UNIVERSIDAD DEL AZUAY

FACULTAD DE MEDICINA

Adherencia entre las diferentes medicaciones disponibles en pacientes con diabetes mellitus tipo 2: Una actualización de una revisión sistemática de la literatura

Trabajo de titulación previo a la obtención de título de Médico

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RESUMEN

La adherencia terapéutica en los pacientes con Diabetes Mellitus tipo 2 (DM2) es esencial para un control glucémico adecuado y prevención de complicaciones vasculares. **Objetivo**: Comparar las tasas de adherencia y persistencia entre las diferentes medicaciones hipoglucemiantes disponibles en pacientes con DM2. **Métodos**: Se realizó una búsqueda avanzada en las bases de datos: MEDLINE, Pubmed, EMBASE, Cochrane Library, Web of Science, Scielo, BIREME y Trip Database en donde se identificaron estudios observacionales e intervencionales incluidos tras pasar 2 fases de filtración. Se desarrolló un metaanálisis en red y se calculó el Riesgo Relativo (RR) para la mala adherencia entre las clases de medicamentos hipoglucemiantes. **Resultados**: En los 136 estudios incluidos se evidenció que los inhibidores de la alfa-glucosidasa tuvieron un mayor riesgo de mala adherencia en comparación con todas las terapias incluidas, mientras que los DPP4i mostraron un menor riesgo de mala adherencia; los GLP-1 RA y SGLT2i tuvieron un menor riesgo de presentar una mala adherencia con respecto a las sulfonilureas (RR= 0.73; IC 95% [0.55; 0.98] y RR=0.70; IC 95% [0.52; 0.94], respectivamente). **Conclusión**: Esta revisión sistemática, ofrece una perspectiva actualizada sobre la adherencia y persistencia en pacientes con DM2. La calidad de los estudios observaciones fue buena y el riesgo de sesgo en ensayos clínicos fue de bajo a indeterminado. Los resultados mostraron una alta heterogeneidad entre estudios, por lo que se debería impulsar el desarrollo de más investigaciones que aborden esta problemática y permitan una estimación más precisa de la adherencia y persistencia en la actualidad.

Palabras clave: Diabetes Mellitus tipo 2, Adherencia, Persistencia, Agentes Hipoglucemiantes, Revisión Sistemática, Meta-Análisis

ABSTRACT

Adherence to treatment in patients with Type 2 Diabetes Mellitus (T2DM) is essential for adequate glycemic control and prevention of vascular complications. **Objective**: To compare adherence and persistence rates among hypoglycemic medications available for the control of hyperglycemia in patients with T2DM. **Methods**: An advanced search was performed in the databases: MEDLINE, Pubmed, EMBASE, Cochrane Library, Web of Science, Scielo, BIREME and Trip Database where observational and interventional studies were identified and included after passing 2 screening phases. A network meta-analysis was developed and the Relative Risk (RR) for poor adherence among different classes of hypoglycemic medications was calculated. **Results**: Inclusion of 136 studies showed that alpha-glucosidase inhibitors had a higher risk of poor adherence compared to all included therapies, while DPP4i was shown to have a lower risk of poor adherence; GLP-1 RA and SGLT2i had a lower risk of poor adherence compared to sulphonylureas (RR= 0.73; 95% CI [0.55, 0.98] and RR=0.70; 95% CI [0.52, 0.94], respectively). **Conclusion**: This systematic review provides an updated perspective on adherence and persistence in patients with T2DM. The quality of the observational studies was good and the risk of bias in clinical trials was between low and undetermined. The results showed a high heterogeneity among studies; therefore, more research should be conducted to address this problem and allow a more accurate estimate of adherence and persistence.

Keywords: Diabetes Mellitus, Type 2, Medication Adherence, Medication Persistence, Hypoglycemic Agents, Systematic Review, Meta-Analysis

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INTRODUCCIÓN

La diabetes mellitus tipo 2 representa una preocupante epidemia global de salud, caracterizada por su naturaleza crónica y prevalencia creciente (1). Según datos de la Federación Internacional de la Diabetes se proyecta que para el año 2045, aproximadamente 783,2 millones de personas padecerán esta enfermedad, sitúandola como una importante carga de morbilidad, mortalidad y altos costes médicos en todo el mundo (2,3). Por este motivo, lograr su control es crucial, y un componente clave es el tratamiento efectivo mediante una adherencia terapéutica adecuada (4).

La identificación de posibles diferencias en las tasas de adherencia entre las distintas clases de medicamentos es esencial para guiar la prescripción médica, y, en última instancia, minimizar las complicaciones asociadas a la diabetes mellitus tipo 2 (5,6). En este contexto, McGovern et al. (7) desarrollaron una revisión sistemática acerca de este tema en el 2017, en donde identificaron algunas diferencias en la adherencia y la persistencia entre los distintos medicamentos hipoglucemiantes. Una de las principales barreras en la investigación fue la falta de una definición universal de adherencia y persistencia, motivo por el cual, únicamente un número limitado de estudios que se incluyeron pudieron evaluar y comparar estos aspectos adecuadamente. En los últimos años, el desarrollo y la disponibilidad de nuevos medicamentos hipoglucemiantes han incrementado significativamente, introduciendo innovaciones en la estrategia de tratamiento para la DM2, donde la adherencia determina la eficacia terapéutica (8).

Por este motivo, para esta investigación, se ha considerado importante realizar una actualización de la revisión sistemática mencionada previamente, tomando en cuenta tanto las innovaciones en los medicamentos disponibles en la actualidad, como la literatura reciente, a fin de que este estudio represente el estado del arte en este ámbito. El objetivo de esta revisión es comparar las tasas

de adherencia y persistencia entre las diferentes medicaciones disponibles para el control de la hiperglucemia en pacientes con diabetes mellitus tipo 2.

MÉTODOS Y MATERIALES

Selección de estudios y población

Se realizó una búsqueda sistemática de la literatura publicada en las siguientes bases de datos electrónicas: *MEDLINE, Pubmed, EMBASE, Cochrane Library*, incluidos el Registro Cochrane de Ensayos Controlados (CENTRAL), *Web of Science*, Scielo, *BIREME y Trip Database* durante el período de enero a febrero del 2024. La estrategia de búsqueda se basó en términos MeSH y otros términos de búsqueda avanzada que se especifican en el **Anexo 1**. Se incluyeron en la presente revisión todos los estudios observacionales y de intervención publicados desde el 2006 hasta el 31 de diciembre del 2023, que comparaban la adherencia o persistencia de diferentes medicamentos hipoglucemiantes orales e inyectables disponibles en la actualidad.

Los estudios fueron incluidos si cumplían con los siguientes criterios:

- Estudios realizados en pacientes con diabetes mellitus tipo 2 que se encuentran tomando la medicación de interés.
- Estudios realizados en el entorno comunitario, ambulatorio o dentro de la atención primaria de salud.
- Estudios que midan la adherencia utilizando métodos como medidas de autoinforme, adherencia estimada por el profesional de salud, tasas de adherencia calculadas a partir de datos de prescripción o dispensación, o seguimiento electrónico del uso de medicamento.
- Estudios que midan de forma suficiente la adherencia y persistencia, para lo cual se utilizarán las definiciones que se describirán en el siguiente apartado.

Los estudios que se realizaron en pacientes con diabetes mellitus tipo 1 o diabetes gestacional, hospitalizados o incapaces de tomar medicación por sí

solos; estudios con medicamentos descontinuados o no disponibles y, especialmente, estudios que no reportaban de manera individual la adherencia por clase de fármaco, fueron excluidos de esta revisión.

Definiciones y medidas usadas para el análisis

Las medidas utilizadas para la medición de adherencia fueron: la Proporción de Días Cubiertos (PDC)[1] y el Índice de Posesión de Medicamentos (MPR[2]). El PDC se refiere al número total de días de suministro dispensados durante el período de observación especificado, dividido para el número total de días en el período de observación desde la primera dispensación hasta el final del seguimiento (9). La proporción de individuos con un PDC >80% se consideró como adherentes al tratamiento. El MPR se calculó dividiendo los días de suministro de medicación dispensada durante un período de tiempo específico para el número de días de este período desde la primera dispensación hasta el final; un MPR>80% se consideró como adherente (9). Por otro lado, varios estudios incluidos reportaron la adherencia con métodos cualitativos como encuestas a pacientes; las encuestas más utilizadas fueron: *Medication Adherence Report Scale* (MARS) y *Morisky Medication Adherence Scale.*

La persistencia fue medida en base a brechas, la ausencia de una nueva dispensación de la medicación prescrita dentro de un período de gracia establecido por cada estudio (30 días, 60 días, 90 días o más de dos veces el tiempo de prescripción del medicamento) se consideró como no persistencia (9).

Proceso de filtración de estudios y extracción de datos

El proceso de filtración se realizó a través de la herramienta Rayyan (10); se reevaluaron todos los estudios incluidos en la revisión realizada por McGovern et al. (7) para determinar su elegibilidad para ser incluidos en esta actualización. Las citas obtenidas de la búsqueda actualizada pasaron a una primera etapa de cribado; de acuerdo con el título y el resumen, los estudios pasaron a la segunda

[1] PDC por sus siglas en inglés Proportion of Days Covered
[2] MPR por sus siglas en inglés Medication Possession Ratio

etapa de cribado si cumplían con los criterios de elegibilidad y, en esta última, se evaluó el texto completo para determinar si se incluían en la revisión. En ambas etapas de cribado, dos autores de la revisión independientes (EC y MA) evaluaron la elegibilidad, y un adjudicador (CS) resolvió los desacuerdos. Todo el proceso de filtración se reporta a detalle en el diagrama de flujo PRISMA **(Figura 1).**

Extracción y análisis de datos

La extracción de datos se realizó a través de la herramienta Covidence (11) . Los datos fueron registrados en una tabla de extracción en la que se describió el tipo de estudio, población, medidas de adherencia o persistencia empleadas, resultados obtenidos y fortalezas o debilidades de cada cita incluida **(Anexo 2).**

Los datos extraídos fueron computados en R y RStudio, y con el paquete "netmeta", se desarrolló un metaanálisis en red. Para la elaboración de este, se usaron todos los estudios que cuantificaban la adherencia mediante PDC para la comparación entre todas las clases de fármacos. El análisis se realizó utilizando el cálculo del Riesgo Relativo (RR) para la mala adherencia (PDC<80%). La heterogeneidad estadística de las estimaciones de RR se cuantificó con varias pruebas como tau^2, la prueba Q de Cochran y la estadística I^2 (28). Adicionalmente, se efectuó un análisis cualitativo con respecto a la adherencia y persistencia de cada clase de medicamentos incluidos en los estudios.

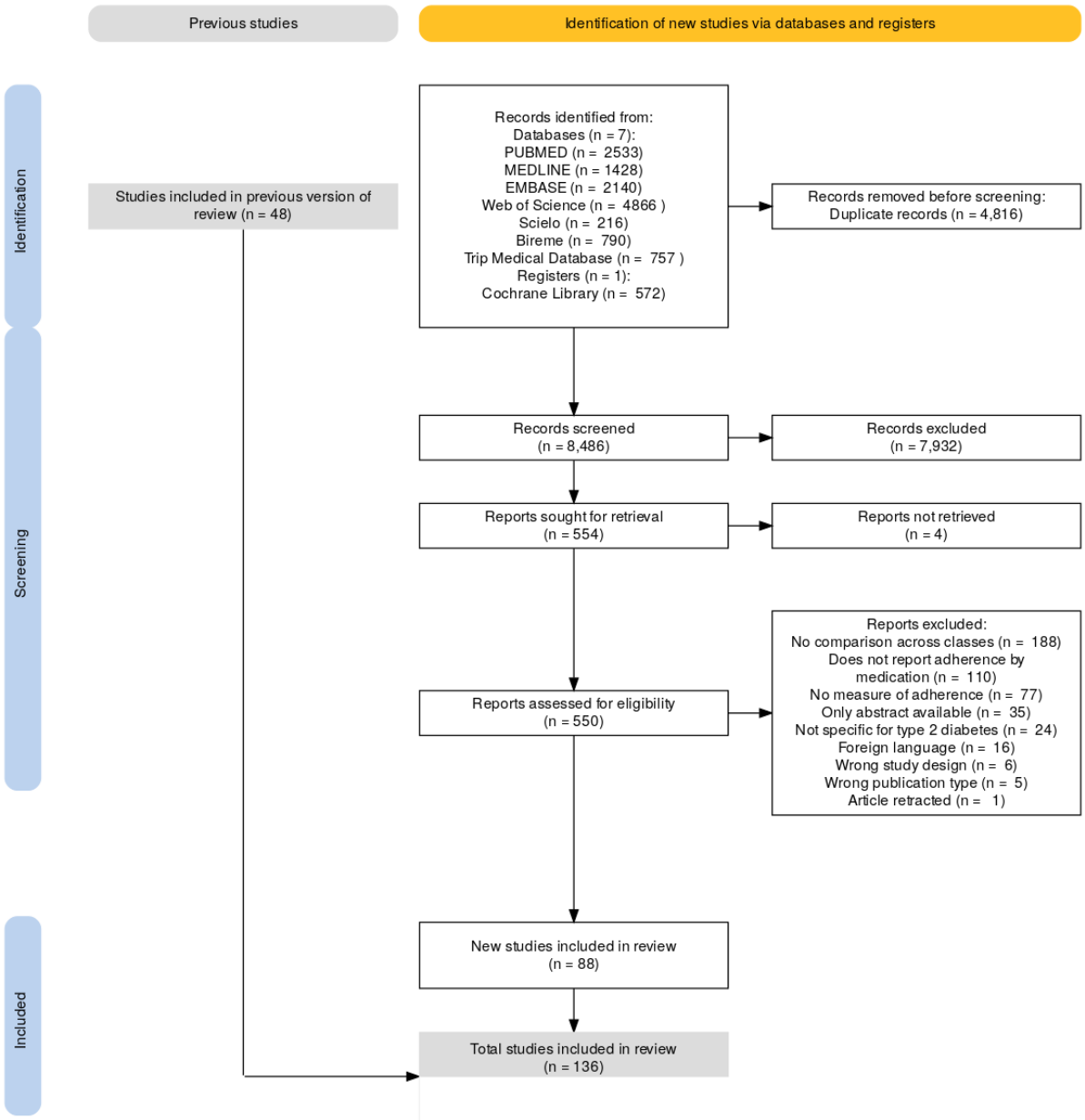
Evaluación de la calidad de los estudios

La calidad de los ensayos controlados aleatorios fue examinada a través de la herramienta Cochrane de Evaluación de Riesgo de Sesgo que permitió clasificar a cada estudio como bajo, indeterminado o alto riesgo (12). Los estudios observacionales se evaluaron mediante la escala de Newcastle-Ottawa (13). La calidad de los estudios con puntuaciones de 7-9 se consideró buena, y las puntuaciones entre 4-6 y ,4 moderada y mala, respectivamente.

RESULTADOS

La nueva búsqueda realizada identificó 8.486 citas, de las cuales 136 fueron incluidas finalmente luego del proceso de filtración. Esta revisión incluye un incremento de aproximadamente el 180% en comparación con el total de estudios incluidos en la revisión previa. El nivel de concordancia entre revisores fue de k=0.85. El diagrama de flujo PRISMA, muestra los resultados de la selección de artículos y se proporciona en la **Figura 1.**

Figura 1. Diagrama de flujo PRISMA



Entre los estudios finalmente seleccionados para esta investigación, 55 compararon exclusivamente terapias orales, 51 terapias inyectables, 29 evaluaron tanto terapias orales como inyectables y 1 estudio comparó la terapia oral con un agente inhalado. La mayoría de los estudios fueron de tipo cohorte (n=105), seguidos de ensayos clínicos aleatorizados (n=16), transversales (n=8), retrospectivos de casos emparejados (n=3) y otros (n=4). Las características de los trabajos incluidos se resumen en la tabla del **Anexo 2.**

Sulfonilureas

El análisis de las tasas de adherencia y persistencia de las sulfonilureas se realizó en un total de 50 estudios (36.76%). De estos, dieciséis estudios (32%) reportaron cifras inferiores en esta clase en comparación con los DPP4i (14–29). Resultados similares fueron evidentes cuando se realizó la comparación con la clase de la biguanidas, demostrando que existen tasas de adherencia y persistencia menores en 16 de los trabajos incluidos (32%) (5,22–24,27,28,30–39). La evidencia de otros estudios no fue consistente con esta tendencia, por lo que se presenta en el **Anexo 2** para su evaluación.

Agonistas del receptor del GLP-1 (GLP1- RA)

Un total de 52 (38,2%) estudios analizaron los medicamentos pertenecientes a la clase de los agonistas del receptor GLP-1. Diecisiete estudios (33%) realizaron comparaciones intraclase en donde se encontró que el GLP1- RA con una mayor proporción de pacientes adherentes o persistentes fue la dulaglutida (40–49), mientras que otras 7 investigaciones (13.4%) observaron que la liraglutida fue la que presentó las tasas de adherencia y persistencia más bajas (41,47,49–53). Cuatro estudios (7%) reportaron una adherencia más baja de los GLP-1 RA en comparación con la clase de los SGLT2i (54–57). Los resultados adicionales se pueden observar en la tabla proporcionada en el **Anexo 2.**

Inhibidores del cotransportador de sodio-glucosa tipo 2 (SGLT2i)

Las tasas de adherencia y persistencia terapéutica de esta clase fueron reportadas en un total de 24 estudios (17.64%). Ocho de estos (30%),

demostraron que tanto las tasas de adherencia y la persistencia fueron superiores en los SGLT2i en comparación con los GLP1-RA (38,55–61). Adicionalmente, se reportó adherencia y persistencia mayor en comparación con las sulfonilureas (23,39,60,61). Sin embargo, estas tasas fueron inferiores en comparación con los DPP4i, como se demostró en cinco estudios (21%) (23,34,39,61,62). En investigaciones que compararon la adherencia y persistencia entre distintos fármacos pertenecientes a esta clase, la canagliflozina destacó por obtener los mejores resultados (54,63).

Insulina

Un total de 32 estudios evaluaron diferentes tipos de insulina. Entre estos, 13 compararon insulinas de distinta acción (intermedia y prolongada), evidenciando que las insulinas de acción prolongada, como detemir o glargina, presentaron mejores tasas de adherencia y persistencia en comparación con la insulina NPH u otras. En cuatro estudios (28,64–66) se identificó a la insulina como el medicamento con la adherencia o persistencia más baja en comparación con otros hipoglucemiantes orales e inyectables (GLP-1 RA). Los detalles de los estudios adicionales se proporcionan en el **Anexo 2.**

Meglitinidas

Quince estudios evaluaron el uso de meglitinidas en pacientes con diabetes mellitus tipo 2. Los resultados fueron mixtos, con algunos mostrando que las meglitinidas tenían las tasas de adherencia o persistencia más bajas en comparación con otros fármacos orales e inyectables (21,65,66). Sin embargo, cuatro estudios encontraron lo contrario, observando una mejor adherencia con las meglitinidas en comparación con otras opciones de tratamiento (62,67–69). El **Anexo 2** contiene información adicional sobre los resultados de los otros estudios.

Inhibidores de la DPP-4 (DPP4i)

La adherencia y persistencia de los medicamentos pertenecientes a la clase DPP4i fue evaluada en un total de 40 estudios (29.41%). Esta clase reportó tasas

de adherencia y persistencia superiores en comparación con las sulfonilureas en 16 investigaciones (14,15,18,19,21,22,25–28,39,61,70–74). Por otro lado, la comparación con las biguanidas se realizó en 10 estudios demostrando resultados inferiores con relación a esta clase (22,24,27,28,30,31,34,38,39,75). Se encontraron resultados contrastantes en otros estudios, por lo que se detallan en el **Anexo 2** para una consulta más completa.

Inhibidores de la alfa-glucosidasa

En total, 11 estudios incluyeron los inhibidores de la alfa-glucosidasa para su análisis. Cuatro investigaciones encontraron que este grupo de medicamentos presentaba las peores tasas de adherencia o persistencia (15,34,68,69). En contraste, el estudio de Shani et al. (33) observó la adherencia más alta con este medicamento. Con respecto a su comparación con las otras clases de medicamentos existieron resultados mixtos, los cuales se detallan en el **Anexo 2.**

Tiazolidinedionas (TZD)

En esta revisión, se analizaron 27 estudios (19.85%) para evaluar las tasas de adherencia y persistencia a las tiazolidinedionas. Este fármaco demostró una mayor adherencia y persistencia cuando fue comparado con las biguanidas, lo cual fue un hallazgo común en 10 estudios (15,25,62,67,76–81). Adicionalmente, se pudo concluir que esta clase ofrece una menor adherencia y persistencia en comparación con los DPP4i, mediante los resultados ofrecidos en 9 de las investigaciones incluidas (15,21–23,28,34,39,62,82). La evidencia de otros estudios no fue consistente, por lo que se presenta en el **Anexo 2** para su revisión.

Terapia combinada

El análisis de los esquemas de tratamiento combinados se efectuó en 16 estudios (11.76%). Dentro de este grupo, cuatro reportaron que la combinación de GLP1-RA + insulina demostró tasas de adherencia y persistencia superiores a la administración de únicamente insulina (83–86). Por otro lado, tres estudios

(87–89), reportaron mayor adherencia y persistencia en la combinación de biguanidas + DPP4i en comparación con otras terapias combinadas como, por ejemplo, metformina + sulfonilureas. Es importante destacar que también se demostró que las combinaciones de medicamentos hipoglucemiantes no ofrecieron ninguna ventaja en las tasas de adherencia estudiadas en comparación con las formulaciones de solamente un medicamento (38,56).

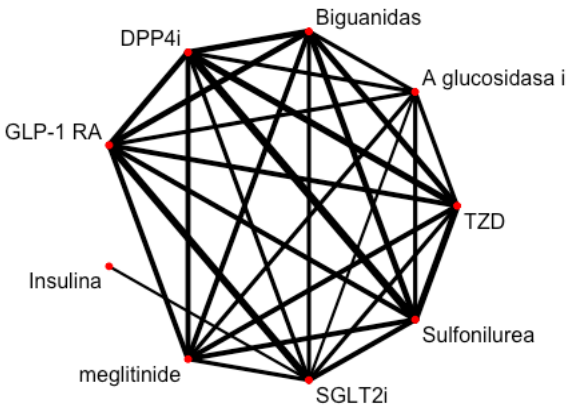
Calidad de los estudios incluidos

La puntuación media en la evaluación de los estudios observacionales en la escala de Newcastle-Ottawa fue 7. La mayoría de los estudios fueron de buena calidad, obteniendo 4 puntos en el dominio de selección, 1 o 2 en el dominio de comparabilidad y 2 en el dominio de resultado/exposición. Sin embargo, una gran proporción de estudios no detalló adecuadamente el seguimiento de los pacientes, ya sea en cuanto a las pérdidas durante el periodo de estudio o al contabilizar el total de individuos hasta el final. El riesgo de sesgo en los ensayos clínicos aleatorizados osciló entre bajo e indeterminado siendo la principal limitación la falta de ocultamiento del tratamiento en estudios de tipo *open label.* **(Anexo 3)**

Síntesis de la evidencia

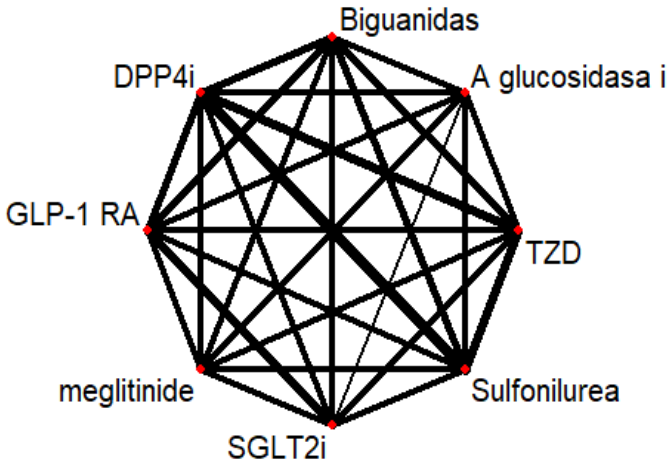
Existieron 16 estudios elegibles para el desarrollo del metaanálisis en red. Se incluyeron todos los que evaluaban la adherencia mediante PDC. Inicialmente, se obtuvo una geometría en red como se visualiza en la **Figura 2.**

Figura 2. Geometría en red de metaanálisis inicial



Al existir solamente un estudio que comparaba la insulina con un fármaco de un clase distinta (59) se decidió excluirlo y realizar un análisis de sensibilidad. Los resultados del metaanálisis que incluyeron dicho estudio se pueden visualizar en el **Anexo 4**. En el metaanálisis en red definitivo se analizaron 15 estudios –todos ellos estudios de cohorte– identificando un total de 88 comparaciones por pares entre 8 tratamientos distintos. La orientación geométrica de la red se puede evidenciar en la imagen presentada en la **Figura 3** a continuación:

Figura 3. Geometría en red de metaanálisis definitivo



En las pruebas de heterogeneidad se halló: tau²= 0.1089; tau = 0.3301; I²= 99.6% [99.5%; 99.6%] y Q= 6207.01 con p <0.01, indicando alta heterogeneidad no explicada por el azar.

En el modelo de efectos aleatorios se identificó que los pacientes en monoterapia con inhibidores de la alfa-glucosidasa tuvieron un mayor riesgo de mala adherencia en comparación con todas las terapias incluidas, en especial con los DPP4i (RR= 4.25; IC 95% [2.88; 6.26]). Por otro lado, los DPP4i presentaron un menor riesgo en comparación con todos los medicamentos incluidos en el análisis.

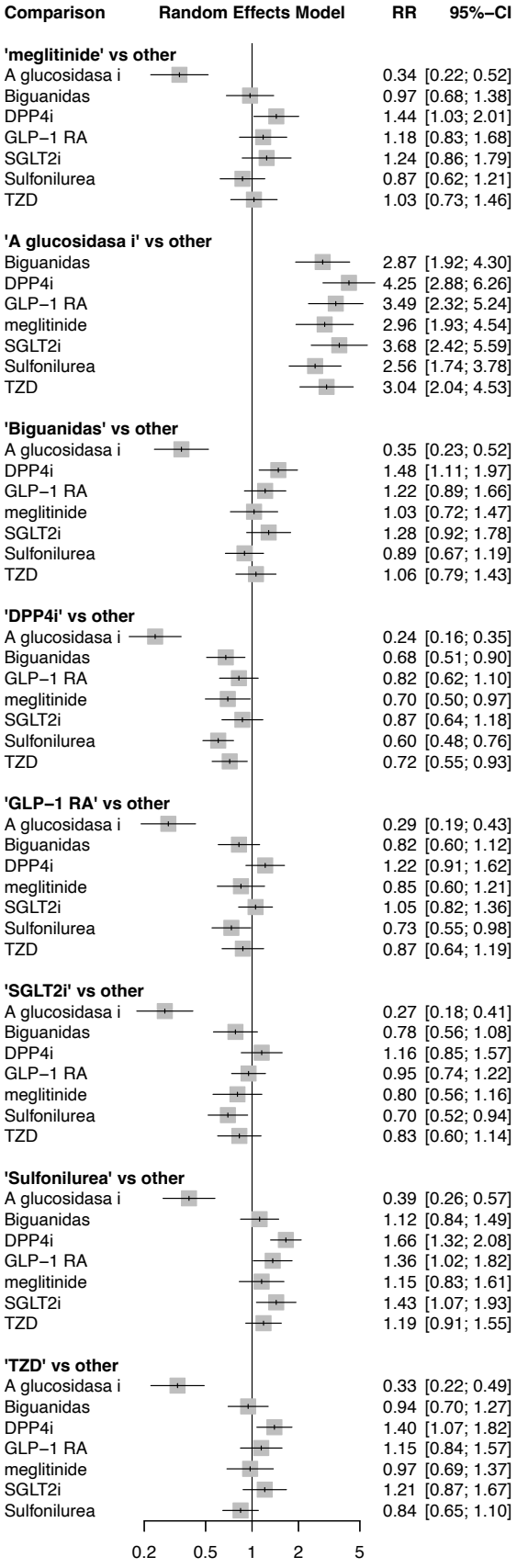
Las meglitinidas tuvieron un menor riesgo de mala adherencia en comparación con los inhibidores de la alfa-glucosidasa (RR=0,34; IC 95% [0.22; 0.52]). No

existió una diferencia significativa en el riesgo para una mala adherencia en las demás comparaciones con otros medicamentos **(Figura 4).**

En el caso de las biguanidas, se observó un menor riesgo de mala adherencia en contraste con los inhibidores de la alfa-glucosidasa (RR=0.35; IC 95% [0.23; 0.52]) y el riesgo para una baja adherencia fue significativamente más alto en comparación con los DPP4i (RR=1.48; IC 95% [1.11; 1.97]), mientras que no se reportaron diferencias importantes con respecto a otros fármacos.

En relación con los GLP-1 RA, se identificó un riesgo significativamente menor de presentar una mala adherencia en comparación con las sulfonilureas (RR= 0.73; IC 95% [0.55; 0.98]). Existió también un riesgo menor en los SGLT2i con respecto a las sulfonilureas (RR=0.70; IC 95% [0.52; 0.94]), mientras que no se encontró una diferencia significativa en las demás comparaciones. Las sulfonilureas reportaron un mayor riesgo de baja adherencia en relación con las demás terapias a excepción de los inhibidores de la alfa-glucosidasa; estas diferencias fueron significativas en las comparaciones contra DPP4i, GLP-1 RA y SGLT2i. Por último, con respecto a las TZD no se encontró un menor riesgo de mala adherencia en comparación con los todos los medicamentos a excepción de DPP4i (RR=1.40; IC 95% [1.07; 1.82]).

