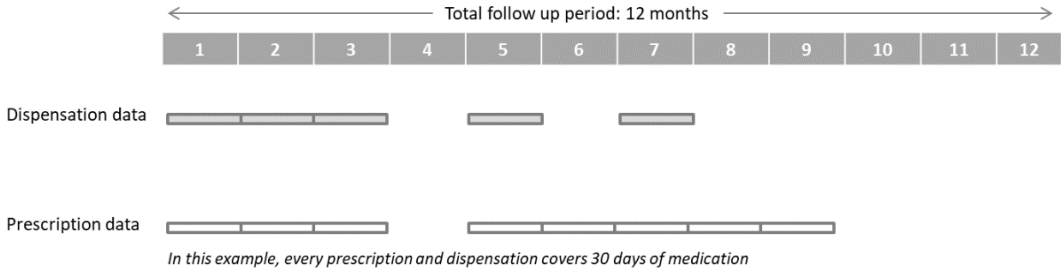
Figure 1a. Example of calculation of PDC using dispensation only data. PDC is calculated using either a fixed interval or a last-refill interval.



In this example, every prescription covers 30 days of medication

Data sources	Specifications	Acronym	Days' supply (numerator)	Follow-up (denominator)	PDC
Dispensation only data	Fixed interval	PDC-DFI	150	360 (whole follow-up period)	41,7%
Dispensation only data	Last-refill interval	PDC-DLR	150	210 (last refill in month 7)	71,4%

Figure 1b. Example of calculation of PDC using linked dispensation and prescription data. PDC is calculated using either any gap or a three-month prescription gap.

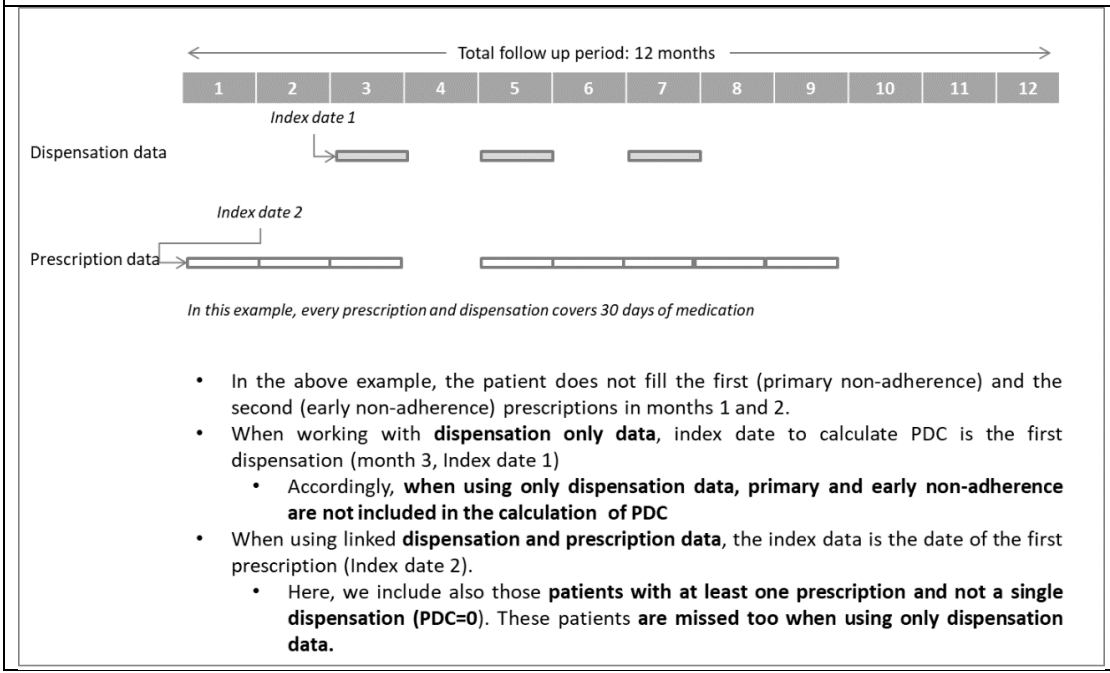


In this example, every prescription and dispensation covers 30 days of medication

Data sources	Specifications	Acronym	Days' supply (numerator)	Follow-up (denominator)	PDC
When working with prescription and dispensation data, numerator is calculated with dispensation data, and denominator is calculated with prescription data					
Prescription and dispensation data	Censoring any period without prescription	PDC-PD	150	240 (period covered with prescription without prescription gaps)	62,5%
Prescription and dispensation data	Censoring periods of three-month gap without prescription	PDC-PD3	150	270 (period covered with prescription without gaps<3months)	55,6%

When using dispensation-only data the index date was defined as the first dispensation, while the first prescription was used as the index date when working with linked dispensation and prescription data. This also has implications with regard to PDC calculations (see Figure 2).

Figure 2. Differences between using dispensation only data or linked dispensation and prescription data with regard to the identification of the index date and patient inclusion for PDC calculation.



Days with available medication during the follow-up period were estimated through the medication regime defined by the physician and the number of pills per package (e.g. for a regime of one pill every 12 h and packages of 30 tablets, each dispensation will entail 15 days of medication available). Stockpiling was set to 90 days. PDC was summarized categorically using the widely accepted cut-off points of PDC<20% (non-adherent), 20%≤PDC<80% (partially adherent), and PDC≥80% (adherent or fully adherent)[23].

Osteoporosis Medications

The treatments for osteoporosis included were bisphosphonates (alendronate, risendronate, ibandronate), raloxifene, bazedoxifene, strontium ranelate and parathyroid hormone/teriparatide.

Statistical Analysis

We first described baseline characteristics for the whole population and then stratified by new and experienced users. Categorical variables were expressed as proportions and compared using chi-square tests.

Second, we estimated the mean PDC for new and experienced users, as well as the percentage of patients categorised as adherent, partially adherent and non-adherent at 12 and 24 months, using four alternatives for PDC estimation (see Figures 1a and 1b). All analyses were conducted using STATA v13 software.

Ethics

All study subjects signed the informed consent granting researchers access to information contained in their medical record for the purposes of the study. All information was handled according to Spanish laws on confidentiality and patients' rights. The ESOSVAL study protocol was reviewed and approved by the Committee for Ethics and Clinical Trials of the Centre for Public Health Research and the Public Health General Directorate of the Valencia Government (Decision March 27, 2009, protocol modification approval October 4, 2012).

Results

Cohort characteristics

We identified 2,260 patients from the ESOSVAL cohort who were prescribed an osteoporotic medication between June 2009 and June 2011. 712 (31.5%) were new users and 1,548 (68.5%) were experienced users (see Table 2). For calculations based on dispensation information only, 696 new users and 1,517 experienced users were considered (missing patients are those who did not fill any of their prescriptions).

Table 2. Baseline characteristics of the ESOSVAL cohort.						
		New users (N=712)		Experienced users (N=1,548)		Total (N=2,260)
		n	%	n	%	n
Age_65	50-64	380	53.4	771	49.8	1,151
	65-99	332	46.6	777	50.2	1,109
Sex	Women	568	79. 8	1447	93.5	2,015
	Men	144	20.2	101	6.5	245
Education	No studies	188	29.2	496	35.2	684
	Primary	287	44.6	618	43.8	905
	Second / Univ	169	26.2	297	21.0	366
Family history of hip fracture	No	485	82.6	1021	79.9	1,506
	Yes	102	17.4	256	20.1	358
Previous fracture	No	553	77.7	1258	81.3	1,811
	Yes	159	22.3	290	18.7	349
Body mass index	<20 kg/m^2	11	1.6	26	1.8	37
	20.0-24.9 kg/m^2	190	28.2	397	26.7	587
	25.0-29.9 kg/m^2	285	42.22	622	41.9	907
	≥30 kg/m^2	189	28.0	439	29.6	628
Falls (≥1 in the last year)	No	486	72.4	1055	72.6	1,541
	Yes	185	27.6	399	27.4	584
10-year risk of hip fracture[1]	<3 %	525	77.8	1098	74.0	1,623
	≥3 %	150	22.2	386	26.0	536
Other osteopenic diseases[2]	No	562	78.9	1241	80.2	1,803
	Yes	150	21.1	307	19.8	457
Glucocorticoid use[3]	No	694	97.5	1515	97.9	2,209
	Yes	18	2.5	33	2.1	51
Other osteopenic drugs	No	407	57.16	809	52.26	1,216
	Yes	305	42.84	739	47.74	1,044
DMO testing	No	416	58.4	979	63.2	1,315
	Yes	296	41.6	569	36.8	865
Bone mineral density (T-score)	Normal	30	10.3	78	14	108
	−1 to −2.5	128	44.0	279	50.1	407
	≤−2.5	133	45.7	200	35.9	333
Sedentarism	No	540	79.8	1218	81.6	1,758
	Yes	137	20.2	274	18.4	411
Polypharmacy	≤6	269	37.8	327	21.1	596
	>6	443	62.2	1221	78.9	1,664
Calcium and/or Vitamin D supplements	No	201	28.2	494	31.9	695
	Yes	511	71.8	1054	68.1	1,565
Copayment	No	533	74.9	1253	80.9	1,586
	Yes	179	25.1	295	19.1	474
Antiosteoporotic treatment	Bisphosphonates[4]	599	84.1	1206	77.9	1,805
	PTH[5]	10	1.4	30	1.9	40
	Raloxifene	38	5.3	180	11.6	218
	Ranelate	65	9.1	132	8.5	197

[1]Fracture Risk Assessment Tool (FRAX®) [2]Type I diabetes, rheumatoid arthritis, untreated long-standing hyperthyroidism, chronic malnutrition or malabsorption, chronic obstructive pulmonary disease, renal disease, prolonged immobility, organ transplantation, and chronic liver disease; [3]≥5mg per day of prednisone or equivalent for at least 3 months in the previous year. [4]Bisphosphonates (alendronate, risendronate, ibandronate),[5]PTH, parathyroid hormone (1-34, and 1-84). Missing data: educational level (205), family history of hip fracture (396), BMI (101), falls (135), FRAX (101), sedentarism (91)

Adherence to osteoporosis medications

The mean PDC at 12 months for new users was 63.1% when using dispensation-only data and a fixed interval, 86.0% when using dispensation-only data and a last-refill interval, 81.0% using linked dispensation and prescription data censoring any period without prescriptions, and 78.3% when using linked prescription and dispensation data but censoring when prescription gaps were 3 months or longer. For experienced users, figures were 80.0%, 88.9%, 83.0% and 81.0%, respectively. At 24 months, PDC slightly decreased using all four calculation methods for both new and experienced users (see Table 3 and Table 4).

Table 3. Mean PDC and categorical PDC at 12 months using dispensation-only data and using linked prescription and dispensation data.

		New users	Experienced users
Mean PDC			
Dispensation-only data		***N=696***	***N=1,517***
PDC-DFI		63.1 (60.5-65.6)	80.0 (78.7-81.2)
PDC-DLR		86.0 (84.5-87.6)	88.9 (88.1-89.7)
Linked prescription and dispensation data		***N=712***	***N=1,548***
PDC-PD3		78.3 (76.2-80.3)	81.0 (79.8-82.3)
PDC-PD		81.0 (78.9-83.1)	83.0 (81.7-84.2)
Categorical PDC			
Dispensation-only data		***N=696***	***N=1,517***
PDC-DFI	**<20%**	18.4 (15.7-21.5)	4.8 (3.9-6.1)
	≥80%	46.1 (42.4-49.8)	67.0 (64.6-69.4)
PDC-DLR	**<20%**	1.3 (0.7-2.4)	0.07 (0.0-0.5)
	≥80%	75.3 (71.9-78.4)	81.0 (79.0-82.9)
Linked prescription and dispensation data		***N=712***	***N=1,548***
PDC-PD3	**<20%**	6.0 (4.5-8.0)	4.9 (3.9-6.1)
	≥80%	65.0 (61.4-68.5)	70.1 (67.8-72.3)
PDC-PD	**<20%**	6.0 (4.5-8.0)	4.8 (3.8-6.0)
	≥80%	69.7 (66.2-72.9)	73.8 (71.6-76.0)

PDC: Proportion of Days Covered; PDC-DFI: PDC, calculated with dispensation-only data and a fixed interval of assessment; PDC-DLR: PDC, calculated with dispensation-only data and an interval of assessment censored at the moment of the last refill; PDC-PD: PDC, calculated with linked prescription and dispensation data and censoring any period of gaps in prescription from the calculation of PDC; PDC-PD3: PDC, calculated with linked prescription and dispensation data and censoring any period of 3 month gaps or longer in prescription from the calculation of PDC.

At 12 months, the percentage of non-adherent patients among new users (PDC<20%) was 18.2% using dispensation-only data and a fixed interval, and 1.3% using dispensation-only data and a last-refill interval, and 6% when using linked prescription and dispensation data, irrespective of the gap specification. The percentage of fully adherent patients at one year for new users

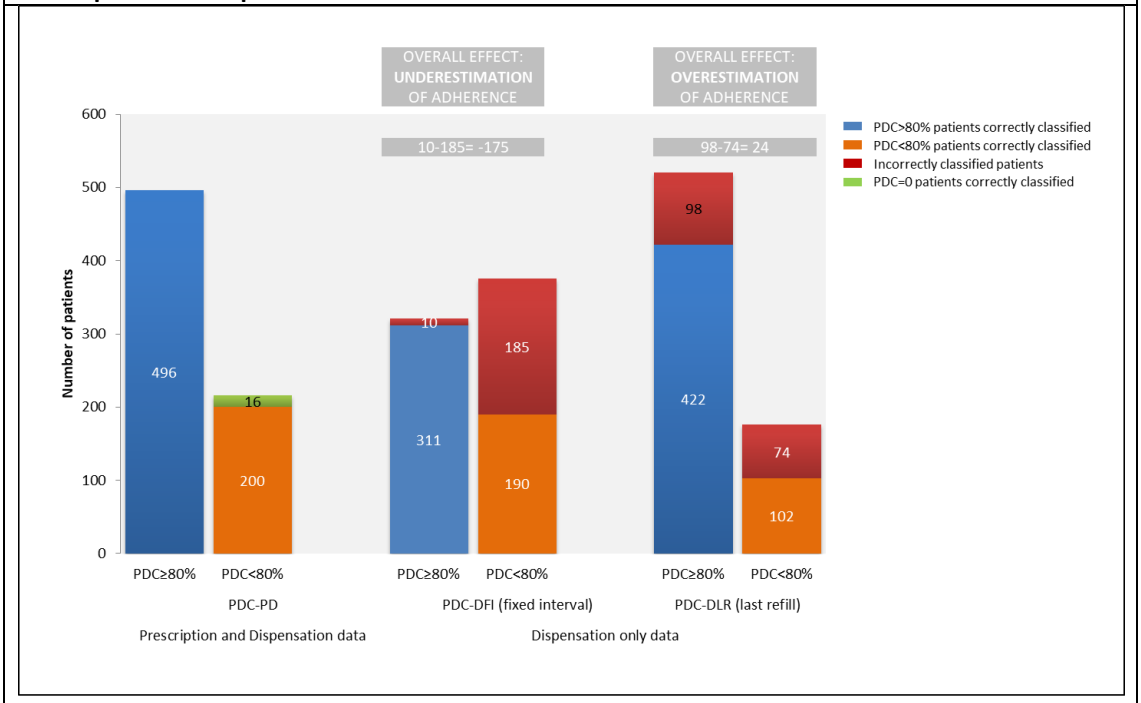
(PDC≥80%) was 46.1% when using dispensation-only data and a fixed interval and 75.3% when the assessment period was censored at the last refill. When using linked prescription and dispensation data, PDC≥80% was achieved by 65% of patients when censoring gaps in prescription equal to or longer than 3 months, and by 69.7% when censoring any gap in prescription. In experienced users, a larger proportion of patients were fully adherent irrespective of calculation methods, and similar differences in magnitude as with new users were observed among the four approaches used to estimate PDC (see Table 3). Overall, PDC-DFI underestimated patient adherence and PDC-DLR overestimated patient adherence with respect to PDC-PD. Patient misclassification using dispensation-only data versus using linked prescription and dispensation data is shown in Figure 3.

