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EFECTIVIDAD Y COSTE-EFECTIVIDAD DE INTERVENCIONES DE TRANSFERENCIA DE CONOCIMIENTO Y MODIFICACIÓN DE ESTILOS DE VIDA EN PACIENTES CON DIABETES MELLITUS 2: ESTUDIO INDICA

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Efectividad y coste-efectividad de intervenciones de transferencia de conocimiento y modificación de estilos de vida en pacientes con diabetes mellitus tipo 2. Estudio INDICA

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Índice

1. Introducción

1.1 La diabetes mellitus tipo 2

La Diabetes Mellitus tipo 2 (DM2) es una de las enfermedades con mayor impacto en el sistema sanitario debido a su alta prevalencia, morbilidad por complicaciones crónicas y mortalidad. Las predicciones para 2045 estiman que se alcancen los 783,2 millones de personas con diabetes entre 20- 79 años, un 12,2% del total de la población mundial. Esta cantidad en 2021 se situaba en 537 millones, lo que supone un incremento del 46% [1]. Este comportamiento "epidémico" de la DM2 tiene base multifactorial, descansando sobre una compleja predisposición genética y epigenética, que interactúa con otra compleja combinación de factores sociales que determinan la incorporación de factores de riesgo ambientales y conductuales como el sedentarismo, la sobrealimentación y, su consecuencia, la obesidad [2].

El estudio de Menéndez Torre et al estimó, a través de los registros asistenciales de atención primaria (AP), una prevalencia ajustada diagnosticada de diabetes para España de 6,66% en 2016 [3], y para Canarias de 9,72%, siendo la Comunidad Autónoma con mayor prevalencia.

La respuesta de los servicios sanitarios al cuidado de los pacientes con DM2 en España, ha sido comprometer un gasto medio anual por persona un 72,4% superior al de las personas sin diabetes (3.110,1€ vs. 1.803,6€), siendo las hospitalizaciones y medicamentos (41,9% y 29,7%, respectivamente) los aspectos que más contribuyen al gasto [4].

Las hospitalizaciones están asociadas en gran medida con la aparición de complicaciones agudas y crónicas, relacionadas con un control glucémico y de otros factores de riesgo cardiovascular inadecuado. Estas complicaciones se producen a pesar de disponer de terapias de efectividad probada frente a la DM2 recomendadas por guías de práctica clínica (GPC) nacionales e internacionales [5-7]. Es posible que las notables diferencias observadas, tanto en España como en otros países desarrollados, entre las recomendaciones de las GPC y las decisiones clínicas adoptadas en la práctica, contribuyan a estos resultados [8,9].

En Canarias, la evaluación del Programa de Atención a la DM realizada mediante la explotación de historias clínicas electrónicas (HCE) en 2015, encontró que sólo el 42% de los pacientes obtuvo valores de HbA1c inferiores a 7,5% [10]; 20 puntos por debajo de los resultados publicados en otras regiones españolas con la misma metodología de *Big Data Analysis* [4]. Estas diferencias se extienden a otros resultados como son la prevalencia de enfermedad renal terminal asociada a DM (65x1.000.000 en Canarias vs 20-30x1.000.000 en el conjunto de España) [11,12] y la mortalidad ajustada asociada a DM (41,8x100.000 en Canarias vs 11x100.000 en España, en 2011) [13].

Es posible que a la mayor tasa de complicaciones y mortalidad contribuya además, el debut más precoz de la DM2 en Canarias, que en el resto de España [14], al prolongarse la exposición a los factores de riesgo cardiovasculares, y por tanto, favorecer la aparición de complicaciones. A esto se une la mayor

prevalencia en Canarias, respecto el resto de España, de otros factores de riesgo cardiovasculares como la obesidad (30%), el sobrepeso (40%), la hipercolesterolemia (32%), el síndrome metabólico (24%) y la hipertensión (38%) [10]. Este escenario para la DM2, caracterizado por prevalencias superiores y peores resultados de salud en Canarias, a pesar del incremento de los recursos sanitarios destinados por el Servicio Canario de la Salud (SCS) al cuidado de las personas con DM [15], explican la necesidad de desarrollar y evaluar intervenciones para mejorar, eficientemente, los resultados de salud de las personas afectadas y contribuir a la sostenibilidad del SCS.

1.2 La concepción del estudio INDICA

En el contexto expuesto en el apartado anterior, y para tratar de aportar valor desde el ámbito investigador en Canarias, en 2010 se reunieron responsables de Unidades de Investigación de los diferentes hospitales de Canarias y de los Servicios Hospitalarios de Endocrinología y Nutrición y Nefrología a petición del Servicio de Evaluación de la Dirección del SCS (SESCS). El propósito era realizar propuestas que pudieran materializarse en un proyecto de investigación, que tuviera como objetivo dar respuesta a la situación epidemiológica y asistencial de la DM2 en Canarias, mediante el desarrollo y evaluación de intervenciones dirigidas a la prevención terciaria de la DM2, siendo este el inicio del estudio INDICA.

En el proceso de construcción del proyecto que ha posibilitado esta tesis, el estudio INDICA, se dieron además una serie de circunstancias que no son habituales. Se creó un equipo de trabajo multidisciplinar incluyendo a todas las personas o instituciones que estaban relacionadas e interesadas en la DM2 en Canarias: profesionales sanitarios de AP, especialistas de endocrinología, nefrología, cardiología, oftalmología y neurología y personal investigador de las Unidades de Investigación de los 4 hospitales de referencia y de las dos Universidades de Canarias, representantes de las Asociaciones de Pacientes de las islas capitalinas (Adigran y ADT) e investigadores/as de las redes nacionales de investigación como el CIBER de Epidemiología y Salud Pública y el CIBER de Obesidad y Nutrición. Además, se configuró un comité de expertos/as externo formado por investigadores/as de la "*Health Economics Research Centre*" [centro de investigación de economía de la salud] (HERC) y la "*Clinical Trials Unit of Primary Care*" [unidad de ensayos clínicos de AP] de la Universidad de Oxford. Todos ellos coordinados por el SESCS, que fue el encargado, a través del personal investigador de la Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC), de solicitar la financiación del estudio INDICA y aportar los métodos de investigación para desarrollar e implementar las intervenciones a evaluar. El equipo de investigación de la FIISC estaba compuesto por profesionales en metodología de investigación, en economía de la salud, en psicología, antropología, sociología, nutrición y educación para la salud, asumiendo la doctoranda, la responsabilidad de coordinación metodológica del proyecto, dirigido científicamente por el Dr. Serrano-Aguilar.

1.3 Intervenciones para promover cambios en los estilos de vida de las personas con DM2

Los cambios en los estilos de vida de la población a partir de las últimas dos décadas del siglo XX, se consideran el factor desencadenante de lo que se ha denominado epidemia de la diabetes. A nivel internacional, sólo entre el 7 y 12% de los pacientes con DM2 alcanza un control adecuado para el conjunto de factores de riesgo vascular más importantes [8,9]; sugiriéndose que las principales causas que explican esta limitada tasa de éxito son la inercia de los profesionales sanitarios y la pobre adherencia de los pacientes a las recomendaciones terapéuticas [16,17].

A pesar de la disponibilidad de GPC de calidad [6,7], que informan de la relación entre los resultados de salud y el autocuidado de los pacientes [18,19], los informes internacionales muestran que solo el 55% de las personas con DM2 reciben educación diabetológica [20] y solo el 16% se adhiere a las actividades de autocuidado recomendadas [21].

El carácter crónico de la DM2 y la relación de su evolución con las decisiones cotidianas del paciente y entorno familiar, hacen de esta un paradigma de enfermedad crónica para el desarrollo de intervenciones de mejora de la capacitación y fortalecimiento. Estas intervenciones deben considerar programas integrados de cuidados centrados en el paciente [22,23].

Conseguir modificaciones en los estilos de vida, requiere que en el diseño de las intervenciones se consideren modelos de co- creación con las personas afectadas y los profesionales que los cuidan, orientados específicamente para promover el cambio, definiendo el marco sobre el que deben aplicar las diferentes intervenciones. El proceso de diseño de intervenciones de cambio de comportamiento, generalmente implica primero determinar el enfoque amplio que se adoptará y luego trabajar en los aspectos específicos del diseño de la intervención [24]. Para esto es necesario definir el objetivo conductual, la población objetivo y el contexto en el que se realizará la intervención. Es habitual que esta actividad se realice en base al conocimiento del equipo investigador, y/o la evidencia científica disponible sobre la efectividad de las intervenciones. Aunque lo óptimo es poder conjugarlo, con la información proporcionada sobre las dificultades y barreras con las que se encuentran las personas que son objeto de intervención para conseguir el cambio. Toda esta información debe ser puesta en relación al modelo de comportamiento a aplicar y los factores que influyen en él.