Figura 4. Forest plot de no-adherencia



DISCUSIÓN

La revisión sistemática y metaanálisis realizados en este estudio proporcionan una visión general actualizada y un resumen cuantitativo de la adherencia y persistencia de los diversos medicamentos hipoglucemiantes disponibles en el tratamiento de la diabetes mellitus tipo 2. En comparación con la versión anterior de esta revisión publicada en el 2017 por McGovern et al. (7), para esta investigación actualizada se reunió un total de 136 estudios, incluidos 88 adicionales. Con los datos obtenidos tras la inclusión de los estudios recientes, se identificaron diferencias significativas en los resultados entre las distintas clases de medicamentos cumpliendo con el objetivo propuesto de la investigación.

Uno de los hallazgos más notables es la mayor adherencia y persistencia observadas en los DPP4i en comparación con otros medicamentos, especialmente los inhibidores de la alfa-glucosidasa y las sulfonilureas, coincidiendo con el estudio realizado previamente (7). Este resultado puede atribuirse a los efectos secundarios leves y la facilidad de administración de los DPP4i, que son bien tolerados, presentan un bajo riesgo de hipoglucemia y aumento de peso, lo que fomenta una alta adherencia y persistencia entre los pacientes (90,91). En contraste, las sulfonilureas, a pesar de ser una clase de medicamentos ampliamente utilizada, presentaron tasas de adherencia y persistencia significativamente inferiores a los otros fármacos antidiabéticos, hallazgo consistente con el estudio realizado por Lee et al. (92). La principal causa de la menor adherencia a las sulfonilureas podría ser sus efectos secundarios, especialmente la hipoglucemia y el aumento de peso (93). Es importante destacar que, incluso cuando se realizaron las comparaciones dentro de una misma clase de medicamentos, las diferencias en los resultados fueron notorias. Esto se evidencia en el caso de los GLP1-RA (40–53), sin embargo, las razones que provocaron estas diferencias no se reportaron específicamente.

Las diferencias en la adherencia y persistencia observadas en este estudio de actualización podrían explicarse por varios factores, incluyendo la frecuencia de administración, los efectos secundarios y la complejidad del régimen de medicación (94,95). Por ejemplo, los DPP4i y los SGLT2i, que requieren solamente una dosis diaria, podrían favorecer una mayor adherencia comparados con las sulfonilureas o la insulina, que requieren múltiples dosis diarias o inyecciones respectivamente (96).

Entre las fortalezas de este estudio se destaca la búsqueda exhaustiva realizada con una amplia gama de bases de datos. La inclusión de diversos estudios observacionales e intervencionales proporciona una visión integral de las tasas de adherencia y persistencia en diversas poblaciones a nivel mundial, mejorando el grado de validez externa. Adicionalmente, el uso del metaanálisis en red permite comparar múltiples tratamientos simultáneamente, estableciendo una jerarquía clara de adherencia y persistencia entre los medicamentos estudiados.

No obstante, existen algunas limitaciones. La alta heterogeneidad en los resultados sugiere una considerable variabilidad entre los estudios incluidos. El valor obtenido de p en las pruebas estadísticas sugiere que es altamente improbable que los resultados observados se deban al azar. Estos datos pueden ser consecuencia de las diferencias en las poblaciones estudiadas y las estrategias de tratamiento (dosis, duración de la administración, tratamientos concomitantes, etc). Además, al ser estudios no aleatorizados, es difícil controlar por factores confusores/confundentes desconocidos. Sin embargo, de acuerdo con las directrices proporcionadas por Guyatt et al. (97), reportamos estos resultados con el objetivo de ampliar la información disponible acerca de este tema. Ya sea médicos o pacientes, todos necesitan una estimación lo más precisa posible del efecto del tratamiento para tomar decisiones informadas. No obstante, la falta de claridad sobre las diferencias entre estudios que investigan la misma pregunta limita de cierta forma la confianza en dicha estimación general. Si bien por ahora es la mejor referencia disponible, la gran

inconsistencia sin explicación entre estudios reduce significativamente la fiabilidad de este valor resumido.

Es importante mencionar que a pesar de utilizar la misma medida de adherencia (PDC), el metaanálisis en red evidenció una heterogeneidad importante, un resultado inesperado dado que la mayoría de los estudios incluidos reportaron porcentajes de adherencia entre el 40% y el 70% (31,35,51,57,60,63,71,98–104). Una posible explicación para esta heterogeneidad es la presencia de estudios con tasas de adherencia muy altas (29,105,106) o muy bajas (32,107), los cuales podrían haber sesgado los resultados del metaanálisis en red.

CONCLUSIÓN

Esta revisión proporciona una visión actualizada y detallada acerca de las tasas de adherencia y persistencia entre diferentes medicamentos hipoglucemiantes, conocimiento que es crucial para guiar la prescripción médica y minimizar las complicaciones asociadas a la diabetes mellitus tipo 2. Al ampliar significativamente la evidencia disponible se identificó una importante variabilidad en la adherencia y persistencia entre clases e incluso en comparaciones intraclase de los medicamentos. El tratamiento con menor riesgo de mala adherencia fue con DPP4i mientras que las sulfonilureas e inhibidores de la alfa-glucosidasa mostraron un mayor riesgo para la baja adherencia en comparación a las demás terapias. La calidad de los estudios observacionales en general fue buena; sin embargo, se detectaron limitaciones, como la falta de especificación en el seguimiento detallado. En contraste, en los ensayos clínicos, la principal dificultad fue la ausencia de ocultamiento. Además, la heterogeneidad derivada de causas no identificadas, subraya la necesidad de realizar más investigaciones que establezcan estándares claros para comprender mejor estas tendencias en la adherencia y persistencia.

Recomendaciones

Para mejorar la comprensión de este tema en el tratamiento de la DM2, futuras investigaciones deberían enfocarse en la estandarización de las definiciones y métodos de medición de adherencia y persistencia. Investigaciones adicionales también podrían explorar los factores que influyen en la adherencia a tratamientos específicos, como las características demográficas, las comorbilidades y las preferencias del paciente. Por último, sería beneficioso realizar estudios cualitativos para entender las barreras y facilitadores de la adherencia desde la perspectiva del paciente.

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Middle East: the VIRTUE study. Curr Med Res Opin [Internet]. 2017;33(1 PG-161–167):161–7. Available from: NS -

Adherencia entre las diferentes medicaciones disponibles en pacientes con diabetes mellitus tipo 2: Una actualización de una revisión sistemática de la literatura. - ANEXOS

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Anexo 1. Estrategia de búsqueda

La estrategia de búsqueda presentada a continuación se usó en la base de datos de PubMed. Esta estrategia se adaptó para su aplicación en las demás bases de datos incluidas.

Search Details	Results
("medication adherence"[MeSH Terms] OR "patient compliance"[MeSH Terms] OR "patient participation"[MeSH Terms] OR "patient preference"[MeSH Terms] OR "treatment refusal"[MeSH Terms] OR ("patient compliance"[MeSH Terms] OR "compliance"[MeSH Terms]) OR "medication adherence"[MeSH Terms] OR "patient compliance"[MeSH Terms] OR "patient dropouts"[MeSH Terms] OR "treatment discontinuation"[All Fields] OR "drug adherence"[All Fields] OR "adher*"[All Fields] OR ("garbage"[MeSH Terms] OR "garbage"[All Fields] OR "refuse"[All Fields] OR "refuses"[All Fields] OR "refusal"[All Fields] OR "refusals"[All Fields] OR "refused"[All Fields] OR "refuser"[All Fields] OR "refusers"[All Fields] OR "refusing"[All Fields]) OR ("withdraw"[All Fields] OR "withdrawal"[All Fields] OR "withdrawals"[All Fields] OR "withdrawing"[All Fields] OR "withdraws"[All Fields]) OR "non-adherence"[All Fields] OR "non-compliance"[All Fields] OR "non-compliant"[All Fields]) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "type II diabetes"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR "case control studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "longitudinal studies"[MeSH Terms] OR "follow up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross sectional studies"[MeSH Terms] OR "observational study"[All Fields] OR "follow-up"[All Fields] OR "follow-up"[All Fields] OR "random*"[All Fields] OR "nonrandom*"[All Fields])	5,319
"clinical trials as topic"[MeSH Terms] OR "case control studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "longitudinal studies"[MeSH Terms] OR "follow up studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "cross sectional studies"[MeSH Terms] OR "observational study"[All Fields] OR "follow-up"[All Fields] OR "follow-up"[All Fields] OR "random*"[All Fields] OR "nonrandom*"[All Fields]	5,375,388
"diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes"[All Fields] OR "type 2 diabetes mellitus"[All Fields] OR "type II diabetes"[All Fields]	241,741
"medication adherence"[MeSH Terms] OR "patient compliance"[MeSH Terms] OR "patient participation"[MeSH Terms] OR "patient preference"[MeSH Terms] OR "treatment refusal"[MeSH Terms] OR "patient compliance"[MeSH Terms] OR "compliance"[MeSH Terms] OR "medication adherence"[MeSH Terms] OR "patient compliance"[MeSH Terms] OR "patient dropouts"[MeSH Terms] OR "treatment discontinuation"[All Fields] OR "drug adherence"[All	634,048

Fields] OR "adher*"[All Fields] OR "garbage"[MeSH Terms] OR "garbage"[All Fields] OR "refuse"[All Fields] OR "refuses"[All Fields] OR "refusal"[All Fields] OR "refusals"[All Fields] OR "refused"[All Fields] OR "refuser"[All Fields] OR "refusers"[All Fields] OR "refusing"[All Fields] OR "withdraw"[All Fields] OR "withdrawal"[All Fields] OR "withdrawals"[All Fields] OR "withdrawing"[All Fields] OR "withdraws"[All Fields] OR "non-adherence"[All Fields] OR "non-compliance"[All Fields] OR "non-compliant"[All Fields]	
"nonrandom*"[All Fields]	49,854
"random*"[All Fields]	1,734,496
"follow up"[All Fields]	1,624,411
"follow-up"[All Fields]	1,624,411
"observational"[All Fields]	339,468
"observational study"[All Fields]	217,590
"cross sectional studies"[MeSH Terms]	490,548
"prospective studies"[MeSH Terms]	678,192
"follow up studies"[MeSH Terms]	695,292
"longitudinal studies"[MeSH Terms]	169,253
"cohort studies"[MeSH Terms]	2,565,426
"retrospective studies"[MeSH Terms]	1,175,229
"case control studies"[MeSH Terms]	1,476,474
"clinical trials as topic"[MeSH Terms]	387,532
"type II diabetes"[All Fields]	10,254
"type 2 diabetes mellitus"[All Fields]	198,000
"type 2 diabetes"[All Fields]	236,797
"diabetes mellitus, type 2"[MeSH Terms]	176,714
"non-compliant"[All Fields]	2,554
"non-compliance"[All Fields]	6,387
"non-adherence"[All Fields]	8,123
"withdraw"[All Fields] OR "withdrawal"[All Fields] OR "withdrawals"[All Fields] OR "withdrawing"[All Fields] OR "withdraws"[All Fields]	135,642
"garbage"[MeSH Terms] OR "garbage"[All Fields] OR "refuse"[All Fields] OR "refuses"[All Fields] OR "refusal"[All Fields] OR "refusals"[All Fields] OR "refused"[All Fields] OR "refuser"[All Fields] OR "refusers"[All Fields] OR "refusing"[All Fields]	72,885
"adher*"[All Fields]	331,615

"drug adherence"[All Fields]	1,242
"treatment discontinuation"[All Fields]	6,246
"patient dropouts"[MeSH Terms]	8,417
"patient compliance"[MeSH Terms]	86,252
"medication adherence"[MeSH Terms]	26,139
"patient compliance"[MeSH Terms] OR "compliance"[MeSH Terms]	90,316
"treatment refusal"[MeSH Terms]	13,949
"patient preference"[MeSH Terms]	10,835
"patient participation"[MeSH Terms]	29,736
"patient compliance"[MeSH Terms]	86,252
"medication adherence"[MeSH Terms]	26,139

Anexo 2. Características de estudios incluidos

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Balkrishnan et al. 2006	Outcomes associated with introduction of thiazolidinedione therapy in Medicaid enrolled patients with type 2 diabetes: An updated and expanded retrospective analysis.	Cohort Study	Retrospective cohort study using a large USA claims database (North Carolina Medicaid) of adults with T2D initiated on a TZD, metformin, or SU between July 1, 2001 and December 31, 2004. 3,191 people included.	1,774 people started on a TZD, 218 started on metformin, and 1,199 started on a SU.	Adherence; Persistence	Adherence measured using MPR. Persistence duration (years). Analysis of new prescriptions. Switching considered as non-persistence.	Mean adherence rates: TZDs 0.49, metformin 0.07, SUs 0.43. Mean persistence: TZDs 0.69, metformin 0.10, SUs 0.97.	Precise definition of medication persistence and adherence rates are unclear. Comparisons used in multivariate analysis are unclear. Limited reporting of patient characteristics.	None	Takeda
Shenolikar et al. 2006	Race and medication adherence in medicaid enrollees with type-2 diabetes.	Cohort Study	Retrospective cohort study in the USA using the North Carolina Medicaid program database of adults with T2D initiated on metformin, SUs, or TZDs between July 2001 and June 2002 inclusive. 3,169 people included for analysis.	216 people initiating metformin, 1,179 initiating SUs, and 1,774 initiating TZDs	Adherence; Persistence	Mean MPR. Analysis of new prescriptions only although measured during the second year of prescription. Approach to interclass switching not described.	Adherence was lowest for metformin (MPR 22%) compared with SUs (57%) and TZDs (60%).	Primary comparison was racial differences in adherence. Characteristics of each medication group not reported. Trends in adherence by class examined across racial groups with same pattern identified (lower adherence with metformin).	Stratification by race and adjustment for other demographic confounders.	None reported
Barnett et al. 2007	Long-term tolerability of inhaled human insulin (Exubera®) in patients with poorly controlled type 2 diabetes.	Randomised controlled trial	RCTs, 104 weeks of intervention, adults (35-80) with T2D not controlled on monotherapy with either metformin (study 1) or SU (study 2). Patients were randomised to inhaled insulin (Exhubera) or glibenclamide (study 2) or metformin (study 1). 922 people started on treatment.	In study 1: 235 people randomised to inhaled insulin and 211 to metformin. In study 2: 243 people randomised to inhaled insulin and 233 to glibenclamide.	Discontinuation	Discontinuation for any reason during the trial period	Discontinuations were similar across the groups. Study 1: inhaled insulin 31, SU 39. Study 2: inhaled insulin 40, metformin 43.	No measure of medication adherence or duration of persistence. Open-label study design.	Randomisation	Pfizer
Holman et al. 2007	Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes.	Randomised controlled trial	RCT in the UK and Ireland, 1 year of intervention, adults with T2D not controlled on metformin and a SU. Patients were randomised to insulin aspart 30 twice daily, prandial insulin aspart thrice daily, or insulin detemir once or twice daily. 708 people randomised to treatment.	235 people started on NovoMix 30 (mean age 61.7 years; SD 8.9; 67.7% male), 239 people started on NovoRapid (mean age 61.6 years; SD 10.5; 63.6% male), 234 people started on Levemir (mean age 61.9 years; SD 10.0; 61.1% male)	Discontinuation	Discontinuation for any reason during 1 year intervention period.	Discontinuation during follow up; NovoMix 30 5.5% (13/235), NovoRapid 7.2% (17/239), Levemir 4.3 (10/234). Withdrawal of participation was more common reason on those on prandial NovoRapid insulin (13), vs biphasic NovoMix (4) or basal Levemir insulin (3).	Only discontinuation reported. Open-label design.	Treatment randomisation	Novo Nordisk and Diabetes UK
Rozenfeld et al. 2008	Oral antidiabetic medication adherence and glycemic control in managed care.	Cohort Study	Retrospective cohort study in the USA using the Providence Primary Care Research Network database in Oregon of adults with T2D initiated monotherapy with metformin, sulfonylureas, thiazolidinediones, meglitinides or AGIs between 2001 and 2004. 2,471 people included for analysis.	1,274 people initiated on metformin (mean age 53.0 years; SD 11.0; 46.0% male), 1,081 on SUs (mean age 55.0 years; SD 12.0; 51.0% male), and 337 taking TZDs (mean age 52.0 years; SD 11.0; 49.0% male). Other groups not reported.	Adherence	Adherence reported as mean PDC and proportion of people with PDC ≥ 80%. Analysis of new prescriptions only. Switching to combination preparations containing the originally prescribed medication was considered ongoing adherence.	Adherence was not significantly different between classes for either measure (mean PDC; proportion with PDC ≥ 80%); metformin (80.7%; 63.9%), SUs (81.8%; 65.8%), TZDs (82.0%; 69.4%). P values not reported.	Small sample size with no adjustment for differences between groups. Attempt to compare all available classes at the time of analysis although insufficient data for AGIs and meglitinides.	None	Novartis
Bergenstal et al. 2009	Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea.	Randomised controlled trial	RCT, 24-weeks duration, in the USA, including people with T2D for longer than 6 months. Patients were randomised 1:1:1 to exenatide twice daily, biphasic insulin aspart 70/30 once daily, or biphasic insulin aspart 70/30 twice daily. 372 people started on treatment.	124 people randomised to exenatide (mean age 52.5 years; SD 10.6; 48.4% male), 124 people randomised to biphasic insulin aspart once daily (mean age 51.8 years; SD 10.9; 48.4% male), and 124 people randomised to biphasic insulin aspart twice daily (mean age 53.4 years; SD 10.0; 47.6% male)	Discontinuation	Discontinuation for any reason during 24-week intervention period.	Discontinuation during follow up; exenatide 29.8%, insulin aspart once daily 16.1%, insulin aspart twice daily 19.4%. Nausea was cited as the most common reason for discontinuation in the exenatide group.	Excluded patients with NYHA class III or IV heart failure, hepatic or renal insufficiency. Study staff monitored subjects for medication compliance.	Treatment randomisation	Novo Nordisk
Fabunmi et al. 2009	Patient characteristics, drug adherence patterns, and hypoglycemia costs for patients with type 2 diabetes mellitus newly initiated on exenatide or insulin glargine	Cohort Study	Retrospective cohort study, in the USA, using HealthCore Integrated Research Database™ research databases of adults with T2D initiated on exenatide or glargine insulin. 6,300 people included.	3,262 people started on exenatide (mean age 53.0 years; SD 10.0; 46.0% male), 3,038 people started on glargine insulin (mean age 56.0 years; SD 12.0; 59.0% male).	Adherence; Persistence; Discontinuation	Mean MPR over 1 year post initiation of therapy and proportion of people with MPR ≥ 80%. Duration of medication persistence (discontinuation gap defined as 60 or 90-days after the prescription supply duration) and adjusted survival analysis for persistence duration. Annual discontinuation rate. Analysis of new prescriptions only. Interclass switching was treated as non-persistence.	MPR was higher with exenatide (0.68 vs 0.29; p<0.001). The proportion of people adherence (MPR ≥ 80%) was higher with exenatide (47% vs 29%; p<0.001). More people in the glargine group discontinued therapy using both 60-day and 90-day discontinuation gap definitions (p<0.001).	Substantial and significant differences reported between groups particularly with gender and comorbidities which may explain observed differences.	None	Amylin Pharma-ceuticals
Garber et al. 2009	Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial.	Cohort Study	RCT, 52 weeks of intervention, adults with T2D with no previous medication or up to half maximum dose single agent. Patients were randomised 1:1:1 to monotherapy with daily liraglutide 1.2mg or 1.8mg or glimepiride (8mg). 746 people randomised.	251 people randomised to liraglutide 1.2mg (mean age 53.7 years; SD 11.0; 47.0% male), 247 to liraglutide 1.8mg (mean age 52.0 years; SD 10.8; 49.0% male), and 248 to glimepiride 8mg (mean age 53.4 years; SD 10.9; 54.0% male).	Discontinuation	Discontinuation for any reason during 52-week intervention period. Non-compliance (not defined in the trial manuscript).	Discontinuation during follow up; liraglutide 1.2mg 35.5%, liraglutide 1.8mg 21.4%, glimepiride 38.7%. Adverse events were the most common reason for discontinuation in the liraglutide groups, ineffective therapy in the glimepiride group. Non-compliance more common in the liraglutide groups (4.4% and 4.4%) than glimepiride group (2.0%).	Number of people non-compliant reported. Reasons for discontinuation reported.	Treatment randomisation	Novo Nordisk

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Haupt et al. 2009	Refill adherence to oral antihyperglycaemic drugs in Sweden.	Cohort Study	Retrospective cohort study using the Swedish prescribed drug register (analysis of the complete population of Sweden). Adults with T2D and no hospital admissions on oral medications between 1st December 2005 and 30 November 2006 included. 171,220 people included.	People currently on monotherapy with metformin (75,125), glibenclamide (20,347), glipizide (7,176), glimepiride (2,791), fixed dose combination with metformin and rosiglitazone (1,534), acarbose (508), rosiglitazone (878), pioglitazone (626), repaglinide (3,647), and nateglinide (166). An additional 36,560 people analysed taking dual therapy.	Adherence	Adherence reported as mean MPR. Analysis of ongoing medication prescriptions. Adherence was measured separately for each drug within each class with interclass switching considered as two separate adherence events.	Adherence (mean MPR) over 12 months; metformin 88.6%, glibenclamide 90.6%, glipizide 91.1%, glimepiride 90.8%, fixed dose combination with metformin and rosiglitazone 87.9%, acarbose 81.1%, rosiglitazone 92.8%, pioglitazone 92.3%, repaglinide 86.4%, and nateglinide 81.3%. Trends were similar in those on dual therapy.	Whole population study. Differentiation between medication use in mono and dual therapy. Analysis over a wide range of oral therapies. No adjustment for confounders. No differentiation between new and established therapy.	None	Lulca University
Patel et al. 2009	Medication adherence in low income elderly type 2 diabetes patients: A retrospective cohort study	Cohort Study	Retrospective cohort study, in the USA, using Medicaid data on adults with T2D on oral antidiabetic medication between July 2001 and June 2002. 3,169 people included.	The number of people initiated on metformin and SUs not reported. Age reported by age groups; 681 people aged 18-44, 2,327 aged 45-64, and 161 aged 65+.	Adherence	Relative adherence rates (measured using MPR) adjusted for confounders. Analysis of ongoing prescriptions. Approach to interclass switching unclear.	Metformin adherence was lower than SUs (adjusted difference in MPR 34.5%, p < 0.05).	Small sample size. Incomplete reporting of patient characteristics.	Multivariate adjustment. Incomplete reporting of factors adjusted for	None reported
Plat et al. 2009	Change of initial oral antidiabetic therapy in type 2 diabetic patients	Cohort Study	Retrospective cohort study, in the Netherlands, using the PHARMO Record Linkage System, of adults with T2D initiated on metformin, SUs, or TZDs from 1999-2004. 33,463 people included here (those on monotherapy).	14,277 people initiated on monotherapy with metformin, 18,876 on SUs, and 310 on TZDs.	Discontinuation	Proportion of people discontinuing therapy within a year. Discontinuation was defined as less than 365 days of continuous use. Analysis of new prescriptions only. Approach to interclass switching unclear.	After 1 year discontinuation was 16.1% with metformin, 20.1% with SUs, and TZDs 25.1%.	Large sample size, except with thiazolidinediones. Long study period with changing guidelines within the study period.	None	Novartis
Russell-Jones et al. 2009	Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial	Randomised controlled trial	RCT, 26 weeks of intervention, adults with T2D not controlled on oral therapies. Patients were randomised 2:1:2 to liraglutide once daily, placebo, or glargine insulin once daily. 581 people randomised to treatment.	230 people randomised to liraglutide (mean age 57.6 years; SD 9.5; 57.0% male), 232 people randomised to glargine insulin (mean age 57.5 years; SD 10.5; 60.0% male).	Discontinuation	Discontinuation for any reason during 26-week intervention period.	Discontinuation during follow up; liraglutide 10.0%, glargine 5.6%. Adverse events cited as the most common reason for discontinuation in the exenatide group (11/23).	No measure of treatment adherence. Short duration of study. No breakdown of which adverse events lead to discontinuation. Open-label design for insulin with blinding to placebo or liraglutide.	Treatment randomisation	Novo Nordisk
Cooke et al. 2010	Persistence with injectable antidiabetic agents in members with type 2 diabetes in a commercial managed care organization	Cohort Study	Retrospective cohort study using a large USA claims database of adults with T2D initiated on glargine, detemir, exenatide, or NPH Vial insulin. 1,769 people included.	785 people started on glargine (mean age 53.0 years; SD 13.2; 52.2% male), 30 people started on detemir insulin (mean age 53.4 years; SD 11.9; 56.7% male), 738 people started on exenatide (mean age 54.6 years; SD 10.3; 45.9% male), 216 people started on NPH insulin (mean age 49.2 years; SD 15.5; 33.3% male).	Persistence	Duration of medication persistence (discontinuation gap defined as 60 days after the prescription supply duration) and adjusted survival analysis for persistence duration. Analysis of new prescriptions only. Interclass switching was treated as non-persistence.	Mean persistence duration was similar for glargine (7.4 months SD 4.4), detemir (7.8 SD 4.1), and exenatide (7.6 SD 4.4), but shorter for NPH insulin (5.6 SD 4.5). In survival analysis persistence with NPH insulin was significantly shorter than with glargine (p=0.01), there was no significant difference between glargine and detemir or exenatide.	Multivariate adjustment for several potential confounders. Small number of people in the detemir group. Unable to exclude people with gestational diabetes only.	Multivariate adjustment for age, gender, co-payments, and number of oral antidiabetic agents at index date.	Amylin Pharma-ceuticals
Diamant et al. 2010	Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial.	Randomised controlled trial	RCT, 26-weeks of intervention, adults with T2D not controlled on metformin alone or in combination with a SUs. Patients were randomised 1:1 to exenatide weekly or glargine insulin once daily. 456 people started on treatment.	233 people randomised to exenatide (mean age 58.0 years; SD 10.0; 52.0% male), 223 people randomised to glargine insulin (mean age 58.0 years; SD 9.0; 55.0% male).	Discontinuation	Discontinuation for any reason during 26-week intervention period.	Discontinuation during follow up; exenatide 10.3%, glargine 6.3%. Adverse events cited as the most common reason for discontinuation in the exenatide group (12/24).	No measure of treatment adherence. Short duration of study. Open-label design.	Treatment randomisation	Amylin Pharma-ceuticals
Filozof et al. 2010	A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study.	Randomised controlled trial	RCT, 52 weeks of intervention, adults with T2D not controlled on metformin alone. Patients were randomised 1:1 to vildagliptin (50mg twice daily) or gliclazide (up to 320 mg/day). 1,007 people started on treatment.	512 people randomised to vildagliptin (mean age 59.2 years; SD 9.9; 52.2% male), 494 people randomised to gliclazide (mean age 59.7 years; SD 10.2; 52.8% male).	Discontinuation	Discontinuation for any reason during 52 week intervention period.	Discontinuation during follow up; vildagliptin 20.6%, gliclazide 16.6%. Adverse events cited as the most common reason for discontinuation in both groups.	No measure of treatment adherence. Reasons for discontinuation reported.	Treatment randomisation	Novartis
Göke et al. 2010	Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial.	Randomised controlled trial	RCT, 52 weeks of intervention, adults with T2D not controlled on metformin alone. Patients were randomised 1:1 to saxagliptin (5mg daily) or glipizide (up to 20mg/day). 858 people randomised.	428 people randomised to saxagliptin (mean age 57.5 years; SD 10.3; 49.5% male), 430 people randomised to glipizide (mean age 57.6 years; SD 10.4; 54.0% male).	Discontinuation	Discontinuation due to adverse events during the 52-week intervention period.	Discontinuation for adverse events during follow up; saxagliptin 2.3%, glipizide 1.6%.	No measure of clear measure of adherence. A large proportion of participants discontinued as no longer meeting study criteria.	Treatment randomisation	Bristol-Myers Squibb and AstraZeneca
Gordon et al. 2010	A comparison of intermediate and long-acting insulins in people with type 2 diabetes starting insulin: An observational database study.	Cohort Study	Retrospective cohort study using a large UK primary care database (The Health Improvement Network; THIN) people with T2D (≥35 years) initiated on NPH, detemir, glargine, or premix insulin. 8,009 people included. Primary outcome measure was change in HbA1c.	357 people started on detemir (mean age 58.9 years; SD 12.1; 47.0% male), 2,197 people started on glargine (mean age 61.1 years; SD 12.2; 45.0% male), and 1,463 people started on NPH insulin (mean age 60.7 years; SD 12.3; 46.0% male)	Persistence	Number of people remaining persistent at 12, 24, and 36 months included as a secondary outcome. Analysis of new prescriptions only. Interclass switching could occur for premixed insulin. The approach to interclass switching for the other groups in unclear.	Persistence at 12 months was: detemir 78%, glargine 83%, NPH 75%. At 36 months persistence was highest with glargine and lowest with NPH (p < 0.001). No 36 month data was available for detemir as it was licensed in mid-2004.	Large population size. No adjustment for confounders. Exclusion of people switching insulin may bias sample. Definition of non-persistence not clear.	None	Sanofi-Aventis
Hansen et al. 2010	A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005.	Cohort Study	Retrospective cohort study using the US MarketScan claims database of adults with T2D on monotherapy with metformin, pioglitazone, or an SU during 2003. 108,592 people included.	52,156 people taking metformin, 11,520 taking pioglitazone, and 44,916 taking an SU. Demographic differences between the cohorts reported.	Adherence	Adherence was reported as the mean MPR and proportion adherent (MPR ≥ 80%). Analysis of ongoing medication prescriptions. Approach to switching not described.	Patients were less adherent to metformin (56.7% of patients) than pioglitazone (59.3%; P<0.001) or SUs (61.3%; P<0.001). Mean MPR; metformin 70.9%, pioglitazone 73.8%, SUs 73.8%.	Very large sample size with comparison across several groups of medication. Contained a mixture of current and new medication users with no adjustment for treatment duration.	None	Takeda