Table 4. Mean PDC and categorical PDC at 24 months using dispensation-only data and using linked prescription and dispensation data.

		New users	Experienced users
Mean PDC			
Dispensation-only data		***N=696***	***N=1,517***
PDC-DFI		56.6 (54.0-59.2)	74.1 (72.7-75.5)
PDC-DLR		81.2 (79.5-83.0)	85.7 (84.7-86.6)
Linked prescription and dispensation data		***N=712***	***N=1,548***
PDC-PD3		77.1 (75.2- 79.1)	80.3 (79.1- 81.5)
PDC-PD		79.0 (77.0-81.0)	82.1 (80.8-83.3)
Categorical PDC			
Dispensation-only data		***N=696***	***N=1,517***
PDC-DFI	**<20%**	23.1 (20.1-26.4)	6.1 (5.0-7.5)
	≥80%	35.3 (31.9-39.0)	57.0 (54.4-59.4)
PDC-DLR	**<20%**	1.7 (1.0-3.0)	0.7 (0.4-1.3)
	≥80%	64.9 (61.3-68.4)	73.9 (71.6-76.0)
Linked prescription and dispensation data		***N=712***	***N=1,548***
PDC-PD3	**<20%**	7.7 (6.0-9.9)	5.7 (4.6-7.0)
	≥80%	61.7 (58.0-65.2)	67.8 (65.5-70.1)
PDC-PD	**<20%**	5.5 (4.0-7.4)	4.5 (3.5-5.6)
	≥80%	60.3 (56.6-63.8)	68.0 (65.7-70.3)

PDC: Proportion of Days Covered; PDC-DFI: PDC, calculated with dispensation-only data and a fixed interval of assessment; PDC-DLR: PDC, calculated with dispensation-only data and an interval of assessment censored at the moment of the last refill; PDC-PD: PDC, calculated with linked prescription and dispensation data and censoring any period of gaps in prescription from the calculation of PDC; PDC-PD3: PDC, calculated with linked prescription and dispensation data and censoring any period of 3 month gaps or longer in prescription from the calculation of PDC.

Figure 3. Patient misclassification in our cohort using Dispensation data only versus using Prescription and Dispensation data.



PDC: Proportion of Days Covered; PDC-PD: PDC using prescription and dispensation data and censoring any prescription gap; PDC-DLR: PDC using dispensation only data and a last-refill interval; PDC-DFI: PDC using dispensation data only and fixed interval. Overall effect calculation does not take into account the 16 patients not captured by methods based on Dispensation data. When considered, overall effect would be an underestimation of 191 patients for PDC-DFI and an overestimation of 8 for PDC-DLR.

Discussion

In the light of our findings, using linked prescription and dispensation data allows for a more accurate estimation of the PDC versus using dispensation data only. When prescription information is available and it is possible to link every prescription individually with every dispensation, the definition of the index date as the first prescription is more accurate than in dispensation-based studies, where the index date is usually the date of the first dispensation. In this way, the estimate is more precise as primary non-adherence and early non-adherence periods, and fully non-adherent patients (those who are prescribed in the period of assessment but do not fill any prescription) are identified and accounted for in PDC calculations (primary non-adherence in our PDC-PD cohort of new users was 6.5%). This may have important implications not only with regard to the accuracy of estimators, but for the design of interventions aimed at improving adherence and outcomes. In this way, it is possible to target

high-risk patients and high-risk periods of non-adherence. Finally, an additional and important element of accuracy associated to the linkage of prescription and dispensation is the ability to censor periods without prescription for the estimation of PDC. Here, the attribution of gaps in days' supply to patients' non-adherence, as happens when using dispensation-only information, is imprecise, as those periods are in fact days not covered by prescription.

In our cohort of the general population of men and women aged 50 and over, we found that PDC figures based on linked prescription and dispensation data sat in the middle of those obtained from dispensation-based measures. When using dispensation-only data, differences between estimators are in turn explained by noticeable differences in the effective assessment period. When the effective period for the measurement of the PDC is censored at the time of the last refill, the effective assessment period is shortened, and thus PDC is overestimated as compared to when the assessment period is a fixed-interval. In fact, we could argue that this particular PDC estimator is inadequate (in the same way that some studies incorrectly censor periods in the presence of persistence gaps). On the other hand, the difference between PDC-DFI (56.6%) and PDC-PD (79%) in the case of new users shows the most noticeable numerical difference between estimators at 12 months, and reflects that, in the absence of prescription information, dispensation-based estimators using a fixed-interval period for secondary adherence assessment underestimate PDC in new users, where a phenomenon of gaps in prescription -that cannot be captured by means of dispensation information- is occurring (Appendix 1). It is commonplace in the literature related to medication adherence that naïve users tend to be less adherent to pharmacotherapy than experienced users; in the light of our results, based on higher quality information than average, this general assumption should be called into question. It is worth noting that the proportion of experienced users was not altered depending of calculation method used, thus this factor is not affecting estimators. Finally, PDC is around 80% in most of our estimates, but a significant proportion of patients (between 25 and 65%) still remain non-adherent or only partially adherent over 24 months. This last finding is

consistent with the widely reported global picture of suboptimal adherence to osteoporosis medications found in the literature, where important differences in magnitude reported among studies also arise, some showing similar figures to those of the present study [24-31]

This study has some limitations. First, our cohort was recruited by doctors that previously underwent a comprehensive, one-year long training programme in the clinical management of osteoporosis. In this sense, we may expect that our results represent high quality care occurring in the real world. This may partly explain the high values of secondary adherence to osteoporosis medications obtained in our study, although it would not affect the differences among assessment methods observed. Second, other measures of secondary adherence are used in the literature, however, PDC (or truncated MPR) is the most commonly used metric and thus more useful for comparative purposes. Third, we compare two methods of calculation of PDC based on dispensation information, while other variations can be found in the literature. For instance, some authors apply censoring when calculating PDC in the presence of persistence gaps, but we discarded these types of approaches as they are usually incorrect for adherence assessment purposes. Fourth, we did not examine the precise reasons for non-adherence, as for instance adverse effects, that may affect treatment continuation by both the physician and patient. Fifth, pharmacy claims data report only prescription filling, not actual medication use. Nevertheless, several studies have shown a high consistency between dispensation and patient consumption [32,33]. Sixth, drugs dispensed at the hospital are not recorded in the database. Patients could be misclassified as non-adherent (non- persistent and low availability) during their hospital stay. Last, exposure/days's supply misclassification may influence estimates of adherence, as shown in other contexts[34], although this is expected to be a minor issue in electronic dispensing systems. Despite the later limitations, retrospective cohort studies currently represent the gold standard for the estimation of real-world medication adherence.

In conclusion, we have shown that linking prescription and dispensation data allows for an accurate, refined estimation of secondary adherence versus using dispensation-only data. This

offers a more complete and realistic view of real-world patient adherence, most notably in new users, where patterns of prescription interruption are quite frequent. Finally, interventions aimed at improving medication adherence may also benefit from a more accurate identification of patients at higher risk of non-adherence.

Transparency section

Funding

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Conflict of Interest/Disclosure

None of the sponsors played any role in the design of the ESOSVAL studies, the collection, analysis or interpretation of data, the writing of the manuscript or in the decision to submit it for publication. FISABIO has received research grants from various pharmaceutical companies (see funding of the ESOSVAL project). The authors declare no additional conflict of interests.

Author contributions

AG, JS, GS, SP were responsible for the study concept, design and, with IH, for data acquisition. AG drafted the manuscript. IH prepared the database and carried out the main statistical analyses. All authors participated in the study design and interpretation of data, and contributed to the critical revision of the manuscript for important intellectual content. All authors agree to be accountable for all aspects of the manuscript.

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Appendix 1

Table 1. Periods of effective assessment when the follow-up is defined at 24 months using different PDC calculation methods

	New users		Experienced users	
PDC	**Periods of follow-up and effective assessment (months)**			
Dispensation-only data	**Formal follow-up**	**Effective assessment period**	**Formal follow-up**	**Effective assessment period**
PDC-DFI	24	23.78	24	23.95
PDC-DLR	24	17.01	24	20.75
Prescription and dispensation data				
PDC-PD3	24	24 (16.3)	24	24 (20.82)
PDC-PD	24	24 (15.94)	24	24 (20.38)

PDC: Proportion of Days Covered; PDC-DFI: PDC, calculated with dispensation-only data and a fixed interval of assessment; PDC-DLR: PDC, calculated with dispensation-only data and an interval of assessment censored at the moment of the last refill; PDC-PD: PDC, calculated with linked prescription and dispensation data and censoring any period of gaps in prescription from the calculation of PDC; PDC-PD3: PDC, calculated with linked prescription and dispensation data and censoring any period of 3 month gaps or longer in prescription from the calculation of PDC.

In the case of estimators built using dispensation-only data, the effective assessment period is shorter than the formal follow-up period, due to censoring for deaths and disenrollment in the case of PDC-DFI, and to additionally censoring the time between the last dispensation and the end of the formal follow-up period in the case of PDC-PLR. The denominator of the formula for calculating the PDC is therefore shorter than the formal follow-up period. When linking prescription and dispensation data, the follow-up period remains stable (24 months), and the denominator for the calculation of the PDC is adjusted by gaps in prescription (figures in brackets).

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Impact of Drug Safety Warnings and Cost-sharing Policies on Osteoporosis Drug Utilization in Spain: a Major Reduction but with the Persistence of Over and Underuse. Data from the ESOSVAL Cohort from 2009 to 2015.

Osteoporosis Drug Utilization in Spain

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ABSTRACT

Background. Recent studies in several countries show a significant decrease in the consumption of osteoporosis drugs from a peak around 2009, mainly attributed to bisphosphonate safety warnings issued by regulatory agencies on jaw osteonecrosis, atypical fractures and esophageal cancer, but no studies have assessed the impact of these warnings by risk of fracture strata.

Aim. The aim of this work is to assess changes in the utilization of osteoporosis drugs in the region of Valencia (Spain) after safety warnings from regulatory agencies and cost-sharing changes, according to patient socio-demographic and risk of fracture characteristics.

Patients and Methods. We constructed a monthly series of osteoporosis drug consumption for 2009-2015 from the ESOSVAL cohort (n=11,035; women: 48%; mean age: 65 years old) and used interrupted time series and segmented linear regression models to assess changes in osteoporosis drug utilization while controlling for previous levels and trends after three natural intervention dates: the issue of the Spanish Agency for Drugs and Medical Products (AEMPS) Osteonecrosis Jaw Warning (Sept 2009), the AEMPS Atypical femur Fracture Warning (Apr 2011) and the modification of the cost-sharing scheme (Jul 2012).

Results. The AEMPS Osteonecrosis Jaw Warning was not associated with a decline in the consumption of osteoporosis drugs, while the warning on Atypical Fracture (a downward trend of 0.11% fewer people treated each month) and the increase in the cost-sharing scheme (immediate change level of -1.07% in the proportion of people treated) were associated with a strong decline in the proportion of patients treated, so that by the end of 2015 osteoporosis drug consumption was around half that of 2009. The relative decline was similar in people with both a high and low risk of fracture.

Conclusion. The AEMPS Atypical femur Fracture Warning of Apr 2010 was associated with a significant decrease in the number of people treated, reinforced by the increase in the

pharmaceutical cost-sharing in 2012. Decreases in treatment affected patients both at a low and higher risk of fracture.

Introduction

Osteoporosis is a common problem, particularly in the elderly population which is more prone to low-impact fragility fractures. Fragility fractures represent a major public health problem because of their contribution to disability, morbidity, mortality, and their cost for health care systems and society in general [1,2]. Pharmacological secondary prevention after hip fracture – with bisphosphonates or alternative drugs– is recommended by virtually all clinical practice guidelines (CPG) [3-5] while pharmacological primary prevention is controversial [6] and CPGs are extraordinarily variable in their assessment of fracture risk factors, risk thresholds, drug risk assessment and recommendations for pharmacological treatment in previously non-fractured patients [7-11]. This uncertainty translates into a great variability in the use of osteoporosis drugs, which combines overuse (osteoporosis treatment in populations with a low risk of fracture, especially young adult women) and underuse (no treatment in men and women with a previous low-impact fracture or at a high risk of fracture) [9,12,13].

While Spain is one of the European (and worldwide) countries with a lower incidence of osteoporotic fracture [2,14], osteoporosis drug consumption experienced a very rapid growth during the 2000s [15,16], Spain being one of the countries with the highest utilization rates at the end of that decade [17]. For instance, the baseline data of the ESOSVAL cohort, recruited in 2009-2010, showed a prevalence of osteoporosis drug treatment of 28% in women aged 50 and over [18]. Notwithstanding, recent studies in several countries show a significant decrease in the consumption of osteoporosis drugs from a peak in around 2009 [19-22], including those for secondary prevention after hip fracture [23,24]. This fall has been mainly attributed to safety warnings issued by regulatory agencies on jaw osteonecrosis, atypical fractures and esophageal cancer [25-27], and also to uncertainty about optimal bisphosphonate treatment duration and recommendations for discontinuation after 3 to 5 years of therapy, as the benefit-risk balance

may become negative in the long term, particularly in patients with a low risk of osteoporotic fracture [28].

In this study, we hypothesize that safety warnings on oral bisphosphonates (the most widely prescribed osteoporosis drug class) issued by the Spanish Agency for Drugs and Medical Products (AEMPS) and the modification of the cost-sharing scheme (with both a 8-10% copayment for retired people who were previously exempt and increases in the copayment for most of the active working population) may have produced a reduction in the global prescription of osteoporosis drugs. Also, we hypothesize that, according to the fact that drug agencies maintained a positive risk-benefit balance in high-risk patients in their warnings, this reduction may occur mainly in people with a low risk of fracture (young people, without risk factors for secondary osteoporosis, without a previous fracture or with low-risk scores in the Fracture Risk Assessment Tool (FRAX®)), thus reducing overuse but keeping –or at least reducing to a lesser extent– appropriate prescription in high-risk patients. The aim of this work, using 2009-2015 data from the ESOSVAL prospective cohort, is to assess changes in the utilization of osteoporosis drugs in the Valencia Region (Spain) after the issue of safety warnings from regulatory agencies and cost-sharing changes, according to patient socio-demographic and risk of fracture characteristics.