El Modelo de Atención al Paciente con enfermedad crónica [25-27], es un marco bien establecido y validado que propone un enfoque integral para la atención de enfermos crónicos, respaldado por una mejora de los resultados funcionales y clínicos. El modelo incluye seis componentes claves e interdependientes, que comprenden: los recursos comunitarios, el apoyo al modelo asistencial, apoyo a la autogestión o autocuidado, diseño del sistema de prestación, apoyo a las decisiones y sistemas de información clínica. La incorporación de las tecnologías de la información y la comunicación, mejora

este modelo, al facilitar un ciclo completo de retroalimentación, haciendo uso de datos e información que contribuye a generar conocimiento y experiencias sobre la gestión de este problema de salud [26].
En el diseño de las intervenciones para los pacientes con DM2 y sus familiares, en el seno del proyecto INDICA, se aplicó el Marco Conceptual de Cambio de Comportamiento propuesto por Michie et al [24]. Además, para maximizar la efectividad de las intervenciones, se incorporaron todos los componentes de un ciclo de retroalimentación de autogestión canalizado a través de la tecnología, conectando a pacientes y profesionales sanitarios bidireccionalmente, analizando el comportamiento del paciente y los datos de salud, llevando a cabo actividades educativas para capacitarlo ante el cambio y personalizando la información que le devuelve el sistema de acuerdo al Modelo de Atención Crónica al Paciente [25-27].
Para la adaptación de estos modelos al problema de la DM2 se realizaron las siguientes acciones:

1) Se incorporó el conocimiento y experiencia de los expertos/as en DM2 e investigadores/as.

2) Se realizó un estudio cualitativo de tipo fenomenológico basado en los principios de la teoría fundamentada [28]. En este estudio se exploraron las dificultades y barreras que se encuentran los pacientes para ser adherentes a las recomendaciones de autocuidado en el contexto de Canarias, a través de entrevistas semi- estructuradas a los pacientes y grupos focales. En concreto, se analizaron las siguientes dimensiones: 1) Percepciones o valoraciones sobre la enfermedad; 2) Adherencia a las recomendaciones de dieta; 3) Adherencia a las recomendaciones sobre actividad física; 4) Recursos que ofrece el sistema sanitario; 5) Relación de los profesionales sanitarios con los pacientes y 6) El uso de las de las tecnologías de la información y la comunicación (TICs) en el contexto sanitario.

3) Se estudió la evidencia científica disponible. Se realizó una revisión sistemática de la literatura sobre intervenciones a pacientes con DM2 en AP para promover cambios en el estilo de vida. También se realizaron otras revisiones de la literatura, de carácter no sistemático, para identificar GPC para pacientes y experiencias de incorporación de la perspectiva de los pacientes conjuntamente con las TICs.

Por último, las características de las intervenciones desarrolladas se planificaron para aumentar la validez de los datos obtenidos y la transferibilidad de las intervenciones evaluadas, fuera del marco del proyecto de investigación, hacia el mundo real.

1.4 Intervenciones para mejorar la gestión clínica por parte de los profesionales sanitarios (de medicina y enfermería), de Atención Primaria

Además del paciente y sus cuidadores, el profesional sanitario (de medicina o enfermería) constituye otro actor fundamental en la prevención terciaria de la DM2. Estos profesionales, trabajando en equipo, conjuntamente con pacientes y entorno familiar, desempeñan un papel importante en las decisiones del día a día de los pacientes, que influyen en sus resultados de salud. Pero a pesar de la alta frecuentación de los pacientes con DM en España (un promedio de 10 visitas anuales), los actuales tiempos de consulta

(7- 10 minutos/ paciente) no favorecen una asistencia de calidad. Además, sólo un 20% de los profesionales admite tener habilidades para gestionar con éxito la consulta de pacientes con DM2 [29], y actualizar periódicamente los conocimientos para su gestión clínica. Las recomendaciones cambiantes constituyen también una barrera identificada, entre otras, para una adecuada asistencia a estos pacientes [30].

De ahí el interés creciente por desarrollar intervenciones de transferencia de conocimiento y apoyo a la toma de decisiones a los profesionales, basadas en las TICs, que complementen su actividad asistencial. Diferentes iniciativas han tratado de mejorar el conocimiento científico de profesionales, por medio de sistemas computarizados de ayuda a las decisiones integrados en la HCE [31-33]. La transferencia de estas iniciativas a los sistemas sanitarios sigue siendo, sin embargo, muy limitada al no disponerse de pruebas científicas robustas sobre su efectividad, factibilidad, aceptabilidad, usabilidad, coste-efectividad e impactos organizativo y presupuestario [34].

El diseño de las intervenciones aplicadas a profesionales sanitarios (de medicina y enfermería) de AP, en el proyecto INDICA, al igual que en la intervención a pacientes, estuvo guiado (parcialmente) por los determinantes del cambio de comportamiento sugeridos por Michie et al [24]. Se incluyeron las recomendaciones sobre la incorporación de técnicas para mejorar habilidades en la comunicación profesional sanitario- paciente, un sistema de avisos y recomendaciones para el apoyo a la toma de decisiones incorporado en la HCE (basado en la evidencia científica) y retroalimentación periódica sobre los resultados, procedimentales y de salud, contrastados en relación a los resultados de sus colegas.

Al igual que en la intervención para los pacientes, el proceso de diseño y desarrollo de las intervenciones a profesionales en el estudio INDICA, se nutrió de las siguientes acciones:

1) Se recogió el conocimiento y experiencia de los expertos en DM2 e investigadores.
2) Se realizó un estudio cualitativo, basado en la misma metodología que el ya descrito para pacientes, en el que se exploraron las dificultades y barreras que afrontan los profesionales sanitarios para conseguir que los pacientes se adhieran a las recomendaciones de autocuidado. Y las dificultades y barreras propias de los profesionales para aplicar las GPC.
3) Se analizó la evidencia científica disponible obtenida a partir de revisiones sistemáticas de la literatura sobre:

    - Las mejores técnicas de transferencia de conocimiento a pacientes y profesionales sanitarios.

    - Herramientas de ayuda a la toma de decisiones en la gestión de la consulta de AP mediante avisos en la HCE para mejorar la adherencia de los profesionales a las GPC.

    - Herramientas de retroalimentación de resultados en salud de los pacientes en las consultas de AP para mejorar la adherencia de los profesionales sanitarios a las GPC.

Adicionalmente, se llevaron a cabo revisiones de la literatura, no sistemáticas, de las mejores técnicas de abordaje terapéutico en la negociación médico paciente.

1.5 El estudio INDICA

El estudio INDICA es un ensayo clínico controlado aleatorizado (ECA) por clúster de corte pragmático en el ámbito de la AP, que ha querido interrumpir la inercia profesional buscando alternativas que ayudasen a mejorar la práctica asistencial y conseguir pacientes más empoderados y adherentes a las recomendaciones para mejorar su estilo de vida.

En el estudio se comparan los resultados de 3 grupos diferentes de intervención frente a un grupo de control, en el que se evalúa la atención habitual ofrecida por el SCS. Los grupos de intervención son: 1) Intervención aplicada directamente a los pacientes y familiares (PTI); 2) Intervención aplicada directamente a los profesionales sanitarios (PFI) y 3) Intervención combinada (CBI), en la que se interviene tanto a los pacientes y familiares, como a los profesionales sanitarios.

La intervención aplicada directamente a los pacientes, tiene como objetivo inicial mejorar su conocimiento sobre la enfermedad y su adherencia a las recomendaciones terapéuticas realizadas por los profesionales sanitarios. Para esto se ha intentado involucrar a pacientes y familiares (implicados en los hábitos alimenticios de los pacientes) en actividades de formación grupal, y se les han dado herramientas para mejorar su autocontrol mediante un apoyo continúo favorecido por la incorporación de las TICs en el diseño de las intervenciones. Esto se ha hecho con la intención de favorecer una mejor toma de decisiones compartidas con los profesionales sanitarios que los atienden, para alcanzar el objetivo intermedio de mejorar el autocuidado de los pacientes, y como objetivo final mejorar sus resultados en salud.

La intervención aplicada directamente a los profesionales sanitarios tiene como uno sus objetivos, que sean más adherentes a la aplicación de las GPC, proporcionándoles herramientas de ayuda para mejorar su nivel de conocimiento sobre la enfermedad y la toma de decisiones clínicas. Otro objetivo, es promover entre los profesionales la aplicación de técnicas de negociación médico - paciente y la toma de decisiones compartidas con las que puedan mejorar la asistencia y en última instancia, los resultados en salud de los pacientes. En todos los componentes de la intervención se ha buscado el apoyo de las TICs para facilitar su aplicación y ofrecer un apoyo continuo en el tiempo.

Los criterios de inclusión y exclusión del estudio, han sido elegidos en base a la premisa de que se iban a evaluar intervenciones para la prevención terciaria de la DM2. Por lo que se incluyeron pacientes de entre 18 y 65, sin complicaciones, independientemente de su nivel de control de la HbA1c. La decisión de incluir tanto pacientes controlados, con niveles de HbA1c $\leq$ 7%, como no controlados, con niveles de HbA1c >7%; siendo el nivel de HbA1c la medida de resultado principal del ECA, se realizó a pesar de ser conscientes de la limitada magnitud de los cambios a observar en los pacientes con niveles de HbA1c bajo control. Sin embargo, el estudio INDICA fue diseñado no solo para mejorar los niveles de HbA1c en los pacientes no controlados, sino para contribuir a mantener el nivel de control a medida que avanza la enfermedad. Esta razón explica la laxitud de los criterios de inclusión, aunque esta decisión

no impidió planificar la realización de análisis por subgrupos con suficiente potencia estadística como para evaluar el efecto diferencial de las intervenciones en los pacientes controlados y no controlados basalmente.