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Barner et al. 2011	Adherence to oral antidiabetic agents with pioglitazone and metformin: comparison of fixed-dose combination therapy with monotherapy and loose-dose combination therapy.	Cohort Study	Retrospective cohort study using a large USA claims database (Texas Medicaid) of adults (18-65) with T2D prescribed pioglitazone or metformin followed by fixed dose combination therapy between January 1, 2004 and August 31, 2007. 210 people from study met inclusion criteria for this analysis.	62 people taking pioglitazone compared with 148 people taking metformin	Adherence	Mean adherence (MPR) and proportion of people adherent (MPR ≥ 80%). Analysis of ongoing users of metformin and pioglitazone. Switching considered as non-persistence.	Mean adherence was lower with metformin (0.71) than pioglitazone (0.84). Similarly, the proportion of people adherent was lower with metformin (86.3%) than pioglitazone (91.2%).	Small sample size. The study was primarily aimed at providing a comparison of fixed and loose dose combination therapies but this proportion of the analysis did not meet our study inclusion criteria.	None	Takeda
Baser et al. 2011	Clinical and economic outcomes in patients with type 2 diabetes initiating insulin glargine disposable pen versus exenatide BID	Case- Control Study	Retrospective case-matched study, in the USA, using IMPACT® claims database of adults with T2D initiated on glargine or exenatide in 2007 or 2008. 2,339 people met the inclusion criteria, 626 people matched.	313 people initiated on insulin glargine (mean age 54.2 years; SD 10.2; 53.0% male) and 313 matched people initiated on exenatide (mean age 54.5 years; SD 8.8; 56.5% male)	Persistence	Proportion of people persisting with medication at one year and average persistence during one year follow-up. Medications were considered discontinued if the prescription was not refilled within the expected time of medication coverage. Analysis of new prescriptions only. Interclass switching was considered to be a discontinuation event.	At one year persistence was 48% with glargine and 15% with exenatide; p<0.0001. Average persistence (days) was 253 with glargine and 144 with exenatide; p<0.0001. Better glycaemic control achieved with glargine (HbAc1 reduction 1.23% vs 0.92%; p=0.0384).	Both study groups well matched for potential confounders including Charlson comorbidity index. Duration of diabetes was not available. Only 26.8% of people meeting in the selection criteria could be matched for inclusion.	Case-matching using propensity scores	Sanofi-aventis
Bonafede et al. 2011	Insulin use and persistence in patients with type 2 diabetes adding mealtime insulin to a basal regimen: a retrospective database analysis.	Cohort Study	Retrospective cohort study, in the USA, from two Thompson Reuters MarketScan® research databases of adults with T2D with mealtime insulin newly added to basal insulin therapy. 4,752 people included.	1,903 people started on meal-time short acting human insulins, 2,849 people started on mealtime rapid acting insulin analogues.	Persistence	Multivariate analysis of ORs for insulin persistence at one year. Two non-persistence definitions used. Measure 1: a 90-day gap in claims, measure 2: failure to make an insulin claim in three-month period. Analysis of new prescriptions only. Interclass switching was not considered to be non-persistence.	Adjusted OR for persistence with short acting human insulin compared to rapid acting analogues - measure 1: OR 0.80 (95% CI 0.68-0.95; p=0.01), measure 2: OR 0.77 (0.67-0.87; p<0.0001).	Demographics of each insulin group not individually reported. Adjustment for a comprehensive range of patient characteristics	Multivariate adjustment for age, gender, region, rural/urban location, health insurance, injection device, Charlson comorbidity index, admissions, diabetes complications, mental health disorders, and insulin co-payments.	Eli Lilly
Buysman et al. 2011	Adherence and persistence to a regimen of basal insulin in a pre-filled pen compared to vial/syringe in insulin-naive patients with type 2 diabetes.	Cohort Study	Retrospective cohort study from a USA large claims database of adults with T2D initiated on Levemir FlexPen or NPH Vial insulin. 1,876 people included.	1,082 people started on Levemir FlexPen (mean age 54.1 years; SD 10.1; 55.6% male), 794 people started on NPH Vial insulin (mean age 53.1 years; SD 15.1; 45.5% male).	Adherence; Persistence	Univariate and multivariate analysis of adjusted MPR (≥80%) and adjusted persistence (time to discontinuation defined by a medication gap greater than the 80th percentile of time between claims in the parent population). Analysis of new prescriptions only. Interclass switching was treated as non-persistence.	Adjusted MPR was higher with Levemir (0.58 vs 0.38; p<0.001). Time to adjusted discontinuation gap was longer with Levemir (167 vs 123 days; p<0.001). Multivariate odds of adherence higher with Levemir (OR 1.39; 95% CI 1.04-1.85). Multivariate HR for discontinuation lower with Levemir (HR 0.62; 95% CI 0.55-0.70)	Multivariate adjustment for a wide range of potential confounders. No sensitivity analysis performed on the impact of adjustment for differences in frequency of claims. Number of non-persistence and non-adherence events not reported.	Multivariate adjustment for age, gender, region, Charlson comorbidity index, prescribing physician, HbA1c test frequency, other medication use, and costs.	Novo Nordisk
Corrao et al. 2011	Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: A population-based cohort study in Italy.	Cohort Study	Retrospective cohort study, in Italy using National Health Service data, of people age 40 to 90 with T2D initiated on metformin or SU monotherapy between 2001 and 2003 (followed until 2007). Data from 70,437 included.	21,810 people started on metformin (mean age 60.0 years; SD 9.8; 53.0% male), 48,627 people started on SUs (mean age 64.8 years; SD 10.5; 54.4% male).	Persistence	Proportion of people persistent at one year (defined as continued therapy without switching, combining with another agent, or discontinuation). Analysis of new prescriptions only.	At one year persistence was 35.5% with metformin and 44.5% with SUs.	Large sample size comparing persistence with initial therapy. Composite measure of non-persistence.	None	Italian Minister for University and Research
Farsaei et al. 2011	Adherence to glyburide and metformin and associated factors in type 2 diabetes in Isfahan, Iran.	Cohort Study	Prospective cohort study of people 35-75 with T2D enrolled from June to September 2007 currently taking metformin or glyburide.	204 people taking metformin and 167 people taking glyburide (including 123 patients taking both medications).	Adherence	Adherence defined as ≥ 90% and ≤ 105% of medication taken as measured by pill count and self-reporting. 248 patients enrolled. Analysis of existing prescriptions only. Approach to medication switching not described.	A higher proportion of people were found to be adherent to glyburide compared to metformin using pill counting (64.7% vs 60.3%) and self-reported adherence (69.5% vs 57.2%). Forgetting, confusion, and Ramadan were reported as the most common reasons for non-adherence.	Prospective design with a considerable number of people included in both medication groups. No adjustment for confounders. Small sample size. Comparison with glyburide rather than other SUs.	None	Isfahan University
Gallwitz et al. 2011	Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia.	Randomised controlled trial	RCT in Germany, 26 weeks of intervention, adults with T2D not controlled on metformin alone or in combination with an SU or meglitininde. Patients were randomised to exenatide twice daily or premixed insulin aspart twice daily. 354 people started on treatment.	181 people randomised to exenatide (mean age 57.0 years; SD 10.0; 59.7% male), 173 people randomised to premixed insulin aspart (mean age 57.0 years; SD 9.9; 55.5% male).	Discontinuation	Discontinuation due to adverse events during 26 week intervention period.	Discontinuation during follow up due to adverse events; exenatide 7.2%, premixed insulin aspart 0.6%; p = 0.0014.	Total number of participants discontinuing for any reason not reported. No measure of adherence. Open-label design.	Treatment randomisation	AstraZeneca and Eli Lilly

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Jermendy et al. 2012	Persistence of initial oral antidiabetic treatment in patients with type 2 diabetes mellitus.	Cohort Study	Retrospective cohort study using the Hungarian National Health Insurance Fund Administration database of adults with T2D initiated on mono or dual therapy with metformin or/and SUs between 1st January 2007 and 31st March 2009. 256,384 people included. Those on a combination of metformin and SUs are excluded here as this group as the definition of persistence in the group was not clear.	115,426 people started on metformin monotherapy, and 125,362 people started on SU monotherapy.	Persistence	Proportion of people persistent at one year. Non-persistence defined as no repeat prescription within 180 days of the last date covered by the previous prescription. Analysis of new prescriptions only. Switching was considered to be a non-persistence event.	A higher proportion of people were found to be persistent at one year with metformin 47.7% (95% CI 47.4-48.0) than with SUs 45.4% (45.1-45.7).	Large population analysis of initial therapy only. No adjustment for confounders. Unusual definition of medication persistence used.	None	None reported
Levin et al. 2012	Combination therapy with insulin glargine and exenatide: Real-world outcomes in patients with type 2 diabetes.	Cohort Study	Retrospective cohort study, in the USA, using a national insurance claims database (the Integrated Health Care Information Services Impact database), of adults with T2D initiated on exenatide and glargine insulin, either in succession or simultaneously. 453 people included.	281 people started on glargine followed by exenatide (mean age 53.9 years; SD 8.7; 52.3% male), 141 people started on exenatide then glargine (mean age 54.2 years; SD 8.4; 58.2% male).	Persistence	Proportion of people remaining persistent at 1 year (discontinuation defined as a prescribing gap longer than the 90th percentile of the time between the first and second prescriptions). Mean duration of persistence. Analysis of new prescriptions only. Interclass switching was treated as non-persistence.	Persistence at 12 months was: glargine before exenatide 68% (mean duration 298; SD 99 days), glargine after exenatide 65% (310; SD 85 days), exenatide before glargine 39% (257; SD 111 days), exenatide after glargine 45% (237; SD 121 days).	Study groups were well characterised. Sensitivity analysis of discontinuation definition performed.	Comparison within the same population	Sanofi-Aventis
Quinzler et al. 2012	Treatment duration (persistence) of basal insulin supported oral therapy (BOT) in Type-2 diabetic patients: comparison of insulin glargine with NPH insulin.	Cohort Study	Retrospective cohort study, in Germany, using claims data from the German Statutory Health Insurance scheme of adults with T2D with initiating glargine, or NPH insulin as part of BOT. 97,998 people included.	61,070 people initiated on glargine and 36,928 people initiated on NPH insulin as part of BOT.	Non-persistence	Proportion of people non-persistent with initial therapy at 1 year. Non-persistence defined as therapy switching. Analysis of new prescriptions only. Approach to Interclass switching unclear.	The annual rate of switching was higher with NPH insulin (24.6 per 100 patients) than glargine insulin (16.8 per 100 patients). Adjusted HR for switching 1.22 (95% CI 1.18 - 1.27).	Large sample size with sensitivity analysis of persistence definition. Limited adjustment for confounders. No reporting or adjustment for patient demographics.	Multivariate adjustment for treatment switching with adjustment for provider type, insurance, and number of previous oral medications.	Sanofi-Aventis
White et al. 2012	Adherence to hypoglycaemic medication among people with type 2 diabetes in primary care	Cohort Study	Prospective cohort study recruiting people in 2001 with T2D currently using oral hypoglycaemic agents, from a single large general practice in England. 60 patients recruited.	32 people taking metformin and 28 people taking an SU.	Adherence	Proportion of people taking ≥ 90% of prescribed doses and proportion of people taking prescribed doses on ≥ 90% of days. Measured using the Medication Event Monitoring System (MEMS). Analysis of ongoing prescriptions. Approach to switching not described.	Metformin adherence was lower than SUs with both measures (≥90% doses taken: 28/32 vs 28/28 and ≥90% days adherent: 17/32 vs 25/28).	More direct measure of medication use. Single centre study (with high quality diabetes care) and small sample size limit generalisability.	None	National Institute for Health Research (NIHR)
Al-Arouj et al. 2013	The effect of vildagliptin relative to sulphonylureas in Muslim patients with type 2 diabetes fasting during Ramadan: the VIRTUE study	Cohort Study	Prospective multicentre cohort study in the Middle East and Asia, of adults with T2D fasting during Ramadan, and taking vildagliptin or a SU as monotherapy or with metformin. 1,315 people included.	684 people taking vildagliptin (mean age 48.0 years; SD 10.9; 57.7% male) and 631 people taking SUs (mean age 51.3 years; SD 10.7; 59.8% male).	Persistence	Mean number of missed doses during a 16 week observation period. Analysis of ongoing prescriptions. Approach to interclass switching not described.	The mean number of missed doses was similar: vildagliptin 0.7 (SD 3.36) and SU 0.8 (SD 2.66)	Prospective design may influence adherence. Specific setting limited generalisability of results outside patients fasting during Ramadan.	None	Novartis
Baser et al.2013	Real-world outcomes of initiating insulin glargine-based treatment versus premixed analog insulins among US patients with type 2 diabetes failing oral antidiabetic drugs.	Case- Control Study	Retrospective case-matched study, in the USA, using IMPACT® claims database of adults with T2D initiated on glargine or a premixed insulin analogue from 2001 to 2009. 2,502 people met the included.	834 people initiated on premixed analogue insulin (mean age 55.9 years; SD 11.1; 52.6% male) and 1,668 matched people initiated on glargine insulin (mean age 55.6 years; SD 11.6; 52.2% male)	Persistence	Proportion of people persisting with medication at one year and average persistence during one year follow-up. Medications were considered discontinued if the prescription was not refilled within the expected time of medication coverage. Average MPR and adjusted MPR. Analysis of new prescriptions only. Interclass switching was considered to be a discontinuation event.	At one year persistence was 45.4% with premixed analogue insulin and 55.9% with glargine; p<0.0001. Average persistence (days) was 254 with premixed and 280 with glargine p<0.0001. Adjusted MPR were similar, 0.64 premixed; 0.66 glargine; p=0.19. No difference in glycaemic control, hypoglycaemic events, or healthcare costs.	Both study groups well matched for potential confounders including Charlson comorbidity index. Duration of diabetes was not available. Not reported how many people meeting the selection criteria could not be matched.	Case-matching using propensity scores	Sanofi-aventis
Curkendall et al. 2013	Predictors of medication adherence in patients with type 2 diabetes mellitus.	Cohort Study	Retrospective cohort study using two large USA claims databases of adults with T2D initiated on saxagliptin, a GLP1 receptor agonist, an SU, or TZD between August 2009 and January 2011 inclusive. 117,702 people included.	8,383 people initiated on saxagliptin, 13,908 people initiated on GLP1 analogues, 65,709 people initiated on SUs, and 29,702 people started on TZDs.	Adherence; Persistence	Adjusted OR of adherence (PDC ≥ 80%). Persistence duration. Analysis of new prescriptions only. Interclass switching was considered to be a discontinuation event.	Adjusted OR for adherence compared with saxagliptin was; GLP1 0.40 (95% CI 0.37-0.42), SUs 0.49 (0.46-0.52), and TZDs 0.54 (0.51-0.57). Persistence was significantly shorter with GLP1s, SUs, and TZDs than saxagliptin (data presented graphically)	Very large sample size with comparison across several groups of medication. DPP4 inhibitor inclusion was limited to saxagliptin only.	Multivariate adjustment for a broad range of confounders	Bristol-Myers Squibb
Davies et al. 2013	Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas.	Randomised controlled trial	RCT, 26-weeks of intervention, adults with T2D not controlled on metformin alone or in combination with an SU. Patients were randomised 1:1 to exenatide weekly or detemir insulin once/twice daily. 216 people started on treatment.	111 people randomised to exenatide (mean age 59.0 years; SD 10.0; 64.0% male), 105 people randomised to detemir insulin (mean age 58.0 years; SD 10.0; 69.0% male).	Discontinuation	Discontinuation for any reason during 26-week intervention period.	Discontinuation during follow up; exenatide 17%, detemir 6%. Adverse events cited as the most common reason for discontinuation in the exenatide group (12/19).	No measure of treatment adherence. Short duration of study. Open-label design.	Treatment randomisation although this was dependant on baseline HbA1c and sulfonylurea use.	Amylin Pharma-ceuticals

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Hanif et al. 2013	Treatment adherence with vildagliptin compared to sulphonylurea as add-on to metformin in Muslim patients with type 2 diabetes mellitus fasting during Ramadan.	Cohort Study	Prospective cohort study of adult Muslims with T2D currently taking an SU or vildagliptin as add on to metformin intending to fast during Ramadan. Followed for up to 16 weeks including observation before and during Ramadan. 72 people enrolled.	23 people taking liraglutide (mean age 58.3 years; SD 13.1; 52.2% male), 36 people taking SUs (mean age 57.3 years; SD 11.0; 58.3% male).	Adherence	Medication adherence was measured using patient reporting of missed doses (using a patient held diary). Total proportion of missed doses and proportion of patients missing more than 20% of doses reported. Analysis of ongoing medication prescriptions. Approach to switching not described.	Patients were more adherent to vildagliptin than SUs; total missed doses 0.2% vs 10.4% (p=0.0292), patients missing > 20% of doses 0% vs 19.4% (p=0.0358). Authors speculate that differences were due to fear of hypoglycaemia with SUs.	Small sample size. Self-reported measure of missing doses. Very specific scenario. Comparison of two different population groups. Prospective data collection may alter adherence.	None	Novartis
Miao et al. 2013	Real world outcomes of adding rapid-acting insulin versus switching to analog premix insulin among US patients with type 2 diabetes treated with insulin glargine.	Case- Control Study	Retrospective case-matched study, in the USA, using IMPACT® claims database of adults with T2D previously on glargine and initiated on rapid acting insulin analogues or switched to pre-mixed insulin analogues. 2,012 patients were eligible, 746 included.	373 people initiated on insulin glargine (mean age 56.7 years; SD 10.1; 56.8% male) and 373 matched people initiated on premixed analogue insulin (mean age 56.1 years; SD 10.0; 58.7% male)	Adherence; Persistence	Proportion of patients persisting with therapy at one year (discontinuation defined as a refill gap longer than the 90th percentile of the time between first and second prescriptions). MPR and adjusted MPR. Analysis of new prescriptions only. Interclass switching was analysed as non-persistence with sensitivity analyses considering it as ongoing persistence.	At one year persistence was 45.4% with premixed analogue insulin and 55.9% with glargine; p<0.0001. Average persistence (days) was 254 with premixed and 280 with glargine p<0.0001. Adjusted MPR was lower with premixed (0.66) than glargine (0.77); p<0.0001. Results were similar when interclass switching was allowed.	Propensity score matching of groups. No measure of adherence or persistence with rapid acting insulin performed.	Case-matching using propensity scores	Sanofi US
Pawaskar et al. 2013	Medication utilization patterns among type 2 diabetes patients initiating Exenatide BID or insulin glargine: A retrospective database study.	Cohort Study	Retrospective cohort study, in the USA, from a Thompson Reuters MarketScan® research database of adults with T2D initiating exenatide twice daily or glargine insulin. 13,696 people met inclusion criteria. 7,548 people matched.	3,774 people initiated on exenatide (mean age 57 years; SD 10; 54.4% male) and 3,774 matched people initiated on glargine insulin (mean age 57 years; SD 12; 54.3% male)	Discontinuation	Average time to discontinuation (discontinuation defined as a 90-day gap in prescription claims). Proportion of people modifying treatment by 18 months and average time to treatment modification. Analysis of new prescriptions only. Interclass switching was treated as non-persistence.	At 18 months treatment modification had occurred in 69.1% with exenatide and 76.0% with glargine insulin; p<0.0001. Treatment discontinuation had occurred in 38.3% with exenatide and 40.0% with glargine; p=0.14. Average time to modification (days) was 159 with exenatide and 123 with glargine p<0.0001. Average time to discontinuation (days) was 156 with exenatide and 105 with glargine p<0.0001.	Propensity score matching of groups. Large sample size. Comparison of treatment discontinuation with treatment modification. No sensitivity analysis performed on definition of discontinuation.	Case-matching using propensity scores	Eli Lilly
Quillam et al. 2013	The association between adherence to oral anti-diabetic drugs and hypoglycaemia in persons with Type 2 diabetes.	Cohort Study	Retrospective cohort study in the USA using the Medstat MarketScan database of adults with T2D initiated monotherapy with metformin, SUs, or TZDs between 2004 and 2008. 93,156 people included for analysis.	55,043 people initiated on metformin monotherapy, 9,817 on SUs, and 8,962 on TZDs.	Adherence	Proportion of people adherent (MPR ≥ 80%) during 12 months of follow up. People switching therapy excluded. Analysis of new prescriptions only. Approach to interclass switching unclear. Interclass switching was not considered as non-adherence.	The proportion of people adherent was: metformin 70.4%, SUs 75.3%, and TZDs 76.4%.	Large sample size. No sensitivity analysis. Only six month baseline period to determine no previous use - some of those included may not be true new users.	None	Takeda
Rathmann et al. 2013	Treatment persistence, hypoglycaemia and clinical outcomes in type 2 diabetes patients with dipeptidyl peptidase-4 inhibitors and sulphonylureas: A primary care database analysis.	Cohort Study	Retrospective cohort study, in Germany, using the Disease Analyzer database of adults with T2D with initiating an SU or DPP4 inhibitor. 50,294 people included.	19,184 people initiated on DPP4 inhibitors (mean age 64.3 years; SD 10.9; 56.2% male), 31,110 people initiated on SUs (mean age 69.2 years; SD 11.7; 50.8% male).	Persistence	Proportion of people persistent with initial therapy at 2 years. Analysis of new prescriptions only. Approach to interclass switching not described.	The proportion of people persisting with DPP4 inhibitors (61%) was higher than with SUs (51%). After adjustment discontinuation was less common with DPP4 inhibitors (HR 0.74; 95% CI 0.71-0.76)	Large sample size, adjustment for a wide range of factors. No sensitivity analysis performed.	Multivariate adjustment for a broad range of confounders	Novartis
Wang et al. 2013	Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study	Cohort Study	Retrospective cohort study, in the USA, from a MarketScan Commercial Claims and Encounters Database 2003-2009 of adults with T2D initiating glargine insulin or NPH insulin. 2,454 people met inclusion criteria. 534 people case matched.	356 people started on glargine insulin (mean age 49.0 years; SD 10.0; 57.1% male), matched with 178 people started on NPH insulin (mean age 49.0 years; SD 10.0; 54.5% male).	Adherence; Persistence	Medication persistence (discontinuation gap defined as a gap longer than the 90th percentile gap between 1st and 2nd claims for each medication or medication switching). Adherence defined as MPR and adjusted MPR over the first year. Analysis of new prescriptions only. Approach to Interclass switching unclear.	At one year persistence was 54.5% with insulin glargine and 43.8% with NPH insulin; p=0.0225. Average persistence (days) was 284 with glargine and 262 with NPH p=0.0178. MPR; 0.50 glargine, 0.45 NPH; p=0.0418. Adjusted MPR; 0.67, glargine 0.61 NPH; p=0.0380.	Propensity score matching of groups. Adjusted and unadjusted measures of MPR reported. Sensitivity analysis of propensity matching method conducted.	Case-matching using propensity scores	Sanofi US
Chong et al. 2014	Prescribing patterns and adherence to medication among South-Asian, Chinese and white people with Type 2 diabetes mellitus: A population-based cohort study	Cohort Study	Retrospective cohort study, in Canada using health administration data between 1997 and 2006, of adults with T2D. Data from 167,243 people analysed.	Medication adherence compared across ethnic groups; 14,084 Chinese, 9,529 South-Asian, 143,630 White people.	Adherence	Proportion with PDC ≥ 80%. Mixture of new and ongoing prescriptions. Approach to interclass switching not described.	Biguanides (BIG) had higher adherence across all ethnicity groups compared with SUs and TZDs: Chinese (MET; 57.5%, SU; 50.5%, TZD; 46.0%), South-Asian (MET; 39.3%, SU; 35.4%, TZD; 35.1%), White (MET; 60.7%, SU; 53.6%, TZD; 55.6%).	Large sample size with comparison across different ethnic groups. No other adjustment performed. Comparison across therapies not primary study outcome.	Comparison within different ethnic groups	Canadian Institutes of Health Research
Degli Esposti et al. 2014	Clinical outcomes and health care costs combining metformin with sitagliptin or sulphonylureas or thiazolidinediones in uncontrolled type 2 diabetes patients.	Cohort Study	Retrospective cohort study, using a linked administrative databases in three Italian local health units, of adults with T2D initiated on SUs, TZDs, or sitagliptin between July 2008 and June 2010 inclusive. 1,341 people included.	928 people started on SUs (mean age 66.1 years; SD 11.4; 52.2% male), 330 started on TZDs (mean age 63.2 years; SD 10.1; 55.2% male), and 83 started on sitagliptin (mean age 56.2 years; SD 9.8; 50.6% male).	Adherence	Mean MPR and adjusted OR of adherence (MPR ≥ 80%). Analysis of new prescriptions only. Interclass switching not considered non-adherent (adherence measured within each class).	MPR was higher with sitaglitpin (79.5%) vs SUs or TZDs (53.9% and 62.8%; p<0.001). Adjusted OR for adherence was lower than sitagliptin for SUs (0.36; 95% CI 0.20-0.64; p<0.001) and TZDs (0.51; 0.28-0.93; p=0.028).	Careful measurement of MPR accounting for hospital dispensing. Small sample size. Approach to switching within class of DPP4 inhibitors unclear.	Multivariate adjustment for a broad range of confounders	Merck Sharp & Dohme