Material and Methods

Design

We use 2009-2015 data from the ESOSVAL prospective cohort to describe changes in osteoporosis drug consumption according to sociodemographic and clinical risk factors at baseline.

Setting

The study was conducted in the VHS, an extensive network of public hospitals and primary healthcare centres which is part of the Spanish National Health System, funded and mostly provided by the Valencia Region Government, free at the point of care (except for some co-payments for out-of-hospital medication, increased in July 2012), and almost universal, covering about 97% of the region's population (approximately 5 million inhabitants).

Population

The ESOSVAL cohort, designed to develop a risk fracture assessment tool for the European Mediterranean population with a prevision of 10 years of follow-up, has been fully described elsewhere [10,18,29,30] and was composed of about 11,000 people aged 50 years and over attending 272 primary healthcare centers in the Valencia Health System (VHS) for any health problem between November 2009 and September 2010. Participants were recruited by 600 general practitioners and primary-care nurses collaborating for free in the ESOSVAL study and following predefined criteria attempting to obtain a similar number of men and women, and with an age distribution as close as possible to the distribution of the region's population.

The baseline characteristics of the ESOSVAL cohort (n=11,035; women: 48%; men: 52%; mean age: 65 years old) have been fully described elsewhere [18] and are summarized in **Table 1**. The exclusion criteria comprised temporary residents, individuals with cognitive impairment, people receiving their usual care through private insurance companies, people physically unable to attend their primary healthcare center, and people of Asian or African descent.

Data sources and study development

The main source of data was the VHS ambulatory electronic medical record (EMR), which among other information includes demographic and clinical data and information on prescriptions and dispensations. In the context of the ESOSVAL project and in collaboration with the VHS, the

ambulatory EMR was modified to include a specific osteoporotic risk sheet to facilitate the registration of fracture risk factors, patient monitoring and decision making about the need for complementary tests or pharmacological treatment. The EMR was modified for all VHS centres, but doctors and nurses participating in the ESOSVAL project were trained to standardize definitions and to fill in the EMR-specific osteoporotic risk sheet.

Main endpoint

Changes associated with the AEMPS safety warnings and cost-sharing changes in the monthly proportion of people filling any osteoporosis drug (bisphosphonates, calcitonin, denosumab, parathyroid hormone [PTH, 1-34 and 1-84], raloxifene or strontium ranelate) between 1 Jan 2009 and 31 Dec 2015. Figures do not include zoledronic acid because inpatient based dispensation is not recorded in the ambulatory EMR, nor over-the-counter medication or treatments prescribed by private doctors not reimbursed by the VHS.

Variables

The variables used in the present study include the patients' sociodemographic and clinical baseline characteristics such as age, sex, educational level (no studies, primary studies, and secondary/university), and personal history of any previous osteoporotic fracture. Using the FRAX® tool calibrated for Spain (www.shef.ac.uk/FRAX/index.htm) we estimated the 10-year risk of hip fracture for each patient [31]. Data in the FRAX® web were introduced by the research team and calculations were based on gender, age, body mass index, personal history of previous fracture, family history of fracture, current smoking, glucocorticoid use, rheumatoid arthritis, other osteopenic diseases, alcohol intake and bone mineral density (BMD) measurement, if available (Women: 25.0%; Men: 5.2%). In accordance with the FRAX® recommendations, missing values were considered as normal. Although in Spain there are no official cutoff points for defining populations at a high or low risk of hip fracture, we tentatively use the criteria of the

Scientific Advisory Council of Osteoporosis in Canada [32] to classify the FRAX® scores as low-risk (10-year risk of hip fracture <3 %) or high-risk (10-year risk of hip fracture ≥3 %).

Statistical analysis

First, we describe the baseline characteristics of the ESOSVAL cohort by gender and age groups at baseline (50–64, 65 and over) with the corresponding 95% confidence intervals calculated using the binomial approach. Second, we estimate the monthly proportion of patients treated with any osteoporosis drug (except zoledronic acid) according to sociodemographic and risk variables at baseline, and we calculate the risk ratio (RR) of being treated each month with respect January 2009 (the first month of the corresponding series). Considering the characteristics of the pharmaceutical package presentations authorized for osteoporosis treatment in Spain (almost all contain doses for four weeks or one month of treatment), we define "treated patients" as patients filling at least one package of any osteoporosis drug in the corresponding month, except for packages of ibandronic acid blister of 3-monthly tablets (we assume a 3 month coverage for that presentation) and denosumab (according to its recommended dosage, we assume a 6 month coverage for each package). Stockpiling was allowed for up to one month of treatment (e.g. for a patient filling two packages one month and none the next, both months were considered as covered by treatment).

Third, we used interrupted time series and segmented linear regression models to assess changes in osteoporosis drug utilization while controlling for previous levels and trends after three natural intervention dates: 1) the issue of the AEMPS Osteonecrosis Jaw Warning (ONJ warning, Sept 2009), 2) the issue of the AEMPS Atypical femur Fracture Warning publication (AF warning, Apr 2011) and, 3) the modification of the cost-sharing scheme on pharmaceuticals (Jul 2012). Trends are presented in natural scale (proportion of people treated) and in RR scale (ratio between the proportion of people treated each month and the proportion of people treated in January 2009) to compare the relative variations between strata in homogeneous terms. Model

parameters and figures for the different segmented regressions are shown in the **Supplementary Files (Tables S2 to S11 and Figures S1 to S10).** Finally, in the supplementary files we analyze separately the annual consumption trends of the different osteoporosis drugs in terms of months of treatment dispensed each year, percentage of market share, and the annual ratio of dispensed treatments with respect to 2009 **(Supplementary Files Table S12 and Figures S11 and S12)**.

In all analyses, people who died were excluded from the respective denominator in the month of death. Cases with missing data in one variable were eliminated from the analyses using that variable. All analyses were performed using the STATA 13.0 (StataCorp, College Station, TX) statistical software.

Ethical aspects

The ESOSVAL project is an observational study with no intervention components apart from the training of participating clinicians, and with no additional tests, visits, evaluations, or treatments provided apart from what the attending physician deemed appropriate. All patients included in the study signed the informed consent form granting the researchers access to the information contained in their medical record for the study purposes. The information relative to the patients was handled according to Spanish and European regulations on data protection and patients' digital rights. The ESOSVAL project was approved by the Committee for Ethics and Clinical Trials of the Centre for Public Health Research and the Public Health General Directorate (decision March 27, 2009).

Results

Mean age at recruitment was 64.3 (SD: 9.3) years for women and 65.6 (SD: 9.9) years for men, with 42.7% of the women and 47.9% of the men being 65 years old and over. Women had a lower educational level than men, and both had a lower educational level in the more aged stratum (**Table 1**). Most prevalent fracture risk factors were falls (20.3%), personal history of

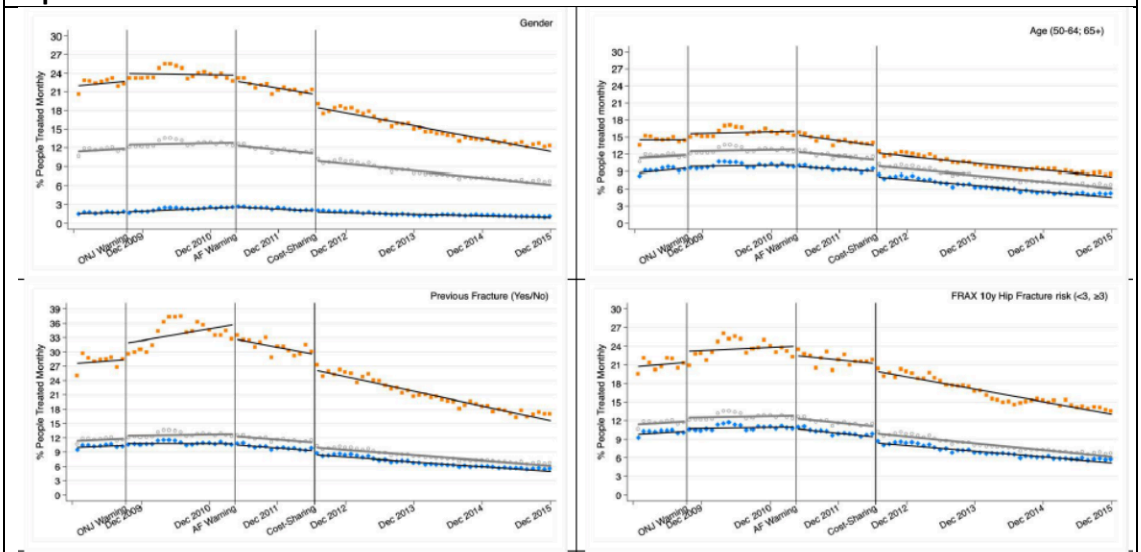
fracture (8.0%), and osteopenic diseases (12.3%) and, in general, risk factors were more prevalent with age. Using the Canadian thresholds [32], 13.5% of the ESOSVAL population showed a high risk (≥3%) of hip fracture (0,4% in people under 65 years old and 29.4% in people of 65 and over). The proportion of the population at a high risk of hip fracture in people under 65 was 0.7% for women and 0.1% for men, while 22% of women and 1.7% of men from this age-group were taking osteoporosis drugs and 20.6% of women and 2.4% of men were taking calcium and/or vitamin D supplements at recruitment.

Table 1. Baseline characteristics of the ESOSVAL cohort at recruitment.

	Women		Men		All		
	50-64 n=3,043	≥65 n=2,267	50-64 n=2,983	≥65 n=2,742	50-64 n=6,026	≥65 n=5,009	All N=11,035
Educational level [% (95CI)]							
No studies	16.1 (14.7;17.5)	50.6 (48.4;52.7)	12.3 (11.1;13.6)	42.4 (40.5;44.4)	14.2 (13.3;15.2)	46.1 (44.7; 47.6)	28.7 (27.8; 29.5)
Primary	50.5 (48.6;52.4)	37.3 (35.3;39.4)	45.1 (43.2;47.0)	37.9 (36.0;39.8)	47.8 (46.5; 49.2)	37.6 (36.2;39.0)	43.2 (42.3;44.2)
Second/University	33.4 (31.7;35.2)	12.1 (10.8;13.6)	42.6 (40.7;44.5)	19.7 (18.2;21.3)	37.9 (36.7;39.2)	16.2 (15.2;17.3)	28.1 (27.3; 29.0)
Personal history of previous osteoporotic fracture [% (95CI)]							
	6.6 (5.8;7.5)	18.0(16.5;19.7)	3.3 (2.7;4.0)	6.2 (5.3;7.1)	5.0 (4.5;5.6)	11.5 (10.7;12.5)	8.0 (7.5;8.5)
Falls (≥1 in the last year) [% (95CI)]							
	22.5 (21.0;24.1)	30.0 (28.1;32.0)	12.2 (11.0;13.5)	18.6(17.1;20.1)	17.4 (16.5;18.4)	23.7 (22.5;24.9)	20.3 (19.5;21.1)
Glucocorticoids use (prednisolone equivalent >5mg/day at least 3 months in the last year) [% (95CI)]							
	0.5 (0.3;0.8)	1.7 (1.3;2.3)	0.9 (0.6;1.3)	1.5 (1.1;2.0)	0.7 (0.1;1.0)	1.6 (1.3;2.0)	0.1 (0.0;1.3)
Osteopenic diseases included in the FRAX tool excluded hypogonadism [% (95CI)]							
	9.5 (8.4;10.6)	14.2 (12.7;15.7)	10.4 (9.3;11.6)	16.2(14.8; 17.6)	9.9 (9.2;10.7)	15.3 (14.3;16.3)	12.3 (11.7;13.0)
Hypogonadism [% (95CI)]							
	5.8 (4.9;6.7)	5.8 (4.8;6.9)	0.7 (0.4;1.1)	1.5 (1. 1;2.1)	3.3 (2.8;3.8)	3.4 (2.9;4.0)	3.3 (3.0;3.7)
FRAX 10-years risk of hip fracture ≥3% [% (95CI)]							
	0.7 (0.4;1.1)	41.6 (39.5;43.7)	0.1 (0.0;0.3)	19.3 (17.9;20.9)	0.4 (0.2;0.6)	29.4 (28.1;30.7)	13.5 (12.9;14.2)
Calcium and/or Vitamin D supplements [% (95CI)]							
	20.6 (19.2;22.1)	35.8 (33.8;37.8)	2.4 (1.9;3.0)	4.9 (4.1;5.8)	11.6 (10.8;12.5)	18.9 (17.8;20.0)	14.9 (14.3;15.6)
Antiosteoporotic treatment (any drug) [% (95CI)]							
	22.0 (20.5;23.5)	36.3 (34.3;38.3)	1.7 (1.3;2.3)	3.1 (2.5;3.8)	12.0 (11.2;12.8)	18.1 (17.1;19.2)	14.8 (14.1;15.4)

The percentage of people treated in the entire cohort grew from 10.6% of the cohort in Jan 2009 to a peak of 13.5% in May 2010, descending from that month to 6.7% in December 2015, a relative reduction of 59% from Jan 2009, and of 104% from the peak of treatment. **Figure 1** shows the results of the segmented linear regression models for the whole ESOSVAL cohort and stratified by gender, age, and previous fracture and FRAX 10-year risk of hip fracture. In all analyses, and despite the ONJ warming in Sept 2009, trends were rising until the AF warning in Apr 2011, starting a downward trend from that moment until the end of the period only altered by a sudden drop associated with the cost-sharing policy change in Jul 2012.

Figure 1. Osteoporosis treatment segmented linear regression trends 2009-2015 for all the ESOSVAL cohort and stratified by gender, age, previous fracture and FRAX 10 years risk of hip fracture.



ONJ: Osteonecrosis Jaw; AF: Atypical Fracture. Marks: circle (all); Orange/Square (Women, ≥65 years, Previous fracture, FRAX ≥3); Blue/Diamond (Men, 50-64 years, No previous fracture; FRAX<3). Lines represent the results of the regression, while marks (circles, squares and diamonds) represent observations.

Table 2 shows the most relevant parameters of the segmented regressions for the entire cohort and the stratum analyzed (**see Supplementary Materials for the complete models: tables S2 to S6 and figures S1 to S5**). In the entire ESOSVAL cohort, the proportion of people treated increased from an initial constant of 11.3% until the release of the AF warning when, with a non-significant immediate level change, a downward trend began with 0.11% fewer people treated

each month. The change in the cost-sharing scheme abruptly reduced by 1.07% the proportion of people treated (immediate level change), but the downward trend initiated immediately after the AF warning was not affected. This pattern of downward trends associated with the AF warning and the level change associated with the cost-sharing change can be observed in all stratified analyses. Also, some of the higher consumption strata showed increases in the level change associated with the issue of the ONJ warning (women, 65 years and over, previous fracture and FRAX risk of hip fracture ≥3%) and level changes associated with the issue of the AF warning (women, previous fracture and FRAX risk of hip fracture ≥3%).