Las medidas de resultado del estudio INDICA incluyen diferentes tipos de variables: resultados clínicos, antropométricos, calidad de vida relacionada con la salud, cambios en el conocimiento y empoderamiento, entre otras medidas proporcionadas por los propios pacientes. Entre los parámetros clínicos se incluyeron algunos de naturaleza analítica obtenidos a partir de análisis de sangre y orina, y los obtenidos en las pruebas oftalmológicas de diagnóstico [retinografías y tomografía de coherencia óptica (OCT)]. Otros parámetros clínicos incluyeron las medidas antropométricas (peso y talla), tensión arterial e índice tobillo/ brazo, además de recogerse la aparición de complicaciones micro y macrovasculares. Entre las medidas reportadas por los pacientes, se incluyeron el cambio en la calidad de vida relacionada con la salud, el conocimiento, el empoderamiento, la adherencia a recomendaciones de estilo de vida y variables afectivas. También en los profesionales se midió el cambio en el nivel de conocimiento y empoderamiento. Todas estas variables fueron medidas en diferentes momentos hasta los dos años de seguimiento, si bien, aquellas relacionadas con las complicaciones vasculares, requieren de una evaluación a más largo plazo, para poder detectar diferencias.

El análisis coste-efectividad es especialmente relevante en la evaluación de intervenciones mediadas por las TICs dirigidas a personas con enfermedades crónicas prevalentes. Al igual que acontece con los programas de salud pública, las intervenciones sobre problemas de salud de gran prevalencia, no solo deben demostrar su efectividad sino también su coste-efectividad para contribuir simultáneamente tanto a la mejora de la salud de las personas afectadas, como a la sostenibilidad del sistema público de salud. En este tipo de intervenciones el mayor coste se atribuye al desarrollo de las intervenciones, reduciéndose progresivamente el coste/paciente a medida que se aplica a un mayor número de pacientes.

En la actualidad, el estudio INDICA sigue estando activo con publicaciones de objetivos secundarios y consiguiendo financiación para abordar nuevos objetivos. Las actividades complementarias más destacadas, son las siguientes:

- **INDICA-DOS:** Seguimiento en el largo plazo de las medidas de resultado del estudio INDICA. Se realiza nueva medición de resultados a los 5 años de incluido el paciente en el estudio. Esto supone una fortaleza frente a la mayoría de los ensayos que evalúan en el corto plazo (6 meses/1 año), y no permiten observar la necesidad de establecer un calendario de refuerzo cuando el efecto de las intervenciones decae.

  Además, en el seguimiento a largo plazo se incorporan medidas de resultado finales como complicaciones micro y macro vasculares y la muerte.

  - **Proyecto PI16/00769**: Efectividad y coste-efectividad de intervenciones complejas de transferencia de conocimiento basadas en TICs a 5 años, para mejorar la salud en pacientes con DM2 (INDICA-DOS). Financiado por el Instituto de Salud Carlos III

    - **Proyecto PIFUN34/17**: Efectividad y coste-efectividad a 5 años de intervenciones complejas de transferencia de resultados basadas en TICS para mejorar la salud en pacientes con DM2, evaluados mediante explotación de registros clínicos electrónicos y entrevista telefónica (INDICA-DOS). Financiado por Funcanis

- **NOVAME:** Este proyecto tiene por objetivo aprovechar el conocimiento generado en INDICA para dar un paso más en el uso de la tecnología y ofrecer una nueva herramienta a los pacientes en forma de app. NOVAME combina el catálogo de conocimiento puesto a disposición de los pacientes mediante videos, infografías y presentaciones con el apoyo de un coach online. Este papel está realizado por una enfermera educadora en diabetes que motiva y resuelve las dudas de los pacientes a través de la aplicación.
    - **Proyecto PIFUN32/17.** Evaluación del impacto de una aplicación móvil de salud para mejorar el autocontrol y los resultados de salud de los pacientes con DM2: estudio piloto "Novame". Financiado por Funcanis.
- **GesPeDia**: Es una herramienta de apoyo a la toma de decisiones de mesogestión generada a partir de INDICA, que trabaja sobre la información ofrecida por la HCE. Pretende incorporar a un nuevo actor en la toma de decisiones que puede venir representado por el endocrino consultor, la dirección de los centros de AP o las Gerencias de AP. GesPeDia ofrece un conjunto de indicadores agregados de proceso y resultado a nivel de cupo, es decir, a nivel de equipo de atención familiar (medicina y enfermería). Y un análisis individualizado a nivel de paciente en relación a los diferentes parámetros clínicos y su cumplimiento. GesPeDia pretende ser una ayuda para evaluar y monitorizar de forma integrada, tanto 1) la calidad del desempeño profesional (y sus necesidades de formación); como 2) los resultados de salud de las personas afectadas por DM2.
    - **Proyecto: ST22/04:** Impacto de la pandemia por Covid-19 sobre la gestión clínica y los resultados de salud de las personas con DM2 en la AP de Canarias. Proyecto GesPeDia-INDICA. Financiado por la FIISC
- **IMPACT-T2D:** Es un estudio multicéntrico de ámbito nacional sobre genética de la DM2 en el contexto de la Convocatoria del Carlos III de Medicina Personalizada que hará uso de las bases de datos de INDICA y de las muestras de ADN almacenadas de sus pacientes. En particular, de aquellas que pertenecen a las personas que han tenido un inicio relativamente temprano de la enfermedad (< 57 años) y sin obesidad (IMC < 27).
    - **Proyecto PMP21/00069:** ImpactT2D: una estrategia genómica para implementar medicina de precisión en la DM2. Financia Instituto de Salud Carlos III.

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3. Hipótesis

Hipótesis general

La hipótesis general del estudio INDICA es que la combinación de intervenciones de transferencia de conocimiento mediadas por las TICs para apoyar las decisiones, mejorarán eficientemente los conocimientos y conductas de gestión de la DM2 por parte de los pacientes (y familiares) y de los profesionales sanitarios (medicina y enfermería) de AP; consiguiendo mejorar, eficientemente y a largo plazo, los resultados de salud de los pacientes con DM2.

Hipótesis específicas:

1. La intervención multicomponente de transferencia de conocimientos y modificación de conducta, mediada por las TICs, y aplicada a pacientes, mejorarán su grado de conocimiento sobre la DM2 y la adherencia de los pacientes a las recomendaciones de autocuidado. Esto hará que mejoren sus resultados de salud clínicos y autopercibidos.
2. La intervención multicomponente de transferencia de conocimientos y toma de decisiones compartidas, mediada por las TICs, y aplicada a los profesionales sanitarios de AP, favorecerá una mejor atención sanitaria con una mayor adherencia de los profesionales a aplicar las recomendaciones basadas en la evidencia sobre el manejo de pacientes con DM2. También mejorará la comunicación de los profesionales con sus pacientes aplicando métodos de toma de decisiones compartidas. Esto hará que mejoren tanto los resultados de salud clínicos como los autopercibidos por los pacientes.
3. La aplicación conjunta de las dos intervenciones anteriormente descritas, conseguirá un mayor efecto que la aplicación de cualquiera de las intervenciones por separado.
4. El efecto de las intervenciones aplicadas tanto a pacientes, como a profesionales sanitarios, será mayor en el grupo de pacientes niveles de HbA1c basal no controlada basalmente.
5. Estas intervenciones son coste-efectivas frente a la atención habitual realizada en AP.

4. Objetivos

Objetivo general

Evaluar mediante un ensayo clínico aleatorizado y controlado (estudio INDICA), la efectividad y coste-efectividad de intervenciones multicomponentes de transferencia de conocimiento mediadas por las TICs, aplicadas a pacientes con DM2 (y familiares) y a profesionales sanitarios (medicina y enfermería) de AP, de forma independiente y combinada, para mejorar sus conocimientos y conductas de gestión de la DM2 consiguiendo mejorar los resultados de salud clínicos y autopercibidos de los pacientes, respecto al grupo de control.

Objetivos específicos:

1) Evaluar el efecto de las intervenciones de INDICA, para disminuir el valor de la medida de resultado principal (HbA1c), respecto al grupo de control.

2) Evaluar el efecto de las intervenciones de INDICA, en el resto de resultados clínicos de los pacientes con DM2 (medidas antropométricas y medidas de laboratorio), respecto al grupo de control

3) Evaluar el efecto de las intervenciones de INDICA, en los resultados autopercibidos por los pacientes con DM2 (medidas cognitivas- actitudinales, medidas de comportamiento, medidas afectivas, calidad de vida relacionada con la salud y percepción de síntomas), respecto al grupo de control.