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Farr et al. 2014	Retrospective analysis of long-term adherence to and persistence with DPP-4 inhibitors in US adults with type 2 diabetes mellitus.	Cohort Study	Retrospective cohort study using the US MarketScan claims database of adults with T2D initiated on saxagliptin, a DPP4 inhibitor, an SU, or TZD between 1st January 2009 and 31st January 2011 inclusive. 238,372 people included.	61,399 people started on DPP4 inhibitors (mean age 56.4 years; SD 11.7; 51.2% male), 134,961 started on SUs (mean age 57.2 years; SD 12.6; 57.2% male), and 42,012 started on TZDs (mean age 55.6 years; SD 11.6; 55.6% male).	Adherence; Discontinuation	Adherence defined as PDC ≥ 0.80 measured over one and two years. Adjusted OR of adherence reported. Discontinuation defined as 60+ day gap in therapy during the first one and two years. Adjusted HR for discontinuation reported. Analysis of new prescriptions only. Switching within class was allowed.	The proportion of people adherent at one year was higher for DPP4 inhibitors (47.3% and 55.0%) than SUs (41.2% and 47.8%) and TZDs (36.7% and 42.9%). Adjusted OR for adherence at one year was higher with DPP4 inhibitors compared with SUs (OR 1.68; 95% CI 1.63-1.73; p<0.001) and TZDs (OR 1.61; 1.56-1.65; p<0.001). Adjusted HR for discontinuation within a year also favoured DPP4 inhibitors compared with SUs (HR 1.39; 1.36-1.41; p<0.001) and TZDs (HR 1.40; 1.38-1.43; p<0.001). Similar trends were seen at two years.	Large sample size. Sensitivity analysis comparing one year and two year outcomes. Also monotherapy and non-mail order patients considered separately with similar trends. Some predictor characteristics not available e.g. HbA1c, BMI, socioeconomic status.	Multivariate adjustment for a broad range of confounders	AstraZeneca
Montilla et al. 2014	Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry.	Cohort Study	Retrospective cohort study in Italy using of patients enrolled into the Italian AIFA Anti-diabetics Monitoring Registry. Those taking exenatide, sitagliptin or vildagliptin and registered between February 2008 and August 2010 included. 75,283 people included.	21,064 people taking exenatide (mean age 58.9 years; SD 9.9; 48.0% male), 38,811 taking sitagliptin (mean age 61.7 years; SD 10.4; 52.7% male), and 17,989 taking vildagliptin (mean age 61.9 years; SD 10.4; 54.1% male).	Persistence	Medication persistence reported as the proportion of people discontinuing for treatment failure during 30 months of follow-up after excluding loss to follow-up. Analysis included new and ongoing medication users. Interclass switching was treated as a discontinuation event.	During 30 months discontinuation for treatment failure occurred; exenatide 7.7%, sitagliptin 3.8%, and vildagliptin 4.1%.	Large registry based analysis. No clear definition of treatment failure provided. A high proportion of loss to follow-up which will skew discontinuation rates.	None although factors associated with discontinuation was explored for each medication	Multiple contributing pharmaceutical companies not individually named
Nauck et al. 2014	Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial	Randomised controlled trial	RCT, 52 weeks of intervention, adults with T2D not controlled on metformin and one other oral therapy. Patients were randomised 1:1 to dapagliflozin or glipizide once daily. 801 people randomised to treatment.	400 people randomised to dapagliflozin, 401 people randomised to glipizide.	Discontinuation	Discontinuation for any reason during 2 week intervention period.	Discontinuation due to inadequate glycaemic control was more common in those treated with glipizide than dapagliflozin (difference -3.6%; 95%CI -5.3 to -1.5). Discontinuation due to adverse events was similar; dapagliflozin 9.1%, glipizide 5.9%.	No measure of treatment adherence. Short duration of study.	None	AstraZeneca and Bristol-Myers
Valensi. 2014	Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: The ODYSSEE observational study.	Cohort Study	Prospective cohort study using data from enrolled general practitioners in France. Adults with T2D initiated on SUs or sitagliptin between July 2009 and December 2010 inclusive. 2,607 people included for analysis.	733 people started on SUs (mean age 64.2 years; SD 11.5; 57.6% male), 1,874 people started on sitagliptin (mean age 62.4 years; SD 10.8; 59.4% male).	Adherence	Median treatment duration (time to addition, switching, or withdrawal of therapy). Analysis of new prescriptions only. Any medication switching was considered to be non-persistence.	Median discontinuation or treatment switching occurred at 20.2 months (95% CI 17.0-25.1) in the SU group and 43.2 months (95% CI 41.4-non-estimable; p<0.0001) in the sitagliptin group.	Large sample size. Discontinuation events included addition of other treatments making study comparison difficult. Median discontinuation was only just achieved at the end of follow up in the sitagliptin group making estimate inaccurate.	Propensity score matched groups	Merck Sharp and Dohme
Calip et al. 2015	Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment	Cohort Study	Retrospective cohort study from an existing breast cancer outcomes cohort with early stage breast cancer. Comparison of metformin and SU adherence during breast cancer treatment. 509 people included.	149 people taking metformin during breast cancer treatment, 195 people taking Sus.	Adherence	Mean MPR and proportion with MPR ≥ 80%. Proportion of people persistent at 1 year (discontinuation defined as a gap of ≥ 90 days). Analysis of ongoing prescriptions. Approach to interclass switching not described.	During treatment for breast cancer more people were adherent to sulfonylurea treatment than metformin (39.0% vs 30.9%). No measure of significance provided.	Small sample size and unadjusted MPR used. Addresses adherence in a very specific population.	None	National Cancer Institute
Grimes et al. 2015	Initial therapy, persistence and regimen change in a cohort of newly treated type 2 diabetes patients	Cohort Study	Retrospective cohort study using an Irish pharmacy claims database (Irish Health Services Primary Care Reimbursement Services database) people with T2D (≥40 years) with initial diabetes treatment with metformin or an SU. 8,995 people included in persistence analysis.	7,539 people had initial therapy with metformin and 1,456 people with SUs.	Persistence	Number of people remaining persistent at 12 months. Non-persistence defined as a 12-week prescribing gap. Analysis of new prescriptions only. Subjects undergoing interclass switching were excluded from the persistence analysis	Treatment persistence was lower with SUs (68.9%) compared with metformin (79.0%). Adjusted HR for non-persistence with sulfonylureas was 1.49 (95% CI 1.36-1.64; p<0.0001).	Large population size. Comparison of first diabetes therapy in both groups. Only a limited number of factors adjusted for.	Multivariate adjustment for age, gender, insurance scheme, and therapy type.	None reported
Pscherer et al. 2015	Treatment persistence after initiating basal insulin in type 2 diabetes patients: A primary care database analysis	Cohort Study	Retrospective cohort study, in Germany, from The Disease Analyzer database (IMS Health) of adults with T2D initiating glargine, basal supported oral therapy (BOT), or intensified conventional therapy (ICT, or NPH insulin as either part of BOT, or ICT. 5,736 people included.	In the BOT group: 1,398 people started on glargine (mean age 67.7 years; SD 11.3; 54.2% male), 292 people started on detemir (mean age 66.4 years; SD 11.4; 54.8% male), and 874 people started on NPH insulin (mean age 65.0 years; SD 11.1; 54.9% male). In the ICT group 866 people started on glargine (mean age 63.8 years; SD 12.8; 57.4% male), 512 people started on detemir (mean age 60.4 years; SD 12.9; 53.7% male), and 1,794 people started on NPH insulin (mean age 63.9 years; SD 11.9; 53.8% male).	Persistence	Average time to discontinuation (discontinuation defined as prescription of a new insulin type). Proportion of people remaining persistent at two years. Analysis of new prescriptions only. Interclass switching was treated as non-persistence.	Persistence in the ICT group (median days; IQR): glargine (421; 252-574), detemir (361; 185-560), NPH (483; 288-683) and in the BOT group: glargine (371; 203-524), detemir (323; 196-447), NPH (334; 195-542). Proportion persistent after 24 months in the ICT group: glargine 84.3%, detemir 85.4%, NPH 85.6% (Log rank p = 0.536) and in the BOT group: glargine 64.5%, detemir 52.7%, NPH 59.2% (Log rank p<0.001). Adjusted HR for discontinuation versus glargine in BOT group: detemir 1.56 (95% CI 1.31-1.87), NPH 1.22 (1.07-1.38). No significant difference in HR for discontinuation between insulins in ICT group.	Adjustment for potential confounders. Unusual definition of discontinuation. Prescribing gap not included as a marker for discontinuation.	Multivariate adjustment for age, gender, diabetes duration >5 years, diabetologist care, health insurance and other medication use.	Sanofi-Aventis

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Cai et al. 2016	Comparative persistence and adherence with newer anti-hyperglycemic agents to treat patients with type 2 diabetes in the United States	Cohort study	Truven Health Analytics Marketscan databases included adult patients with type 2 diabetes whose first pharmacy claim for a newer anti-hyperglycemic agent was between February 1, 2014 and July 31, 2014.	A total of 11,961 patients met all patient selection criteria. Proportion of women was 45% for canagliflozin 100 mg (reference cohort) and ranged from 38–55% in the other cohorts.Mean patient age was 54.3 years for canagliflozin 100 mg and ranged from 52.0–59.5 years in the other cohorts.	Adherence; Persistence	Persistence: no gap > 90 days between the end of one pharmacy claim and the start of the next pharmacy claim post-index. Adherence: PDC and MPR.	Persistence rates at 12 months: canagliflozin 100 mg, 61%; canagliflozin 300 mg, 64% (p =0.037); dapagliflozin 5 mg, 40% (p < 0.001); dapagliflozin 10 mg, 41% (p < 0.001); sitagliptin, 48% (p < 0.001); saxagliptin, 42% (p < 0.001); linagliptin, 52% (p < 0.001); liraglutide, 47% (p < 0.001); exenatide, 23% (p < 0.001); and long-acting exenatide, 39% (p < 0.001) Adherence OR (95% CI): PDC > 80%: Canagliflozin 300 mg 1.151 (0.991–1.337) p= 0.066; Dapagliflozin 5 mg 0.480 (0.401–0.575) p<0.001; Dapagliflozin 10 mg 0.522 (0.413–0.660) p<0.001; Sitagliptin 0.660 (0.579–0.752) p<0.001; Saxagliptin 0.610 (0.492–0.755) p<0.001; Linagliptin 0.717 (0.591–0.870) p= 0.001; Liraglutide 0.445 (0.387–0.513) p<0.001; Exenatide 0.209 (0.148–0.294) p<0.001; Long-acting exenatide 0.439 (0.367–0.526) p<0.001 MPR> 80%: Canagliflozin 300 mg 1.153 (0.991–1.342)p= 0.065; Dapagliflozin 5 mg 0.486 (0.408–0.579) p<0.001; Dapagliflozin 10 mg 0.493 (0.393–0.619) p<0.001; Sitagliptin 0.656 (0.577–0.747) p<0.001; Saxagliptin 0.596 (0.483–0.735) p<0.001;	Strengths: large sample size. Limitations: common to all claim based studies (data collected from payment and prescription form doesn't account for if the medication was actually consumed or not).	Multivariate adjustment for a broad range of confounders	Janssen Scientific Affairs
Farmer et al. 2016	Adherence to Oral Glucose Lowering Therapies and Associations With 1-Year HbA1c: A Retrospective Cohort Analysis in a Large Primary Care Database	Cohort study	Patients with T2DM with a record of treatment with metformin, sulfonylurea, DPP4i, or thiazolidinediones for at least 1 year. All patients were selected from the Clinical Practice Research Data-base (CPRD) and the Genetics of Diabetes and Audit Research Tayside Study(GoDARTS) databases.	A total of 32 634 patients were included, 28.7% of patients were taking no other oral antihyperglycemic treatments, 51.8% were taking one other treatment, and 19.1% were taking two other treatments.	Adherence	Adherence: MPR >80% was considered as adherent while those with a MPR <80% were non adherent.	A higher non adherence was observed in patients taking metformin in both CRPD and GoDARTS cohorts (18.8 and 18.1 respectively). The percentage of patients with a MPR< 80 by drug class in both cohorts were: sulfonylurea 11.9%/16.2%, thiazolidinedione 8,6%/11.4% and DPP4i 9.1%/10.7%. Also participants with MPRs>90% had better reductions in baseline-adjusted HbA1c.	Strengths:The association between adherence to oral antihyperglycemic medication in T2DM over 1 year and changes in HbA1 was assessed in this study. Limitations: There is no mention of characteristics that could have an effect on lower adherence.	None	Oxford NIHR Biomedical Research Center
Farr et al. 2016	Comparison of adherence and persistence among adults with type 2 diabetes mellitus initiating saxagliptin or linagliptin	Cohort study	T2DM patients >18 years old with at least 1 prescription claim for saxagliptin or linagliptin and continuous enrollment for 24 months (12 months pre-index date and 12 post-index date) between January 2009 and June 2013 were included.	A total of 27 385 patients were included, from these 21 599 were on saxagliptin and 5786 were on linagliptin. Average age was 55–57 years old (SD 11.2–11.8), and more than 50% were male.	Adherence; Persistence	Adherence: PDC> 0.80 . Persistence: period of time from the index date to the last day with the index drug before a > 60 days gap or the end of follow up, non persistence was considered when the gap was more than 60 days.	A higher mean PDC was observed with saxagliptin (65%) compared with linagliptin (62%). Adherence rates (PDC>80%) were 45.9% for saxagliptin and 42.4% for linagliptin. The days persistent on the index drug were 240 for linagliptin and 249.9 for saxagliptin. Discontinuation was lower with saxagliptin (46.%).	Limitations: Data about reasons for discontinuation were not available in databases and therefore, not evaluated.	Multivariate adjustment for a broad range of confounders	AstraZeneca
Hassoun et al. 2016	The effect of vildagliptin relative to sulfonylurea as dual therapy with metformin (or as monotherapy) in Muslim patients with type 2 diabetes fasting during Ramadan in the Middle East: the VIRTUE study	Cohort study	T2DM patients >18 years old who planned to fast during Ramadan and were treated with vildagliptin or sulfonylurea either alone or associated with metformin for at least 1 month before Ramadan.	A total of 573 patients were included for the final sample, from these 308 were on vildagliptin and 265 on sulfonylurea.The mean age was 50.6 (10.54) and 54.2 (10.33) for vildagliptin and sulfonylurea respectively. Most of the population were <65 years old (91.3%) and predominantly male in both cohorts (60.7%).	Adherence; Discontinuation	Adherence: proportion of patients on each index therapy that did not miss more than 20% of prescribed doses during the fasting period. Discontinuation: not mentioned.	Discontinuation: Vildagliptin 8%, Sulfonylurea 6% Adherence: Vildagliptin 7.7%, 3.4%.	Strengths: Hypoglycemic events and adverse effects were evaluated with each cohort (vildagliptin and sulfonylurea). Limitations: Adherence was measured for a short time period in Ramadan and can not reflect accurately long term adherence.	None	Novartis Pharma services AG
Iglay et al. 2016	Risk factors associated with treatment discontinuation and down-titration in type 2 diabetes patients treated with sulfonylureas	Cohort study	MarketScan Commercial Claims and Encounter Database and the Medicare Supplemental Database from 2008 and 2012, included T2DM taking sulfonylurea.	Total of 104,082 patients. 56.2% was male, and the average patient age was 57.0 years.	Discontinuation	Discontinuation: if the date of a subsequent prescription fill for a sulfonylurea was more than 90 days apart.	Sulfonylurea 2nd generation: 65.2%. Sulfonylurea 3rd generation 34.7%. Metformin 61% (HR 0.82 p<0.01) . Thiazolidinediones 10.8% (HR 0.94 p<0.01). Meglitinides 0.6% (HR 0.99 p=0.82). GLP-1 agonists 1.6% (HR 0.92 p=0.02) . DPP-4 inhibitors 9.2% (HR 0.88 p<0.01). Alpha-glucosidase inhibitors 0.1% (HR 1.07 p=0.57). Amylin analog 0% (HR 1.03 p=0.96). Insulin 2.7% (HR 1.48 p<0.01).	Limitations: due to claims database nature.	Multivariate adjustment for a broad range of confounders	Merck & Co. Inc

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Kurtyka et al. 2016	Adherence to dipeptidyl peptidase-4 inhibitor therapy among type 2 diabetes patients with employer-sponsored health insurance in Japan	Cohort study	T2DM patients between 18-64 years old who started DPP-4 treatment as monotherapy or dual therapy between January 2010 and July 2013; dual therapy was defined as a DPP-4i prescribed with other antidiabetic medication. All data was collected from the Japan Medical Data Center database and individuals were followed up for at least 3 months with a maximum of 24 months.	A total 14 449 individuals initiated a DPP-4i but the final sample included 2 874 patients on monotherapy and 3 016 on dual therapy; most of population, including both monotherapy and dual therapy groups, was male (74.9 and 74.4), the mean age was (51. 3% and 50.8%) and over half of the study population had hypertension (51.5% and 51.8%).	Adherence; Persistence	Adherence: PDC ≥80% Persistenced: proportion of patients who continued the medication at the end of 12 and 24 months with no gap in therapy ≥90 days.	The mean PDC was 76.6% (75.1–78.2) for monotherapy and 82.5%(81.2–83.7) dual therapy in the first year of follow up. The proportion of adherent patients (PDC>80%) was: monotherapy 67.2% (64.9–69.5) and dual therapy 74.6 (72.6–76.5). Persistence at 12 months was: 72.2% for monotherapy and 79.2% for dual therapy.	Strengths: The exclusion of individuals older than 65 years from the analysis could have underestimated adherence because in previous studies older patients tended to have better adherence. Limitations: The study sample was mostly male, which might be a limit if we want to generalize the results to female type 2 diabetes patients.	Multivariate adjustment for a broad range of confounders	Merck & Co
Nguyen et al. 2016	Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) Therapy Adherence for Patients with Type 2 Diabetes in a Medicare Population	Cohort study	Medical and pharmacy claims between 2010 and 2013 for Medicare members in a United States health plan diagnosed with T2D and between the ages of 65 and 89 years.	Total of 5133 patients. final sample sizes for each cohort were : exenatide QW = 537, exenatide BID = 923, liraglutide QD = 3673, liraglutide QD 1.2 mg = 1980 and liraglutide QD 1.8 mg = 1693. The percentage of males in each cohort ranged between 44% (exenatide BID) and 49%(exenatide QW).	Adherence	Adherence: PDC of 80% or 90%	PDC > 80%: exenatide QW (43.2%), liraglutide QD (35.0%; P<0.001), exenatide BID (39.0%; P<0.01), liraglutide QD 1.8 mg (30.0%; P<0.001), liraglutide QD 1.2 mg (39.3%). PDC > 90%: exenatide QW (37.24%; P<0.001) ,liraglutide QD (23.31%), exenatide BID (20.6%), liraglutide QD 1.2 mg (26.36%) or liraglutide QD 1.8 mg (19.73%). Mean PDC: exenatide QW (63.5%), exenatide BID (57.7%; P<0.01), liraglutide QD 1.8 mg (58.3%), liraglutide QD (61.5%) and liraglutide 1.2 mg (64.2%).	Limitations: Potential coding error from administrative claims, results may not translate to uninsured patients.	Inverse propensity treatment score weighting, multivariable logistic regression.	AstraZeneca Pharmaceutica
Peng et al. 2016	Treatment progression in sulfonylurea and dipeptidyl peptidase-4 inhibitor cohorts of type 2 diabetes patients on metformin	Cohort study	T2DM patients >18 years old, with background metformin therapy who started sulfonylurea or DPP-4i from January 2010 to December 31 with a continuous pharmaceutical enrollment for 12 months before and after index date (day in which the index medication was initiated).	A total of 27 105 individuals met the inclusion criteria and were included, from these 19 621 were SU users and 7484 were DPP-4i. After propensity score matching each cohort had 6758 patients.	Adherence; Persistence	Adherence: PDC >80%. Persistence: period of time before evidence of discontinuation (a >60 days gap between two continuous drug claims).	Higher persistence was observed with DPP-4i users (52.5%) compared with sulfonylurea (48%) (P<0.001). The mean PDC for SU was 63.3% and for DPP-4i (65.5%). Adherence (PDC>80%) was higher in the DPP-4i (43.4%) compared with SU (40.5%).	Strengths: Larga sample was used in this study and propensity score matching was obtained to avoid bias. Limitations: Data regarding HbA1c was not available to determine associations between treatment outcomes and persistence.	Logistic regression model .	Eli Lilly and Company
Qiao et al. 2016	Adherence to GLP-1 receptor agonist therapy administered by once-daily or once-weekly injection in patients with type 2 diabetes in Germany	Cohort study	Patients taking GLP-1 RA (exenatide once weekly and liraglutide once daily) between January 1, 2011 and December 31, 2013 who had a minimum of 6 months follow up data after the index date.	A total of 30 097 patients between January 2011 and September 2014 were selected from the longitudinal prescriptions database (LRx) (IMS Health, Frankfurt am Main, Germany) . 5 449 had therapy with exenatide once weekly and 24 648 with liraglutide once daily.	Adherence	Adherence: PDC ≥80%.	Adherence was higher among patients taking exenatide (53,4%) than those with liraglutide (48,1%).The median PDC was higher for exenatide (88%) compared with liraglutide (77%) especially in patients between 51-70 years old.	Strengths: (OR) was calculated in patients with a PDC ≥80% using variables such as age, the type of medication used (Exenatide once weekly vs liraglutide once daily) and concomitant medication (metformin, sulfonylurea, insulin and other combinations). Limitations: Factors like diabetes duration, diabetes-related complications and glycated hemoglobin levels could not be evaluated. Another limitation is that there was not a randomized assignment to receive treatments.	Logistic regression model	None
Roussel et al. 2016	Persistence with Insulin Therapy in Patients with Type 2 Diabetes in France: An Insurance Claims Study	Cohort study	Patients >18 years old with a T2DM diagnosis who started a new insulin regimen between January 2011 and December 2013.	A total of 1909 patients were included in the 2012-2013 cohort , from these 1180 started basal insulin only, 286 basal-fast-acting and 443 other insulin regimens. The mean age was 65.7 ± 16 and 53% were male. A total of 1969 individuals were included in the 2011-2012 cohort, the mean age was 66.4 and mostly male (51.9%).	Discontinuation	Discontinuation: lack of dispensation of medication within a 6 month period or 1 year after the index date.	Insulin discontinuation including deaths at 6 months: basal insulin (19%), basal-fast-acting (23.4%) and other regimens (37.2%). Discontinuation rates after 12 months including deaths: basal insulin (27.5%), basal-fast-acting insulin (35.5%) and other regimens (46.9%).	Strengths: Discontinuation was measured at 2 endpoints: 6 and 12 months taking into acount deaths. Limitations: Small sample size, no adjustment for confounders and reasons for discontinuation not mentioned.	None	Sanofi
Saundankar et al. 2016	Predictors of Change in Adherence Status from 1 Year to the Next Among Patients with Type 2 Diabetes Mellitus on Oral Antidiabetes Drugs	Cohort study	Humana Medicare Advantage Database included patients with T2DM and continuous enrollment between 2010 and 2012.	Total of 238,402 patients subdivided into 2 groups (baseline adherent and nonadherent). Mean age of the 2 groups was 72.0 and 72.3 years. Use of each antidiabetic agent was: Biguanideas 186704, Sulfonylureas 128336, Thiazolidinediones 43608, Meglitinides 2767, Alpha-glucosidase inhibitors 1100, Glucagone-like peptide-1 receptor agonists 1973, DPP-4 inhibitors 7681.	Adherence	Adherence: PDC> 80%.	Patients adherent: Biguanideas 120021(64%), Sulfonylureas 89684 (70%), Thiazolidinediones 30571 (70%), Meglitinides 999 (36%), Alpha-glucosidase inhibitors 485 (44%), Glucagone-like peptide-1 receptor agonists 966 (49%), DPP-4 inhibitors 5933 (77%).	Strengths: large number of patient treatment and disease-related variables. Limitativos: those common to claim study design.	None	Eli Lilly and Company

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Tan et al. 2016	Oral antidiabetic drug use and associated health outcomes in cancer patients	Cohort study	Patients with T2DM and any cancer diagnose >65 years old and took at least one oral antidiabetic drug between July 2008 and December 2009 were included in this study.	A total of 1918 individuals met the inclusion criteria and were included, from these, 56.5% were female with average age of 56.7 years, prostate and breast cancer were more prevalent 50% and 36 7%, respectively than other cancers.	Adherence	Adherence :medication possession ratio (MPR) > 0.8.	Adherence rates were higher among metformin users (38.5%) followed by DPP4i (36.5%), sulfonylureas (32.6%) and TZD (30.2%). The highest mean MPR was observed with metformin (0.61).	Strengths:Adherence was measured for every medication type. Limitations:sample size was small.	Multivariate adjustment for a broad range of confounders	None
Wei et al. 2016	A real-world study of treatment patterns and outcomes in US managed-care patients with type 2 Diabetes initiating injectable therapies	Cohort study	Linked insurance claims and medical record data were collected from 2 large US health insurers (April 1, 2010 to March 31, 2012) of T2DM adults initiating treatment with glargine (GLA) or liraglutide (LIRA).	A total of 4490 patients were included (GLA, 2116; LIRA, 2374). GLA patients were older and more likely to be men, and had more comorbid diagnoses.	Persistence	Persistence: percentage of patients remaining on therapy without discontinuation using the 90th percentile.	At 12-month follow-up, overall treatment persistence was 64% for GLA and 49% for LIRA patients, and the mean number of persistent days was 306.2 for GLA and 263.3 for LIRA.	Strengths: real world study, large amount of patient data. Limitations: observational study and, as such, the analyses may be subject to selection bias and confounding, data analysed were from a commercially insured US managed-care population, and may not be fully representative of other populations and limitations due to persistence definition and innnability to foresee patient consumption.	Propensity score matching	Optum™
Yu et al. 2016	Liraglutide Versus Exenatide Once Weekly: Persistence, Adherence, and Early Discontinuation	Cohort study	Data from Truven Health MarketScan 2008 to 2013 Commercial Claims and Encounters and Medicare Supplemental and Coordination of BenefitsDatabase on T2D patients initiating once weekly (QW) exenatide or daily liraglutide over a 6-month follow-up period.	Before executing propensity score matching, the exena- tide QW cohort included 13,274 patients and the lira- glutide cohort included 31,675 patients. Each matched cohort included 12,306 patients with a mean age of 55.3 years and 51% female.	Adherence; Persistence	Persistence: percentage of patients who continued to take the index drug over an index period of 182 days with an allowable gap of 60 days. Adherence: PDC ≥ 0.8.	Persistence: Exenatide QW 63%, Liraglutide 66%.HR (95% CI) for exenatide QW versus liraglutide was 0.865 (0.829–0.902). Adherence: Exenatide QW (mean SD 0.692 (0.307)), PDC>/= 0.8 51%; Liraglutide (mean SD 0.686 (0.283)), PDC>/= 47%. Liraglutide had lower odds (OR and 95% CI) of being adherent compared with exenatide QW (OR =0.84; 95% CI, 0.80–0.89)	Limitations: secondary to claims database study (misclassification bias, inclusion of only commercially insured individuals).	Propensity score matching	Eli Lilly and Company
Alatorre et al. 2017	Treatment patterns in patients with type 2 diabetes mellitus treated with glucagon-like peptide-1 receptor agonists: Higher adherence and persistence with dulaglutide compared with once-weekly exenatide and liraglutide	Cohort study	T2DM patients > 18 years old who were new GLP-1 RA users with at least 1 prescription claim from November 214 to April 2015 were included in this study.	A total of 2470 patients met the inclusion criteria, from these 1250 took albiglutide, 5022 exenatide QW, 1369 exenatide BID and 8705 liraglutide. After matching dulaglutide and exenatide QW comparison included 2415 individuals in each group and the same for dulaglutide and liraglutide comparison where 2037 patients were included for each cohort.	Adherence; Persistence	Adherence:PDC ≥ 0.80 Persistence:days from the index date to the end of day's supply with no 60 days gap.	The mean PDC mas higher for dulaglutide (73%) and (71%) for both matched cohorts followed by liraglutide (67%) and exenatide QW (61%). Adherence rates (≥80%) by each drug were: dulaglutide (54.2%) and (53.5%) for each matched cohort, liraglutide (44.9%) and exenatide QW (37.9%). In the 6-month post-index period, 26.2% of dulaglutide and 48.4% of exenatide once-weekly patients discontinued treatment.	Strengths: Large sample size of patients enrolled in diverse health plans across the USA were included. Limitations: Propensity score matching was used for confounding. A short follow up period (6 months) was used in this study which can not estimate long term adherence and persistence.	Propensity score matching	Eli Lilly and Company
Bell et al. 2017	Comparing Medication Adherence and Persistence Among Patients with Type 2 Diabetes Using Sodium-Glucose Cotransporter 2 Inhibitors or Sulfonylureas	Cohort study	Patients were included if they were diagnosed with type 2 diabetes, had ≥18 years with ≥1 outpatient pharmacy claims for an SGLT-2 inhibitor or a sulfonylurea between January 1, 2015, and December 31, 2015. People with type 1 diabetes, gestational diabetes, or pregnancy during the baseline or follow-up periods were excluded.	151 514 patients with 1 claims for an SGLT-2 inhibitor and 470 284 patients with ≥1 claims for a sulfonylurea in the 3 databases combined. After applying the study inclusion and exclusion criteria, the final sample were 17 724 taking SGLT-2 inhibitor and 25 490 taking sulfonylurea.	Adherence; Persistence	Adherence: (PDC) during the 6 months follow-up period Persistence: period of time from the index date until a >60 days gap without the medication or the end of follow-up.	The mean PDC were higher in the SGLT-2 with 75.6% compared with sulfonylurea (71.8%) but a higher adherence (PDC ≥ 80) was observed in patients using SGLT-2 inhibitor rather than those using sulfonylurea.	Limitations: Patient characteristics that could affect adherence such as race, socioeconomic status, glycemic control or others were not available in the databases, also it was assumed that patients took their medications for the duration of the days of supply on the medication claim which can not be accurate.	Propensity score matching	AstraZeneca
Bloomgarden et al. 2017	Adherence, persistence, and treatment discontinuation with sitagliptin compared with sulfonylureas as add-ons to metformin: A retrospective cohort database study*	Cohort study	US administrative-claims database (MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases; Truven Health Analytics, Ann Arbor, MI, USA) from 1 January 2008 through 31 March 2013.	Cohorts of: 34 113 patients sulfonylurea +metformin and 14 947 sitagliptin+ metformin.	Adherence; Persistence; Discontinuation	Adherence: PDC ≥80 %. Persistence: proportion of patients who continued to use their index medications at 1, 2, and 3 years after the index date. Only adherence to MET + SU and MET + SITA was evaluated.	-Mean PDC: 0.736 +/- 0.3 for sitaglipin +metformin and 0.72 +/- 0,308 for sulfonylurea+ metformin (P < 0.001). -Adherence (PDC ≥80 %) to sitaglipin +metformin was 59.1 % (P < 0.001) at 1 year, 52.6 % (P= 0.007) at 2 years and 48.3% at 3 years (P=0447) -Adherence (PDC ≥80 %) to sulfonylurea+ metformin was 55.9 % (P < 0.001) at 1 year, 49.9 % (P= 0.007) at 2 years, 47.1% at 3 years (P=0447) -Persistence to sitaglipin +metformin was 64.3 % (p<0.001) at 1 year,51.96% (p<0.001) at 2 years and 43.3% (p=0.042)at 3 years. -Persistence to sulfonylurea+ metformin was 61.5% (p<0.001) at 1 years, 48.46% (p<0.001) at 2 years and 40.2% (p=0.042) at 3 years.	Strengths:Large numbers of patients. Limitations:The requirement of a continuous health plan enrollment may have overestimated adherence.	Multivariate adjustment for a broad range of confounders	None