Table 2. Segmented regression parameters for all people, and stratified by gender, age, previous fracture and FRAX 10 years risk of hip fracture.

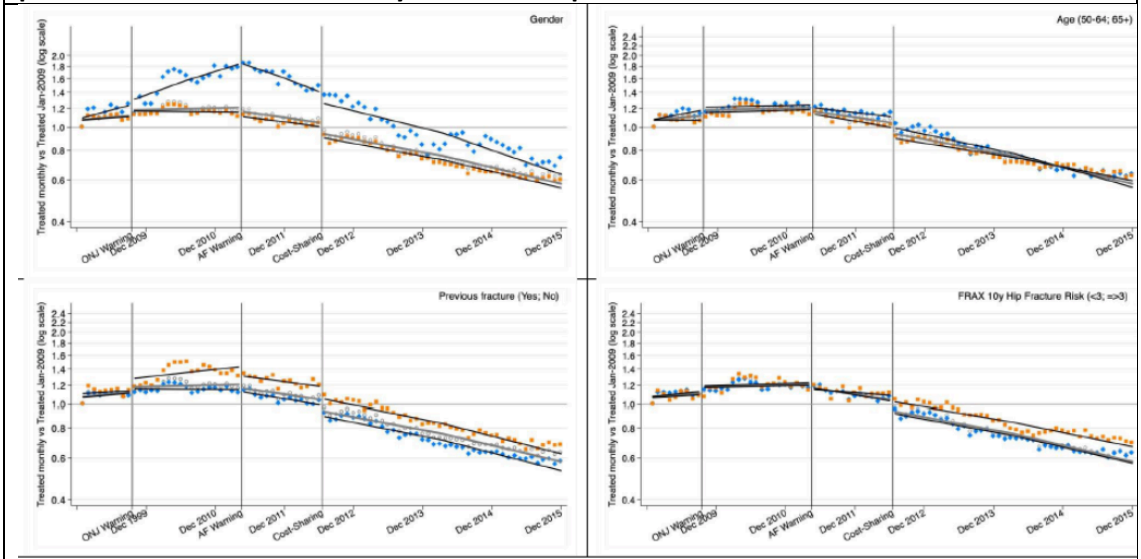
	All	Gender		Age		Previous Fracture		Hip FRAX ≥3%	
		Men	Women	50-64	65+	No	Yes	No	Yes
Initial Constant	11.31*	1.50*	21.89*	8.66*	14.51*	9.92*	27.47*	9.76*	20.63*
Trend from Start to ONJ Warning	0.05	0.02	0.09	0.10*	-0.001	0.05	0.09	0.06	0.08
Constant 2nd period/ONJ Warning issue	0.65*	0.67	1.31*	0.30	1.07*	0.43	3.42*	0.42	1.83*
Trend from ONJ Warning to AF Warning	-0.04	0.17	-0.10	-0.09	0.02	-0.05	0.12	-0.04	-0.04
Constant 3rd period/AT Warning issue	-0.40	0.05	-0.90*	-0.24	-0.60	-0.20	-2.87*	-0.19	-1.47*
Trend from AF Warning to Cost-Sharing change	-0.11*	-0.09*	-0.14*	-0.07*	-0.16*	-0.09*	-0.44*	-0.11*	-0.14
Constant 4th period/Cost-Sharing change	-1.07*	-0.20*	-2.02*	-0.87*	-1.32*	-0.87*	-3.21*	-0.97*	-1.14*
Trend from Cost-Sharing change	0.001	0.02*	-0.02	-0.03	0.04	0.01	-0.03	0.02	-0.07

ONJ: Osteonecrosis Jaw; AF: Atypical fracture
n=84 months; R^2: from 0.93 to 0.98 according models. *p<0.05

Figure 2 shows the segmented regressions with the ratio between the proportion of patients treated each month and the proportion treated in January 2009 **(see Supplementary Materials –Tables S7 to S11, Figures S6 to S10- for model parameters)**. The downward trends initiated after the AF warning were similar for the different risk strata, somewhat more pronounced in men (who had previously experienced greater growth), although the relative decline at the end

of the period was slightly lower in men and in people with a previous fracture (at the expense of a greater relative increase in the period prior to the AF warning), or with a FRAX hip fracture risk ≥3 % (at the expense of a lower level change associated with the change in the cost-sharing scheme). By age, the reduction was similar in people both under and over 65 years old.

Figure 2. Ratio of osteoporosis treatment each month regarding January 2009. Segmented linear regression trends 2009-2015 for all the ESOSVAL cohort and stratified by gender, age, previous fracture and FRAX 10 years risk of hip fracture.



ONJ: Osteonecrosis Jaw; AF: Atypical Fracture. Marks: circle (all); Orange/Square (Women, ≥65 years, Previous fracture, FRAX ≥3); Blue/Diamond (Men, 50-64 years, No previous fracture; FRAX<3). Lines represent the results of the regression, while marks (circles, squares and diamonds) represent observations.

Discussion

Our study shows that osteoporosis drug utilization in the Valencia region increased until mid-2011 and then started to decline, so that by the end of 2015 global consumption was around a half of 2009 and almost two thirds less than the maximum peak in 2010. The AF safety warning of April 2011 and to a lesser extent the increase in the pharmaceutical cost-sharing (associated with a sudden descent in the months immediately after July 2012 but without altering the temporary trend) seem to have had a strong influence on this decline, which nonetheless does not seem to be related to the clinical characteristics of patients, as we observe a similar relative

decline in those with both a high and low risk of fracture. To the best of our knowledge, no previous studies in this field have assessed the impact of warnings on several risk strata (age, gender, risk of fracture).

The beginning of the decrease in the consumption of osteoporosis drugs happened at an earlier moment in Australia [19], the UK [20] or the US [21,22], with a maximum peak in 2009 and starting to fall in 2010, coinciding with the FDA Warning on the association between long-term use of bisphosphonates and atypical fractures (requiring drug manufacturers to include a recommendation for considering discontinuation after 3-5 years of treatment in patients at a low risk of fracture). However, certain parallels exist as the Spanish Agency for Medicines and Medical Devices did not publish the warning on atypical fractures (simultaneously with the European Medicines Agency) until mid-2011, a year after the FDA warning. None of these previous studies in Australia, the UK or the US evaluated the appropriateness of treatment according to patient risk factors, so these results cannot be compared with those of our study, but the decline of secondary prevention with osteoporosis drugs after hip fracture in the US started before 2010 intensified after the FDA 2010 warning [23,24]. A cross-national study also seems to show a declining trend in bisphosphonate use following hip fracture after 2010 in Spain, the US and Korea, compensated for in this last country by the use of other osteoporosis drugs [33].

In addition to bisphosphonate safety warnings issued by regulatory agencies, other factors may have contributed to the decline in the consumption of osteoporosis drugs in Spain. First the expiration of most patents, with the associated cessation of pharmaceutical promotion and proprietary firm efforts to neutralize the impact of warnings (note that warnings on jaw osteonecrosis with some bisphosphonate patents in force had little impact, if any, on osteoporosis drug utilization); Second, the contagion from safety warnings on other osteoporosis drugs, including the practical withdrawal of calcitonin and strontium ranelate [see ***Supplementary Material Table S1***]; Third, the influence from the previous FDA atypical fracture

warning, with a wide repercussion in medical journals, scientific meetings and guidelines, including an important controversy about the suspension of the treatment and its duration (the so-called “therapeutic holidays"). And finally, and as studies in other therapeutic areas [34] and the results of our study show, the introduction of a new cost-sharing scheme with an 8-10% copayment for retired people (previously exempt) and increases in the copayment for most of the active working population and their families.

The benefit in terms of fracture prevention provided by bisphosphonates far outweighs the potential risks of atypical fracture and jaw osteonecrosis in most patients at a high risk of fracture [35,36]. Although our study does not directly address treatment appropriateness (or its absence), the analysis of fracture risk factors strongly suggests the existence of a high proportion of inappropriate treatment in low risk people (for instance, approximately three quarters of treatments in 2015 were dispensed to patients with FRAX 10-year risk of hip fracture below 3%) and also of a high proportion of inappropriate absence of treatment (only 14% of the ESOSVAL cohort patients with a 10-year risk of hip fracture equal to or above 3% were receiving treatment at the end of 2015). Therefore, and despite the decrease in osteoporosis drug consumption, a significant concern about overuse remains and is even reinforced with regard to underuse in patients at risk.

Strengths and Limitations

Our study has strengths and limitations. Among the former, it should be noted that –even if introduced in the EMR– the baseline data was collected prospectively by doctors and nurses trained in osteoporosis and in the operational definitions of the study. Additionally, data from the VHS electronic prescription information system is of high quality, and includes paperless electronic prescription, the registration of any dispensation in any community pharmacy and reimbursement to pharmacies in a traceable way for each pharmaceutical package and each patient.

Among the limitations, the first is the use of the baseline characteristic of the ESOSVAL cohort to stratify the risk of fracture, when several of these characteristics (e.g. the incidence of previous fracture or the FRAX scores) may have changed with advancing age in the 5-6 years of the cohort follow-up and the risk level of some patients could be misclassified in the final years of the study. Second, we have no information on zoledronic acid consumption, which is restricted to inhospital use in our country. Although it is likely that some patients may still be treated with this drug (thus our study would underestimate the proportion of patients treated), studies in other countries indicate that zoledronic acid has undergone a decrease in consumption similar to that of other bisphosphonates [37]. Third, we have not analyzed the importance of the possible mechanisms operating in the decrease in osteoporosis drug consumption (non-adherence, discontinuation, therapeutic holidays, decrease of initiators or others), an essential aspect for the design of underuse improvement strategies or to assess the impact of this decrease on clinical outcomes, an essential element to establish the substantive importance of over and underuse. In any case, the current evidence would support a negative risk-benefit balance in the case of low-risk patients and positive in high-risk patients, with large gray areas in the intermediate risks and with respect to the duration of treatment or possible temporary discontinuations. Finally, doctors who enrolled patients in the ESOSVAL cohort were the object of an educational intervention coinciding with the cohort recruitment period (2009-2010), an aspect that could have modified the initial prescription behavior.

Despite these limitations, our study shows a worrying evolution of treatment for the prevention of osteoporotic fracture in our environment, where an important problem of overuse still remains, while the problem of underuse is intensified. This situation urgently requires approaches (professional and organizational) focused on high-risk population (especially in secondary prevention after hip and vertebral fracture) that selectively addresses underutilization, while continuing efforts to avoid treatments in low-risk people.

Conclusion

The AEMPS ONJ warning of Sept 2009 was not associated with a decline in the consumption of osteoporosis drugs, while the AEMPS AF warning of Apr 2010 was associated with a significant decrease in the number of people treated, reinforced by the increase in the pharmaceutical cost-sharing occurred in 2012. As a result, in December 2015 only half of the patients that of May 2010 (the month with the highest proportion of treatment) were under treatment. Decreases in treatment affected patients both at a low and higher risk of fracture.

Acknowledgements

We are grateful to all doctors and nurses at the Valencia Health Agency primary healthcare centres participating in the ESOSVAL study for their collaboration, and to the Valencia Ministry of Health for its enthusiastic and continued support of the ESOSVAL research projects.

Author Contributions Statement

G.S.G. had full access to all the data in the study and takes responsibility for their integrity and of the accuracy of their analysis. G.S.G., J.S.G., I.H. and S.P. were responsible for the study concept, design and data acquisition. G.S.G., I.H., A.G.S. and C.L.R.B. carried out the data preparation and the statistical analysis and A.G.S. drafted the manuscript. All authors participated in the analysis and interpretation of data, critical revision of the manuscript for important intellectual content, all approved the final version submitted for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Supplementary Material

Table S1. AEMPS warnings and informative notes on osteoporosis drugs (2009-2015)	
Nov 8, 2005	Bisphosphonates for parenteral administration and jaw osteonecrosis.
Set, 2009	Recommendations for the prevention of jaw osteonecrosis associated with treatment with bisphosphonates.
Apr, 2011	Bisphosphonates and risk of atypical femur fractures.
Mar, 2012	Strontium ranelate (Osseor®, Protelos®): risk of venous thromboembolism and serious dermatological reactions. New contraindications for use.
Jul, 2012	Calcitonin: use restricted to short-term treatments.
Apr, 2013	Calcitonin: suspension of the commercialization of intranasal preparations and restriction in the use of injectable preparations to short-term treatments.
Apr, 2013	Strontium ranelate (Osseor®, Protelos®): risk of acute myocardial infarction
Jan, 2014	Strontium ranelate (Osseor®, Protelos®): the European review concludes that the benefit-risk balance is unfavorable
Feb, 2014	Completion of the review of the benefit-risk balance of strontium ranelate (Osseor®, Protelos®): restrictions in use.
Jul, 2014	Strontium ranelate (Osseor®, Protelos®): qualified as a hospital diagnosis drug.
Set, 2014	Denosumab (Prolia®, Xgeva®): risk of jaw osteonecrosis and hypocalcemia.

Table S2. Proportion of people treated (ESOSVAL Cohort). Segmented regression analysis.