4) Analizar el efecto de las intervenciones de INDICA, según el grado de control de la HbA1c basal, respecto al grupo de control.

5) Evaluar el coste-efectividad de las diferentes intervenciones, a corto y medio plazo, desde la perspectiva de los servicios de salud.

5. Resultados

A continuación, se expone el listado de las publicaciones incluidas en esta tesis por compendio. La primera publicación es el protocolo del ECA del estudio INDICA, la segunda contiene el efecto de las intervenciones de INDICA sobre las medidas de resultado clínicas, mientras que la tercera contiene el efecto de las intervenciones de INDICA sobre las medidas de resultado autopercibidas por los pacientes (PROM). Por último, se publicó el análisis coste-efectividad de las intervenciones.

1. **Ramallo-Fariña Y**, García-Pérez L, Castilla-Rodríguez I, Perestelo-Pérez L, Wägner AM, de Pablos-Velasco P, Carrillo Domínguez A, Boronat Cortés M, Vallejo-Torres L, Estupiñán Ramírez M, Pedrianes Martín P, García-Puente I, Salinero-Fort MA, Serrano-Aguilar PG, INDICA team. Effectiveness and cost-effectiveness of knowledge transfer and behavior modification interventions in type 2 diabetes mellitus patients—the INDICA study: a cluster randomized controlled trial. Implement Sci. 2015;10:47. doi: 10.1186/s13012-015-0233-1

   Citado por 10 artículos

   Factor de impacto de la revista en 2015: 3,20; *Posición*: 16 /88; *Cuartil*: 1

   Factor de impacto de la revista en 2021: 8; *Posición*: 5 /109; *Cuartil*: 1
2. **Ramallo-Fariña Y,** García-Bello MA, García-Pérez L, Boronat M, Wägner AM, Rodríguez-Rodríguez L; de Pablos-Velasco P; Llorente Gómez de Segura I, González- Pacheco H; Carmona Rodríguez M; Serrano-Aguilar P, INDICA Team. Effectiveness of Internet-Based Multicomponent Interventions for Patients and Health Care Professionals to Improve Clinical Outcomes in Type 2 Diabetes Evaluated Through the INDICA Study: Multiarm Cluster Randomized Controlled Trial. JMIR Mhealth Uhealth. 2020;8(11):e18922. doi: 10.2196/18922

   Citado por 9 artículos

   Factor de impacto de la revista en 2020: 4,77; *Posición*: 17 /107; *Cuartil*: 1

   Factor de impacto de la revista en 2021: 4,95, *Posición*: 21 /109; *Cuartil*: 1
3. **Ramallo-Fariña Y**, Rivero-Santana A, García-Pérez L, García-Bello MA, Wägner AM, Gonzalez-Pacheco H, Rodríguez-Rodríguez L, Kaiser-Girardot S, Monzón-Monzón G, Guerra-Marrero C, Daranas-Aguilar C, Roldán-Ruano M, Carmona M, Serrano-Aguilar PG; INDICA Team. Patient-reported outcome measures for knowledge transfer and behaviour modification interventions in type 2 diabetes-the INDICA study: a multiarm cluster randomised controlled trial. BMJ Open. 2021;11(12):e050804. doi: 10.1136/bmjopen-2021-050804

   Citado por 3 artículos

   Factor de impacto de la revista en 2021: 3,01; *Posición*: 86 /172; *Cuartil*: 2
4. García-Pérez L, **Ramallo-Fariña Y**, Vallejo-Torres L, Rodríguez-Rodríguez L, González-Pacheco H., Santos-Hernández B, García-Bello MA, Wägner AM, Carmona M, Serrano-

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Factor de impacto de la revista en 2021: 3,01; *Posición*: 86 /172; *Cuartil*: 2

Publicación 1.

Ramallo-Fariña *et al. Implementation Science* (2015) 10:47
DOI 10.1186/s13012-015-0233-1

IMPLEMENTATION SCIENCE

STUDY PROTOCOL Open Access

Effectiveness and cost-effectiveness of knowledge transfer and behavior modification interventions in type 2 diabetes mellitus patients—the INDICA study: a cluster randomized controlled trial

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Abstract

Background: Type 2 diabetes mellitus is a chronic disease whose health outcomes are related to patients and healthcare professionals' decision-making. The Diabetes Intervention study in the Canary Islands (INDICA study) aims to evaluate the effectiveness and cost-effectiveness of educational interventions supported by new technology decision tools for type 2 diabetes patients and primary care professionals in the Canary Islands.

Methods/design: The INDICA study is an open, community-based, multicenter, clinical controlled trial with random allocation by clusters to one of three interventions or to usual care. The setting is primary care where physicians and nurses are invited to participate. Patients with diabetes diagnosis, 18–65 years of age, and regular users of mobile phone were randomly selected. Patients with severe comorbidities were excluded. The clusters are primary healthcare practices with enough professionals and available places to provide the intervention. The calculated sample size was 2,300 patients.

Patients in group 1 are receiving an educational group program of eight sessions every 3 months led by trained nurses and monitored by means of logs and a web-based platform and tailored semi-automated SMS for continuous support. Primary care professionals in group 2 are receiving a short educational program to update their diabetes knowledge, which includes a decision support tool embedded into the electronic clinical record and a monthly feedback report of patients' results. Group 3 is receiving a combination of the interventions for patients and professionals. The primary endpoint is the change in HbA1c in 2 years. Secondary endpoints are cardiovascular risk factors, macrovascular and microvascular diabetes complications, quality of life, psychological outcomes, diabetes knowledge, and healthcare utilization. Data is being collected from interviews, questionnaires, clinical examinations, and records. Generalized linear mixed models with repeated time measurements will be used to analyze changes in outcomes. The cost-effectiveness analysis, from the healthcare services perspective, involves direct medical costs per quality-adjusted life year gained and two periods, a 'within-trial' period and a lifetime Markov model. Deterministic and probabilistic sensitivity analyses are planned.

(Continued on next page)

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(Continued from previous page)

Discussion: This ongoing trial aims to set up the implementation of evidence-based programs in the clinical setting for chronic patients.

Trial registration: Clinical Trial.gov NCT01657227

Keywords: Behavior modification, Care management, Decision support aids, Electronic communication, Knowledge transfer, Mobile phone technology, Multicomponent intervention, Primary care, Type 2 diabetes mellitus

Background

Type 2 diabetes mellitus (T2DM) is a paradigmatic chronic disease in which health outcomes are related to patients' decision-making on adherence to life-style changes and pharmacologic recommendations. Besides patients, other relevant stakeholders, such as family members, as well as healthcare professionals, mainly at the primary care level, also play a relevant role in supporting patients' decision-making.

In the Canary Islands, Spain, the prevalence of T2DM in the population over 15 years is 7.74%, slightly higher than the Spanish average (6.99%) [1]. However, the Canary Islands have an increased prevalence of diabetes-related end-stage renal disease [2-4] and diabetes-related mortality [5], when compared to the rest of Spain, with 65 vs 20–30 cases/million population and 7.8% vs 2.5%, respectively. This happens despite the fact that patients with diabetes mellitus (DM) have a mean number of ten visits/year to their primary care physician/nurse in the Canary Islands [6]. Furthermore, public healthcare resources earmarked to care for people with diabetes in the Canary Islands increased from 2.13% in 1998 to 5.9% in 2004 [7].

Despite the availability of evidence-based clinical practice guidelines [8,9] and clinical trials reporting better health outcomes linked to interventions promoting patients' self-care [10,11], international reports still show that only 55% of people with T2DM receive diabetes education [12]; 16% adhere to recommended self-management activities [13], 37% meet the glycated hemoglobin (HbA1c) target of 7.0%, and only 7% meet combined glycemic, lipid, and blood pressure goals [14-17].

The socio-economic and public health consequences of T2DM in the Canary Islands prompted the Canary Islands Health Service (CIHS) to assess the effectiveness and efficiency of new interventions to improve both patient healthcare outcomes and the sustainability of publicly funded healthcare services. In this context, information and communication technology (ICT) offers the opportunity of efficiently supporting knowledge transfer and behavior modification interventions to improve decision-making by T2DM patients [18-22] and healthcare professionals [23-25]. Indeed, more than 70% of Canary Island families and 90% of inhabitants have daily access to internet and mobile phones, respectively [26].

Although there are many publications addressing the use of different ICT applications to support patient and professional decision-making [23,27], few studies have assessed the health and economic impact of complex interventions by means of large and long-term randomized clinical trials reporting on effectiveness and cost-effectiveness.

The Diabetes Intervention study in the Canary Islands (INDICA study) is a randomized controlled trial (RCT) that assesses the effectiveness and cost-effectiveness of three different complex interventions for knowledge transfer and behavior modification of patients, families, and healthcare professionals (physicians and nurses) at the primary care level in the Canary Islands. The interventions include a diabetes-coaching system using a combination of conventional educational workshops with mobile phones, a patient web-based platform, electronic decision aids, and periodic feedback on patients' outcomes to guide them and healthcare professionals in decision-making related to T2DM management.