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Buysman et al. 2017	Real-world comparison of treatment patterns and effectiveness of albiglutide and liraglutide	Cohort study	Claims data from the Optum Research Database (ORD) included adult commercial health plan members with evidence of T2DM and one or more pharmacy claims for albiglutide or liraglutide between 29 July 2014 and 31 December 2015.	4426 patients in the post- matched study sample (n = 2213 each in the albiglutide and liraglutide groups). Mean patient age was 52 years.	Adherence; Persistence; Discontinuation	Adherence: mean PDC and PDC >0.80 Discontinuation: gap in therapy of the index drug of more than 60 days. Persistence: number of days to discontinuation of the index therapy.	Adherence: mean ([SD) PDC was 0.69 (0.29) for albiglutide versus 0.64 (0.29) for liraglutide (p < 0.001). PDC ≥0.80 albiglutide 48.3 % vs liraglutide 42.3% (p < 0.001). Persistence: albiglutide 142.1 mean days vs liraglutide 134.7 day mean days. p ≤ 0.002 Discontinuation: albiglutide 33.2% vs liraglutide 37.8%.	Strengths: real world data. Limitations: secondary to prescription claim nature.	Propensity score matching	GlaxoSmithKline
Cai et al. 2017	Adherence and persistence in patients with type 2 diabetes mellitus newly initiating canagliflozin, dapagliflozin, dpp-4s, or glp-1s in the United States	Cohort study	QuintilesIMS PharMetrics Plus Health Plan Claims Database from February 1, 2013 through June 30, 2015.	Total of 23,702 patients: 6,546 canagliflozin (57.0% started on 100 mg) mean age 54.4 ; 3,087 dapagliflozin (66.1% started on 5 mg) mean age 53.8 ; 7,796 DPP-4 (76%sitagliptin) mean age 55.9 ; and 6,273 GLP-1 mean age 53.2.	Adherence; Persistence	Adherence: PDC and MPR. Persistence: measured over the 12-month follow-up and calculated based on the number of consecutive days from index until discontinuation, or end of the 12-month study period, whichever occurred first.	Adherence: Mean PDC: Canagliflozin 0.71 (56.2% adherent) ; Dapaglifozin 0.64 (41.8% adherent) ; DPP-4 0.62 (42.7% adherent) ; GLP-1 0.56 (32.8% adherent) Mean MPR: Canagliflozin 0.72 (56.6 % adherent) ; Dapaglifozin 0.65 (42.1 % adherent) ; DPP-4 0.62 (43% adherent) ; GLP-1 0.57 (33.7 % adherent) Persistence:	Limitations: Study results may not be generalizable to the overall, national population, or to patients who are uninsured or covered by other payers.	None	Janssen Research & Development, LLC.
Curington et al. 2017	Clinical outcomes of switching from insulin glargine to NPH insulin in indigent patients at a charitable pharmacy: The Charitable Insulin NPH: Care for the Indigent (CINCI) study	Cohort study	29 patients recruited from the SVdP Charitable Pharmacy from January 15, 2014, to March 13, 2014	29 patients enrolled, only 17 completed the study. Control group (NPH insulin) n=15, mean age 53+/- 5.1, 73.3% female. Intervention (glargine to NPH) n=14, mean age 56.9+/- 4.9, 64.3% female.	Adherence	Morisky Medication Adherence Scale (MMAS). Ideal adherence =8	Control (NPH): Baseline 6.6 +/-1.9 (p=0.6). Week 24 6.7+/- 1.3 (p=0.83) Intervention (glargine to NPH): Baseline 6.2+/- 2 (p=0.6).Week 24 6.5 +/-2 (p=0.83)	Strenghts: results imply cost savings in future patients. Limitations: study population of single pharmacy for indigent patients limits generalisability. Small sample size.	None	None
Divino et al. 2017	GLP-1 RA Treatment Patterns Among Type 2 Diabetes Patients in Five European Countries	Cohort study	Patients with T2DM from 5 European countries (France, Germany, The Netherlands, Sweden and Belgium) >18 years who were new users of GLP-1 RA therapy class with no prescription for these medication within the 180 days before index date and did not take other injectable antihyperglycemic therapy on the index date other than the index therapy.	The final sample included 4339 exenatide BID patients, 1499 exenatide QW patients, 20 955 liraglutide patients and 1751 lixisenatide patients. Most patients were between 50–64 years old (41.8–59.1%) with a mean age from 57.1 to 62.9 years. Approximately half or more of patients were female.	Persistence; Discontinuation	Discontinuation: gap in a series of successive index therapy prescriptions >2 x the expected duration of the first prescription. Persistence:proportion of patients who kept continuous prescriptions until evidence of discontinuation or switching (new antihyperglycemic prescription within 30 days before or after discontinuation of the index medication).	Persistence rates by each drug were: liraglutide 29.0% (Belgium), 51.5% (France), 43.1% Germany, 60.8% (The Netherlands), 59% Sweden; exenatide BID: 17.5% (Belgium), 29% Germany, 31.4% (Sweden), 34.1% (The Netherlands) and 44.4% (France); exenatide QW 32.8% (Germany), 42.75 Sweden and 50.8% (The Netherlands); lixisenatide; 50.0% (Belgium) and 4.2% (Germany).	Limitations: Patients included in the LRx databases may not represent accurately all patients in the respective country, as data was collected only from participating pharmacies. Lack of medical diagnosis codes in LRx and unavailability of diagnosis codes from the primary care in Sweden made it difficult to confirm the presence/absence of T1DM or T2DM.	None	Eli Lilly and Co.
Lee et al. 2017	Assessing oral medication adherence among patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: a cross-sectional study	Cross sectional study	Patients with T2DM diagnosis confirmed from their medical records between 35-84 years old treated with one or more oral antihyperglycemic agents in a primary care center located in SengKang, Singapore	The sample size was computed using a confidence interval of 5% and study power of 95%, 382 patients with T2DM participated in this study.	Adherence	Medication Adherence Report Scale (MARS-5) :total score of less than 25 points is defined as low adherence to the medication.	The highest medication adherence was observed in patients taking DPP4 (sitagliptin 67.7%), followed by sulfonylureas (gliclazide 56.5%, glipizide 53.5% and tolbutamide 53.1%), AGI (acarbose 50.1%) and biguanides (45.2%).	Limitations: The measurement of medication adherence based on self reporting by patients can not be accurate sometimes. A response rate in the study was not computed to avoid double counting as potential subjects could be approached multiple times by research assistants at different locations at the study site.	Logistic regression model .	None
Linnemann Jensen et al. 2017	Long-term patterns of adherence to medication therapy among patients with type 2 diabetes mellitus in Denmark: The importance of initiation	Cohort study	T2DM patients referred to the outpatient clinic at Steno Diabetes Center (Steno) during 1998–2009.	5,232 patients, 58% men with a median age of 59.5 year	Adherence; Persistence	Persistence: proportion of days in persistence of all days prescribed with the medicine in question. Adherence: having filled prescriptions and having sufficient supply of medication to cover the daily prescribed dose	Adherence (first five years): metformin (77.4% [95%CI: 77.2–77.6%]); SUs (77.7% [95%CI: 77.5–78.0%].	Limitations: populations primarily from tertiary care facilities, thus complicating generalisability of results.	None	None
Peper et al. 2017	Evaluación de la adherencia primaria a medicamentos en pacientes con enfermedades crónicas afiliados al Seguro de Salud del Hospital Italiano de Buenos Aires: estudio de cohorte retrospectiva	Cohort study	Patients with T2DM affiliated with the Health Insurance of the Italian Hospital of Buenos Aires who had at least 1 electronic prescription for insulin or metformin from 2012 to 2013.	A total of 747 patients were included, from these 236 were on metformin,117 on insulin and 394 took other medication for different diseases (88 bifosfonates and 306 tamoxifen). The median age for metformin and insulin were 69(62,5-76) and 67 (59,5-75) respectively. The 48.4% of metformin users were women.	Adherence	Patients with drugs prescriptions, even without evidence of dispensation,were contacted to confirm that they didn't acquired medication and be categorized as non adherent.After confirming non adherence individuals were asked about reasons for discontinuing with a questionnaire.	The proportion of patients adherent to metformin was 195/221 with a media (CI 95%)of 88 (84-93) and to insulin 112/117 with a media (CI 95%) of 96 (92-99). The bivariate analysis showed a significant association between adherence to metformin and the median years of insurance affiliation[7.5 (2-12.8); p= 0.007).	Limitations:Possible recall bias because calls were made one year after the medication was prescribed. The sample size was small which can not reflect the adherence of the total population.	Multivariate adjustment for a age and gender.	None.

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Shani et al. 2017	Diabetes medication persistence, different medications have different persistence rates.	Cohort study	T2DM patients with a diagnose before 2008 who were treated by the same family physician and had filled a minimum of 1 prescription per year between 2008-2010 in the Central District of CHS.	A total of 21 357 individuals were included, 48.9% were men and a significant proportion had other concomitant diseases like hypertension (76.8%), hyperlipidemia (88.5%) and ischemic heart disease (32.5%).	Persistence	Persistence: calculated for each drug class, a logistic regression model was used to calculate odds ratio and analyze the effect of specific variables in medication persistence. No definition of persistence was mentioned.	Persistence rates by each drug class were: acarbose 67.8%, metformin 58.6% and glibenclamide 55.3%. Increased age, BMI and higher medication burden was associated with increased medication persistence and mean HbA1c levels were lower in patients with good persistence compared to lower persistence.	Limitations: There is no mention of a specific measure for persistence and medication purchasing was used to estimate medication persistence which can not guarantee that patients took their medication.	Multivariate adjustment for a broad range of confounders.	None
Wu et al. 2017	Comparative assessment of the efficacy and safety of acarbose and metformin combined with premixed insulin in patients with type 2 diabetes mellitus	Observational	Subgroup analysis of OPENING study, in which 1511 subjects with T2DM from 48 centers in China enrolled and required to discontinue prior oral hypoglycemic treatments except for biguanides and a-glucosidase inhibitors (acarbose).	80 patients were treated with acarbose +insulin (mean age 57.93 +/-10.25 p= 0.14, 46.25% male) and were 192 treated with metformin + insulin (mean age 55.96 +/- 10.06 p=0.14, 48.44% male).	Adherence	Morisky Medication Adherence Scale (MMAS). Score of 0 as high adherence, 1 to 2 as medium adherence, and 3 to 4 as low adherence.	Mean scores of MMAS improved in both groups at endpoint: 0.46±0.73 versus 1.29±1.30 (P<.0001) in the acarbose group and 0.41±0.79 versus 1.20±1.46 (P<.0001) in the metformin group, (P > .05)	Limitations: small sample size and short duration.	None	None
Jermendy et al. 2018	Persistence to Treatment with Novel Antidiabetic Drugs (Dipeptidyl Peptidase-4 Inhibitors, Sodium-Glucose Co-Transporter-2 Inhibitors, and Glucagon-Like Peptide-1 Receptor Agonists) in People with Type 2 Diabetes: A Nationwide Cohort Study	Cohort study	T2DM patients who were taking DPP4i, SGLT2i, GLP-1 RA, metformin and sulfonylurea from January 2014 to October 2016.	A total of 103 284 patients were included, from these 59 900 were on DPP4i, 26 052 on SGLT2i and 17 332 on GLP-1 RA.	Persistence	Persistence :period of time from initiation to discontinuation of medication with a flexible gap of 180 days between the last day on therapy and the next refill of prescription.	The persistence rates at 1 year by each drug class were: DPP4i (69.6%), SGLT2i (67.8%), GLP-1 RA (66.3%),SU (52.4%) and metformin (47%). Persistence decreased at year 2: DPP4i (57.3%), SGLT2i (56.8%), GLP-1 RA (52.2%), SU (41.8%) and metformin (41.8%).	Strengths: The sample size of the population was large. Limitations:There is not assessment for possible confounders such as severity of the disease,comorbidities, glycemic control, HbA1c values, BMI, renal function, socioeconomic status, or incidence of side effect	None.	None.
Kadowaki et al. 2018	Persistence of oral antidiabetic treatment for type 2 diabetes characterized by drug class, patient characteristics and severity of renal impairment: A Japanese database analysis	Cohort study	T2DM patients ≥40 years old from Japan who had hypoglycemic drug prescriptions between January 2014 and September 2016 were included.	A total of 161 116 individuals were included, the mean SD age of patients was 70.7 (11.2) years, 73% of patients were aged ≥65 years while 40% were aged ≥75 years; more than half were male (61%).	Persistence; Discontinuation	Persistence: number of days from the index date until evidence of discontinuation for medicacion (treatment gap of ≥30 days between two subsequent prescriptions). Discontinuation : switching to another drug class.	Discontinuation (median 95% IC) time in months: DPP4I 13.7 (11.1-17.7); BG 11.1 (9.6-14.2); SU 5.5 (3.5-8.3); alfa-GI 6.3 (4.9-8.7); Glinide 8.4 (5.8-12.1); TZD 6.2 (3.9-14).	Strengths: Large sample size; database used covered 300 hospitals which provided care to a big part of the population. Limitations: Factors that could have affected persistence, reasons for discontinuation duration of DM, social background and lifestyles were not evaluated due to the lack of information in the database.	None.	Nippon Boehringer Ingelheim Co. Ltd and Eli Lilly Japan K.K.
McGovern et al. 2018	A Class Comparison of Medication Persistence in People with Type 2 Diabetes: A Retrospective Observational Study	Cohort study	Primary care records collected from 1,238,909 people. Within the adult T2D population we identified all new medication prescriptions between January 1, 2005 and December 31, 2015.	Total of 60327 adults with T2D. Mean age was 66.1 years, and 41.3 % were female. Number of people on each medication class: Metformin 41317, Sulfonylureas 20819, DPP-4 inhibitors 9614, Thiazolidinediones 6084, SGLT2 inhibitors 1642, Meglitinides 602, Alpha-glucosidase inhibitors 307.	Persistence; Non persistence	Non-persistence:gap in prescriptions of 90 days. Duration of persistence: time interval between the first prescription and the last identified prescription consistent with persistence.	Median persistence years (95% CI): Metformin 3.04 - Sulfonylureas 2.12 - DPP-4 inhibitors 1.69 - Thiazolidinediones 1.55 - SGLT2 inhibitors NA - Meglitinides 0.81 - Alpha-glucosidase inhibitors 0.64 Non persistence (cox regression HR): Metformin (1; p< 0.001) - Sulfonylureas (1.2; p<0.001) - DPP-4 inhibitors (1.43; p<0.001) - Thiazolidinediones (1.71; p<0.001) SGLT2 inhibitors (1.04; p=0.45) Meglitinides (2.25; p<0.001) Alpha-glucosidase inhibitors (2.45; p<0.001)	Strenghts: The large population size, long duration of follow-up and completeness of the patient record. Limitations: Definition of non adherence may have inflated apparent persistence for medications not available for long periods.	Cox regression model.	Eli Lilly and Company
Mody et al. 2018	Adherence, persistence, glycaemic control and costs among patients with type 2 diabetes initiating dulaglutide compared with liraglutide or exenatide once weekly at 12-month follow-up in a real-world setting in the United States.	Cohort study	Patients with type 2 diabetes and ≥ 1 pharmacy claim for dulaglutide, liraglutide or exenatide once weekly from the HealthCore Integrated Research Database between 1 November 2014 and 31 May 2016.	Matched cohorts: dulaglutide vs liraglutide (n = 2427) mean age 54 years and 52% men; dulaglutide vs exenatide once weekly (n = 1808) mean age of 54 years and ~51% men.	Adherence; Persistence	Adherence: PDC ≥80%. Persistence: number of days of continuous therapy from initiation until the end of 12 months' follow-up, allowing a maximum gap of 45 days between fills.	Matched dulaglutide vs liraglutide: Adherence: dulaglutide 51.2%, liraglutide 38.2% (p<0.001). Persistence (mean days SD): dulaglutide 252.8 (55% persistent) ; liraglutide 218.2 (43.8% persistent). Matched dulaglutide vs exenatide once weekly : Adherence: dulaglutide 50.7%, exenatide 31.9% (p<0.001). Persistence (mean days SD): dulaglutide 251.4 (54.9% persistent) ; exenatide 192.5 (34.4% persistent).	Limitations: Potential for bias attributable to unmeasured confounders. Data from medical and pharmacy claims may have contained undetected coding errors.	Propensity-score matching.	None

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Nishimura et al. 2018	Comparison of persistence and adherence between fixed-dose combinations and two-pill combinations in Japanese patients with type 2 diabetes	Cohort study	Patients with a diagnosis of T2DM > 18 years old who initiated fix-dose combination (FDC) or two-pill combination (TPC) of oral hypoglycemic drugs and received >1 prescription of these for a period of January 2011 to December 2015. A total of five subgroups were defined based on T2DM therapies: TZ+DBG,TZD+SU, aGI+glinide, TZD+DPP-4i and DPP-4i+BG.	Adherence (>0.8): MET 26%, GLP-1 99%, DPP4i 78%, alpha-glucosidase inhibitors 26%, SGLT2i 80%, Meglitinides 13%, MET + DPP4i 8%, MET + TZD 22%, MET + SLGT2i 6%, MET + SLF 30%, SLF 56%, TZD 72%, TZD + DPP4i 78%, TZD + SLF 78%. Persistence: not reported numerically	Adherence; Persistence	Adherence :PDC >80% in a 12 month follow up period. Persistence:period of time from the index date to the first discontinuation of the OAD.	The highest persistence rates in the JMDC group at 12 months were observed with DPP-4i + BG fixed dose combination (FDC) combination (83.5%) and DPP-4i + BG two pill combination (TPC) (72.5%), this is followed by TZD + DPP-4i on FDC (70.9%), TZD + DPP-4i on TPC (67.5%), TZD + SU both combinations (66.7%), TZD + BG on FDC (66.5%), a-GI + glinide on TPC (60.4) and a-GI + glinide on FDC (53.8%). The highest adherence (PDC>80%) were observed among TZD + DPP-4i/FDC (98.60%) and the lowest TZD + SU/FDC (82.14).	Limitations: No method for confounding or analysis of variables that can affect adherence and persistence.	None	Takeda Pharmaceutical Company Limited
Nishimura et al. 2018	Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study	Cohort study	Patients with T2DM diagnosis >18 years old from Japan who initiated new treatment with at least 1 prescription for hypoglycemic medication between January 2011 and December 2015 were included in this study.	A total of 131 329 individuals from 2 administrative claims databases in Japan were included, from these, 40 908 were registered in the Japan Medical Data Center (JMDC) and 90 421 in the Medical Data Vision (MDV) database. The mean age in the JMDC and MDV was 51.7 years and 67.6 years, respectively, majority of the population was male (72.3% and 60.8%) and had concomitant hypertension (47.8% and 70.1%). In the population, 32 155 were on DPP4i monotherapy, 7911 on biguanides monotherapy, 3070 on sulfonylurea monotherapy, 3763 on α-GI monotherapy, 1244 on TZD monotherapy, 1038 on glinide and 1168 on SGLT2i monotherapy.	Adherence; Persistence	Adherence: PDCf ≥ 0.80 . Persistence :period of time from the index date until evidence of discontinuation for 12 months.	Persistence rates at 12 months in the JMDC cohort were higher with DPP4i (67.4%) followed by biguanides (57.3%), SGLT2i (53.5%), thiazolidinedione (51.2%), sulfonylurea (50.4%), a--glucosidase inhibitor (45.5%) and glinide (38.8%). Persistence rates were also higher with DPP4i (73.5%) in the MDV database compared with other medication. Adherence rates in both JMDC and MDV groups were higher with DPP4i (87% and 96.8%) compared with other antidiabetic agents.	Strengths: Larga sample of population. Limitations:Reasons for discontinuation and clinical outcomes were not evaluated due to lack of information in the databases.	Cox regression model.	Takeda Pharmaceutical Company.
Orsini et al. 2018	Utilization Patterns of Glucagon-Like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus in Italy: A Retrospective Cohort Study	Cohort study	T2DM patients >20 years old who initiated GLP-1 RAs from August 2015 to January 2017 in Italy were included in this study.	A total of 7319 patients were included for the final sample, from these 2268 were on DULA, 2573 on LIRA, 970 exQW, 316 on LIXI and 92 on exBID. Most of the individuals were males (54%), and 89% were > 50 years	Persistence; Discontinuation	Persistence: proportion of patients who remain on the index therapy until evidence of discontinuation (a gap between successive prescriptions >2 times the duration of the last prescription) or switch (prescription of a new drug within 30 days following discontinuation).	Persistence rates at 6 months were higher among dulaglutide users (69.1%) followed by liraglutide (50.2%), exenatide QW (46.5%), lixisenatide (39.9%) and exenatide BID (24.8%). Discontinuation was more common with exenatide BID (59.8%) compared with other GLP-1 RAs.	Limitations: A large sample size was used to compare persistence among 5 cohorts that included each type of GLP-1 RA. Bias and confounding were not assessed.	None	Eli Lilly and Co.
Thorsten et al. 2018	Utilization patterns of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus in Germany: a retrospective cohort study	Cohort study	T2DM patients from Germany who initiated GLP-1 RA treatment for the first time (cohort 1) and those switching to another GLP-1 RA during the index time period (cohort 2).	A total of 13 417 individuals were included for cohort 1, from these, (47.9%) were on LIRA, (34.1%) DULA, (9.1%) exQW and (8.8%) exBID. The mean (±SD) age of the cohort was 57.7 ± 11.1 years and proportion of males and females were the same (37.3%). Cohort to had 4264 patients, from these (76.3%) initiated DULA as a second or therapy and (49.5%) switched from LIRA; 36.4% were male and 40.0% female.	Persistence; Discontinuation	Persistence:proportion of patients who remain on the index treatment until any evidence of discontinuation (a gap between continuous prescriptions > 2 times the duration of one prescription) or switching (prescription of a new medication within 1 month after discontinuation).	Persistence rates in cohort 1 were: dulaglutide (50.9%) compared with liraglutide (48.1%), exenatide QW (35.3%) and exenatide BID (27%). A higher discontinuation was observed with exenatide BID. In cohort 2, persistence was higher in dulaglutide users (56%) followed by liraglutide (39.9%), exenatide QW (32.4%) and exenatide BID (28.1%). Discontinuation was most common with exenatide QW compared with other GLP-1 RAs.	Limitatios: A large sample was used for the analysis including 2 cohorts with different characteristics. Bias was not evaluated in this study.	None	Eli Lilly and Company.
Balkhi et al. 2019	Oral antidiabetic medication adherence and glycaemic control among patients with type 2 diabetes mellitus: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia	Cross sectional study	T2DM patients >18 years old, who were taking oral hypoglycemic medication at outpatient clinics of King Saud University Medical City from January to December 2016, with at least 2 prescriptions for sulfonylureas, metformin, thiazolidinediones, meglitinide analogues, acarbose, DPP4i and combination therapy were included in the study.	A total of 5457 individuals were included in the study, from these the majority were women (62.3%), 60 years and older (43.2%) and had concomitant diseases like hypertension (65.6%) and dyslipidaemia (66.0%).	Adherence	Adherence: (MPR) for a 12 month follow up period. Patients were considered adherent if the MPR was ≥0.80, poor adherence was described as a MPR <0.80 and oversupply as a MPR >1.2.	Adherence rates were higher with repaglinide (71.7%) and pioglitazone (65%) followed by sitagliptin (59.9%), acarbose (58.1%), glibenclamide (56.6%), combination (43.9%) and metformin (43.3%).	Strengths: The study uses a reliable method to measure adherence, also, an association between medication adherence and glycemic control (HbA1C). Limitations: Study results may not reflect adherence ar the whole Saudi population residing in the other geographical areas of the country.	Multivariate adjustment for a broad range of confounders	None.

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Capehorn et al. 2019	Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10)	Randomised controlled trial	Phase 3b, open-label trial, 577 adults with type 2 diabetes on 1–3 oral antidiabetic drugs were randomized 1:1 to subcutaneous once-weekly semaglutide 1.0 mg or subcutaneous once-daily liraglutide 1.2 mg with a treatment period of 30 weeks.	577 patients were randomized and 576 were exposed to treatment. A total of 287 (99.0%) subjects in the once weekly semaglutide 1.0 mg arm and 282 (98.3%) subjects in the once daily liraglutide 1.2 mg arm completed the trial; 249 (85.9%) and 261 (90.9%) completed treatment, respectively. The overall mean age was 59.5 years.	Discontinuation	Treatment discontinued by the end of the 30 week trial.	Discontinuation with semaglutide (n = 33, 11.4%) vs liraglutide (n = 19, 6.6%).	Strengths: applicable to real world clinical practice. Limitations: open label design, short duration, not all dosages of the medication were included.	Randomization	Novo Nordisk A/S.
Divino et al. 2019	GLP-1 RA Treatment and Dosing Patterns Among Type 2 Diabetes Patients in Six Countries: A Retrospective Analysis of Pharmacy Claims Data	Cohort study	Patients with a T2DM diagnosis > 18 years old who were new GLP-1 RAs users from January to December of 2016 in 6 different countries (Belgium, France, Germany, Italy, The Netherlands and Canada) were included.	A total of 99 914 patients were included, from this 34 649 were on dulaglutide (389 Belgium, 3464 France, 23 039 Germany, 5795 Italy, 180 Netherlands, 1782 Canada); 3616 on exenatide BID (68 Belgium, 487 France, 2579 Germany, 393 Italy, 18 Netherlands, 71 Canada); 11 138 on exenatide QW (1058 Belgium, 3111 France, 2181 Germany, 4346 Italy, 86 Netherlands, 356 Canada); 48 317 on liraglutide (997 Belgium, 8012 France, 15 792 Germany, 9557 Italy, 1225 Netherlands, 12 734 Canada); and 2204 on lixisenatide (407 Belgium, 1772 Italy, 25 Netherlands).	Persistence; Discontinuation	Persistence: proportion of patients who remain on treatment until evidence of discontinuation. Discontinuation: gap between successive prescriptions > 2 times the expected duration of the previous prescription.	Persistence at 1 year in each country by each GLP-1 RA drug were: Belgium DULA (36.8%), exQW (28.1%), LIRA (22.2%), LIXI (15.5%) and exBID (5.9%); France DULA (50.9%), LIRA (36.7%), exQW (35%) and exBID (20.9%); Germany DULA (49.7%), LIRA (46.4%), exQW (34.3%) and exBID (27.5%); Italy DULA (50.4%), LIRA (40.1%), exQW (35.7%), LIXI (27.7%) and exBID (11.7%), Netherlands DULA (67.2%), LIRA (57.5%), exBID (44.4%), exQW (44.2%) and LIXI (40%); Canadá DULA (51.8%), LIRA (46.4%), exQW (24.7%) and exBID (14.1%). Discontinuation was most common with exenatide BID in 5 countries (BE 67.6%, FR 50.5%, DE 55.8%, IT 64.6% and CA 66.2%).	Strengths: Large sample that included individuals from different countries. Limitations: Variables or factors that could have affected persistence and discontinuation were not evaluated in this study. Adjustment for confounding or bias was not evaluated.	None	Eli Lilly and Company.
Durden et al.2019	The Effect of Early Response to GLP-1 RA Therapy on Long-Term Adherence and Persistence Among Type 2 Diabetes Patients in the United States	Cohort study	U.S. electronic medical record data from the IBM Watson Health Explorys Universe Dataset from July 1, 2009, to January 1, 2017 identified adults aged ≥18 years with T2D initiated with GLP-1 RA therapy.	8,329 identified patients. The mean [SD] age of the study population was 57 (10.8) years, and (54%) were female. 3 response cohorts were analysed: 1. A1c with no early effect (n= 5558) and dropped >1% (n=2771). 2. Body weight with no early effect (n=5731) and dropped >3% (n=2598). 3.A1c and weight with no early effect (n=7211) and early effect (n=1118). Cohort 1: no early effect (Albiglutide 1.5%, Dulaglutide 1.6%, Exenatide 17.4%, Exenatide QW 17.7%, Liraglutide 61.8%) . Dropped >1%: (Albiglutide 1.5%, Dulaglutide 2%, Exenatide 13.3%, Exenatide QW 18%, Liraglutide 65.2%). Cohort 2:No early effect (Albiglutide 1.7%, Dulaglutide 1.9%, Exenatide 16.6%, Exenatide QW 18.4%, Liraglutide 61.3%). Dropped >3% (Albiglutide 1.1%, Dulaglutide 1.3%, Exenatide 14.7%	Adherence; Persistence; Discontinuation	Adherence: PDC ≥80% Non-persistence - discontinuation: gap in therapy ≥60 days. Persistence: indexing line of therapy lasting for at least 12 or 18 months, respectively.	Cohort 1.Adherent: no early effect 37.1%; dropped > 1% 45%. PDC, mean (SD): no early effect 0.61 (0.32); dropped > 1%0.67 (0.31). Discontinued: no early effect 67.9%, dropped> 1% 61.4%. Days on medication mean SD: no early effect 343.8 (1176.5), dropped > 1% 378.5 (170.8). p<0.001 Cohort 2.Adherent: no early effect 38%; dropped > 3% 43.3%. PDC, mean (SD): no early effect 0.62 (0.32); dropped > 3%0.66 (0.32). Discontinued: no early effect 67.5%, dropped> 3% 61.9%. Days on medication mean SD: no early effect 348.8 (175.6), dropped > 3% 369.8 (174). p<0.001 Cohort 3.Adherent: no early effect 38.6%; early effect 46.4%. PDC, mean (SD): no early effect 0.63 (0.32); early effect 0.68 (0.31). Discontinued: no early effect 66.7%, early effect 60%. Days on medication mean SD: no early effect 351.1 (175.7) , early effect 382.8 (170.3). p<0.001	Strenghts: large scale study. Limitations: mainly from database research.	Multivariate adjustment for a broad range of confounders	IBM Watson Health by Novo Nordisk A/S
Lingvay et al. 2019	Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial	Randomised controlled trial	52 weeks double-blind, parallel-group, phase 3b, randomised controlled trial done at 111 centres in 11 countries. Patients were randomly assigned (1:1) to subcutaneous semaglutide 1·0 mg once weekly or oral canagliflozin 300 mg once daily.	788 patients were randomly assigned to semaglutide 1·0 mg (394 patients) or canagliflozin 300 mg (394 patients). 739 patients completed the trial (367 in the semaglutide group and 372 in the canagliflozin group).	Discontinuation	Discontinuation of treatment prior to trail finalisation.	Premature discontinuation occurred in 38 (10%) of 392 patients with semaglutide and in 20 (5%) of 394 patients with canagliflozin.	Strengths: substantial size, global population, double-blind nature, relatively long treatment period, and relevant head-to-head comparison with a well-established glucose-lowering medication. Limitations: evaluation of persistence was unobtainable due to trial duration.	Treatment randomisation and masking.	Novo Nordisk.
Moreno et al. 2019	Treatment Patterns of Diabetes in Italy: A Population-Based Study	Cohort study	Patients with a T2DM diagnosis ≥ 40 years old with at least 1 prescription of hypoglycemic medication between January and December 2016 from the primary health care centers in Campania, Italy where included in this study.	A total of 19,546 patients aged over 40 years were new users of antidiabetic drugs, from these just 14,679 patients met the inclusion criteria and were recruited. The mean age (± SD) of the cohort was 64 ± 11.6 year and approximately more than 50% were male (54.8).	Persistence	Persistence: proportion of patients who continued their treatment for 1 year from the index date without a gap between two dispensations greater than two and a half times the duration of the previous prescription (grace period).	Persistence rates in 1 year were higher among patients taking metformin (80.1%) compared with sulfonylurea (67.9%). The average number of days between the index date and discontinuation of medication was 330 days (95%CI 328.6; 331.7) for metformin and 303 days (95%CI 296.6; 309.7) for sulfonylurea. A higher non-persistence was observed in the oldest age group (≥80 years), sulfonylurea users and polymedicated patients.	Strengths:The study assessed predictor for non-adherence (age, sex, type of medication, polypharmacy etc) using HR. Limitations: Data regarding changes in lifestyle, glycated haemoglobin values and medical reasons for treatment discontinuation was not available for analysis. Medication dispensation can not guarantee that the patient took their medication.	Cox regression model.	Fundación Instituto de Investigación Sanitaria Aragón.