	AGE: <65 AT RECRUITMENT			
	Coef.	p	95%CI	
Initial Constant	11.31	<0.001	10.78	11.85
Trend from Start to ONJW	0.05	0.260	-0.04	0.15
Constant 2nd period/ONJW	0.65	0.026	0.08	1.22
Trend from ONJW to AFW	-0.04	0.466	-0.93	0.06
Constant 3rd period/AFW	-0.40	0.131	-0.93	0.12
Trend from AFW to Cost-sharing change	-0.11	<0.001	-0.17	-0.05
Constant 4th period/Cost-sharing change	-1.07	<0.001	-1.51	-0.63
Trend from Cost-Sharing change	<0.01	0.930	-0.05	0.05
n=84 months; R^2: 0.976. ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning				

Figure S1. Segmented linear regression. Entire ESOSVAL Cohort

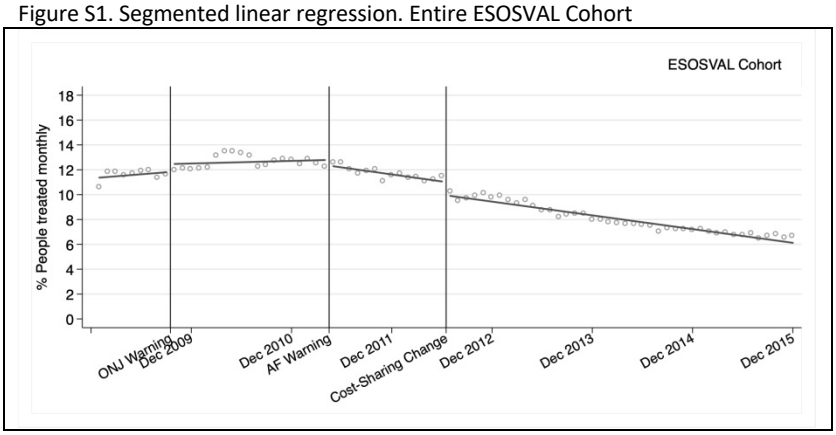
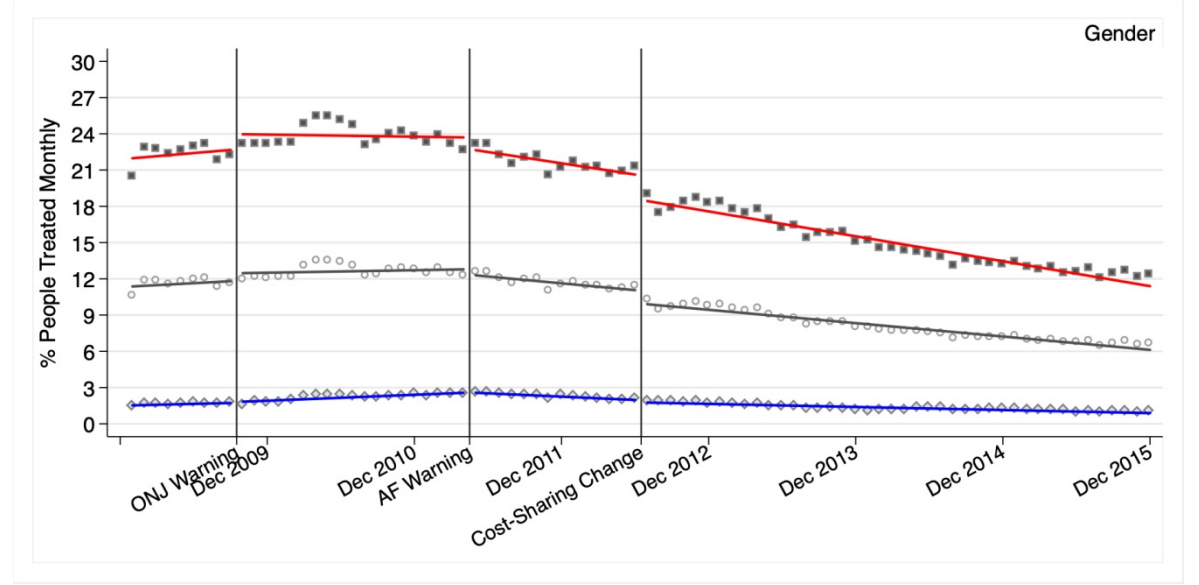


Table S3. Proportion of people treated by gender. Segmented regression analysis.								
	WOMEN					MEN		
	Coef.	p	95%CI			Coef.	p	95%CI	
Initial Constant	21.89	<0.001	20.93	22.85		1.50	<0.001	1.31	1.69
Trend from Start to ONJW	0.09	0.317	-0.08	0.26		0.02	0.156	-0.01	0.06
Constant 2nd period/ONJW	1.31	0.013	0.28	2.33		0.07	0.514	-0.16	0.27
Trend from ONJW to AFW	-0.10	0.267	-0.28	-0.08		0.02	0.352	-0.02	0.05
Constant 3rd period/AFW	-0.90	0.062	-1.85	0.04		0.05	0.586	-0.13	0.24
Trend from AFW to Cost-sharing change	-0.14	0.008	-0.24	-0.04		-0.09	<0.001	-0.11	-0.07
Constant 4th period/Cost-sharing change	-2.02	<0.001	-2.81	-1.23		-0.20	0.013	-0.35	-0.04
Trend from Cost-Sharing change	-0.02	0.714	-0.11	0.07		0.02	0.007	0.01	0.04
n=84 months; R^2: 0.932 (men); 0.977 (Women). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning									

Figure S2. Segmented linear regression by gender



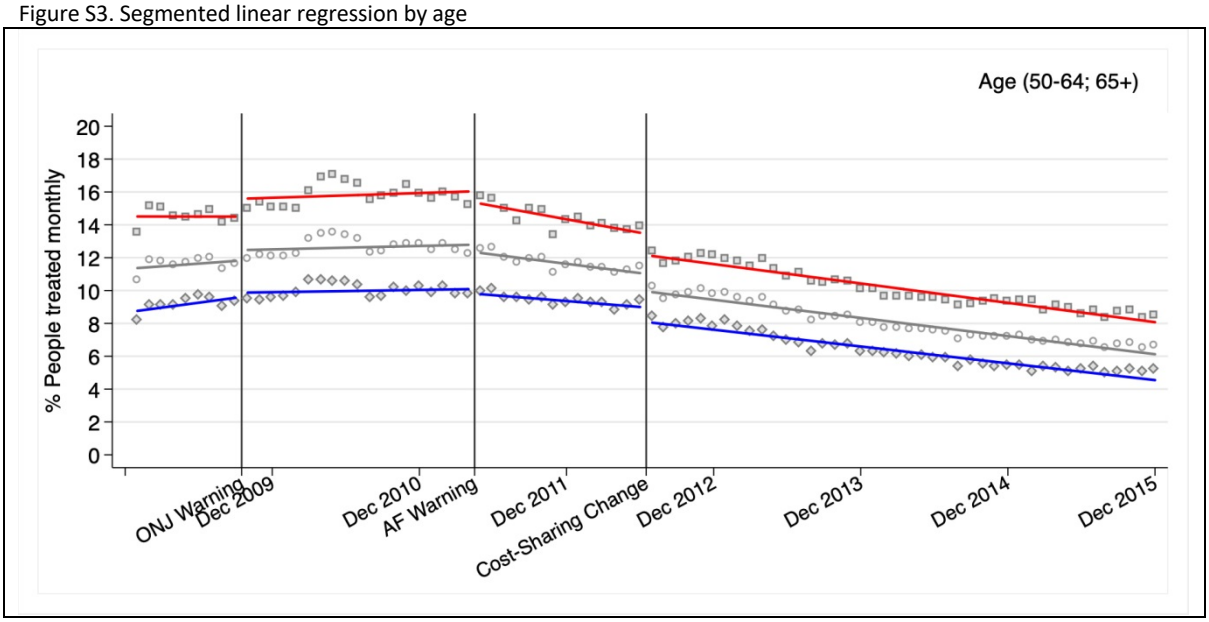
Women: red line; Men: blue line; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S4. Proportion of people treated by age. Segmented regression analysis.

	50-64 years old				65 years and over			
	Coef.	p	95%CI		Coef.	p	95%CI	
Initial Constant	8.66	<0.001	8.18	9.14	14.51	<0.001	13.83	15.18
Trend from Start to ONJW	0.10	0.024	0.01	0.19	<-0.01	0.991	-0.12	0.12
Constant 2nd period/ONJW	0.30	0.248	-0.21	0.82	1.07	0.004	0.35	1.80
Trend from ONJW to AFW	-0.09	0.057	-0.18	<0.01	0.02	0.699	-0.10	0.15
Constant 3rd period/AFW	-0.24	0.313	-0.72	0.23	-0.60	0.074	-1.23	0.06
Trend from AFW to Cost-sharing change	-0.07	0.008	-0.12	-0.02	-0.16	<0.001	-0.23	-0.09
Constant 4th period/Cost-sharing change	-0.87	<0.001	-1.27	-0.47	-1.32	<0.001	-1.87	-0.77
Trend from Cost-Sharing change	-0.02	0.268	-0.07	0.02	0.04	0.233	-0.02	0.10

n=84 months; R^2: 0.973 (65y and over); 0.968 (50-64y). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning

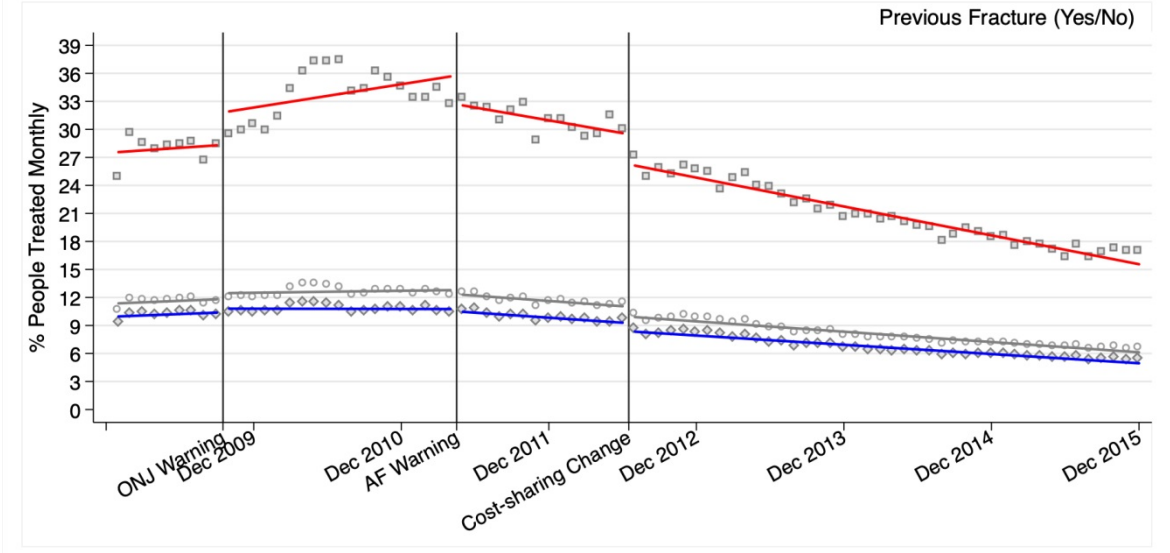
Figure S3. Segmented linear regression by age



65y and over: red line; 50-64y: blue line; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S5. Proportion of people treated by antecedent of previous fracture. Segmented regression analysis.								
	No previous fracture					Previous fracture		
	Coef.	p	95%CI			Coef.	p	95%CI	
Initial Constant	9.92	<0.001	9.48	10.36		27.47	<0.001	25.44	29.50
Trend from Start to ONJW	0.05	0.201	-0.03	0.13		0.09	0.616	-0.27	0.45
Constant 2nd period/ONJW	0.43	0.075	-0.04	0.90		3.42	0.002	1.25	5.60
Trend from ONJW to AFW	-0.05	0.202	-0.14	0.03		0.12	0.542	-0.26	0.49
Constant 3rd period/AFW	-0.20	0.354	0.64	0.23		-2.87	0.006	-4.87	-0.86
Trend from AFW to Cost-sharing change	-0.09	<0.001	-0.14	0.04		-0.44	<0.001	-0.66	-0.22
Constant 4th period/Cost-sharing change	-0.87	<0.001	-1.24	-0.51		-3.22	<0.001	-4.88	-1.55
Trend from Cost-Sharing change	0.01	0.714	-0.03	0.05		-0.03	0.762	-0.22	0.15
n=84 months; R^2: 0.954 (Previous fracture); 0.979 (No previous fracture). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning									

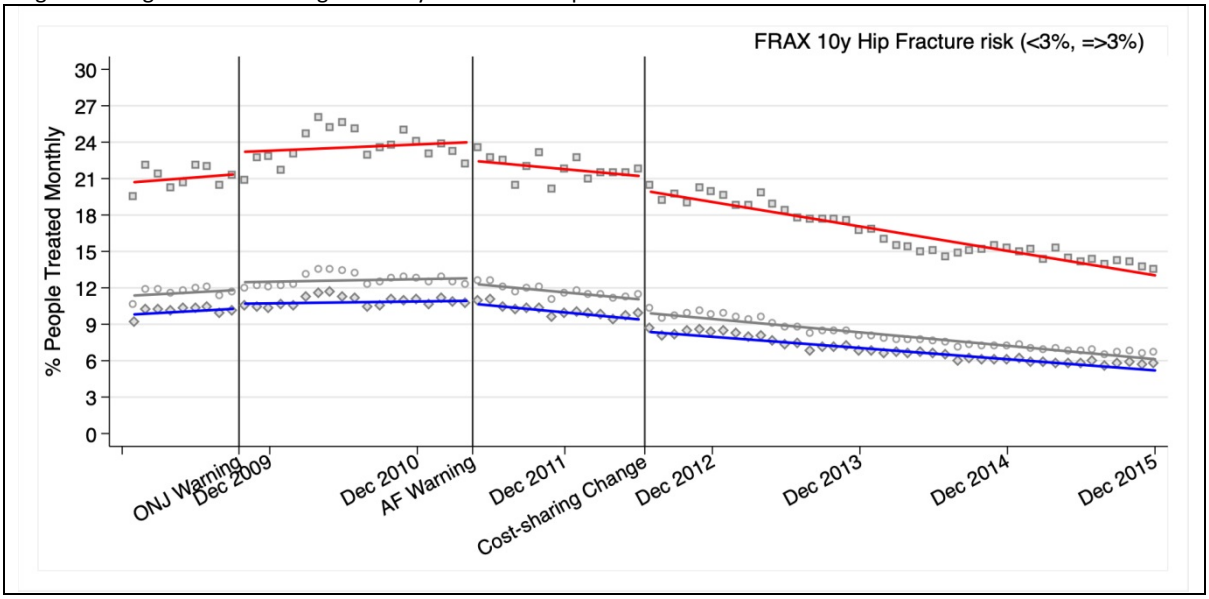
Figure S4. Segmented linear regression by previous fracture antecedent



Yes: red line; 50-64y: No; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S6. Proportion of people treated by FRAX risk of hip fracture. Segmented regression analysis.									
	<3%					≥3%			
	Coef.	p	95%CI			Coef.	p	95%CI	
Initial Constant	9.76	<0.001	9.30	10.21		20.63	<0.001	19.28	21.97
Trend from Start to ONJW	0.06	0.171	-0.02	0.14		0.08	0.514	-0.16	0.32
Constant 2nd period/ONJW	0.42	0.092	-0.07	0.91		1.83	0.013	0.39	3.27
Trend from ONJW to AFW	-0.04	0.312	-0.13	0.04		-0.04	0.779	-0.29	0.22
Constant 3rd period/AFW	-0.19	0.410	-0.64	0.26		-1.47	0.030	-2.80	-0.14
Trend from AFW to Cost-sharing change	-0.11	<0.001	-0.16	-0.06		-0.14	0.067	-0.28	0.01
Constant 4th period/Cost-sharing change	-0.97	<0.001	-1.35	-0.60		-1.14	0.043	-2.25	-0.04
Trend from Cost-Sharing change	-0.02	0.392	-0.02	0.06		-0.08	0.233	-0.20	0.05
n=84 months; R^2: 0.977 (<3%); 0.931 (≥3%). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning									

Figure S5. Segmented linear regression by FRAX risk of hip fracture.



≥3%: red line; <3%: blue line; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S7. Ratio of monthly osteoporosis treatment regarding January 2009. Segmented regression analysis for the entire ESOSVAL cohort.