We hypothesize that this combination of conventional educational activities complemented with timely and continuous ICT decision support tools will efficiently improve disease management skills and behavior, both in patients and in healthcare professionals, in addition to health outcomes (HbA1c change over 2 years) in T2DM patients.

Methods

Trial design

The INDICA study is an open, community-based, multicenter, clinical controlled trial with random allocation by clusters to usual care or one of the following different interventions of knowledge transfer and behavior modification.

Group 1 corresponds to *intervention only for patients and family members*, group 2 to intervention only for *healthcare professionals at primary care*, and group 3 is a *combined intervention* for patients and professionals. In the control group, neither patients/families nor physicians/nurses receive any additional educational or supporting activities beyond the usual activities provided by the CIHS.

Subjects

Patient inclusion criteria

1) Patients with T2DM diagnosed at least 1 year prior to study enrolment
2) 18–65 years of age
3) Formal consent to participate in the study
4) Regular use of mobile phone

Patient exclusion criteria

1) Chronic kidney disease ≥ stage 3b, as defined by the National Kidney Foundation's Kidney Disease Outcomes and Quality Improvement Initiative (KDOQI), urinary albumin to creatinine ratio (UACR) ≥ 300 mg/g, and/or urinary protein excretion ≥ 300 mg/24 h.
2) Acute coronary syndrome (documented angina or myocardial infarction) or stroke in the last 6 months or class III or IV heart failure, according to the New York Heart Association (NYHA).
3) Proliferative diabetic retinopathy or clinically significant diabetic macular edema requiring previous treatment with retinal photocoagulation, vitrectomy, or intravitreal injections of anti-vascular endothelial growth factor or triamcinolone acetonide 6 months prior to study inclusion.
4) Uncorrected severe hearing or visual impairment or corrected visual acuity ≤ 20/40 by any cause.
5) Diabetic foot with ulcers ≥ 2 according to the Wagner scale.
6) Liver cirrhosis
7) Cancer unless disease free 5 years after diagnosis
8) Other terminal illnesses
9) Intellectual retardation, dementia, psychotic diseases
10) Active substance abuse, alcohol, or drugs (must be sober for 1 year)
11) Pregnancy
12) Insufficient (Spanish) language skills
13) Physical disability limiting participation in group education activities
14) Concurrent participation in another clinical trial or any other investigational study.

Primary care professionals

The unit of recruitment for primary care professionals was the Family Care Unit (FCU), composed of a family physician and a nurse. Given the interventions' nature and the organizational characteristics in primary care at CIHS, it was agreed that physicians and nurses working together as FCUs independently sign the informed consent to participate. Family physicians and nurses either planning or awaiting placement changes among primary healthcare practices (PHCP) in the first 6 months after project initiation were excluded.

Only PHCP with at least eight FCUs and availability of appropriate places to provide group sessions were included.

Setting and recruitment

PHCP were randomly recruited in four of the seven Canary Islands (Tenerife, Gran Canaria, Lanzarote, and La Palma). Tenerife and Gran Canaria are the main and most populated islands, providing 12 PHCP each (four from metropolitan areas, four from the south, and four from the north). La Palma and Lanzarote are less populated islands and provided four PHCP each. The Human Resources Department of the CIHS at every island supplied us with an updated list of publicly available physician/nurses for every selected PHCP. FCUs' recruitment in PHCPs was supported by informative meetings preceded by meetings with local health authorities as well as with the directors of all selected PHCP on every island. In these meetings, a 60–80-min presentation describing the study objectives, planned time frame and tasks to be developed by healthcare professionals, expected resources utilization, and funding procedures were detailed.

After FCUs agreed and consented to participate, the electronic clinical records (ECR) of all potentially eligible patients in the selected FCU were screened to verify all inclusion and exclusion criteria. Once identified, patients received a phone call to explain the study objectives, informing that they might be eligible to participate and inviting them to an initial meeting in their respective PHCP. In this meeting, the study staff provided face-to-face extended information about the study, confirmed patient eligibility, and invited them to sign individual patient informed consent.

When a participant physician/nurse left their practice, they were excluded from the study and replaced by the new physician/nurse. In groups 2 and 3, the educational intervention was given to the new healthcare professionals on an individual level. Their corresponding patients were kept in the study without changes.

Random assignment

Randomization was applied at different levels in every island included in the trial. Three different strata or geographic areas were set in Tenerife and Gran Canaria (metropolitan, northern, and southern areas). Four PHCP were randomly allocated to every stratum. Each PHCP was assigned to one of the three interventions or control arms by block permutation. La Palma and Lanzarote were geographically divided into four zones with only one PHCP available in each zone. Each of these PHCP was randomly assigned to one of the study arms. In every island, all arms were equally distributed.

Six FCUs were randomly selected from all those consenting participants at each PHCP. From all patients fulfilling inclusion criteria and consenting to participate in each PHCP, 15 were randomly selected per FCU. Exceptionally, more than six FCUs or more than 15 patients per FCU were selected, in order to recruit 90 patients at every PHCP.

While PHCP randomization was performed using block permutation at three different levels, second (FCUs) and third (patients) stage randomizations were performed by simple generation from a list of random numbers. PHCP assignment to interventions or control group was performed by the data manager.

In order to prevent potential contamination among study interventions, all FCUs at every PHCP were allocated to the same study group.

Blinding

Participating FCUs were not told about their intervention assignment (groups 1–4) until the last patient agreed to participate at every FCU. To warrant patient participation and cooperation, interventions could neither be blinded to patients nor to healthcare professionals. Data analysis will be blinded to the intervention assignment.

Interventions

The study will assess the effectiveness and cost-effectiveness of three different complex interventions of knowledge transfer and decision guiding for primary care healthcare professionals and/or patients and families, according to intervention assignment (Figure 1). These three interventions are compared with a control group receiving usual care.

Patient interventions

Groups 1 and 3 receive a complex intervention of knowledge transfer and behavior modification combining the following: A) an educational and interactive group program plus continuous monitoring by means of B) daily use of paper workbooks and weekly utilization of a web-based platform and C) tailored semi-automated mobile phone messages.

A) Interactive educational group program:
Patients accompanied, if appropriate, by one family member responsible for buying food and cooking and serving meals are invited to receive a set of eight quarterly 3-h group sessions during the 2 years of intervention. The aim of this program is to empower patients in self-control and monitoring as well as to involve relevant family members in supporting appropriate decisions about nutritional, pharmacologic, and physical activity issues. An experienced nurse, trained in diabetes education, conducts every session, with groups of ten patients and their corresponding family members. Every session contains theoretic and practical interactively delivered activities about the most important diabetes topics: understanding T2DM, cooking, understanding nutritional food labels, glycemic target, foot care, drug adherence, tobacco, stress management, exercise, chronic complications, etc., according to Funnel et al.'s recommendations [28]. The specific contents and procedures of every session were developed based on several systematic literature reviews. The best documented and assessed educational interventions that provided valid and longer term data on improvements in relevant T2DM health outcomes were selected [29-31]. In every session, interactive activities are used to reinforce knowledge transfer and self-motivation. The first session included information and training about the adequate use of the other components of the intervention, such as the web platform, the workbooks, and the short message service (SMS) sent to mobile phones. In order to develop an educational tool for future use in research or clinical practice, these sessions are video recorded, after consent of all group participants. This recording is available on-line to patients.

B) Patient logs for continuous self-monitoring and periodic reporting:
To provide continuous support to patients and to reinforce self-care and lifestyle changes, two different types of workbooks were developed, which show patients the dynamics and relationships of food intake, physical activity, and medication adherence with blood glucose levels. Patients are invited to use a paper-supported workbook and a web workbook embedded in a patient web-based platform. The paper version gathers daily information on the amount of physical activity, nutritional intake, medication adherence, mood, blood pressure, and blood glucose levels. In addition, this information is summarized and filled in, weekly, in the web workbook, to allow for continuous monitoring and feedback by means of automated SMS. Once the web-based questionnaire is completed, graphical feedback is displayed in the web platform, showing the variation in all selected variables over time. The web platform also offers additional information on diabetes self-management extracted from the contents of the group educational program. Additionally, every month, patients are requested to complete a longer, web-based questionnaire, collecting information on tobacco use, foot care, and weight control. This monthly questionnaire is also used to provide continuous feedback in the form of automated SMS (see below). A free phone service is available to fill in