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Ofori-Asenso et al. 2019	Dynamics of switching, adherence, and persistence of dipeptidyl peptidase-4 inhibitors use: A nationwide cohort study	Cohort study	Data from the PBS records covering a 10% random sample of Australians dispensed PBS medications. Adults aged 18 years and older who were newly dispensed DPP-4is from 1 January 2015 to 31 August 2017 were included.	A total of 15,915 adults who were initiated DPP-4is, The mean age was 62.7 (standard deviation [S.D] ± 13.3) years and 42.8% were female. Sitagliptin (n = 9,576), vildagliptin (n = 1,130), saxagliptin (n = 1,126), linagliptin (n = 3,560), and alogliptin (n = 523)	Non adherence; Non persistence	Adherence: PDC in 12 month follow up period. Non adherence: PDC<0.8 Persistence: continuous use of medication until a gap of 90 or more days without medication on hand.	Non-adherent (PDC<0.8) sitagliptin 36.3% (OR 1), vildagliptin 34.2% (OR 0.99; 0.86-1.13), saxagliptin 43.4% (OR 1.41; 1.23-1.6), linagliptin 37.2% (OR 0.93; 0.85-1.01), alogliptin 38% (OR 1.13; 0.93-1.36) p<0.001. Non- persistence: sitagliptin 29.6% (OR 1), vildagliptin 31.7% (OR 1.11; 0.98-1.24), saxagliptin 35.9% (OR 1.27; 1.15-1.42), linagliptin 31.2% (OR 1.01; 0.94-1.09), alogliptin30.4% (OR 1.06; 0.90-1.24) P<0.001	Strengths: first study to describe medication patterns in DPP-4is, significant real world data. Limitations: single in class analysis, PDC over the one-year analysis period could likely be underestimated leading to misclassification as nonadherent or nonpersistent.	Multivariate adjustment for a broad range of confounders	None
Patel et al. 2019	Effect of medication adherence on clinical outcomes in type 2 diabetes: analysis of the SIMPLE study	Randomised controlled trial	Analysis of the SIMPLE study, 120 adults with T2DM and HgbA1c≥10% were randomized to detemir plus liraglutide, or detemir plus aspart before each meal; 6-month follow-up.	120 participants were randomized with an average age of 47 years, 71% female.	Adherence	Adherent: patients with at least two (out of three) visits where adherence could be assessed (product was returned) and the calculated time-adjusted average adherence rate for the entire duration of the study was≥80%.	The percentage of participants with ≥80% adherence to detemir insulin was higher in the GLP1RA+BI group (n=32, 59.3%) versus the BBI group (n=20, 35.7%) (p=0.021 between groups). The percentage of participants with ≥80% adherence to liraglutide was 57.4% compared with aspart insulin 30.4% (p=0.007 between groups). The percentage of participants with ≥80% adherence with metformin was similar between groups (66.7% in the GLP1RA+BI group and 60.7% in the BBI group, p=0.556 between groups)	Strengths: results translatable to real world usual clinical practice, adherence measurement more accurate than pharmacy fill rates. Limitations: underestimation of adherence rate due to calculation method, small sample in subgroups, free medication in study doesn't related to real world results.	Randomisation	Novo Nordisk
Sefah et al. 2019	Adherence to Oral Hypoglycemic Drugs among Type 2 Diabetic Patients in a Resource-Poor Setting	Cross sectional study	Patients with T2DM >18 years old who took antidiabetic medication and were registered in 4 district/municipal hospitals in the Volta Region of Ghana between January and March of 2015 were included in this study.	A total of 400 patients were included, patients were divided in 2 groups: non adherent and adherent. The majority of the population including both adherent and nonadherent were female (67.5% and 76.1%), had between 41-60 years (43.9% and 55.5%), were unemployed (27.7% and 26.4%), were Christian (89% and 89.5%) and had no history of taking alcohol or smoking (86.4% and 83.2%) respectively.	Adherence	Adherence:8-item Morisky Medication Adherence Scale (MMAS-8). Patients were considered as adherent if the MMAS-8 score was 6-8 an non adherent if it was <6.	47.7% of patients were adherent, among these, 42.4% took metformin+glibenclamide, 19.4% metformin+gliclazide+pioglitazone, 9.4% metformin+glimepiride, 7.9% metformin (p=0.547), 4.7% glibenclamide, and 2.6% metformin+glimepiride+pioglitazone. The main reason for non adherence was forgetfulness (30.87%). Significant variables after aOR were: fasting blood glucose of 1-6 mmol/L [OR=1.920; 95% CI (1.110-3.319)], higher educational status [OR=3.01; 95% CI (1.445-6.269)]and the number of oral hypoglycemic agents prescribed but unavailable [OR=1.734; 95% CI (1.008-2.984)].	Strengths: multivariate analysis was developed to predict adherence in statistically significant independent variables obtained after cross-tabulation. Limitations: The use of self-reported data can overestimate adherence rates due to a pottencial patient bias.	Multivariate adjustment for a broad range of confounders	Nil
Singhal et al. 2019	Effectiveness, treatment durability, and treatment costs of canagliflozin and glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes in the USA	Cohort study	Data from the HealthCore Integrated Research Database on patients initiating canagliflozin 300 mg or any dose of a GLP-1 receptor agonist from 1 April 2012 to 28 February 2017.	3171 patients met all inclusion and exclusion criteria, 755 initiated on canagliflozin 300mg, and 2416 initiated on any dose of a GLP-1 receptor agonist.	Adherence; Discontinuation	Adherence: PDC >/= 80% Discontinuation: failure to refill index medication within 90 days after the depletion of the previous days' supply.	Adherence: PDC > 80% Canaglifozin 300mg 47.5%, GLP-1 agonist 37.5%. PDC mean (SD) Canaglifozin 300mg 0.67 (0.29), GLP-1 0.59 (0.31). p<0.0001* Discontinuation: Canaglifozin 300mg 49.6%, GLP-1 57.4%. Mean (SD) Canaglifozin 300mg 187 (120), GLP-1 163 (120) p=0.001	Strengths: large and accurate data sample. Limitations: focused only on canagliflozin and not include other SGLT2 inhibitors, patients were included only with 300mg canagliflozin rather than 100mg.	Propensity score matching	Janssen Scientific Affairs.
Trejo-Bastidas et al. 2019	Adherencia farmacológica de pacientes con diabetes mellitus en un programa de nefroprotección: una responsabilidad compartida	Cohort study	Patients with type two diabetes mellitus in a nephroprotection programme in the municipalities of Pasto and Túquerres in 2017.	Total of 282 patients.18.1% were taking Metformin + glibenclamide, 1.4% Metformin + vildagliptin, 1.1% Vildagliptin, 67.7% Metformin, 1.4% glibenclamide. Median age was 67 years (interquartile range -RIQ- 16), 66.7% were women.	Adherence	Morisky Medication Adherence Scale	Adherence: Metformin + glibenclamide 12.5% (adjusted PR 1), Metformin + vildagliptin 1.6% (adjusted PR 1.07 95% CI 0.08-15.90), Vildagliptin 1% (adjusted PR 1.43 95% CI 0.14-38.25), Metformin 75% (adjusted PR 1.68 95% CI 1.76-10.15), Glibenclamide 1% (adjusted PR 1.74 95% CI 0.14-38.25). 43 95% CI 0.14-38.25) , Metformin 75% (adjusted PR 1.68 95% CI1.76-10.15) , Glibenclamide 1% (adjusted PR 1.74 95% CI 0.26-101.08) , None 8.9%. Non-adherence: Metformin + glibenclamide 30%, Metformin + vildagliptin 1.1%, Vildagliptin 1.1%, Metformin 52.2%, Glibenclamide 2.2%, None 13.3%.	Limitations: use of secondary source for secondary source for collection of various data.	Binary logistic regression with independent factors and probability sampling.	Self-funding

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Xu et al. 2019	Use of non-insulin diabetes medicines after insulin initiation: A retrospective cohort study	Cohort study	MarketScan Commercial Claims and Encounters data from 2010–2015 examining 72,971 patients with type 2 diabetes aged 18–65 years old who initiated insulin and had filled a prescription for a non-insulin diabetes medication in the 90 days prior to insulin initiation.	Total of 72,971 individuals included in the final cohort. Mean age was 51.5 years and 54.0% were male. Metformin used in 72.7%, sulfonylureas 34.9%, DPP4 inhibitors 11.7%, and TZDs 10.2%, GLP-1 receptor agonists 8.3% and SGLT-2 inhibitors 1.6% .	Discontinuation	Discontinuation : used medication before the index date but had no drug on hand for 90days or more after insulin initiation. Continuation: used medication in the 90 days prior to index date and filled at least one prescription of it after insulin initiation.	Continuation: Metformin 84.6%, Sulfonylurea 73.6%, Dipeptidyl peptidase 4 inhibitor 78.3%, Glucagon-like peptide-1 receptor agonist 77.8%, Sodium glucose cotransporter inhibitor 81.9%, Thiazolidinedione 79.3%. Discontinuation (months): Metformin median 26.4 95%CI (26.1, 26.8), Sulfonylurea median 23.3 95% CI (22.8, 23.8), Dipeptidyl peptidase 4 inhibitor median 17.9 95%CI (17.3, 18.7) , Glucagon-like peptide-1 receptor agonist median 10.7 95%CI (10.1, 11.3) , Sodium glucose co-transporter inhibitor median 3 95%CI(3.0, 3.0) , Thiazolidinedione median 19.2 95%CI (18.6, 19.6).	Strengths: large, nationally representative data source.Definition of discontinuation allows flexible regimen adjustments with gaps of up to 90 days. Limitations: due to prescription records, use of ICD-9 codes during the 90 days prior to the index date to exclude patients with type 1 diabetes could be imprecise.	None	None
Climens et al. 2020	Understanding Reasons for Treatment Discontinuation, Attitudes and Education Needs Among People Who Discontinue Type 2 Diabetes Treatment: Results from an Online Patient Survey in the USA and UK	Qualitative research	Patients with a T2DM diagnosis > 18 years old from the USA and UK who had discontinued treatment within the previous 6 months were included in this study.	A total of 161 individuals, 98 from the USA and 90 from the UK met the inclusion criteria and were selected to respond the survey.	Discontinuation	An online questionnaire was used to ask patients the treatment that they discontinued in the past 6 months. The survey included one closed-ended and three open-ended questions to identify reasons for initiating treatment, discontinuing medication and factors to prevent this.	Discontinuation among oral hypoglycemic drugs was higher with metformin (59%), followed by sitagliptin (13%) and glipizide (8%) and SGLT2i (3%). Regarding to injectable therapies, discontinuation was more common with insulin (25%) followed by GLP-1 RAs (8%).	Strengths: Discontinuation was measured for each drug class. Limitations: Small sample size, participant basal characteristics were not mentioned and discontinuation was measured just in a 6 month period.	None.	Sanofi.
Deval Gor et al. 2020	Adherence and Persistence with DPP-4 Inhibitors Versus Pioglitazone in Type 2 Diabetes Patients with Chronic Kidney Disease: A Retrospective Claims Database Analysis	Cohort study	Truven MarketScan administrative claims databases from 2009-2015 that included patients with T2DM and non - dialysis CKD that were new users of DPP-4 inhibitor or pioglitazone. New users were defined as the ones who started the medication without any prescription claim for both DPP-4 inhibitor or pioglitazone within a year before the index date (first prescription claim date)	Total of 1 111 645 individuals taking DPP-4 inhibitors or pioglitazone, from that population there were 43 559 patients with T2DM and CKD, 17 439 had a continuous enrollment 1 year before and after the index date, 8420 were excluded for different reasons and 9019 patients were considered as the final sample.	Adherence; Persistence	Adherence: PDC > 0,8. Persistence: days between the index date and last day with the medication on hand, based on a period of 365 days or at the end of follow-up. Flexible gaps of 2 times the days supply, 60 and 90 days without index medication was allowed in between the prescriptions before classifying an individual as nonpersistent.	Adherence: 59.5% with DPP-4 inhibitors and 52.4 with pioglitazone. Persistence with an allowed gap of 90 days was of 58.2% with DPP-4 inhibitors and 47.6 with pioglitazone.	Strengths: Adherence and Persistence measures were well defined. Limitations: Adherence was calculated based on pharmacy claims data that can not be accurate regarding how patients use their medication. Reasons for non adherence and the effect of adherence on clinical outcomes were not analyzed.	None	None
Irani et al. 2020	Evaluation of Adherence to Oral Hypoglycemic Agent Prescription in Patients with Type 2 Diabetes	Cross sectional study	136 patients with T2D between September 2018 and March 2019 in the clinics of internal diseases and endocrinology, which are affiliated with Islamic Azad University.	Of the 136 diabetes patients, 85 (62.5%) were women and 51 (37.5%) were men. The number of patients on each medication were: Metformin 86 , Glibenclamide 43, Gliclazide 21, Linagliptin 3 , Repaglinide 5 , Sitagliptin 11 , Pioglitazone 4.	Adherence	Not reported	Adherence: Metformin 77.5% (LR = 1.53 P-value = 0.287) , Glibenclamide 71.7% (LR = 3.92 P-value = 0.048), Gliclazide 84.0 (LR = 0.41P-value = 0.512) , Linagliptin 100.0% , Repaglinide 71.4% , Sitagliptin 73.3%, Pioglitazone 100%.	Limitations: no specification of adherence.	None	None
Juste et al. 2020	Initial Therapy, Regimen Change, and Persistence in a Spanish Cohort of Newly Treated Type 2 Diabetes Patients: A Retrospective, Observational Study Using Real-World Data	Cohort study	T2DM patients >15 years old from Spain who initiated any antidiabetic drug between October 2013 and September 2014 were included in this study.	A total of 4247 patients were included, from these 57.6% were male, the mean age was 64.6 ± 12.8 years, more than half lived in urban areas (58.6%) and had polypharmacy (51%).	Persistence; Discontinuation	Persistence: proportion of patients who continued drug dispensation during 1 year from the index date, patients were considered non-persistence if the gap between two dispensations was >90 days. Discontinuation: if the patient stopped treatment without receiving new prescriptions after the established gap.	Persistence was higher with DPP4i (76.7%), followed by metformin (68.8%), sulfonylureas (63.8%) and repaglinide (61.1%). Discontinuation was more common with repaglinide (38.9%), followed by sulfonylureas (36.2%), metformin (31.2%) and DPP4i (23.3%).	Strengths: Large sample size, persistence was measured for all medication class included. Limitations: Reasons for discontinuation were not evaluated.	Multivariate adjustment for a broad range of confounders	Gobierno de Aragón and the European Regional Development Fund (ERDF).
Machado et al. 2020	Medication non-adherence in patients with type 2 diabetes mellitus with full access to medicines	Cross sectional study	T2DM patients > 18 years old, who took at least one oral antidiabetic agent provided by the public health system were recruited at the "Centro de Saúde Teodorico Teles" between January and December of 2017.	A total of 300 patients were included in the study, most of them were females (64.3%), married (69.7%) and had children (91.7%) also hypertension was the most common comorbidity, with 63.3%.	Adherence	Adherence: 4-item Morisky Medication Adherence Scale (MMAS-4); individuals with the minimum score (0 points) were considered as high adherent and those with 1 point or more low adherent.	High adherence: 42.6% (p=0.014) for metformin, 33.8% for association without insulin, 20.6% for association with insulin and 2.9% for sulphonylurea. Low adherence : association without insulin (49.5%), metformin (26.3%), association with insulin (15.5%) and sulphonylurea (8.6%).	Strengths: This study assessed factors that can affect non-adherence like sex, number of prescribed medicines, age and others. Limitations: Patients were selected from the same health center and recruitment was performed non-randomly.	None.	None.
Mody et al. 2020	Adherence and persistence among patients with type 2 diabetes initiating dulaglutide compared with semaglutide and exenatide BCise: 6-month follow-up from US real-world data	Cohort study	T2DM patients who took dulaglutide, semaglutide or exenatide between February 2018 and December 2018 with ≥1 pharmacy claim for these medication during the index period and continuous enrolment in the 6 months pre-index (baseline) and 6 months post-index (follow-up).	Prior to propensity-score matching a total of 18 650 met the inclusion criteria, after score matching 3852 pairs for the dulaglutide versus semaglutide cohort and 1879 pairs for the dulaglutide versus exenatide were included.	Adherence; Persistence	Adherence: PDC ≥80%. Persistence: period of time of continuous therapy from the beginning of treatment to discontinuation (failure to refill the medication within a gap of 45 days or 60 days) or end of the 6-month follow-up period.	The mean PDC was higher among patients taking dulaglutide (75%) compared with semaglutide (67%) and exenatide (63%). The adherence rates (PDC ≥80%) were also higher with dulaglutide (59.7%) and (58.1%) compared with semaglutide (42.7) and exenatide (40.3%) regarding to the matched cohorts. Dulaglutide initiators had better persistent compared with semaglutide initiators (69.2% vs. 59.2%).	Limitations: There was a risk for bias attributable to unmeasured confounder, patient information and characteristics that could have affected the outcomes were not available for analysis.	Propensity score matching	Anthem Inc. HealthCore, Inc.

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Oh et al. 2020	Comparison of persistence and adherence between DPP-4 inhibitor administration frequencies in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study	Cohort study	Data from the Japanese nationwide hospital-based Medical Data Vision (MDV) administrative claims database for patients given a new DPP-4i prescription between May 2015 and June 2017 with 1-year follow-up until May 2018.	Total of 39,826 patients met the inclusion criteria, 82.4% were receiving once-daily DPP-4i, 15.6% twice-daily DPP-4i, and 2.0% once-weekly DPP-4.	Adherence; Persistence	Persistence: total duration of continuous prescription. Adherence: PDC>0.80.	12-month persistence rate: once-daily DPP-4i (66.3%); twice-daily DPP-4i (64.7%); once weekly (38.8%). HR for discontinuation: twice daily 1.022 [95% CI: 0.994–1.050]; p= .1187, once weekly1.699 [95% CI:1.585–1.822]; p < .0001 Adherence: once daily 97.8%, twice daily 97.8%, weekly 65.8%.	Strengths: large number of patients with continuous enrollment in the MDV claims database (largest in Japan) Limitations: observational nature, adjusted regression analysis limited to confounders available in database, absence of data linkage to other medical facilities.	Multivariate adjustment for a broad range of confounders	Takeda Pharmaceutical Company Limited
Pishdad et al. 2020	A time to revisit the two oldest prandial anti-diabetes agents: acarbose and repaglinide	Randomized, double-blind, prospective study,	Type 2 diabetic patients who were being seen and followed in our diabetes and endocrinology clinics between January 1, 2012 and December 31, 2014	Total of 358 patients: 119 received repaglinide, 132 acarbose, 107 and repaglinide + acarbose.	Adherence	Not mentioned	Treatment adherence rate: repaglinide 75.6%, acarbose 61.4%, repaglinide-plus-acarbose 81.3%. (p = 0.001)	Strengths: analysis of cost effective and globally available agents. Limitations include reduced sample size.	Random allocation	Shiraz University of Medical Sciences
Pishdad et al. 2020	Acarbose versus Repaglinide in Diabetes Treatment: A New Appraisal of Two Old Rivals	Non-randomised experimental study	Patient's aged 20-65 years with endocrinologist-ascertained T2D of less than 2-years since diagnosis selected from local diabetes and endocrinology clinics between January 1, 2010 and December 31, 2011.	Acarbose group with 82 patients, 46.3% male, mean age of 52.3. Repaglinide group with 82 patients, 49% male, mean age of 49.5 years.	Adherence	Not mentioned	Adherence: acarbose 52.4%, repaglinide 72%. P = 0.01	Strengths: patients included have a recent diagnosis leading to better response to insulin secretagogue. Limitations: lack of randomisation and blinding.	None	None
Svensson et al. 2020	Treatment persistence in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists in clinical practice in Sweden	Cohort study	T2DM patients > 18 years old who were new GLP-1 RA users from May 2015 to October 2017.	A total of 17 361 patients were included, from these 713 initiated exenatide QW, 12 461 liraglutide, 797 lixisenatide and 3390 dulaglutide. All four groups were similar in age, sex, diabetes duration, HbA1c, body mass index, comorbidities and among others.	Persistence	Persistence: proportion of patients who continue their medication dispensation until evidence of a 45 gap or more between the last claim and the date of the next claim for the same medication.	Treatment persistence rates at 1 year using a 45 day gap were higher among dulaglutide users (85%) followed by liraglutide (75.5%), exenatide QW (69.4%) and lixisenatide (66.6%). Treatment persistence was higher using 60 days gap: (87.7%) for dulaglutide, (80.9%) liraglutide, (72.6%) exenatide QW and (71.2%) lixisenatide. According to HR patients on exenatide QW, liraglutide and lixisenatide were 2.2, 1.7 and 2.5 times more probable to discontinue medication compared with those on dulaglutide.	Strengths: Changes in HbA1c levels, body weight associated with persistence and predictors of discontinuation were analyzed in this study. Bias was managed with propensity scores including more than 50 variables.	Propensity score matching	None.
Uzoigwe et al. 2020	Semaglutide Once-Weekly Persistence and Adherence Versus Other GLP-1 RAs in Patients with Type 2 Diabetes in a US Real-World Setting	Cohort study	Patients with T2DM diagnosis > 18 years old who were taking GLP-1 RA treatment in the 360 days prior to the index period (January 2018 to April 2019) with at least 1 pharmacy claim of the index medication.	A total of 56 715 patients initiated GLP-1 RA, from these 3279 were on semaglutide, 27 891 dulaglutide, 17 186 liraglutide and 8359 exenatide QW.	Adherence; Persistence	Persistence:proportion of patients who kept taking the medication from the initiation of the medication until evidence of discontinuation (60 day gap). Persistence was estimated at 180 and 360 days. Adherence: PDC>80%	Persistence with semaglutide QW was higher than that observed for all comparators. Persistence rates at 180 days were: semaglutide QW (74%), dulaglutide (66.4%), liraglutide (54.1%) and for exenatide QW (48.6%) and at 360 days: semaglutide (67%), dulaglutide (56%), liraglutide (40.4%) and (35.5%) exenatide QW. Adherence at 180 days (PDC>80%) was higher for semaglutide QW (41.9%) compared with dulaglutide (43.6%%) and similarly at 360 days	Strengths:Large sample size was used. Persistence and adherence were measured at 180 and 360 days.	Propensity score matching	Novo Nordisk Inc.
Zhang et al. 2020	Assessment of basal insulin adherence using 2 methodologies among Texas Medicaid enrollees with type 2 diabetes	Cohort study	Texas Medicaid prescription claims data from January 1, 2014, to June 30, 2017.	5,034 patients included: 187 (3.7%) received NPH; 4,522 (89.8%) received FGLA; and 325 (6.5%) received SGLA insulin at index. Overall, the mean age (SD) was 50.9 (9.9) years, and the majority was female (65.9%).	Adherence	Adherence: MPR and aMPR >/= 0.8 over the 12-month post-index period.	MPR (SD): NPH: 0.55, FGLA: 0.59, SGLA: 0.68; (P<0.0001) aMPR (SD): NPH: 0.73, FGLA: 0.78, SGLA: 0.83 (P=0.0001) MPR ≥ 80%: (NPH:21.4%, FGLA: 27.6%, SGLA: 39.7%; P< 0.0001) aMPR ≥ 80%: (NPH: 49.2%, FGLA: 60.0%, SGLA: 67.1%; P=0.0004).	Limitations: As an observational study, selection bias may be present. No validated threshold exists for aMPR	Multivariate adjustment.	None
Abitbol et al.2021	Persistence of GLP-1 RA in combination with basal insulin among adults with type 2 diabetes in Canada	Cohort study	Individuals from the IQVIA Canadian LRx database were included in the study if they were taking basal insulin and GLP-1 RA as a loose-dose combination at least once during the selection period	12 411 people inexperienced with the combination therapy at index and 17 016 people with or without previous experience on loose-dose combination therapy.	Persistence	Persistence: overlapping prescriptions. Non-persistence was defined as a gap period greater than 90 days between prescriptions. Patients were followed for 12 months.	Persistence with loose-dose combination over 12 months was was 46.8% , from these, 47.2% were persistent for GLP-1 RA + NPH insulin combination, 46.3% for QD GLP-1 RA + basal insulin and 48.6% for QW GLP-1 RA + basal insulin.	Limitations: Results were obtained from a non-clinical prescription database (IQVIA Canadian LRx database) which uses pharmacies registers therefore, the use of medication is interpreted based on the transaction history. Database used does not mention diagnostic information hence, they assumed that people taking GLP-1 RA were people with type 2 diabetes. The study do not analyze the reasons for poor adherence and considered variables which can affect adherence.	None	Sanofi