	AGE: <65 AT RECRUITMENT			
	Coef.	p	95%CI	
Initial Constant	1.069	<0.001	1.019	1.119
Trend from Start to ONJW	0.005	0.260	-0.004	0.014
Constant 2nd period/ONJW	0.061	0.026	0.007	0.116
Trend from ONJW to AFW	-0.003	0.466	-0.013	0.006
Constant 3rd period/AFW	-0.038	0.131	-0.088	0.011
Trend from AFW to Cost-sharing change	-0.011	<0.001	-0.016	-0.005
Constant 4th period/Cost-sharing change	-0.101	<0.001	-0.142	-0.060
Trend from Cost-Sharing change	<0.001	0.930	-0.004	0.004
n=84 months; R^2: 0.976. ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning				

Figure S6. Ratio monthly treatment / Jan 2009. Segmented linear regression.

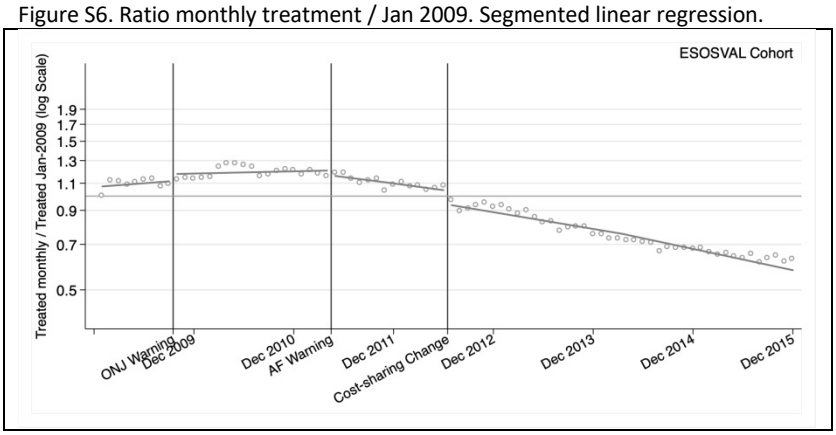
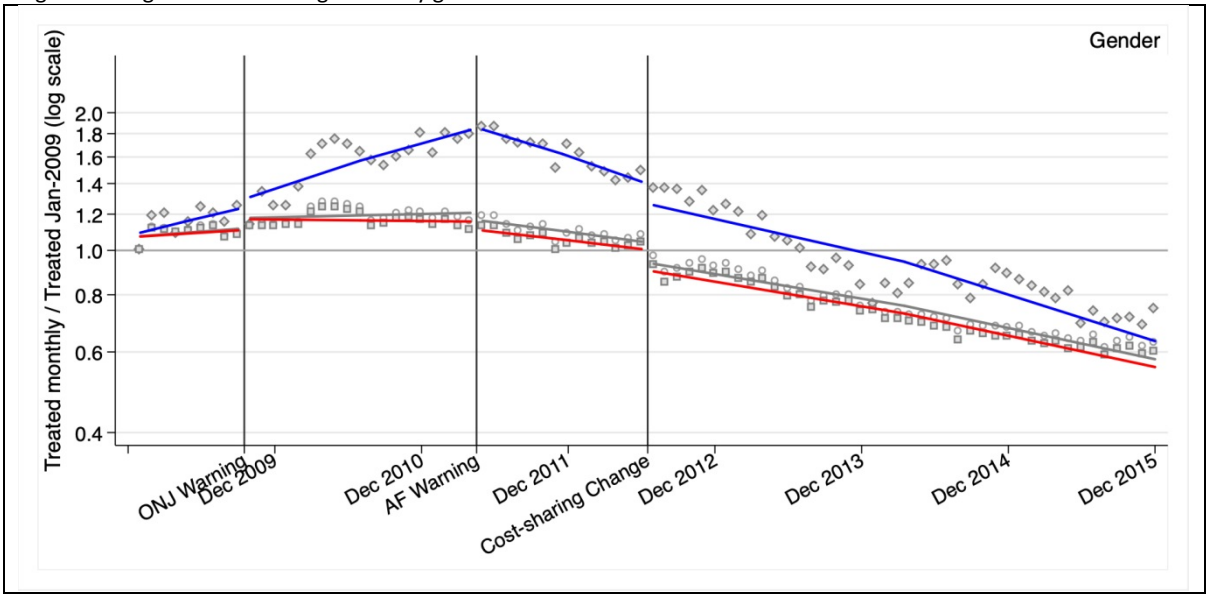


Table S8. Ratio of monthly osteoporosis treatment regarding January 2009. Segmented regression analysis stratified by gender.

	MEN					WOMEN			
	Coef.	p	95%CI			Coef.	p	95%CI	
Initial Constant	1.076	<0.001	0.941	1.211		1.068	<0.001	1.022	1.115
Trend from Start to ONJW	0.017	0.156	-0.007	0.041		0.004	0.317	-0.004	0.012
Constant 2nd period/ONJW	0.478	0.514	-0.097	0.193		0.064	0.013	0.013	0.114
Trend from ONJW to AFW	0.012	0.352	-0.013	0.037		-0.005	0.267	-0.14	0.004
Constant 3rd period/AFW	0.037	0.586	-0.097	0.170		-0.044	0.062	-0.090	0.002
Trend from AFW to Cost-sharing change	-0.062	<0.001	-0.076	-0.047		-0.007	0.008	-0.012	-0.002
Constant 4th period/Cost-sharing change	-0.142	0.013	-0.253	-0.031		-0.099	<0.001	-0.137	-0.060
Trend from Cost-Sharing change	0.018	0.007	0.005	0.030		-0.001	0.714	-0.005	0.003

n=84 months; R^2: 0.932 (men); 0.979 (Women). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning

Figure S7. Segmented linear regression by gender



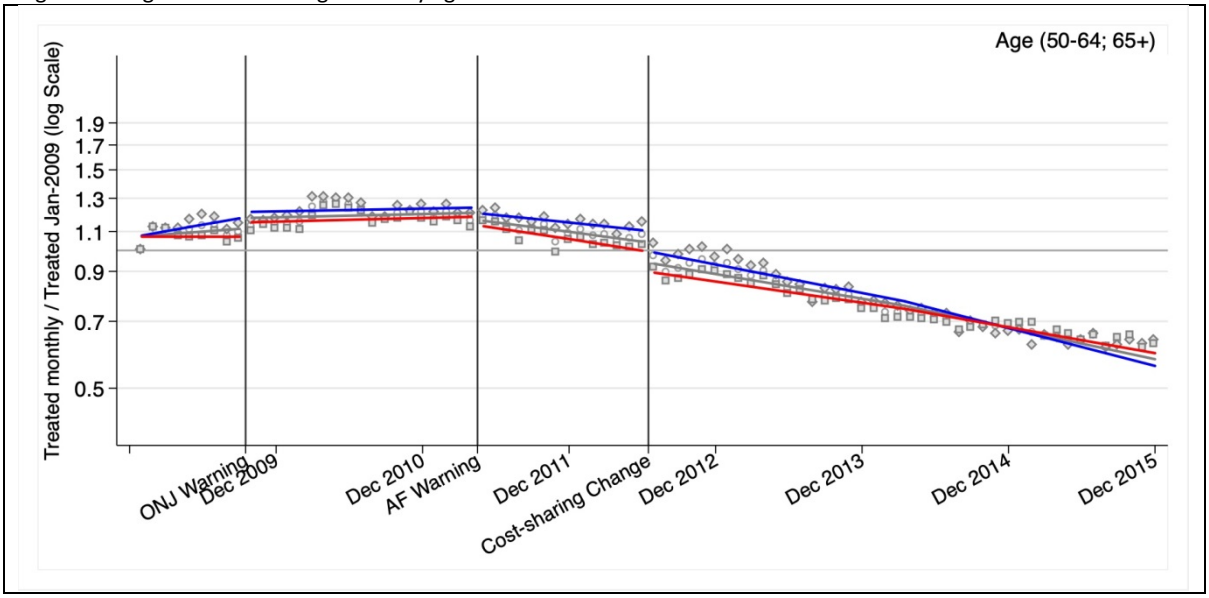
Women: red line; Men: blue line; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S9. Ratio of monthly osteoporosis treatment regarding January 2009. Segmented regression analysis stratified by age.

	50-64 years old				65 years and over			
	Coef.	p	95%CI		Coef.	p	95%CI	
Initial Constant	1.065	<0.001	1.006	1.125	1.072	<0.001	1.022	1.121
Trend from Start to ONJW	0.012	0.024	0.002	0.023	<0.001	0.991	-0.009	0.009
Constant 2nd period/ONJW	0.037	0.248	-0.026	0.101	0.079	0.004	0.026	0.133
Trend from ONJW to AFW	-0.011	0.057	-0.022	<0.001	0.002	0.699	-0.007	0.011
Constant 3rd period/AFW	-0.030	0.313	-0.089	0.029	-0.045	0.074	-0.093	0.004
Trend from AFW to Cost-sharing change	-0.009	0.008	-0.015	-0.002	-0.012	<0.001	-0.017	-0.006
Constant 4th period/Cost-sharing change	-0.107	<0.001	-0.156	-0.058	-0.097	<0.001	-0.138	-0.057
Trend from Cost-Sharing change	-0.003	0.268	-0.009	0.002	0.003	0.233	-0.002	0.007

n=84 months; R^2: 0.971 (65y and over); 0.971(50-64y). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning

Figure S8. Segmented linear regression by age



65y and over: red line; 50-64y: blue line; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

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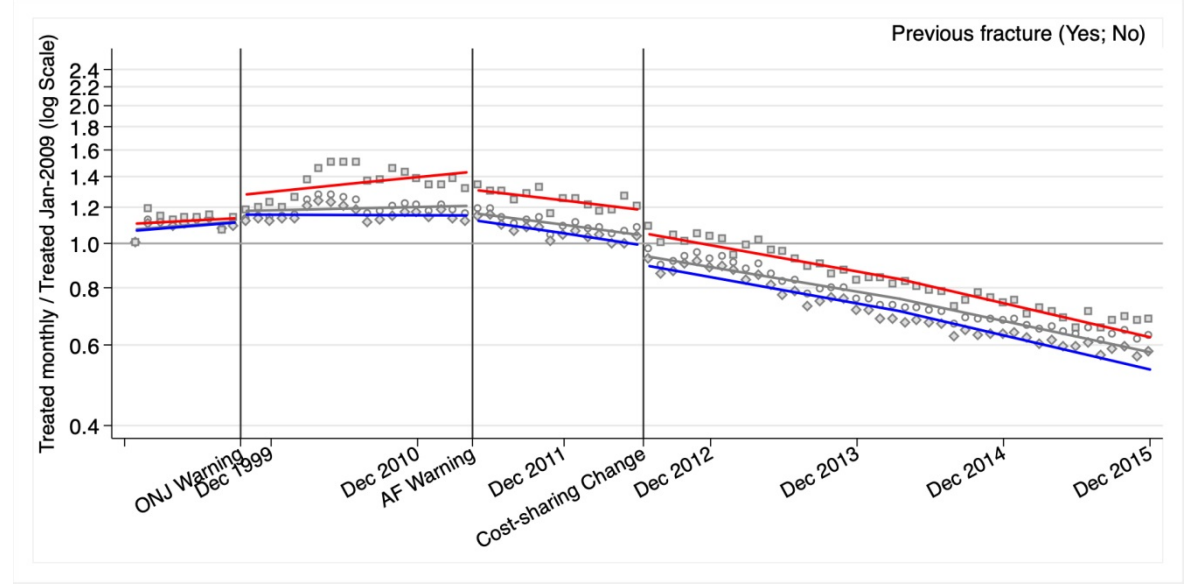
Table S10. Proportion of people treated by antecedent of previous fracture. Segmented regression analysis.									
	No previous fracture					Previous fracture			
	Coef.	p	95%CI			Coef.	p	95%CI	
Initial Constant	1.061	<0.001	1.014	1.109		1.101	<0.001	1.020	1.183
Trend from Start to ONJW	0.005	0.201	-0.003	0.014		0.004	0.616	-0.011	0.018
Constant 2nd period/ONJW	0.046	0.075	-0.005	0.097		0.137	0.002	0.050	0.224
Trend from ONJW to AFW	-0.006	0.202	-0.014	0.003		0.005	0.542	-0.010	0.020
Constant 3rd period/AFW	-0.022	0.354	-0.068	0.025		-0.115	0.006	-0.195	-0.035
Trend from AFW to Cost-sharing change	-0.009	<0.001	-0.014	-0.004		-0.017	<0.001	-0.026	-0.009
Constant 4th period/Cost-sharing change	-0.093	<0.001	-0.132	-0.055		-0.129	<0.001	-0.196	-0.062
Trend from Cost-Sharing change	0.001	0.714	-0.004	0.005		-0.001	0.762	-0.009	0.006
n=84 months; R^2: 0.954 (Previous fracture); 0.979 (No previous fracture). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning									

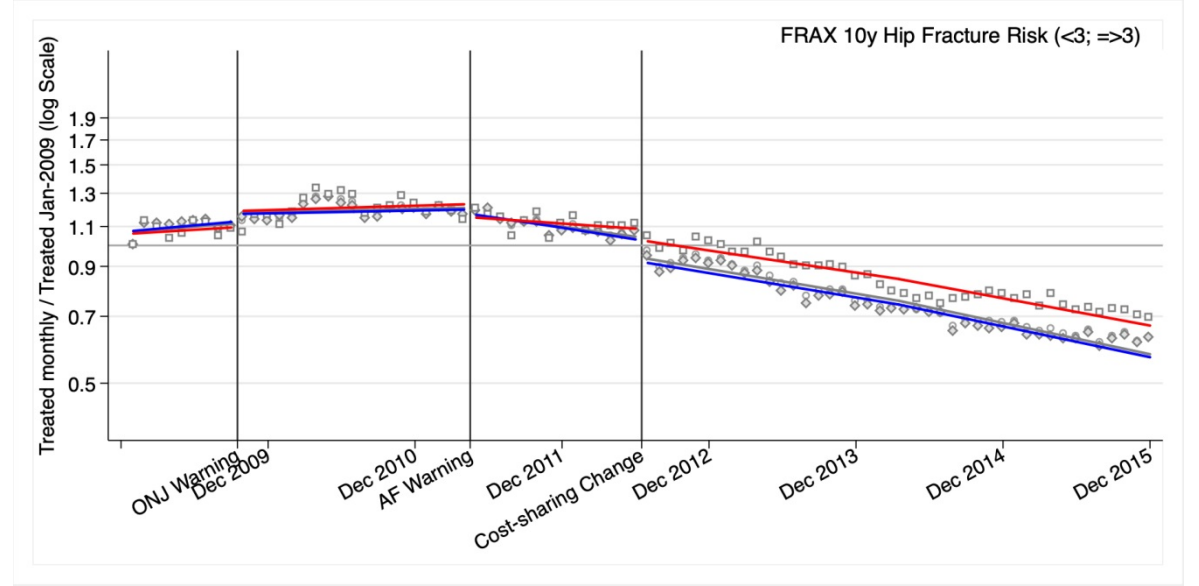
Figure S9. Segmented linear regression by previous fracture antecedent



Yes: red line; 50-64y: No; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S11. Proportion of people treated by FRAX risk of hip fracture. Segmented regression analysis.									
	<3%					≥3%			
	Coef.	p	95%CI			Coef.	p	95%CI	
Initial Constant	1.069	<0.001	1.019	1.119		1.058	<0.001	0.989	1.127
Trend from Start to ONJW	0.006	0.171	-0.003	0.015		0.004	0.514	-0.008	0.016
Constant 2nd period/ONJW	0.046	0.092	-0.008	0.099		0.094	0.013	0.020	0.168
Trend from ONJW to AFW	-0.005	0.312	-0.014	0.005		-0.002	-0.779	-0.015	0.011
Constant 3rd period/AFW	-0.020	0.410	-0.070	0.029		-0.075	-0.030	-0.143	-0.007
Trend from AFW to Cost-sharing change	-0.012	<0.001	-0.017	-0.006		-0.007	-0.067	-0.014	0.001
Constant 4th period/Cost-sharing change	-0.107	<0.001	-0.148	-0.066		-0.058	-0.043	-0.115	-0.002
Trend from Cost-Sharing change	0.002	0.392	-0.003	0.007		-0.004	-0.233	-0.010	0.003
n=84 months; R^2: 0.977 (<3%); 0.937 (≥3%). ONJW: Osteonecrosis Jaw Warning; AFW: Atypical femur Fracture Warning									

Figure S10. Segmented linear regression by FRAX risk of hip fracture.