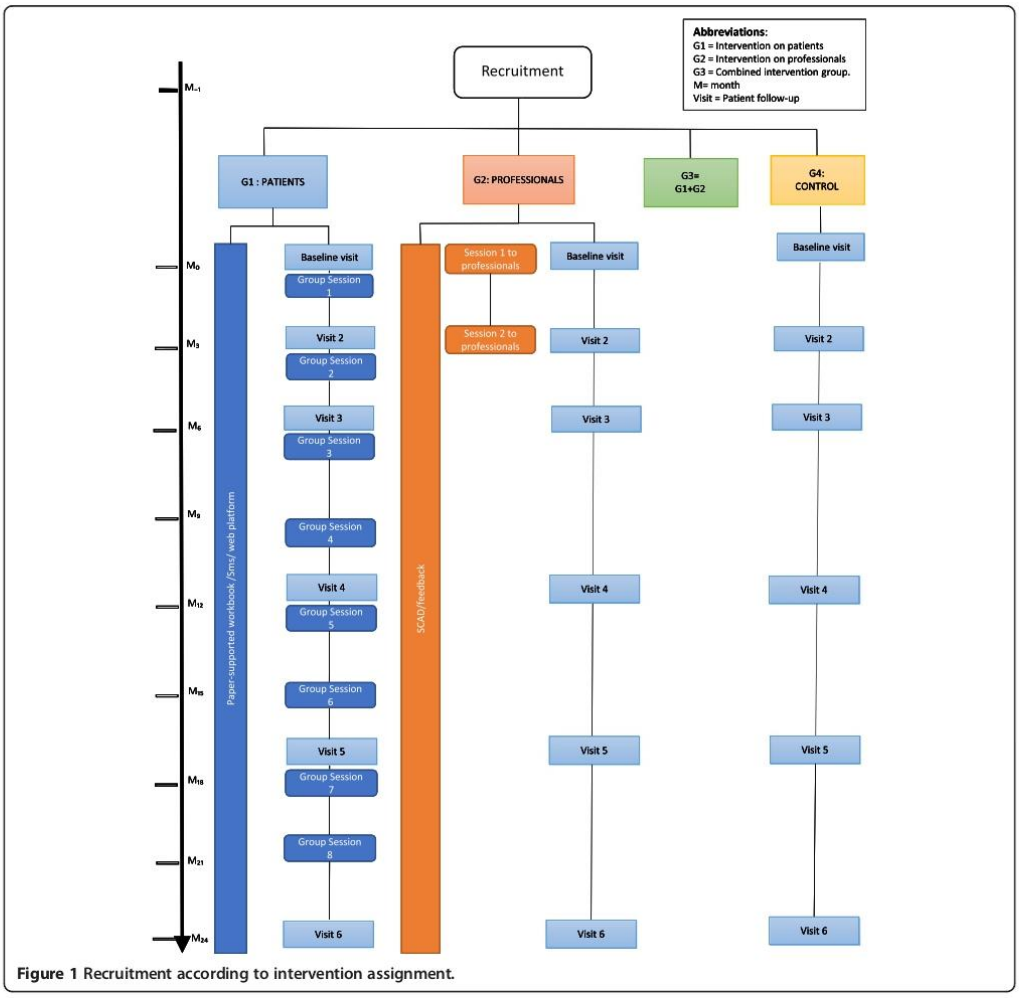

Figure 1 Recruitment according to intervention assignment.

the online workbooks, as an alternative to the website access.

C) Tailored semi-automated mobile phone messages for continuous patient support:
Mobile phones are used to warrant reception of tailored continuous support by means of semi-automatic periodic delivery of predefined SMS to support diabetes self-management about healthy diet, tobacco use, physical activity, treatment adherence, stress management, and foot care [18]. SMS contents are progressively fitted according to the topics discussed in the successive group sessions and to the degree of achievement of the different targets required to attain adequate self-management. SMS are sent weekly, focused on two different targets each week (eight targets per month). Specific SMS are selected according to a computer algorithm that reviews patient compliance for every target monthly. Compliance is classified as either 'adequate control,' 'partial improvement,' or 'inadequate control' for every target. The eight targets with the poorest results are selected monthly, on a two-per-week basis. Two messages a week are sent when targets attained 'adequate control' or 'partial improvement.' For targets under 'inadequate control,' four messages a week are activated. In addition, all patients receive one

general education SMS and another as a reminder to complete questionnaires every week, up to a maximum of one SMS a day. The ICT-based interventions (components B and C of the patient intervention) were designed according to the best available evidence by means of a literature review [18,20,32,33].

Interventions for primary care physicians and nurses

Primary care professionals (physicians and nurses) assigned to groups 2 and 3 receive a complex intervention of knowledge transfer and decision-making composed of the following: A) an educational and interactive group program, B) continuous support by means of an automated decision aid tool embedded into the electronic clinical record of patients included, and C) periodic feedback on process and outcome measures for all T2DM patients of the corresponding FCU.

A) Educational interactive group intervention for FCUs: The six FCUs (physician-nurse couples) selected in every PHCP received 5 hours of education, in two interactive sessions, 3 months apart. The objectives and contents of the first session are designed to update evidence-based clinical knowledge on T2DM management, improve communication and negotiation abilities, and develop skills to promote patient-centered care [34] and shared decision-making [29]. Role-playing exercises with a set of short video-films representing different types of complex sham patients are used to deliver this intervention. The session also includes an explanation about the use of the automated decision aid tool (see below). The second session is designed to promote shared decision-making and motivational interviewing methods in the context of the patient-centered care model [29,34]. Shared decision-making is promoted throughout the sessions to help patients explore and identify their personal preferences. These sessions are led by an endocrinologist and a primary care physician with proven expertise in communication skills and patient-centered care methods [35-37]. They are video-recorded in order to standardize training and to ensure intervention reliability [38].
The evidence-based information to update knowledge on clinical management for T2DM was obtained from the clinical practice guidelines (CPG) of the National Institute for Health and Clinical Excellence of the United Kingdom (NICE) [9] and was complemented with those developed by the American Diabetes Association (ADA) [8]. These two guidelines were selected after a process that included 1) a systematic search of guidelines in several databases (MEDLINE, PREMEDLINE, Trip Database, GuíaSalud (CPG database in Spain), and National Guideline Clearinghouse) and 2) the assessment of their quality by means of the AGREE instrument and their degree of updating [39]. Contents from these two CPG were collapsed and contextualized to obtain the INDICA CPG.

B) Decision support tool embedded in the ECR: Physicians and nurses have access to an automated decision support tool (DST) built by means of a computational algorithm from the previously developed INDICA CPG and integrated into the primary care ECR to adapt the recommendations to the specific needs of every patient included. This DST is passively activated, providing dynamic and interactive support for clinical management of decision-making. The tool is made available for the 15 patients included in every FCU [23-25]. As previously mentioned, the DST takes into consideration both the best available scientific knowledge [8,9] and relevant clinical information of every patient stored in the ECR (blood pressure, glucose, and cholesterol levels; renal function, comorbidities, missed tests or appointments, etc.).

C) Feedback screen:
Every month, physicians and nurses in participating FCUs receive feedback, consisting of a computer screen displaying a personalized graphical summary of relevant processes and outcome indicators compared to mean results obtained by participating PHCP [25]. Every month, this informative screen is automatically displayed when the healthcare professional switches on his/her work PC. The screen displays combined indicators, periodically generated by automated proprietary analytical models from the ECR of all T2DM patients in the FCU and not just the 15 study participants. Process indicators assessed include the measurements HbA1c, blood pressure, body mass index (BMI), and lipid profile, as well as the performance of periodic screening for retinopathy and nephropathy, according to the INDICA CPG recommendations. Outcome indicators are based on the levels of HbA1c, blood pressure, BMI, and every component of the lipid profile. Outcome indicators are classified into three levels depending on whether the patients are in the expected target, not in target but better than the previous visits, or out of target and with no improvement. An overall severity indicator is also calculated by taking into consideration the number of outcome indicators out of the expected goal by patient. For every indicator displayed on the screen, mean reference values obtained from all FCUs at the same PHCP are used as dynamic comparators.

Ethics

The Scientific and Ethics Committees of both the University Hospital of Canarias and the University Hospital Nuestra Señora de la Candelaria approved the study protocol. Moreover, a Data Safety and Monitoring Board was appointed to review and monitor the study procedures and potential adverse events. The study is being performed in accordance with Good Clinical Practice standards, applicable local regulatory requirements, and the recommendations of the Declaration of Helsinki.

Endpoints

Primary endpoint

The primary endpoint of the study is the mean change in HbA1c from baseline until 24 months later. We considered a change in HbA1c of 0.4 percentage points to be clinically significant [40]. In addition to the measurements at baseline and at 24 months, HbA1c is also measured at 3, 6, 12, and 18 months (Table 1).

Secondary endpoints

A broad set of secondary outcomes are measured (Table 1), including the following:

- *Cardiovascular risk factors*: mean change of BMI, waist circumference, and waist-to-hip ratio, systolic and diastolic blood pressure, total cholesterol and its fractions (low-density lipoprotein (LDL), high-density lipoprotein (HDL), and nonHDL), and triglycerides. Blood pressure is measured twice in one arm (right when possible) in a sitting position, with a digital sphygmomanometer trademark OMRON© model M6, and the average of the two readings will be recorded. Smoking status is determined by self-report of whether the subject currently smoked.
- *Macrovascular diabetes complications*: new ischemic heart events (angor pectoris, myocardial infarction, surgical or percutaneous coronary revascularization), hospitalization for congestive heart failure, peripheral artery disease (surgical or percutaneous peripheral arterial revascularization, nontraumatic lower limb amputation), carotid stenosis fulfilling criteria for endarterectomy, or confirmed ischemic or hemorrhagic stroke. The annual occurrence of cardiovascular events, surgical procedures, or hospitalization is verified by reviewing the medical records.
- *Microvascular diabetes complications*: Incidence and progression of diabetic nephropathy: mean change in UACR, UACR ≥ 30 mg/g, mean change in estimated glomerular filtration rate (eGFR), eGFR < 60 mL/min/1.73 m^2 and need for renal replacement therapy (dialysis or renal transplantation).