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Khan et al. 2021	Assessment of Drug Compliance Among Diabetic Patients	Descriptive study	Patients diagnosed with T2DM above 18 years old taking hypoglycemic agents for at least 6 months were included in this study.	The size of the sample was calculated using the WHO Sample Size Calculator, with 95% confidence level, a total of 196 diabetic patients were included.	Adherence	Adherence: PDC >80%.	Adherence by drug class were: biguanides (16.27%), sulphonylureas (1.16%), DPP4i (15.11%), GLP 1 RA (13.95%) and combination of drugs (53.48%).The highest adherence rates were observed in patients taking biguanides and combination of drugs. The medication with the poorest adherence was GLP 1 RA with 18.18%.	Limitations: The study was conducted in Private Consultation Clinic where the patient's reported adherence might not be an accurate representation of community. Also this study did not analyze variables which could have affected adherence.	None	None
Luo et al. 2021	Incidence and Predictors of Primary Nonadherence to Sodium Glucose Co-transporter 2 Inhibitors and Glucagon-Like Peptide 1 Agonists in a Large Integrated Healthcare System	Cohort study	Data of adult patients from a large health system who had at least one prescription order for a SGLT2i or GLP-1 agonist between 2012 and 2019.	Total of 5146 patients newly prescribed a SGLT2i or GLP-1 agonist. 47.3% were taking GLP-1 agonist and 52.7% SGLT2 inhibitor. 91% of the overall cohort was under the age of 65, 47% were female.	Non adherence	Non-adherence: no dispensed claim within 30 days of an electronic prescription order.	Non-adherence: GLP-1 agonist 29.8%, SGLT2 inhibitor 33.6%.	Limitations: estimates of primary nonadherence may be subject to misclassification, limits due to unmeasurable confounding, limited generalisability.	None	National Center For Advancing Translational Sciences of the National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases.
Norrbacka et al. 2021	Glucagon-Like Peptide 1 Receptor Agonists in Type 2 Diabetes Mellitus: Data from a Real-World Study in Spain.	Cohort study	T2DM patients >18 years old who initiated a new treatment with a GLP-1 RA (dulaglutide, exenatide-QW or liraglutide) from 1 November 2015 to 30 June 2017.	All data collected for the study came from the BigPac database (Atrys Health-Real Life Data, Madrid, Spain). A total of 49 101 patients met the inclusion criteria, after applying exclusion criteria 492 patients on dulaglutide, 438 patients on exenatide-QW and 472 patients on liraglutide were included.	Persistence; Discontinuation	Persistence: time from the index date until evidence of non-persistence, either by discontinuation (a gap of 60 days in successive dispensations) or switching (new dispensation of a different hypoglycemic drug within 30 days before or after discontinuation) in a follow-up period of 18 months.	Persistence at 6, 12 and 18 months was higher among dulaglutide users (78%), (69.7%) and (59.1%) respectively. The rates of discontinuation at 6 months were higher with exenatide (26.9%), at 12 months with liraglutide (24.6%) and at 18 months also with liraglutide (25.2%).	Strengths: An association between the use of GLP-1 RAs and changes in (HbA1c) levels from baseline to 12 months was studied. Limitations: The reasons for treatment non-persistence were not assessed in detail.	None	Eli Lilly and Co.
Polonsky et al. 2021	Higher Rates of Persistence and Adherence in Patients with Type 2 Diabetes Initiating Once-Weekly vs Daily Injectable Glucagon-Like Peptide-1 Receptor Agonists in US Clinical Practice (STAY Study)	Cohort study	Data from individuals identified in the US IBM MarketScan Explorys Claims-EMR Data Set. Index date was the first claim for GLP-1 RA. Index period was 1 July 2012 to 31 January 2019.	Total of 4311 patients receiving once-weekly injectable GLP-1 RAs and 5639 patients receiving daily injectable GLP-1 RAs. Following PS matching, each of the GLP-1 RA cohorts included 784 individuals, and the matched cohorts had similar baseline characteristics.	Adherence; Persistence	Adherence: PDC> 80% Persistence: >60 days covered by medication, >90 days for sensitivity analysis.	Persistence: At 12 months 48% for once weekly GLP-1 RAs and 41% for once daily. Median stay time was 333 days for once-weekly GLP-1 RAs and 269 days for daily GLP-1RAs. Adherence: At 6 months once-weekly GLP-1 RA 54% and once daily 44%; p <0.01. At 12 months once-weekly 46%, once daily 34%; p <0.01.	Strengths: Use of linked EHR and claims data, which allowed for a comprehensive analysis. Limitations: A proportion of the eligible patients in the database could not be PS matched, persistence and adherence couldn't be evaluated for individual GLP-1 RAs.	Propensity score matching	Novo Nordisk A/S
Rea et al. 2021	Comparing medication persistence among patients with type 2 diabetes using sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists in real-world setting	Cohort study	T2DM patients 40 years or older who received at least one prescription of metformin between 2007 and 2015 and who initiated treatment with P1-RA or SGLT2-I and with a follow up period of 1 year after the index date defined as que date of the first prescription of the medication.	The study started with 473 121 patients on treatment with metformin between 2007 and 2015, but 126 493 were incident users. A total of 6977 individuals were included : 965 initiated GLP 1-RA and 3012 SGLT2-I. A 1:1 matched cohort design was adopted for each individual initiating GLP1-RA therapy, a patient starting SGLT2-I was randomly identified.	Adherence; Discontinuation	Discontinuation: if the gap between the end of one prescription and the beginning of the following one was >60 days. Adherence :PDC	Treatment discontinuation was higher with SGLT2I (28.8%) compared with GLP1-RA (24.1%). Individuals taking GLP1-RA had 15% (95% CI, 3% to 25%) lower risk of discontinuation of the treatment. PDCs in patients taking metformin and SGLT2 or GLP1-RA were 55%.	Strengths: Large sample size. Limitations: Discontinuation was estimated with drug prescriptions that can not guarantee a consumption of the medication by the patient.	Multivariate adjustment	Italian Ministry of the Education
Romagnoli et al. 2021	Drug utilisation pattern over 3 years in the real-world treatment of type II diabetes	Cohort study	Claims from pharmacy of the Hospital of Pescara from 1 January 2011 to December 2019.	Total of 19 600 patients. 14 211 were treated with MET, 1521 with GLP-1, 1754 with DPP4i, 1723 with alpha-glucosidase inhibitors, 839 with SGLT2i, 2597 with meglitinides, 1696 with MET + DPP4i, 650 with MET + TZD, 757 with MET + SGLT2i, 888 with MET + SLF, 4089 with SLF, 637 with TZD, 93 with TZD + DPP4i, 18 with TZD + SLF. 52% of patients were male, while the median age was 70 years.	Adherence; Persistence	Adherence: ratio between Received Daily Dose (RDD) and Prescribed Daily Dose (PDD). Persistence: difference in the number of days between the beginning and the end of the therapy. Failure to refill the drug after 60 days was classified as non-persistence.	Adherence (>0.8): MET 26%, GLP-1 99%, DPP4i 78%, alpha-glucosidase inhibitors 26%, SGLT2i 80%, Meglitinides 13%, MET + DPP4i 8%, MET + TZD 22%, MET + SLGT2i 6%, MET + SLF 30%, SLF 56%, TZD 72%, TZD + DPP4i 78%, TZD + SLF 78%. Persistence: not reported numerically	Limitation: overestimation of adherence due to study nature.	None	None
Unger et al. 2021	Maintenance of glycaemic control with liraglutide versus oral antidiabetic drugs as add-on therapies in patients with type 2 diabetes uncontrolled with metformin alone: A randomized clinical trial in primary care (LIRA-PRIME)	Randomised controlled trial	Adults (n = 1991) with T2D receiving metformin were randomized 1:1 to liraglutide (≤1.8 mg/d) or one OAD, selected by the investigator, added to metformin, for up to 104 weeks.	Total of 1991 patients (liraglutide, n = 996; OAD, n = 995), 47.6% were female, mean age was 57.4 years and mean HbA1c was 8.2%. OADs included glucosidase inhibitor, DPP-4i, meglitinide, SGLT-2i, SU, or thiazolidinedione.	Discontinuation	Discontinuation before finalisation of trial (104 weeks)	Premature treatment discontinuation: Liraglutide 80.4 weeks, OAD 52.3 weeks (p < .0001). SGLT-2i (52 weeks), DPP-4i (63 weeks), and SU (38 weeks)	Strengths: pragmatic design, large scale. Limitations: open-label nature, investigator selection of OADs, and external funding of treatment as potential sources of bias.	Randomisation and masking	None

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Vlacho et al. 2021	Analysis of the Adherence and Safety of Second Oral Glucose-Lowering Therapy in Routine Practice From the Mediterranean Area: A Retrospective Cohort Study	Cohort study	Data were obtained from the primary care SIDIAP database (The Information System for the development of Primary Care Research). Inclusion of subjects initiating add-on treatment with DPP-4i, SGLT-2i, or SU to metformin between January 1st, 2010, and December 31st, 2017.	Total of 75,808 subjects initiating a second antidiabetic drug in addition to metformin were included: 27,878 (36.7%) initiated a DPP-4i, 2,198 (2.89%) a SGLT-2i and 45,732 (60.3%) an SU.	Adherence; Persistence	Adherence: MPR >0.8 good adherence, <0.8 poor adherence. Persistence: time between index treatment initiation and the first discontinuation event (gap of 90 days).	MET+ DPP-4i: MPR>0.8 (53.6%); persistence Mean SD 372 MET+SGLT-2i: MPR>0.8 (68.7%); adjusted OR (98% CI) 1.72 p=0.017; persistence Mean SD 385 MET+ SU: MPR>0.8 (43%); adjusted OR (98% CI) 0.35- 0.59 p=0.017; persistence Mean SD 343	Strenghts: population-based cohort, long follow-up of two years, propensity matching and outcomes for adherence,persistence and adverse events. Limitations: study population is a highly selected sample which potentially diminishes the external validity.	Propensity score matching	AstraZeneca, Spain
Yen et al. 2021	Persons with type 2 diabetes and high insulin persistence were associated with a lower risk of mortality: A nationwide retrospective cohort study	Cohort study	Taiwan's NHI Research Database administrative data collected from 1 January 2000 to 31 December 2015. Included data of newly diagnosed type 2 diabetes mellitus patients in 2001–2014, with the age at diagnosis ≤90 years.	222,440 matched patients (111,220 in each cohort). The mean age was 62.8 and 62.6 years in patients with high and low insulin persistence, respectively.	Persistence	Persistence: continual insulin treatment without a 90- day discontinuation gap in the 2-year observation period. Days of persistence were measured as the number of days of continuous insulin treatment before a 90-day discontinuation gap. The degree of persistence was the number of persistent days divided by 730.	Cohort 1 (persistence > 90%): Metformin 81%, Sulfonylurea 82%, Meglitinide 20%, AGI 36%, TZD 38.7%, DPP-4i 23%, Basal Insulin 66.5%, Premixed insulin 40.7%, Fast acting insulin 20%. p<0.001 Cohort 2 (persistence >90%): Metformin 82.3%, Sulfonylurea 81.4%, Meglitinide 21%, AGI 33.8%, TZD 34.8%, DPP-4i 29.8%, Basal Insulin 70.8%, Premixed insulin 37.1%, Fast acting insulin 23.8%	Limitations: lack of information in database (lifestyle, blood test results). Insulin persistence did not represent injection persistence.	Propensity score matching	None
Cho et al. 2022	Long-term clinical outcomes of oral antidiabetic drugs as fixed-dose combinations: A nationwide retrospective cohort study	Cohort study	T2DM patients who initiated metformin or sulphonylurea from January 2002 to December 2013, from this cohort, individuals taking fixed-dose combination (FDC) or two-pill combination (TPC)of MET+SU and MET+DPP4i were included in the study.	From 195 691 patients with T2DM, 10 973 and 5143 were taking TPC and FDC respectively, after propensity score matching 5143 pairs were included.	Adherence; Persistence	Adherence: PDC. Persistence: period of time from the index date until evidence of discontinuation (absence of a refill prescription within 150% of the previous prescription supply). Adherence and Persistence were obtained at 12 and 24 months.	Persistence rate at 12 months for MET + DPP4i were: TPC (47.35%) and FDC (42.7%) while for MET + SU were: TPC (30%) and FDC (32.5%). The mean PDC for MET + DPP4i at 12 months was: 70% for TPC and 69% for FDC while for MET + SU was: 54% for TPC and 56% for FDC. Overall persistence and adherence at 12 and 24 months were higher with FDC compared with TPC.	Limitations: Potential confounders were assessed, however, HbA1c levels, stress and family history of chronic diseases, were unavailable for assessment from the NHIS-NSC database.	Propensity score matching	Ministry of Food and Drug Safety of South Korea.
Edelman et al. 2022	Treatment persistence and adherence in people with type 2 diabetes switching to iGlarLixi vs free-dose combinations of basal insulin and glucagon-like peptide 1 receptor agonist	Cohort study	US Optum Clinformatics (January 2017 to November 2019) database and included data from adults (aged≥18 years) with type 2 diabetes and a glycated hemoglobin A1c (A1c) of 8% or more.	After propensity score matching, there were 1,357 patients in each group (iGlarLixi and free-dose combination of a GLP-1 RA and BI). In the free-dose combination group, 65.6% started on BI, then added GLP-1 RAs; 28.5% started on GLP-1 RAs, then added BI; and 5.9% started on GLP-1 RAs and BI on the same day.	Adherence; Persistence	Persistence: number of days of continuous therapy from the point of initiation until the end of 12 months of follow-up. Maximum gap of 45 days was allowed. Adherence: PDC>/= 80%	Persistence: iGlarLixi 44.8% and 150 (63, 360) median number of persistent days, free-dose combinations 36.3% and 120 (60, 310) median number of persistent days. Hazard ratio=1.22, 95% CI=1.11-1.35; P<0.001 Adherence: iGlarLixi 41.3% and median number of adherent days of 200.Free-dose combinations 18.7% and median number of adherent days of 99. Odds ratio=3.06, 95% CI=2.57-3.65; P<0.001.	Strengths: large population with long-term follow-up and breadth of coverage, resulting in considerable statistical power. Limitations: Data provided from clinical practice database resulting in possible bias for research purposes. Generalisability may be limited.	Propensity score matching	Sanofi US
Lajara et al. 2022	iGlarLixi versus premixed insulin initiation in adults with type 2 diabetes advancing from basal insulin therapy: The SoliComplex real-world study	Cohort study	Data from adults (age ≥ 18 years) with T2D in the US Optum Clinformatics database who had previously received basal insulin and newly initiated iGlarLixi or premixed insulin from 1 January 2017 to 30 June 2020.	1082 (iGlarLixi) and 1786 (premixed insulin) patients were propensity-score matched, yielding groups each comprising 834 participants with a mean age of approximately 65 years.	Adherence; Persistence	Persistence at 12 months: no discontinuation (gap > 45 days) of the index treatment until the end of the follow-up period. Adherence: PDC > 80%	Persistence: iGlarLixi 42.5%, pre mixed insulin 39.1%. Adherence: iGlarLixi 41.4%, premixed insulin 38.0%.Mean (SD) number of days covered of 232 (107.9) for iGlarLixi and 216 (117.4) for premixed insulin.	Strengths: large sample and coverage, strong statistical power. Limitations: size of propensity score matched cohort.	Propensity score matching.	Sanofi
Mody et al. 2022	Greater Adherence and Persistence with Injectable Dulaglutide Compared with Injectable Semaglutide at 1-Year Follow-up: Data from US Clinical Practice	Cohort study	Administrative claims data from three IBM MarketScan research databases. Data from adult patients with type 2 diabetes newly initiating treatment with dulaglutide or semaglutide between January 2018 and January 2020.	Prior to propensity-score matching, 48,113 and 32,308 dulaglutide initiators were assigned to 6M and 12M cohorts, respectively, and 26,284 and 13,837 semaglutide initiators for the 6M and 12M cohorts. After matching, the 6M cohort included 26,284 pairs and the 12M cohort included 13,837 pairs. Mean age was 53 years, and 50% of patients were women.	Adherence; Persistence	Adherence: PDC >/= 80% Persistence: lack of any treatment gap of ≥45 days	Adherence: PDC >80% (dulaglutide 63.4% for 6 months cohort, 54.4% for 12 month cohort). (semaglutide 47.8% for 6 months, 43.3% for 12 months). p<0.0001 Persistence: dulaglutide 71.9% for 6 months and 62.2% for 12 months, semaglutide 55.5% for 6 months and 45.3% for 12 months. P < 0.0001	Strengths: similar follow-up times across cohorts, and all patients had data available from follow-up times sufficient for the event of interest (discontinuation) to have occurred, large sample sizes. Limitations: potential for bias exists due to unmeasured confounders.	Propensity score matching	None
Prázný et al. 2022	Real-world characteristics, modern antidiabetic treatment patterns, and comorbidities of patients with type 2 diabetes in central and Eastern Europe: retrospective cross-sectional and longitudinal evaluations in the CORDIALLY® study	Cross sectional study	Data were retrospectively collated by medical chart review for patients initiating empagliflozin, another SGLT2i, DPP4i, or GLP-1 RA from September - December 2018 in Bulgaria, Czech Republic, Hungary, Poland, and Russia.	4055 total included patients. Medication percentages were: empagliflozin (48.5%), DPP4i (28.2%), other SLGT2i (14.4%), and GLP-1 RA (8.9%).	Discontinuation	Discontinuation at 1 year +/- 2 months of treatment.	Discontinuation: 7.9% for empagliflozin, 12.3% for DPP4i, 11.4% for GLP-1RA, 11.2% for other SGLT2i. Mean time to discontinuation was 14.0 months (SE 0.1) for other SGLT2i, 18.3 months (SE 0.4) for DPP4i, 19.5 months (SE 0.7) for empagliflozin, and 20.6 months (SE 0.6) for GLP-1 RA.	Strengths: sizeable population across 5 countries. Limitations: outcomes may have been affected by confounding factors (e.g. imbalanced patient enrolment per country, selection of primary reasons for discontinuation rather than being able to select more than one reason per patient)	None	Boehringer Ingelheim

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Silva-Tinoco et al. 2022	Adherence to antidiabetic treatment in primary health care in individuals with type 2 diabetes. A survey including socio-demographic, patient related and clinical factors	Cross sectional study	Patients receiving diabetes care in 18 primary care units in Mexico City between August 2019 and November 2021.	Total of 319 participants. 48.3% (n = 154) were adherent to their antidiabetic medication, mean age was 53.1 ± 12.9 years, 58.6% were fe-male. 256 were on metformin, 44 on sulphonylureas, 8 on pioglitazone, 54 on DP4 inhibitors and 192 on insulin.	Adherence	Adherence assessed with Morisky Green Levine (MGL) questionnaire. Score >3 classified as adherent.	Adherence: 81.5% for metformin (p=0.9) , 10.9% for sulphonylureas (p=0.112), 1.8% for pioglitazone (p=0.593) , 13.9% for DP4 inhibitors (p=0.09) , 67.8% for insulin (p=0.01).	Limitations: small sample size, self reported adherence	Multivariate adjustment for a broad range of confounders	None
Vlacho et al. 2022	Adherence to antidiabetic treatment among patients managed in primary care centres in Spain: the INTENSE study	Cross sectional study	Patients > 30 years old with a T2DM diagnosis for more than a year and in treatment with oral antidiabetic medication only. The individuals were recruited from primary care centers in Spain based on their disposition to participate as they arrived to the clinic	A total of 515 individuals were included in the study and population was divided in 2 groups: good adherence and poor adherence, mean age in both groups was 65.7 ± 10.6 and 64.6 ± 9.9 respectively, the majority were male (60% and 56.5%) and had hypertension (70.8% and 72.5%).	Adherence	Adherence :PDC> 80%	Adherence: metformin 67.3% (p=0.27) DPP-4 54.6% (p=0.88), SGLT2i 15.4% (p=0.006), SU 5.8% (p=0.44), glinides 4.2% (p>0.99), GLP1-RA 3.1% (p<0.001) and TZDs 0.8% (>0.99). The mean PDC by medication class was: 75 (SU), 73.5 (metformin), 70.7 (DPP4i), 68.7 (SGLT2i), 64.6 (glinides), 59.5 (TZDs) and 8.2 (GLP 1-RA). Adjusted OR for poor adherence (PDC<80%) was 4.94 (95% CI: 2.17-11.21) for GLP 1-RA and 1.82 (95% CI: 1.15-2.89) for SGLT2i.	Strengths: Investigation of factors related to adherence which included mental illnesses, patient age, sex and adverse events. The study calculated the Adjusted Odds Ratios for poor adherence according the variables related.	Multivariate adjustment for a broad range of confounders	RedGDPS Foundation and Almirall, S.A.
Wright et al. 2022	Real-world persistence, adherence, health care resource utilization, and costs in people with type 2 diabetes switching from a first-generation basal insulin to a second-generation (insulin glargine 300 U/mL) vs an alternative first-generation basal insulin	Cohort study	Optum Clinformatics claims data from adults with T2D who had received BI (neutral protamine Hagedorn, Gla-100, IDet) in the 6-month baseline period, and switched to either Gla-300 or an alternative first-generation BI (Gla-100 or IDet; treatment switch=index date) between April 1, 2015, and August 31, 2019.	Propensity score matching generated 3,077 participants for each group (mean age: 68 years, 52% female). At baseline, 51.3% were receiving Gla-100, 42.8% IDet, and 5.9% were receiving NPH.	Adherence; Persistence	Persistence: no discontinuation of the index BI until the end of the 12 month follow-up period. Adherence: PDC> 80%	Persistence: Insulin glargine 300 U/mL 45.5%, mean (SD) number of persistent days was 234.6 (130.1); 1st gen BI (neutral protamine Hagedorn, insulin glargine 100 U/mL or insulin detemir 100 U/mL) 42.1%, mean (SD) number of persistent days was 218.7 (131.9) p=0.0001 Adherence: Insulin glargine 300 U/mL 42.8%, mean (SD) number of adherent days was 214.5 (111.1); 1st gen BI 38.2%, mean (SD) number of adherent days was 194.5 (112.6). p=0.0006	Strengths: large population with long-term follow-up provided considerable statistical power. Limitations: those common to administrative claims database studies, assessment of persistence with injectable therapies using claims data is challenging as the dosing schedules are not fixed, and the rules routinely used to measure persistence with oral therapies, cannot be applied	Propensity score matching	Sanofi US.
Alkabbani et al. 2023	Post-initiation predictors of discontinuation of the sodium-glucose cotransporter-2 inhibitors: A comparative cohort study from the United Kingdom	Cohort study	Data from the UK Clinical Practice Research Datalink (CPRD) with linked data to hospital and death records. Study included newmetformin users who initiated either SGLT2 inhibitors or DPP-4 inhibitors between January 2013 and October 2019.	There were 2550 users of SGLT2 inhibitors and 8195 new users of DPP-4 inhibitors. Users of SGLT2 inhibitors were younger (mean [SD] age 56.5[10.45] years) compared to new users of DPP-4 inhibitors (63.12 [12.60]).	Discontinuation	Discontinuation (non persistence): first 90-day gap after the estimated treatment end date.	Discontinuation: 69% for SGLT2 inhibitor and 74% of DPP-4 inhibitors. Median time to discontinuation in years: 1.51 (95% CI 1.40-1.60) for SGLT2 inhibitor users and 1.39 (95% CI 1.34-1.46) for DPP-4 inhibitor users.	Limitations: study based on prescribing record data, prescriptions from specialist were not included, residual confounding	Inverse probability of treatment weighting based on the high-dimensional propensity score.	Canadian Institute of Health Research
Cherupally et al. 2023	Treatment Modification After Initiating Second-Line Medication for Type 2 Diabetes	Cohort study	T2DM patients >18 years old from the US who initiated a second-line hypoglycemic medication between January 2014 and June 2017 and had a continuous enrollment for 12 months were included in this study.	A total of 82 624 individuals were included, from these 51% received sulfonylurea as index medication followed by DPP4is (24%), SGLT2is (11.6%), GLP-1 RAs (8.1%), and TZDs (5.3%). More than half of the cohort were men (54.0%) and had no diabetes complications (61.5%).	Discontinuation	Discontinuation: lack of refilling the index medication or initiate a new drug from another class within 60 days.	Discontinuation was most common with GLP-1 RA (50.3%) followed by DPP4i (39.5%), SGLT1i (39.4%), sulfonylurea (36.6%) and TZD (34.2%). After adjusting for risk of discontinuation, this was 7% higher (HR, 1.07; 95% CI, 1.04-1.10) among patients initially prescribed DPP4is and 28% higher (HR, 1.28; 95% CI, 1.23-1.33) among patients initially prescribed GLP-1 RAs.	Strengths: Confounding was assessed with several covariates. Limitations: Reasons for discontinuing medication were not mentioned.	Multivariate adjustment for a broad range of confounders	Northwestern University from UnitedHealth Group.
Damachi et al. 2023	Comparing Adherence in Patients with Type 2 Diabetes Initiating Glucagon-like Peptide-1 Receptor Agonists or Sodium-Glucose Cotransporter-2 Inhibitors	Cohort study	T2DM patients who were new users of GLP-1 and SGLT2 without previous use of the index medication in the past 6 months and with a continuous enrollment from January 2013 to December 2019.	A total of 10 307 individuals were included in this study, from these, 5218 were SGLT2i users and 5089 GLP 1 RA users. Most of the population in both SGLT2i and GLP 1 RA groups were 45-54 years old, (37% and 33.3%). The 57.1% of the SGLT2i cohort was male and 53.3% of the GLP 1 RA cohort was female .	Adherence	Adherence: PDC ≥80% within a period of 270 days of follow up.	The mean PDC was 0.80 with SGLT2I and 0.75 with GLP-1 agonists. Adherence rates (PDC>80%) were: 65.5% (p<0.01) for SGLT2i and 57.7% (p<0.01) for GLP-1 agonists during a 9 month follow up period. Adjusted OR for adherence was: SGLT1i (OR=1.36; 95% CI: 1.24-1.49) with p< 0.01, baseline insulin use (OR=0.91; 95% CI: 0.83-1.02) with p= 0.10 and baseline DPP4 use (OR= 1.51; 95% CI: 1.36-1.68) with p<0.01.	Strengths: Confounding was assessed by obtaining adjusted odds ratio for adherence in both SGLT2i and GLP 1 RA groups. Limitations: There is not any mention of association between glycemic control and the adherence.	Logistic regression model .	None

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Edelman et al. 2023	Real-World Persistence, Adherence, Hypoglycemia, and Health Care Resource Utilization in People With Type 2 Diabetes Who Continued With the Second-Generation Basal Insulin Analog Insulin Glargine 300 Units/mL or Switched to a First-Generation Basal Insulin (Insulin Glargine 100 Units/mL or Detemir 100)	Cohort study	US Optum Clinformatics Data Mart with Socio-Economic Status database and included data from adults with type 2 diabetes receiving the second-generation BI Gla-300 and either continued treatment or switched to a first-generation BI between 1 January 2016 and 30 April 2021.	After PSM, there were 1,104 participants in each group (Gla-300 and first-generation BI). The mean ages were 67.9 and 67.2 years, respectively, with 50.3 and 51.9% of females in each group.	Adherence; Persistence	Persistence: no discontinuation of the index treatment until the end of the follow-up period (12 month). Adherence: PDC>80%	Persistence: Gla-300 64.6 % mean (SD) number of persistent days was 237 (130.7); First-generation BI 44.1% mean (SD) number of persistent days was 191 (138.6); hazard ratio [HR] 0.59, 95% CI 0.52–0.68). Adherence: Gla-300 34.1 %, mean (SD) number of adherent days was 214 (115.1); first-generation BI 32.3%, mean (SD) number of adherent days 192 (125.65) ; odds ratio 0.91, 95% CI 0.76–1.10).	Strengths: large population with long term follow up Limitations: generalisability may be limited, bias due to lack of randomization	Propensity score–matching	Sanofi US
Ekenberg et al. 2023	Socioeconomic factors associated with poor medication adherence in patients with type 2 diabetes	Cohort study	T2DM patients >18 year old from primary healthcare centers in Uppsala, Sweden who took hypoglicemic agents between January 2012 to December 2019.	A total of 8515 patients were included in this study, from these, 77.2% were prescribed metformin, (9.1%) insulins, (8.4%) other antidiabetic monotherapy and (5.4%) polytherapy. The mean age of the population was 59.8 SD=15.2, the majority were male, had secondary education (44.4%), has hypertension (47%) and were retired (49.1%).	Persistence; Other	Persistence: period of time after initiation in which patients continued the medication prescription and nonpersistence as the discontinuation of medication within 3 months before and after the endpoint of 12 (P12) months and 24 months (P24) after the first dispensing date.	The persistence rates at 12 months were 71.7% for metformin, 64.9 for other monotherapy, 42.1 for polytherapy, and 28% for insulins. At 24 months persistence percentages were: 67.2% for metformin, 41.1% for other monotherapy, 34.9% for polytherapy and 22.2% for insulins.	Strengths: Persistence was measured at two points which can estimate the proportion of patients who were persistent at medium and long term. The effect of variables like age, education level, unemployment among others was assessed with logistic regression.	Multivariate adjustment for a broad range of confounders	Uppsala University.
Essien et al. 2023	Association of Prescription Co-payment With Adherence to Glucagon-Like Peptide-1 Receptor Agonist and Sodium-Glucose Cotransporter-2 Inhibitor Therapies in Patients With Heart Failure and Diabetes	Cohort study	Optum Insight's Clinformatics Data Mart Database of enrollees with commercial and Medicare health insurance plans. Individuals aged 18 years or older with T2D and/or HF who had a prescription claim for a GLP1-RA or SLGT2i from January 1, 2014, to September 30, 2020,	94 610 individuals (mean [SD] age, 61.8 [11.4] years; 51 226 [54.1%] male). 39149 were prescribed GLP1-RA and 50892 SGLT2i therapy.	Adherence	PDC >/= 80%	Adherence rates: GLP1-RA: 71.9%, 65.7%, 59.8% (P<0.001) respectively for low, medium and high copayment. SGLT2i: 77.1%, 71.5%, 73%(P<0.001) respectively for low, medium and high copayment. Combination: 78.7%, 74.8%, 68.7% (P<0.001) respectively for low, medium and high copayment.	Strenghts: results strengthened by broad adjustment for social and ecumenic variables, large and nationally representative sample of insured individuals. Limitations: inability to exclude residual confounding from any unmeasured individual-level social factors.	Multivariate adjustment.	Magnani
Giorgino et al. 2023	The real-world observational prospective study of health outcomes with dulaglutide and liraglutide in patients with type 2 diabetes (TROPHIES): Final, 24-month analysis of time to first significant treatment change, treatment persistence and clinical outcomes.	Cohort study	T2DM patients >18 years old, who initiated dulaglutide or liraglutide as their first injectable drug, from France, Germany and Italy between July 2017 and May 2019.	A total of 2005 individuals were included at the final sample, from these 1014 were on dulaglutide and 991 on liraglutide; the mean age was 59.2 years, more than half were male (56.4%) and predominantly obese with a mean BMI of 33.8kg/m2.	Persistence; Discontinuation	Persistence: period of time with the medication until discontinuation. Discontinuation: proportion of patients who stop taking dulaglutide or liraglutide or switching to insulin, oral GLM or another GLP-1 RA.	Kaplan-Meier analysis showed higher probabilities of persistence at 24 months with both dulaglutide 0.82 (0.80-0.85) and liraglutide 0.75 (0.72-0.78). Discontinuation rates were higher with liraglutide (23.9%) compared with dulaglutide (17.3%). Main causes of discontinuation were: tolerability (dulaglutide: 6.7%, liraglutide: 7.1%), glycaemic control (2.4%, 5.2%) and patient decision (2.1%, 2.4%).	Strengths: Confounding factors were evaluated. Limitations: There were fewer patients with information available at the end of follow-up compared to the beginning of the study in both groups.	Inverse probability of treatment weighting (IPTW) using propensity score matching.	Eli Lilly and Company.
Ouchi et al. 2023	Impact of Second-Line Combination Treatment for Type 2 Diabetes Mellitus on Disease Control: A Population-Based Cohort Study	Cohort study	Patients with T2DM diagnosis who initiated metformin monotherapy followed by a combination therapy and had prescriptions for this medication between 2015 and 2020 in Catalonia, Spain.	A total of 43 068 patients started metformin treatment, from these 28,425 individuals had an addition of a combination therapy and met the inclusion criteria.	Adherence	Adherence :MPR >80% .	The highest mean MPR was found with th metformin + DPP4i combination (92.23%) and the lowest with metformin + insulin (70.17%). The rates of adherence (MPR ≥80%) by each therapy combination were: metformin + DPP4i (87.8%), metformin + SGLT2i (77.2%), metformin + SU (76.7%), metformin + others (71.3%), metformin + GLP1 (70.3%) and metformin + insulin (48.8%).	Strengths: Large study sample with complete sociodemographic characteristics and a report of adherence rates by each medication, effect of adherence on HbA1c control was measured among all combinations comparing adherent versus non-adherent patients. Limitations:There was not adjustment for confounding.	None.	None.
Palanca et al. 2023	Real-World Evaluation of GLP-1 Receptor Agonist Therapy Persistence, Adherence and Therapeutic Inertia Among Obese Adults with Type 2 Diabetes	Cohort study	T2DM patients >18 years old from the Department of Health of Valencia Clínico Malvarrosa who were taking hypoglycemic agents and with at least one prescription of medication between January 2014 to December 2019 were included in the study.	A total of 26,944 T2DM patients met the inclusion criteria, from these, 1848 were on GLP-1RA, 5034 were on SGLT2i, 4813 on insulin and 15,249 were miscellany users. Gender, age, preexisting cardiovascular disease and heart failure were significantly different among groups. After propensity score matching all drug classes groups had 1848 users.	Adherence; Persistence	Adherence :PDC >80%. Persistence:proportion of individuals who continue therapy until evidence of discontinuation. Adherence and Persistence was obtained for 1 and 2 years.	Persistence rated at 1 year by each medication class were: GLP-1 RA (81.5%), SGLT2i (81%), miscellany (25.2%) and insulin (25.1%) while at 2 year was: SGLT2i (77.2%), miscellany (73.9%), SGLT2i (60.3%) and GLP-1 RA (45.5%). Adherence rates were higher in insulin (90.2%) followed by GLP-1 RA (73.8%), SGLT2i (65.5%) and miscellany (51.1%).	Strengths:Clinical outcomes like death, heart failure, hospitalization, severe hypoglycaemia requiring hospitalization and reduction in HbA1c were assessed with the medication used. A propensity score matching and logistic regression model were developed. Limitations: There was no available information to explain possible reasons for treatment discontinuation and low medication adherence.	Propensity score matching	Novo Nordisk.