≥3%: red line; <3%: blue line; All: grey line. ONJ: Osteonecrosis Jaw; AF: Atypical fracture

Table S12. Annual consumption (months of treatment) of osteoporosis drugs, ratio to 2009 and market share in the ESOSVAL cohort (2009-2016)							
	2009	2010	2011	2012	2013	2014	2015
Total							
Months treat (n)	15,487	16,941	15,846	13,715	11,282	9,379	8,375
Ratio to 2009	1.00	1.09	1.02	0.89	0.73	0.61	0.54
Bisphosphonates alone							
Months treat (n)	9,588	10,685	9,642	7,911	6,288	4,882	4,030
Ratio to 2009	1.00	1.11	1.01	0.83	0.66	0.51	0.42
Market Share (%)	61.91	63.07	60.85	57.68	55.73	52.05	48.12
Bisphosphonates in combination							
Months treat (n)	2,318	2,964	2,824	2,438	2,042	1,783	1,511
Ratio to 2009	1.00	1.28	1.22	1.05	0.88	0.77	0.65
Market Share (%)	14.97	17.50	17.82	17.78	18.10	19.01	18.04
Raloxifen							
Months treat (n)	1,760	1,446	1,445	1,477	1,265	1,100	1,012
Ratio to 2009	1.00	0.82	0.82	0.84	0.72	0.63	0.58
Market Share (%)	11.36	8.54	9.12	10.77	11.21	11.73	12.08
Calcitonins							
Months treat (n)	460	390	314	197	11	2	2
Ratio to 2009	1.00	0.85	0.68	0.43	---	---	---
Market Share (%)	2.97	2.30	1.98	1.44	0.10	0.02	0.02
Strontium ranelate							
Months treat (n)	1,082	1,207	1,369	1,225	896	234	13
Ratio to 2009	1.00	1.12	1.27	1.13	0.83	0.22	---
Market Share (%)	6.99	7.12	8.64	8.93	7.94	2.49	0.16
Denosumab							
Months treat (n)	---	---	17	340	670	1,194	1,615
Ratio to 2012	---	---	---	1.00	1.97	3.51	7.45
Market Share (%)	---	---	---	2.48	5.94	12.73	19.28
Parathyroid hormone							
Months treat (n)	279	249	235	127	110	184	192
Ratio to 2009	1.00	0.89	0.84	0.46	0.39	0.66	0.69
Market Share (%)	1.80	1.47	1.48	0.93	0.98	1.96	2.29

In 2009 and from a total annual volume of 15,487 months of osteoporosis treatment dispensed, bisphosphonates alone accounted for 61.9% of the market share, and up to 76.9% when bisphosphonates in combination were added. Raloxifene accounted for 11.4% and ranelate for 7.0%, with minimal consumption of calcitonin (3.0%) and parathyroid hormones (1.8%). Single bisphosphonates experienced a fall of 2.7 fold (from 10,685 to 4,030 packages filled), while combinations fell by 2 fold. Use of raloxifene and parathyroid hormone was halved while calcitonin and strontium ranelate disappeared after the warnings and restrictions of use from the AEMPS. In 2015, and over a total volume of 8,375 months of treatment (roughly half of 2009), bisphosphonates -alone or in combination- still accounted for 66.6% of the market share, followed by denosumab (19.3%), which experienced a notable growth in the period. Raloxifene (12.1%) and parathyroid hormone (2.3%) maintained their market share although on a much smaller market than in 2009.

Figure S11. Annual consumption of osteoporosis drugs 2009-2015

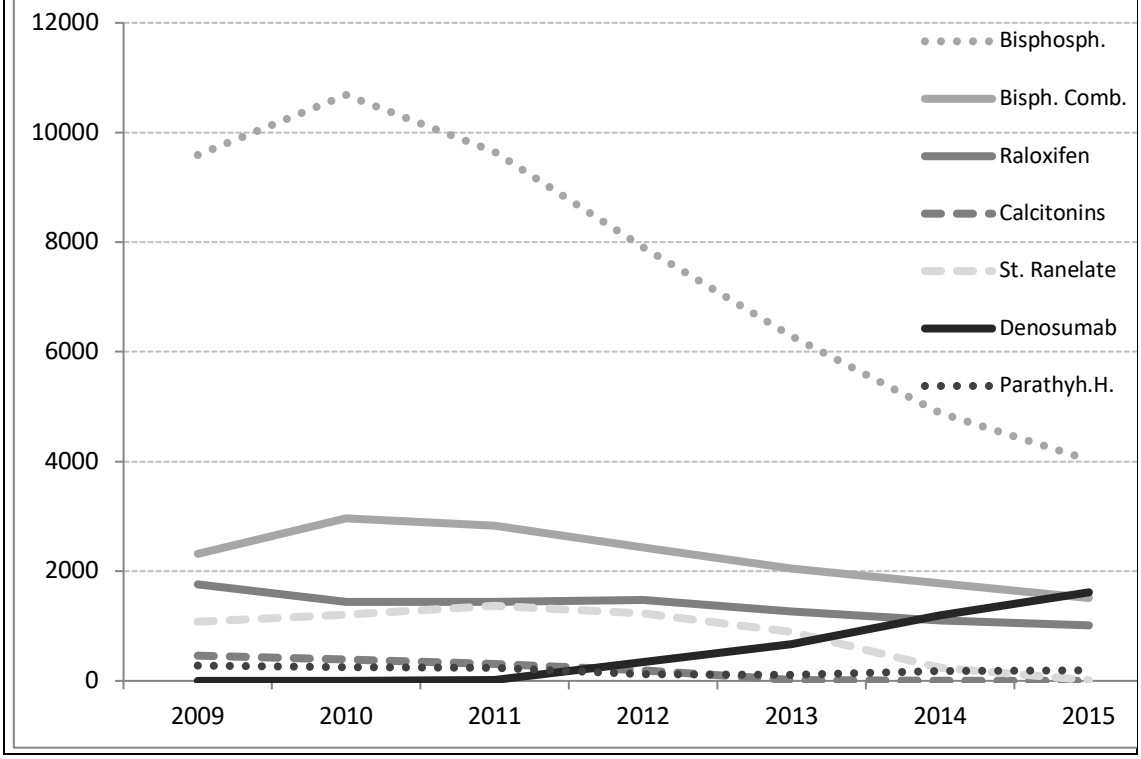
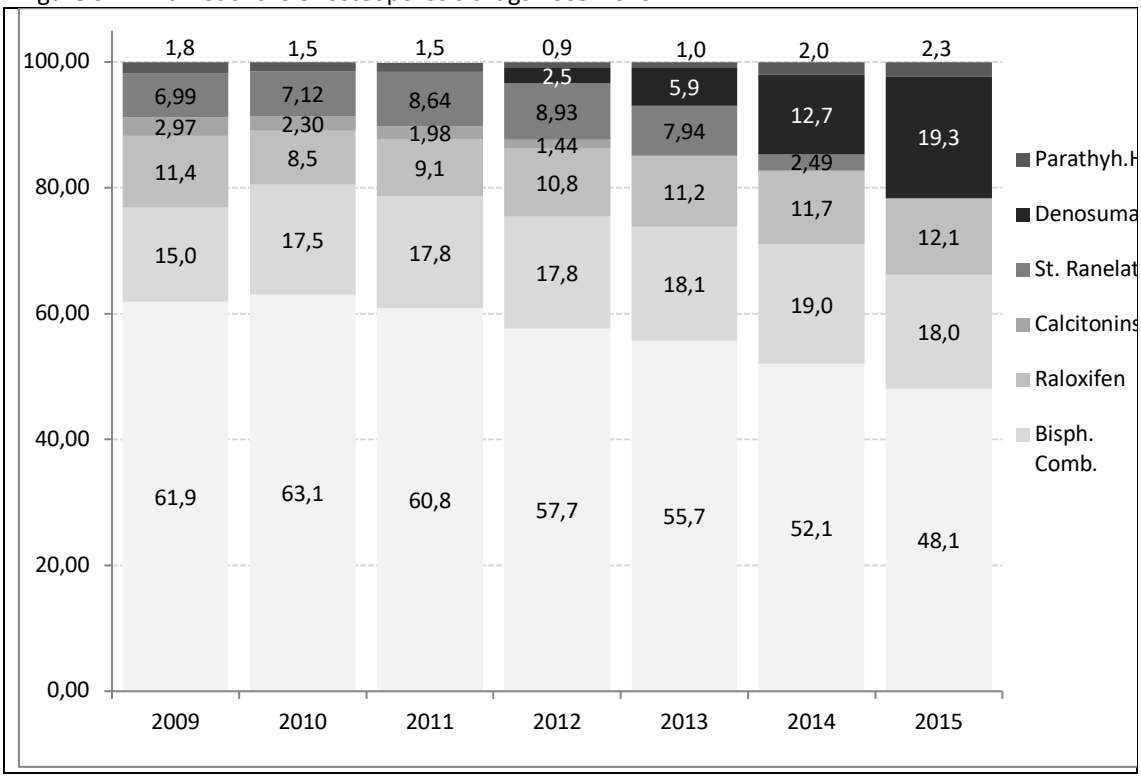


Figure S12. Market Share of osteoporosis drugs 2009-2015.



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Discusión

La eclosión de los sistemas de información electrónicos que permiten el registro de grandes volúmenes de datos de actividad clínica que se realiza en la práctica asistencial en el Sistema Nacional de Salud está abriendo un nuevo campo de posibilidades para la mejora de la evaluación y consecuentemente de la gestión de la provisión sanitaria en nuestro entorno, si bien este fenómeno tiene un alcance global y está sucediendo con mayor o menor intensidad en todas las economías desarrolladas.

En el ámbito de la farmacoterapia, los estudios basados en dichos sistemas de información que proveen de datos de vida real son cada vez más apreciados por los agentes sanitarios. De una parte, las principales agencias reguladoras de medicamentos ya han desarrollado o están en proceso de desarrollo de directrices para la utilización de dichos estudios para la toma de decisiones de autorización y reembolso, así como para la determinación de indicaciones aprobadas y directrices de uso de los fármacos, dado el enorme valor que supone disponer de evidencia sobre los patrones de utilización, efectividad y seguridad de los medicamentos en práctica clínica real de forma complementaria a la evidencia tradicionalmente empleada por dichas agencia proveniente de ensayos clínicos aleatorizados de carácter experimental. De otra, los estudios con datos de vida real ofrecen a los gestores sanitarios a nivel macro, meso y micro la posibilidad de conocer cómo se están empleando los medicamentos en su área de responsabilidad, si dicha utilización se adecua a la mejor evidencia disponible, si sus resultados en términos de resultados en salud están en línea con los demostrados en el ámbito experimental (ensayos clínicos), o cuál es el impacto real de las medidas regulatorias y de política farmacéutica sobre dicha utilización y resultados.

En este sentido, no es de extrañar que las industrias proveedoras de productos farmacéuticos se hayan sumado también al movimiento de los estudios con grandes bases de datos, a pesar de sus reticencias iniciales, dada la importancia cada vez mayor que se confiere a dicho tipos de estudios por los principales decisores en regulación y política farmacéutica. En definitiva, los estudios con grandes bases de datos de práctica clínica real abren un nuevo campo para la evaluación y la mejora de la calidad de la asistencia que brindamos a nuestros pacientes, y en el ámbito de los medicamentos aportan un inmenso valor por cuanto tienen el potencial de mejorar el manejo y resultados de las terapias en su utilización diaria, así como de diseñar nuevas y mejores intervenciones de mejora de la calidad de la prestación farmacoterapéutica.

Los medicamentos constituyen un recurso pivotal para la mejora de la salud de las poblaciones atendidas en los servicios de salud en todo el mundo. Sin embargo, tanto los patrones de utilización de medicamentos en práctica clínica habitual como sus efectos pueden distar mucho de las condiciones experimentales de los ensayos clínicos aleatorizados en que se determinan sus perfiles de eficacia y seguridad. En este sentido, los estudios farmacoepidemiológicos con datos de vida real obtenidos mediante la utilización de grandes bases de datos de corte poblacional aportan información para conocer cómo se utilizan los fármacos por parte de los profesionales sanitarios y los pacientes, cuáles son los resultados en términos de beneficios clínicos de dicha utilización, o cómo afectan las medidas de gestión farmacéutica a dicho uso. Esta información es de gran valor para poder identificar áreas de mejora en la prestación farmacéutica, así como para el diseño de intervenciones orientadas a mejorar la calidad de la atención sanitaria que prestamos a los pacientes.

En este sentido, los trabajos reunidos en esta tesis doctoral son ejemplos de contribuciones nuevas, originales y relevantes para la mejora del Sistema Valenciano de Salud y por ende del SNS.

Dos de los trabajos presentados analizan la calidad del manejo farmacoterapéutico de la prevención de ictus isquémico con fármacos anti-vitamina K de los pacientes con fibrilación atrial. En el primero de ellos se describe la situación de dicho manejo durante el año 2015, analizando las diferencias por género. Se observa que la calidad del control de INR en estos pacientes es subóptima, con entre un cuarto y dos tercios de los pacientes mal controlados en función de las diferentes definiciones empleadas, en línea con la evidencia internacional en este ámbito (Hart RG et al, 2007; Kirchhof P et al, 2016). De forma importante, los resultados reflejan una peor situación de las mujeres, plasmada de forma significativa en cada uno de los indicadores y definiciones empleados. Existe un notable cuerpo de evidencia en relación con la mayor vulnerabilidad de la mujer en cuanto al control de la anticoagulación, pero dicha evidencia parte de entornos experimentales, registros o poblaciones pequeñas, siendo el estudio que forma parte de la presente tesis el primero que confirma dichos resultados con datos de vida real de base poblacional (Alonso Roca R et al, 2015; Barrios V et al, 2015; Cinza-Sanjurjo S et al, 2015; Fernández López P et al, 2016; Aguirre Rodriguez JC et al, 2017; Barrios V, 2017; Boned-Ombuena A et al, 2017; Esteve-Pastor MA et al, 2018).