Table 1 Outcome measurements according to periods of follow-up and type of collection

Time		Outcome measurements
Outcomes measured on patients		
M0, M3, M6, M12, M18, M24 (F to F)		Demographic data, health history, history of DM, DM health status, current medications, risk factors for complications of poorly controlled DM
Laboratory measurements		
M0, M12, M24 (CT)		HbA1c; fasting glucose; total cholesterol; HDL, LDL, and non-HDL cholesterol; triglycerides; serum creatinine; albumin/creatinine ratio; and glomerular filtration rate
M3, M18 (CT)		HbA1c, fasting glucose
M6 (CT)		HbA1c, fasting glucose, total cholesterol, HDL, LDL cholesterol, and triglycerides
Anthropometric measurements		
M0, M3, M6, M12, M18, M24 (F to F)		BMI, waist/hip ratio, systolic and diastolic blood pressure, heart rate
Macro and microvascular complications		
M0, M12, M24 (F to F, ECR)		Incidence of new ischemic heart events, hospitalization for congestive heart failure, peripheral artery disease, carotid stenosis fulfilling criteria for endarterectomy or confirmed ischemic or hemorrhagic stroke, incidence or progression of diabetic retinopathy, incidence or progression of diabetic nephropathy
Eye examination		
M3, M24 (CT)		Retinography and macular examination by OCT
Instruments used for self-reported outcomes measures		
M0, M12, M24	(SRI)	ADDQoL-19, BDI-II, DES-SF, DDS2, DIATEK, IPAQ, MEDAS, STAI-S, INDICA-LSQ
	(F to F)	EQ-5D-5 L, MMAS
M6, M18	(SRI)	ADDQoL-19, IPAQ, MEDAS
	(F to F)	EQ-5D-5 L, MMAS
Healthcare utilization		
M0, M3, M6, M12, M18, M24 (F to F, ECR)		Visits to primary care services, nurses, specialists; hospital admissions, emergency room visits, laboratory procedures, and other diagnostic tests; medication
Satisfaction		
M24 (SRI)		INDICA-SATP
Outcomes measured on physicians and nurses		
M0 (F to F)		Demographic data, years in practice, practice descriptors
M0, T3 (SRI)		INDICA-KNOW, LATCon
M24 (SRI)		INDICA-SATC

BMI: body mass index; F to F: face to face interview; CT: clinical test; DM: diabetes mellitus; ECR: electronic clinical records; HDL: high-density lipoprotein; LDL: low-density lipoprotein; OCT: optical coherence tomography; SRI: self-reported interview.
Note: see description of the questionnaires in Table 2.

Incidence and progression of diabetic retinopathy, according to the results of a retinography, and incidence and progression of diabetic macular edema, according to the results of an optical coherence tomography (OCT) and a retinography, are measured at months 3 and 24 of the study. Incidence of diabetic polyneuropathy is measured using the Michigan Neuropathy Screening Instrument (MNSI), an emergent instrument used to assess distal diabetic peripheral polyneuropathy. Only the 15-item self-administered MNSI, which is scored by adding up abnormal responses [41] will be applied. MNSI was translated into and back-translated from Spanish for its use in the INDICA study.

- *Health-related quality of life* (*HRQoL*), *distress, anxiety, depression, satisfaction with the interventions, health behaviors, and changes in knowledge about diabetes self-management*: all instruments selected to measure these outcomes are reported in Table 2.
- *Attitude toward concordance and knowledge about the clinical management of diabetes*: these instruments, reported in Table 2, are used to evaluate the interventions on physicians and nurses included in groups 2 and 3.

Table 2 Instruments used for self-reported outcomes measures

Instruments	Outcome measurements
Outcomes measured on patients	
EQ-5D-5L [59]	Generic HRQoL questionnaire. The self-reported description assesses five domains: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression
ADDQoL-19, Audit of Diabetes-Dependent Quality of life [60]	Specific HRQoL questionnaire for DM. It assesses 19 domains: leisure activities, working life, travel, holiday, physical activities, family life, social life, personal life, sex life, physical appearance, self-confidence, motivation, reaction from others, feelings about the future, financial situation, living conditions, reliance on others, freedom to eat, and freedom to drink
DDS2, Diabetes Distress Scale [61]	It is a validated two-item diabetes distress-screening instrument that asks respondents to rate on a six-point scale the degree of distress caused by the two following items: (1) feeling overwhelmed by the demands of living with diabetes and (2) feeling that I am often failing with my diabetes regimen
STAI-S, State Trait Anxiety Inventory [62]	It is a self-description questionnaire including two non-dependent scales, the applied state-anxiety scale (STAI State) and the trait-anxiety scale (STAI Trait). It assesses transient emotional state or condition as characterized by subjective feelings of tension and apprehension that can fluctuate in time and intensity
BDI-II, the Beck Depression Inventory II [63]	It is a validated 21-item self-report inventory that measures depressive symptoms such as sadness, pessimism, suicidal thoughts or wishes, tiredness or fatigue, loss of energy, and loss of pleasure, among others
DES-SF, Diabetes Empowerment Scale-Short Form [64]	This questionnaire assesses patient empowerment on T2DM management, including eight items with responses on a five-point Likert scale
IPAQ, International Physical Activity Questionnaire. [65]	This questionnaire checks physical activity and provides information on the time spent on walking, moderate-intensity activities, and vigorous and sedentary activities
MEDAS, Mediterranean Diet Adherence Screener [66]	This questionnaire assesses diet recommendation adherence. It consists of 14 targets for food consumption rated with one point for each target achieved
MMAS, Morisky Medication Adherence Scale [67]	This questionnaire assesses the medication adherence, including a four-item self-report measure with an established concurrent and predictive validity
INDICA-SATP	Patient satisfaction and usability of the web portal and the mobile phone communication system are assessed with a specific instrument created in the context of this project
Diatek	It is a specific instrument created in the context of this project, to assess potential changes in patient knowledge about DM based on the CPG INDICA
INDICA-LSQ	It is a specific instrument created in the context of this project used to assess attitudinal changes of patients regarding lifestyles, based in the Transtheoretic Model of Behavior Change [68]
Outcomes measured on physicians and nurses	
LATCon, Leeds Attitude toward Concordance scale [69]	It is a 12-item self-reported scale to assess patients' and health professionals' attitudes toward concordance in medicine-taking
INDICA-KNOW	Knowledge change among healthcare professionals will be measured with the aid of an instrument with 20 questions based on the contents of the INDICA CPG
INDICA-SATC	Acceptability and usability of the DST and the feedback screen is measured according to four different dimensions: acceptability of interactions and time devoted using the software communication technology, impact on patients, impact on the clinician's practice, and communications issues such as quality of feedback and formats used [70]

DST: decision support tool.

Healthcare utilization Costs because of the clinical management of T2DM in all groups will be assessed from the healthcare services perspective, including the costs related to the development and use of all components for each intervention assessed (group sessions, ICT system, SMS services, computer-assisted aids, etc.). The analysis will also include costs because of patient contacts with primary care services, hospital admissions and length of stay, outpatient visits, emergency attendances, and prescribed medications. The volume of resource used for each cost component will be measured with the aid of patient questionnaires and ECR; unit costs will be taken from standard published sources when available and from the specific providers.

Measurement procedures

Information needed from patients are being collected by several procedures, including face-to-face interviews, clinical examinations, analysis of data stored in the ECR, downloading of information from the INDICA web platform, and self-completed questionnaires. Results of laboratory tests will be downloaded from ECR by trained staff blinded to patient group assignment.

Information needed from FCUs is being obtained by means of personal interviews and self-reported questionnaires.

The planning of information collection for every outcome measured throughout the project is shown in Table 1.

Biochemical determinations

Blood and urine samples are being collected after an overnight fast, by research nurses, using the available facilities of the participating PHCPs. After centrifugation, samples are being immediately transported to the biochemistry laboratory of the corresponding reference hospital. HbA1c is being quantified according to the Diabetes Control and Complications Trial assay. LDL cholesterol will be estimated using the Friedewald formula, and nonHDL cholesterol will be calculated as the difference between total cholesterol and HDL cholesterol. Estimated glomerular filtration rate will be calculated using the Modification of Diet of Renal Disease formula (MDRD4).