Anexo 2 (Continuación)

Author - year	Study Title	Study design	Population	Sample size and characteristics	Measure of adherence or persistence	Description of measurement	Study results	Strengths and Limitations	Adjustment for confounding	Funding sources
Pantalone et al. 2023	Initiation of iGlarLixi Versus Basal-Bolus Insulin in Adults With Type 2 Diabetes Advancing From Basal Insulin Therapy: The SoliComplex Real-World Study	Cohort study	U.S. Optum Clinformatics claims database with data from adults with type 2 diabetes who previously received basal insulin and were newly initiated on iGlarLixi or basal-bolus insulin between 1 January 2017 and 30 June 2020.	After propensity score matching, there were 1,070 participants in each group (iGlarLixi and basal-bolus insulin). The mean age was 64 years. Insulin used in the iGlarLixi grupo was: NPH 1.5%; Insulin glargine 100 units/L 51.7%; Insulin glargine 300 units/mL 17.2%; Insulin detemir 24%; Insulin degludec 100 or 200 units/mL 9.3%. Insulin used in the basal bolus group was: NPH 1.2%; Insulin glargine 100 units/L 52.1%; Insulin glargine 300 units/mL 17%; Insulin detemir 24.1%; Insulin degludec 100 or 200 units/mL 9.6%.	Adherence; Persistence	Persistence at 12 months: No discontinuation (gap<45 days) of the index treatment until the end of the follow-up period. Adherence: PDC >/= 80%	Persistence: iGlarLixi 43.7% (mean number of persistent days was 216 ± 4.3) and basal-bolus insulin 22.3% (mean number of persistent days 142 ± 3.9) . Adjusted HR 0.51, 95% CI 0.46–0.57, adjusted P <0.001) Adherence: iGlarLixi 42.1% (mean number of days was 236 ± 107.1); basal-bolus insulin 15.4% (mean number of days was 147 ± 110.7); adjusted OR 4.00, 95% CI 3.25–4.91).	Strengths: large population, propensity score matching. Limitations: those common to administrative claims database study, sampling bias or confounding bias by indication and changes in practice and/or disease biology, generalisability may be limited to populations of the Optum Clinformatics database.	Propensity score matching	Sanofi
Sim et al. 2023	Impact of COVID-19 Lockdown on Glycemic, Weight, Blood Pressure Control and Medication Adherence in Patients with Type 2 Diabetes	Cohort study	T2DM patients >18 years who took hypoglycemic agents such as metformin, insulin, sulfonylureas, DPP4i, SGLT2i and statins between January 2012 and December 2020 during COVOD-19 pandemic in Malaysia.	A total of 1985 patients were included in this study. Most of patients were taking metformin (74.8%), followed by insulin (61%), DPP4i (56.3%), sulfonylureas (29.2%), SGLT2i (20.9%), and GLP 1-RA (0.9%).	Adherence	Adherence:PDC ≥0.8 .	There was a higher adherence to medication on the post-index date compared with pre-index period: metformin (PDC 0.985 vs 0.978,), sulfonylureas (PDC 0.988 vs 0.979), DPP4i (PDC 0.987 vs 0.98).	Strengths: Differences in HbA1c, weight and systolic Blood pressure values pre- and post-Index date were obtained and analysed. Limitations: The study was conducted in tertiary hospitals so findings may not represent primary care level. Unmeasured confounding bias may exist.	None.	None.
Zamanillo-Campos et al. 2023	Non-adherence to non-insulin glucose-lowering drugs: Prevalence, predictors and impact on glycemic control and insulin initiation. A longitudinal cohort study in a large primary care database in Spain	Cohort study	Data extracted from the electronic health records of the Balearic Islands (Spain) between 2016 and 2018.	Sample of 18,119 patients.The mean (SD) age was 63.44 (12.54) and 40.53% were female. The number of patients taking each medication were the following: Biguanides 6,774; Sulfonylureas 1,320; DPP4i 2,263; GLP-1 555; SGLT2i 1,721;Combination biguanides and DPP4i 3,273; Combination biguanides and SGLT2i 1,545.	Non adherence	Non-adherence: MPR <80%	Biguanides:84 (58.14–95.64) MPR, median (IQR) ; 73.83 (26.84) MPR, mean (SD) ; (44.63) MPR <80% Sulfonylurea: 95.12 (80.55–99.21) MPR, median (IQR) ; 85.28 (21.44) MPR, mean (SD) ; (27.77) MPR <80% DPP4 inhibitors: 96.73 (87.75–99.73) MPR, median (IQR) ; 87.91 (20.57) MPR, mean (SD) ; (17.63) MPR <80% GLP-1 analogues: 95.71 (85.71–100) MPR, median (IQR) ; 87.65 (19.69) MPR, mean (SD) ; (17.12) MPR <80% SGLT2 inhibitors: 95.28 (83.67–99.18) MPR, median (IQR) ; 86.03 (21.31) MPR, mean (SD) ; (21.67) MPR <80% Combination biguanides and DPP4: 93.26 (77.12–98.66) MPR, median (IQR) ; 83.54 (21.86) MPR, mean (SD) ; (27.86) MPR <80% Combination biguanides and SGLT2: 93.59 (80.32–98.44) MPR, median (IQR) ; 84.79 (20.61) MPR, mean (SD) ; (24.85) MPR <80%	Strengths: representative population from a validated database and robust analytic methods Limitations:secondary to MPR measurement, patients not identified by diagnosis code.	Multivariate adjustment for a broad range of confounders.	Ministerio de Ciencia, Innovacion y Universidades and co-funded by the European Regional Development Fund

Anexo 3. Evaluación de calidad de los estudios

Tabla 1. Calidad de los ensayos clínicos aleatorizados mediante la herramienta Cochrane de evaluación del riesgo de sesgo

	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Barnett et al. 2007	L	H	H	H	L	?	L
Holman et al. 2007	L	H	H	H	L	L	L
Bergenstal et al. 2009	L	H	H	H	L	L	L
Garber et al. 2009	L	L	L	L	L	L	L
Russell-Jones et al. 2009	L	H	H	H	L	L	L
Diamant et al. 2010	L	H	H	H	L	L	L
Filozof et al. 2010	?	?	L	L	L	?	L
Göke et al. 2010	L	L	L	L	L	L	L
Gallwitz et al.2011	?	H	H	H	?	L	L
Davies et al. 2013	?	H	H	H	L	L	L
Hauck et al. 2014	L	L	L	L	L	L	L
Capehorn et al. 2019	L	H	H	H	L	?	?
Lingvay et al. 2019	L	L	L	L	L	L	L
Patel et al. 2019	L	h	h	?	?	L	?
Pishdad et al. 2020	?	L	L	L	L	L	?
Unger et al. 2021	L	H	H	?	L	L	?

Nota: L - Bajo riesgo de sesgo; ? - Riesgo de sesgo desconocido; H - Riesgo de sesgo alto.

Tabla 2. Calidad de los estudios observacionales evaluados mediante la escala Newcastle-Ottawa.

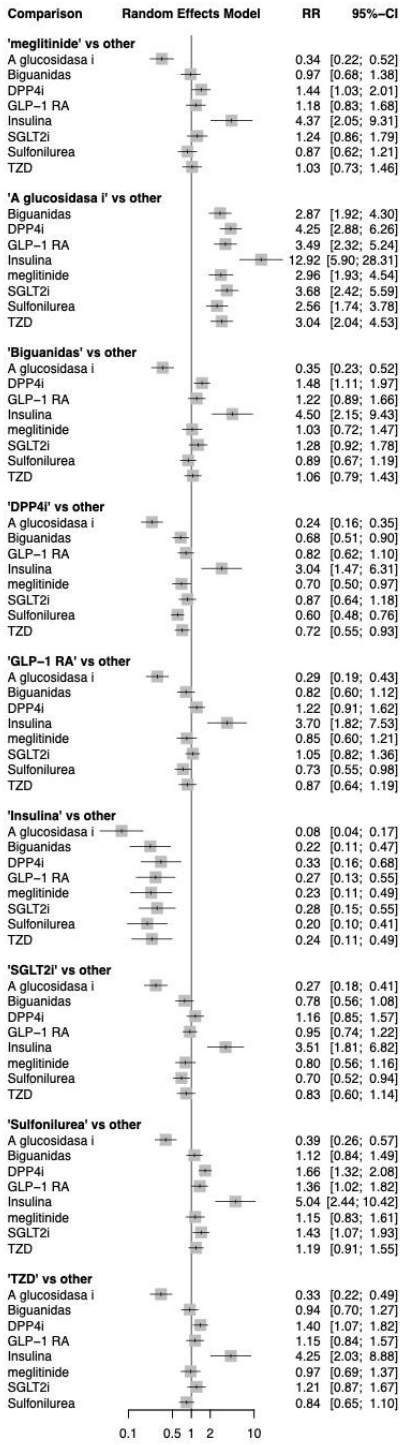
Study	Selection (4 max)	Comparability (2 max)	Outcome (3 max)	Total (9 max)
Al-Arouj et al. 2013	2	0	2	4
Balkrishnan et al.2006	4	0	3	7
Cai, et al. 2016	4	1	2	7
Nguyen, et al. 2016	4	1	2	7
Barner et al. 2011	4	0	3	7
Calip et al. 2015	2	0	3	5
Tan, et al. 2016	3	1	3	7
Divino, et al. 2017	4	0	2	6
Chong et al. 2014	3	1	3	7
Corrao et al. 2011	4	0	3	7
Degli Esposti et al. 2014	4	2	3	9
Svensson, et al. 2020	4	2	2	8
Farr et al. 2014	4	2	3	9
Linnemann Jensen, et al. 2017	4	2	3	9
Farsaei et al. 2011	3	0	3	6
Grimes et al. 2015	4	2	3	9
Hanif et al. 2013	2	0	2	4
Wu, et al. 2017	2	0	1	3
Abitbol, et al. 2021	4	0	2	6
Luo, et al. 2021	4	0	2	6
Hansen et al. 2010	3	0	3	6
Haupt et al. 2009	3	0	3	6
Jermendy et al. 2012	4	0	3	7
Patel et al. 2009	2	1	2	5
Plat et al. 2009	4	0	3	7
Quillam et al. 2013	4	0	3	7
Rathmann et al. 2013	4	2	3	9
Rozenfeld et al. 2008	4	0	3	7
Ekenberg, et al. 2023	4	2	2	8
Zhang, et al. 2020	4	2	3	9
Shenolikar et al. 2006	4	1	3	8
Valensi et al. 2014	3	2	3	9
Kadowaki, et al. 2018	4	0	1	5
White et al. 2012	3	0	3	6
Curkendall et al. 2013	4	2	1	7

Montilla et al. 2014	3	0	3	6
Singhal, et al.2019	4	2	3	9
Baser et al. 2011	4	2	3	9
Baser et al. 2013	4	2	3	9
Bonafede et al. 2011	4	2	3	9
Buysman et al. 2011	4	2	3	9
Juste, et al. 2020	4	2	2	8
Cooke et al. 2010	4	2	3	9
Fabunmi et al. 2009	4	0	3	7
Gordon et al. 2010	4	0	3	7
Levin et al. 2012	4	1	3	8
Peper, et al. 2017	4	2	2	8
Miao et al. 2013	4	2	3	9
Pawaskar et al. 2013	4	2	3	9
Pscherer et al. 2015	4	2	3	9
Quinzler et al. 2012	4	1	3	8
Wang et al. 2013	4	2	3	9
Deval Gor, et al. 2020	3	1	2	6
Oh, et al.2020	4	2	2	8
Luo, et al. 2021	4	2	2	8
Romagnoli, et al. 2021	4	0	2	6
Hassoun, et al. 2016	2	0	3	5

Nota: se tomó una muestra aleatoria representativa del 60% de los estudios observacionales para la evaluación de la calidad.

Anexo 4. Resultados metaanálisis 1

Figura 1. Forest plot de no-adherencia (insulina incluida)



Anexo 5. Metaanálisis 2

- Número de estudios: k = 15
- Número de comparaciones por pares: m = 88
- Número de observaciones: o = 727661
- Número de tratamientos: n = 8
- Número de diseños: d = 10

Modelo de efectos aleatorios

Tabla 3. Estimación del tratamiento ('RR', comparación: otros tratamientos frente a 'Sulfonilurea')

	RR	95%-CI	z	p-value
A glucosidasa i	25.632	[1.7398; 3.7764]	4.76	< 0.0001
Biguanidas	0.8931	[0.6718; 1.1875]	-0.78	0.4368
DPP4i	0.6035	[0.4800; 0.7587]	-4.32	< 0.0001
GLP-1 RA	0.7345	[0.5499; 0.9810]	-2.09	0.0366
meglitinide	0.8668	[0.6208; 1.2104]	-0.84	0.4015
SGLT2i	0.6970	[0.5188; 0.9366]	-2.39	0.0166
TZD	0.8426	[0.6460; 1.0989]	-1.26	0.2062

Cuantificación de la heterogeneidad / inconsistencia: tau^2, = 0,1089; tau = 0,3301; I^2 = 99,6% [99,5%; 99,6%].

Tabla 4. Pruebas de heterogeneidad

	Q	d.f.	p-value
Total	6207.01	27	0
Within designs	2022.63	5	0
Between designs	4184.39	22	0

Tabla 5. Datos originales (con errores estándar ajustados para los estudios multibrazo)

Medication 1	Medication 2	TE	seTE	seTE.adj	n=arms	multiarm
GLP-1 RA	meglitinide	-24.937	0.2605	0.9521	8	*
meglitinide	SGLT2i	-0.5032	0.0869	0.6701	8	*
Biguanidas	meglitinide	18.103	0.0531	0.6428	8	*
DPP4i	meglitinide	0.5976	0.0694	0.6544	8	*
A glucosidasa i	meglitinide	18.103	0.0548	0.6438	8	*
meglitinide	TZD	-0.8365	0.0827	0.6661	8	*
meglitinide	Sulfonilurea	-12.905	0.0557	0.6445	8	*
GLP-1 RA	SGLT2i	-29.969	0.2643	0.9683	8	*
Biguanidas	GLP-1 RA	43.041	0.2552	0.9288	8	*
DPP4i	GLP-1 RA	30.914	0.2591	0.9456	8	*
A glucosidasa i	GLP-1 RA	43.040	0.2555	0.9303	8	*
GLP-1 RA	TZD	-33.302	0.2629	0.9624	8	*
GLP-1 RA	Sulfonilurea	-37.842	0.2557	0.9312	8	*
Biguanidas	SGLT2i	13.071	0.0692	0.6537	8	*
DPP4i	SGLT2i	0.0944	0.0823	0.6656	8	*
A glucosidasa i	SGLT2i	13.071	0.0705	0.6548	8	*
SGLT2i	TZD	-0.3333	0.0939	0.6774	8	*
SGLT2i	Sulfonilurea	-0.7873	0.0712	0.6554	8	*
Biguanidas	DPP4i	12.127	0.0452	0.6384	8	*
A glucosidasa i	Biguanidas	-0.0000	0.0151	0.6281	8	*
Biguanidas	TZD	0.9739	0.0638	0.6498	8	*
Biguanidas	Sulfonilurea	0.5199	0.0183	0.6287	8	*
A glucosidasa i	DPP4i	12.127	0.0472	0.6395	8	*
DPP4i	TZD	-0.2388	0.0779	0.6616	8	*
DPP4i	Sulfonilurea	-0.6928	0.0483	0.6401	8	*
A glucosidasa i	TZD	0.9739	0.0652	0.6508	8	*
A glucosidasa i	Sulfonilurea	0.5199	0.0227	0.6297	8	*
Sulfonilurea	TZD	0.4540	0.0660	0.6515	8	*
GLP-1 RA	meglitinide	0.0174	0.0518	0.6197	7	*
meglitinide	SGLT2i	0.1243	0.0618	0.6260	7	*
Biguanidas	meglitinide	-10.719	0.0907	0.6501	7	*
DPP4i	meglitinide	-0.7494	0.0796	0.6399	7	*
meglitinide	TZD	-0.0418	0.0457	0.6163	7	*
meglitinide	Sulfonilurea	0.0179	0.0622	0.6263	7	*
GLP-1 RA	SGLT2i	0.1418	0.0482	0.6177	7	*
Biguanidas	GLP-1 RA	-10.893	0.0820	0.6415	7	*
DPP4i	GLP-1 RA	-0.7669	0.0696	0.6314	7	*

GLP-1 RA	TZD	-0.0244	0.0244	0.6081	7	*
GLP-1 RA	Sulfonilurea	0.0353	0.0488	0.6180	7	*
Biguanidas	SGLT2i	-0.9475	0.0887	0.6480	7	*
DPP4i	SGLT2i	-0.6251	0.0774	0.6379	7	*
SGLT2i	TZD	-0.1662	0.0416	0.6144	7	*
SGLT2i	Sulfonilurea	-0.1065	0.0593	0.6244	7	*
Biguanidas	DPP4i	-0.3224	0.1019	0.6624	7	*
Biguanidas	TZD	-11.137	0.0783	0.6380	7	*
Biguanidas	Sulfonilurea	-10.540	0.0890	0.6484	7	*
DPP4i	TZD	-0.7913	0.0652	0.6280	7	*
DPP4i	Sulfonilurea	-0.7316	0.0777	0.6382	7	*
Sulfonilurea	TZD	-0.0597	0.0422	0.6147	7	*
GLP-1 RA	meglitinide	-0.0285	0.0590	0.6325	7	*
Biguanidas	meglitinide	-0.6208	0.0441	0.6237	7	*
DPP4i	meglitinide	-10.793	0.0553	0.6301	7	*
A glucosidasa i	meglitinide	0.5409	0.0532	0.6288	7	*
meglitinide	TZD	0.8715	0.0455	0.6245	7	*
meglitinide	Sulfonilurea	0.7591	0.0442	0.6238	7	*
Biguanidas	GLP-1 RA	-0.5924	0.0401	0.6219	7	*
DPP4i	GLP-1 RA	-10.509	0.0522	0.6282	7	*
A glucosidasa i	GLP-1 RA	0.5693	0.0500	0.6270	7	*
GLP-1 RA	TZD	0.8431	0.0417	0.6226	7	*
GLP-1 RA	Sulfonilurea	0.7307	0.0403	0.6220	7	*
Biguanidas	DPP4i	0.4585	0.0343	0.6195	7	*
A glucosidasa i	Biguanidas	11.617	0.0310	0.6183	7	*
Biguanidas	TZD	0.2507	0.0140	0.6140	7	*
Biguanidas	Sulfonilurea	0.1383	0.0090	0.6134	7	*
A glucosidasa i	DPP4i	16.202	0.0455	0.6246	7	*
DPP4i	TZD	-0.2078	0.0362	0.6202	7	*
DPP4i	Sulfonilurea	-0.3202	0.0346	0.6196	7	*
A glucosidasa i	TZD	14.124	0.0330	0.6190	7	*
A glucosidasa i	Sulfonilurea	13.000	0.0312	0.6184	7	*
Sulfonilurea	TZD	0.1124	0.0146	0.6141	7	*
DPP4i	GLP-1 RA	-0.0255	0.0837	0.4108	3	*
Biguanidas	GLP-1 RA	-0.0575	0.1167	0.4340	3	*
Biguanidas	DPP4i	-0.0320	0.1081	0.4268	3	*
GLP-1 RA	SGLT2i	0.2644	0.0101	0.3302	2	
Biguanidas	Sulfonilurea	0.0534	0.0563	0.4043	3	*
Biguanidas	TZD	0.1667	0.0902	0.4217	3	*
Sulfonilurea	TZD	0.1132	0.0923	0.4232	3	*
GLP-1 RA	SGLT2i	0.3260	0.0137	0.3303	2	

DPP4i	Sulfonilurea	-0.0499	0.0117	0.3303	2	
Sulfonilurea	TZD	-0.0738	0.0044	0.4043	3	*
DPP4i	Sulfonilurea	-0.1095	0.0045	0.4043	3	*
DPP4i	TZD	-0.1833	0.0053	0.4043	3	*
DPP4i	Sulfonilurea	-0.0466	0.0202	0.3307	2	
DPP4i	Sulfonilurea	-20.557	0.0438	0.3330	2	
SGLT2i	Sulfonilurea	-0.1775	0.0142	0.3304	2	
GLP-1 RA	SGLT2i	0.1753	0.0381	0.3323	2	
GLP-1 RA	SGLT2i	0.2041	0.0251	0.3310	2	
DPP4i	TZD	-0.1591	0.0275	0.3312	2	

Tabla 6. Resultados (modelo de efectos aleatorios)

Medication 1	Medication 2	RR	95%-CI
GLP-1 RA	meglitinide	0.8473	[0.5953; 1.2061]
meglitinide	SGLT2i	12.436	[0.8632; 1.7916]
Biguanidas	meglitinide	10.304	[0.7237; 1.4669]
DPP4i	meglitinide	0.6962	[0.4980; 0.9732]
A glucosidasa i	meglitinide	29.570	[1.9260; 4.5399]
meglitinide	TZD	10.288	[0.7275; 1.4550]
meglitinide	Sulfonilurea	0.8668	[0.6208; 1.2104]
GLP-1 RA	SGLT2i	10.537	[0.8181; 1.3573]
Biguanidas	GLP-1 RA	12.160	[0.8926; 1.6566]
DPP4i	GLP-1 RA	0.8216	[0.6157; 1.0964]
A glucosidasa i	GLP-1 RA	34.898	[2.3224; 5.2439]
GLP-1 RA	TZD	0.8717	[0.6390; 1.1893]
GLP-1 RA	Sulfonilurea	0.7345	[0.5499; 0.9810]
Biguanidas	SGLT2i	12.813	[0.9226; 1.7795]
DPP4i	SGLT2i	0.8657	[0.6377; 1.1753]
A glucosidasa i	SGLT2i	36.773	[2.4185; 5.5912]
SGLT2i	TZD	0.8273	[0.5983; 1.1439]
SGLT2i	Sulfonilurea	0.6970	[0.5188; 0.9366]
Biguanidas	DPP4i	14.801	[1.1116; 1.9707]
A glucosidasa i	Biguanidas	28.699	[1.9166; 4.2972]
Biguanidas	TZD	10.600	[0.7856; 1.4304]
Biguanidas	Sulfonilurea	0.8931	[0.6718; 1.1875]
A glucosidasa i	DPP4i	42.476	[2.8808; 6.2631]
DPP4i	TZD	0.7162	[0.5508; 0.9313]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
A glucosidasa i	TZD	30.422	[2.0422; 4.5317]
A glucosidasa i	Sulfonilurea	25.632	[1.7398; 3.7764]

Sulfonilurea	TZD	11.869	[0.9100; 1.5479]
GLP-1 RA	meglitinide	0.8473	[0.5953; 1.2061]
meglitinide	SGLT2i	12.436	[0.8632; 1.7916]
Biguanidas	meglitinide	10.304	[0.7237; 1.4669]
DPP4i	meglitinide	0.6962	[0.4980; 0.9732]
meglitinide	TZD	10.288	[0.7275; 1.4550]
meglitinide	Sulfonilurea	0.8668	[0.6208; 1.2104]
GLP-1 RA	SGLT2i	10.537	[0.8181; 1.3573]
Biguanidas	GLP-1 RA	12.160	[0.8926; 1.6566]
DPP4i	GLP-1 RA	0.8216	[0.6157; 1.0964]
GLP-1 RA	TZD	0.8717	[0.6390; 1.1893]
GLP-1 RA	Sulfonilurea	0.7345	[0.5499; 0.9810]
Biguanidas	SGLT2i	12.813	[0.9226; 1.7795]
DPP4i	SGLT2i	0.8657	[0.6377; 1.1753]
SGLT2i	TZD	0.8273	[0.5983; 1.1439]
SGLT2i	Sulfonilurea	0.6970	[0.5188; 0.9366]
Biguanidas	DPP4i	14.801	[1.1116; 1.9707]
Biguanidas	TZD	10.600	[0.7856; 1.4304]
Biguanidas	Sulfonilurea	0.8931	[0.6718; 1.1875]
DPP4i	TZD	0.7162	[0.5508; 0.9313]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
Sulfonilurea	TZD	11.869	[0.9100; 1.5479]
GLP-1 RA	meglitinide	0.8473	[0.5953; 1.2061]
Biguanidas	meglitinide	10.304	[0.7237; 1.4669]
DPP4i	meglitinide	0.6962	[0.4980; 0.9732]
A glucosidasa i	meglitinide	29.570	[1.9260; 4.5399]
meglitinide	TZD	10.288	[0.7275; 1.4550]
meglitinide	Sulfonilurea	0.8668	[0.6208; 1.2104]
Biguanidas	GLP-1 RA	12.160	[0.8926; 1.6566]
DPP4i	GLP-1 RA	0.8216	[0.6157; 1.0964]
A glucosidasa i	GLP-1 RA	34.898	[2.3224; 5.2439]
GLP-1 RA	TZD	0.8717	[0.6390; 1.1893]
GLP-1 RA	Sulfonilurea	0.7345	[0.5499; 0.9810]
Biguanidas	DPP4i	14.801	[1.1116; 1.9707]
A glucosidasa i	Biguanidas	28.699	[1.9166; 4.2972]
Biguanidas	TZD	10.600	[0.7856; 1.4304]
Biguanidas	Sulfonilurea	0.8931	[0.6718; 1.1875]
A glucosidasa i	DPP4i	42.476	[2.8808; 6.2631]
DPP4i	TZD	0.7162	[0.5508; 0.9313]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
A glucosidasa i	TZD	30.422	[2.0422; 4.5317]
A glucosidasa i	Sulfonilurea	25.632	[1.7398; 3.7764]
Sulfonilurea	TZD	11.869	[0.9100; 1.5479]
DPP4i	GLP-1 RA	0.8216	[0.6157; 1.0964]

Biguanidas	GLP-1 RA	12.160	[0.8926; 1.6566]
Biguanidas	DPP4i	14.801	[1.1116; 1.9707]
GLP-1 RA	SGLT2i	10.537	[0.8181; 1.3573]
Biguanidas	Sulfonilurea	0.8931	[0.6718; 1.1875]
Biguanidas	TZD	10.600	[0.7856; 1.4304]
Sulfonilurea	TZD	11.869	[0.9100; 1.5479]
GLP-1 RA	SGLT2i	10.537	[0.8181; 1.3573]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
Sulfonilurea	TZD	11.869	[0.9100; 1.5479]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
DPP4i	TZD	0.7162	[0.5508; 0.9313]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
DPP4i	Sulfonilurea	0.6035	[0.4800; 0.7587]
SGLT2i	Sulfonilurea	0.6970	[0.5188; 0.9366]
GLP-1 RA	SGLT2i	10.537	[0.8181; 1.3573]
GLP-1 RA	SGLT2i	10.537	[0.8181; 1.3573]
DPP4i	TZD	0.7162	[0.5508; 0.9313]

Anexo 6. Referencias

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