También el análisis de *switch* de anti-vitamina-K a otros fármacos anticoagulantes en el conjunto de la población tratada es novedoso en nuestro ámbito, y atendiendo a la regulación nacional que establece el criterio de mal control con VKA como razón principal para el cambio a otras

terapias sugiere la existencia de un notable fenómeno de inercia terapéutica (Agencia Española de Medicamentos y Productos Sanitarios, 2016). En definitiva, este artículo señala dos ámbitos de actuación muy claros: la necesidad de incorporar el gradiente de género en las estrategias de mejora de la calidad de anticoagulación oral en el territorio, así como el abordaje del fenómeno de inercia terapéutica como elementos esenciales para impactar positivamente el manejo de estos pacientes en el SNS.

En el tercer artículo se aborda de nuevo el manejo con VKA de los pacientes con fibrilación atrial pero adoptando una aproximación metodológica inédita hasta la fecha en este campo como es la aplicación de la metodología de análisis de clases latentes *Group-based Trajectory Models* (GBTM) al estudio de la calidad de la anticoagulación con VKA. Las medidas tradicional y habitualmente empleadas para determinar la calidad del manejo de los pacientes con VKA, como son el tiempo en rango terapéutico (TRT) o el porcentaje de determinaciones de INR en rango en un período, ofrecen resultados promedio de un período concreto, pero no capturan la naturaleza dinámica del control del INR a lo largo de tiempo. En este sentido, dos pacientes con el mismo valor de TRT en un mismo período de tiempo pueden tener comportamientos muy diferentes a lo largo de dicho período, y por tanto sus riesgos pueden también ser muy diferentes a lo largo de dicho período. Los resultados obtenidos reflejan de hecho dichas diferencias, puesto que aquellos pacientes clasificados en trayectorias de control óptimo o en mejora presentan un menor riesgo de muerte que los pacientes clasificados en trayectorias de empeoramiento o mal control.

El presente artículo demuestra, por primera vez, como la técnica de GBTM permite caracterizar la naturaleza longitudinal del proceso de control de INR, así como identificar subgrupos de pacientes con diferente propensión a estar adecuadamente anticoagulados. Además, se comprueba que la determinación de trayectorias funciona de un modo consistente con las medidas tradicionales de calidad del INR, aportando así una visión más completa de la calidad del control de INR y suponiendo un verdadero hito en el abordaje de la evaluación de la calidad del INR.

La adherencia a la medicación es un elemento esencial para la obtención en práctica clínica real de los beneficios demostrados en los ensayos clínicos (Brown MT et al, 2011). La gran mayoría de estudios de adherencia y persistencia a la medicación con datos de vida real se llevan a cabo utilizando información sobre dispensación de medicamentos. Sin embargo, en ausencia de información sobre prescripción es difícil conocer el momento real de inicio de la terapia (esencial, por ejemplo, para calcular la adherencia primaria). Del mismo modo, en ausencia de

dicha información sobre prescripción, los gaps detectados en dispensación se atribuyen necesariamente a una falta de adherencia del paciente, ignorando el hecho de que dichos gaps podrían deberse a una interrupción del tratamiento por parte del médico.

El cuarto artículo aborda esta problemática comparando la obtención de estimadores de adherencia con información de prescripción y dispensación relacionadas, con los obtenidos únicamente con información sobre dispensación. Tomando como ejemplo una cohorte de alrededor de 11.000 pacientes mayores de 50 años tratados con medicación osteoporótica, se demuestra como con información relacionada de prescripción y dispensación se obtienen indicadores de adherencia farmacoterapéutica refinados. En este sentido, la determinación del momento de inicio terapéutico es mucho más exacta que basándose únicamente en datos de dispensación. Igualmente, los estimadores de adherencia son mucho más precisos puesto que tienen en cuenta tanto la no-adherencia primaria (pacientes que no recogen la primera receta prescrita), como la no-adherencia temprana (pacientes que no recogen las primeras recetas prescritas) o la falta total de adherencia (aquellos pacientes que reciben alguna prescripción, pero nunca recogen la medicación). Esto tiene importantes implicaciones no sólo con relación a la mejora de la calidad de los estimadores, sino también con respecto a la identificación de los pacientes con mayor riesgo o de los períodos con mayor riesgo de no-adherencia (Zhao B et al, 2013; García-Sempere A et al, 2017).

Por último, aunque no menos importante, este trabajo pone en entredicho una asunción extraordinariamente extendida en el estudio de adherencia a medicamentos, como el que los pacientes que inician tratamiento tienen una peor adherencia terapéutica que aquellos pacientes más experimentados (que llevan más tiempo en tratamiento). Al emplear información de prescripción, se mejora la atribución de los gaps de tratamiento en estos pacientes, y se observa que en pacientes iniciadores las menores tasas observadas de exposición a los fármacos se deben en gran medida a un patrón de interrupciones por parte de médico y no siempre a una menor adherencia de los pacientes. En este sentido, este estudio ofrece una visión más precisa y realista del fenómeno de la no adherencia terapéutica en práctica clínica real y permite refinar las intervenciones de mejora de la adherencia gracias a una mejor identificación de los pacientes con un mayor riesgo de no ser adherentes.

Finalmente, el análisis del impacto de las alertas por osteonecrosis mandibular y fracturas atípicas, así como del cambio de copago sobre la utilización de medicación antiosteoporótica muestra como se ha reducido a la mitad la utilización de dichos fármacos a lo largo del período, y como la segunda alerta y el cambio de copago han tenido un papel importante en dicho

declive, aunque no la primera. Más allá de la atribución de los cambios en utilización al impacto de las citadas medidas, el presente trabajo constituye una aportación muy relevante al análisis de la calidad de los patrones de utilización de medicación osteoporótica en nuestro ámbito. En primer lugar, se trata del primer estudio que evalúa el impacto de las alertas en diferentes estratos de riesgo (edad, género, riesgo de fractura), hallando que dicho impacto tuvo un efecto similar en pacientes de alto y bajo riesgo, lo que pone en entredicho la efectividad de dichas medidas en cuanto a la mejora de la adecuación de la prescripción. En este sentido, el estudio señala áreas claras de potencial intervención desde la gestión, debido a que, a pesar de la intensa reducción en la utilización de estos fármacos, parece persistir un notable problema de sobreutilización (en 2015 alrededor de tres cuartos de los tratamientos fueron dispensados a pacientes con un riesgo de fractura de cadera a los 10 años inferior a 3%), a la vez que ~~se~~ apunta a la intensificación de un problema de infrautilización en pacientes de riesgo (tan sólo un 14% de los pacientes de nuestra cohorte con riesgo de fractura de cadera a los 10 años superior al 3% recibían tratamiento en 2015).

Limitaciones

Los trabajos presentados adolecen de ciertas limitaciones que suelen estar presentes en la mayoría de estudios observacionales retrospectivos basados en datos de vida real. En primer lugar, pueden existir sesgos de información, fundamentalmente derivados de problemas de infra-registro o de variabilidad en dicho registro por parte de los profesionales sanitarios en las bases de datos clínico-administrativas.

En segundo lugar, no es descartable que se omita información relevante para los análisis realizados (por ejemplo, las dificultades para acceder a la monitorización de INR o la presencia de contraindicaciones al tratamiento con anti-vitamina K), debido a que dicha información no se registra rutinariamente en las bases de datos. En este sentido, no es descartable que existan factores de confusión no medidos *(unmeasured confounding)* que pueden estar mediando en la obtención de estimadores.

En tercer lugar, cabe apuntar que la evaluación de la adherencia a medicamentos en grandes bases de datos se extrapola a partir de la identificación de prescripciones y/o dispensaciones, pero no en base al consumo final por parte del paciente, si bien diversos estudios han demostrado una gran consistencia entre la dispensación y el consumo por parte del paciente (Steiner JF et al, 1997; Grymonpre R et al, 2006).

En cuarto lugar, no tenemos información integrada en el sistema de información sanitaria de la prescripción de medicación intrahospitalaria, lo que podría dar problemas de mala clasificación de los pacientes como no-adherentes en caso de estancias hospitalarias. A pesar de estas limitaciones, los estudios de cohortes retrospectivos representan el *gold standard* para la estimación de adherencia a la farmacoterapia en vida real.

Por último, todos los trabajos se llevaron a cabo en el ámbito de la Comunidad Valenciana. Además, en varios de los estudios presentados se aplicaron criterios de inclusión y exclusión para la conformación de cohortes óptimas para el análisis. Dichas restricciones pueden limitar la generalizabilidad de los resultados presentados, y su extrapolación a poblaciones diferentes a la estudiadas se ha de realizar con extrema cautela.

En definitiva, la presente tesis ofrece una visión pormenorizada de las características de los datos de vida real y las bases de datos en que se registran, y aporta información inédita hasta la fecha en relación con el manejo farmacoterapéutico en práctica clínica real de patologías crónicas de alta prevalencia en la Comunidad Valenciana, empleando además aproximaciones metodológicas innovadoras. Los resultados presentados señalan potenciales áreas de mejora sobre las que actuar desde la gestión, y a su vez pueden contribuir a informar sobre el diseño de intervenciones de mejora más efectivas.

Conclusiones

1. El Sistema de Información Sanitaria de la Comunidad Valenciana es el resultado de la unión, gracias a un identificador único de paciente, de un conjunto de bases de datos clínico-administrativas, de titularidad pública y de alcance poblacional, que aportan información sobre el conjunto de la población de la Comunidad Valenciana y permiten analizar la práctica clínica habitual. Gracias a dicho sistema se han podido realizar los estudios que conducen a las siguientes conclusiones.

2. La calidad del control de INR de los pacientes con fibrilación atrial tratados con fármacos anti-vitamina K para la prevención de ictus en la Comunidad Valenciana en el año 2015 fue subóptima. Las mujeres presentaron un mayor riesgo de mal control y se observaron tasas de *switching* muy bajas en pacientes mal controlados.

3. Los pacientes con fibrilación atrial tratados con anti-vitamina K en la Comunidad Valenciana pueden agruparse utilizando la metodología *de Group-based Trajectory Models* (GBTM), según el grado de control del INR en el tiempo, en cuatro trayectorias de control durante el primer año de tratamiento: buen control, mejora, empeoramiento, y mal control. Los pacientes clasificados en trayectorias de mejora y buen control presentaron un menor riesgo de muerte que aquellos agrupados en trayectorias de empeoramiento o mal control.

4. Utilizar datos relacionados de prescripción y dispensación permite obtener estimadores de adherencia secundaria más precisos y refinados que los obtenidos empleando únicamente datos de dispensación, ya que permiten una aproximación más completa y realista de la adherencia a la medicación por parte de los pacientes, especialmente en el caso de los iniciadores de terapia, dónde es frecuente la existencia de patrones de interrupción por parte de los prescriptores.

5. La alerta emitida por la Agencia Española de Medicamentos y Productos Sanitarios en septiembre de 2009 de riesgo de osteonecrosis maxilar por consumo de bifosfonatos no se asoció con un descenso en el consumo de fármacos para la osteoporosis. Sin embargo, la alerta de abril de 2011 de riesgo de fracturas atípicas de fémur sí se asoció con un descenso significativo en el volumen de pacientes tratados, descenso que se vio reforzado por el cambio en el sistema de copago de 2012. Como resultado, el volumen de pacientes tratados en diciembre de 2015 era la mitad de los tratados en mayo de 2010. Dicha disminución afectó por igual al volumen de pacientes con bajo y alto riesgo de fractura.

6. Los resultados, en su conjunto, ofrecen una visión pormenorizada de las características de los datos de vida real y las bases de datos en que se registran, aportan información inédita hasta la fecha en relación con el manejo farmacoterapéutico en práctica clínica real de patologías crónicas de alta prevalencia en la Comunidad Valenciana y permiten plantear actuaciones dirigidas a la optimización farmacoterapéutica.

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TESIS DOCTORAL

Programa de Doctorado en Biomedicina y Farmacia

ANEXO 1. PUBLICACIONES

Datos de vida real para la mejora de la utilización y la efectividad de los medicamentos en el Sistema Nacional de Salud: contribuciones esenciales

Aníbal García Sempere

Artículo 1.

García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, Hurtado I, Peiró S, Sanfélix-Gimeno G, Diez-Domingo J. **Data resource profile: the Valencia Health System Integrated Database (VID).**

International Journal of Epidemiology, 2020.
doi:10.1093/ije/dyz266

Factor de impacto: 7,339
Ranking: D1 (97,03%; 6/185; Category: Public, Environmental and Occupational Health)

Artículo 2.

García-Sempere A, Hurtado I, Bejarano-Quisoboni D, Rodríguez-Bernal C, Santa-Ana Y, Peiró S, Sanfélix-Gimeno G. **Quality of INR control and switching to non-Vitamin K oral anticoagulants between women and men with atrial fibrillation treated with Vitamin K Antagonists in Spain. A population-based, real-world study.**

PLoS One. 2019.
doi:10.1371/journal.pone.0211681.

Factor de impacto: 2,776
Ranking: Q1 (77,34%; 36/155; Category: Multidisciplinary Sciences)

Artículo 3.

García-Sempere A, Hurtado I, Bejarano D, Santa-Ana Y, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. **Group-based Trajectory Models to Assess Quality of INR Control and its Association with Clinical Outcomes.**

Medical Care, 2020.
doi:10.1097/MLR.0000000000001253

Factor de impacto: 3,795
Ranking: Q1 (85,14%; 28/185; Category: Public, Environmental & Occupational Health); Q1 (83,51%; 16/98; Category: Health Care Sciences & Services) ; D1 (92.07%; 7/82; Category: Health Policy & Services)

Artículo 4.

García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. **Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs.**

Current Medical Research and Opinion, 2019.
doi: 10.1080/03007995.2019.1601944.

Factor de impacto: 2,345
Ranking: Q1 (77,1%; 15/64; Category: Medicine, General & Internal)

Artículo 5.

Hurtado-Navarro I, García-Sempere A, Rodríguez-Bernal C, Sanfélix-Genovés J,Peiró S, Sanfélix-Gimeno G. **Impact of Drug Safety Warnings and Cost-Sharing Policies on Osteoporosis Drug Utilization in Spain: A Major Reduction But With the Persistence of Over and Underuse. Data From the ESOSVAL Cohort From 2009 to 2015.**

Frontiers in Pharmacology. 2019.
doi: 10.3389/fphar.2019.00768.

Factor de impacto: 3,845
Ranking: Q1 (78,09%; 59/267; Category: Pharmacology & Pharmacy)