Biological samples for future research questions

To facilitate efficient answers to potential future research questions on T2DM in the Canarian population, urine and blood samples of patients are being frozen and stored. This will enable collating a collection of biological specimens from a wide and representative sample of the overall T2DM population in the Canary Islands. Urine and serum samples are being obtained at baseline and 24 months, while DNA samples are only being obtained at baseline. Every patient will be specifically informed and asked to consent to storage of DNA and nonDNA biological samples. These samples are being stored in the biobanks of the hospitals of the Canary Islands belonging to the Spanish National Biobanks Network. This process is in accordance with prevailing Spanish laws on protection of personal data [42], patient autonomy [43], and biomedical research [44]. These materials will subsequently be used to search for genetic or biological markers that could either characterize the T2DM patient population or predict clinical disease course.

Statistical methods

Generalized linear mixed models with repeated time measurements will be used to analyze changes in outcomes over time. To compare the three interventions and the control group after different follow-up periods (Baseline, 3, 6, 12, 18, and 24 months), the intervention groups will be treated as a 'factor within.' First, we will examine whether the intervention in Groups 1 and 2 are better than usual care, and then, we will examine whether the most intensive intervention (group 3) is better than less intensive interventions (groups 1 and 2). The purpose of these analyses is to obtain preliminary estimates regarding the incremental benefits of the intervention components [45]. For multiple comparisons, the *P* value will be adjusted with Bonferroni correction (Pc Z corrected value). In addition, the models will include a subset of covariates that are imbalanced at baseline. To identify the covariates to be included in the model, we will first fit separate models including each covariate, one at a time. The final model will include those covariates such that their inclusion changes the estimates' treatment effect by at least 10%. As suggested in the CONSORT statement, decisions about covariates will not be based on *P* value [46,47].

To incorporate the effect of cluster analysis, a multilevel model (MLM) approach will be implemented. MLM adjusts for the clustering effects across three levels (patients, FCU, and PHCP) of the hierarchical data structure.

For the main intention-to-treat analysis comparing outcomes, all patients will be included. Standard imputation methods (i.e., mean value imputation, last observation carried forward) will be used to impute missing data depending on the pattern of missing data. All tests will be two-sided with a type I error of 5%. Statistical analyses will be performed using Statistical Package for social Sciences (SPSS v.21, Chicago, IL, USA).

Sample size calculation We estimated that 393 patients per arm (total in the study = 1,572) were needed to detect an absolute difference in Hba1c of 0.4%, assuming a common standard deviation of 1.4% [40], a two-tailed power of 90%, and an alpha of 0.05. After an additional

adjustment for clustering of patients within FCU by the design effect [48], assuming 15 patients per FCU and an intra-class correlation coefficient of 0.01 (interquartile range: 0 to 0.032) based on data from the literature [49], the estimated number of patients per arm was 448 (total in the study = 1,792). Although the unit of allocation was the PHCPs, these are formed of several healthcare centers throughout the territory that only share administrative management and some services. Also, this effect was already controlled by means of the stratification. Therefore, we considered that the intra-class correlation within PHCP was insignificant, and we used instead the intra-class correlation for FCU, that is, among patients served by the same FCU. Although small, we consider that this correlation is significant.

However, sample size was increased by an additional 30% to accommodate for expected losses to follow-up and to warrant the presence of each arm in the study in the different islands. Hence, we aimed for a total sample size of 2,330.

Cost-effectiveness analysis

We will undertake a detailed analysis of the cost and the cost-effectiveness of each of the four groups in comparison to the others. Our analysis will conform to accepted economic evaluation methods. We will estimate cost and cost-effectiveness for the 'within-trial' period (2 years/short-run model) and also over the expected lifetime of the patient (lifetime/long-run model).

Short-run model The cost-effectiveness measures in the two-year model will be the incremental cost per quality-adjusted life year (QALY) gained. QALYs will be calculated based on the HRQoL data collected during the trial. HRQoL will be measured according to the EQ-5D-5 L, which will be collected at baseline and at each follow-up visit for each individual patient. Patient-specific utility profiles will be constructed assuming a straight line relation between each of the patients' EQ-5D-5 L scores at each follow-up point. The QALYs experienced by each patient from baseline to 2 years will be calculated as the area underneath this profile. We will investigate differences in baseline characteristics and, if necessary, use regression methods to control for them. As explained above, costs included in the analysis are those incurred by the healthcare service. Cost-effectiveness will be calculated as the incremental cost-effectiveness ratio (ICER) by dividing the estimated differences in costs by the differences in effects observed. Nonparametric methods to calculate confidence intervals around the ICER based on bootstrapped estimates of the mean cost and effect differences will be used. The bootstrap replications will also be used to construct a cost-effectiveness acceptability curve, which will reveal the probability that each alternative is cost-effective at 2 years for different values of willingness to pay for an additional unit of effectiveness. We will also subject the results to extensive deterministic (one-, two-, and multiway) sensitivity analysis.

Long-run model The interventions under evaluation in this study are likely to have an impact beyond the trial period. To capture these potential effects, we will extrapolate the results to an extended time horizon in the analysis, i.e., considering the remaining life expectancy of the patients.

We will consider the potential application of the Centers for Disease Control-Research Triangle Institute (CDC-RTI) Diabetes Cost-Effectiveness Model [50] to estimate long-term outcomes in our population. The CDC-RTI Diabetes Cost-Effectiveness Model is a validated simulation model of disease progression and cost-effectiveness for T2DM based on data from the UK Prospective Diabetes Study (UKPDS) [51] and other sources. The aim of this model is to simulate the development of T2DM-related complications on three microvascular disease paths (nephropathy, neuropathy, and retinopathy) and two macrovascular disease paths (coronary heart disease and stroke). The model structure is based on a Markov model which simulates the progression of a patient based on estimated transition probabilities between possible disease states. In the CDC-RTI Diabetes Cost-Effectiveness Model, transition probabilities depend on risk factors—including HbA1c and cholesterol concentrations.

Following decisions about model structure to estimate future outcomes, a list of parameter estimates required for the model will be developed. Data from the trial will be used to input the model in order to estimate the long-term cost-effectiveness of the different alternatives, alongside relevant data from the published literature. The specific details of the data to be used to populate the model will be determined following the development of the structure and the systematic literature searches to identify available evidence. The cost-effectiveness measure will again be expressed in terms of the ICER for each alternative after discarding dominated strategies. We will undertake deterministic (one-, two-, and multiway) and probabilistic sensitivity analysis, the latter assuming appropriate distributions and parameter values [52].

Duration of fieldwork

Fieldwork is estimated to last 3 years. The first year to complete recruitment of patients and healthcare providers in primary care and the following 2 years for follow-up and measurement. As interventions are maintained over time, the period of intervention and follow-up overlap (Figure 1).

Monitoring

Trial monitoring is the responsibility of a research team in charge of all quality control activities, assessing adherence to the trial protocol: timely work plan execution and comprehensiveness of data acquisition and data quality (databases have been designed to avoid downloading inappropriate values for every variable). The interactive group sessions for patients and family members, as well as those for primary care physicians and nurses, are being recorded to monitor the quality of the intervention and its adherence to the predefined script.

Trial status

Recruitment is complete and the trial is ongoing.

Discussion

The ongoing INDICA study is a four-arm RCT involving all main actors playing a role in decision-making in T2DM (patients, families, physician and nurses). The INDICA study will assess the comparative effectiveness and cost-effectiveness of usual care for T2DM patients against three multicomponent education and coaching interventions. These interventions combine conventional group educational and training activities with different ICT-based interventions to guide the decisions of T2DM patients, families, and primary care healthcare professionals, according to evidence-based guidelines. The primary analysis is aimed at comparing the mean 24-month HbA1c (operationalized as HbA1c % change from baseline) among patients with T2DM whose PHCPs were assigned to the usual care group with the mean 24-month HbA1c % change among patients with T2DM whose PHCPs were assigned to the three different intervention groups. The study used cluster randomization to reduce the risk of contamination bias, since the educational parts of the multicomponent interventions for patients and healthcare professionals were applied to groups.

The importance of glucose control in T2DM has been confirmed in a meta-analysis [53]. The high incidence of macrovascular complications, such as myocardial infarction, stroke, and lower-limb amputations, are a major cause of disability, mortality, and economic losses. Microvascular complications, including retinopathy, neuropathy, and kidney disease also account for a highly significant morbidity, mortality, and economic burden [54] among patients with T2DM. The incidence of these complications and their healthcare and social and economic consequences is higher in the Canary Islands than in the rest of Spain and most western countries [2-4].

The interventions assessed by the INDICA study are based on the conceptual framework of behavioral change and patient-centered care [29,34]. There is increasing evidence that good self-care is related to improved T2DM outcomes [10,11,55,56]. Provider education and continuous feedback to patients and the use of reminders have been associated with improvements in provider adherence to guidelines and with clinically significant improvements in patient outcomes [10,11,55,56]. Although ICT-based studies to improve diabetes self-management have grown rapidly, there is a substantial discrepancy between the demand for this healthcare delivery mode and the scientific evidence supporting its efficacy and cost-effectiveness. Most published studies are focused on single interventions exclusively aimed at patients and are limited by methodologic deficiencies related to small-sample sizes and inconsistent selection of outcomes and measurement instruments, as well as short follow-up periods [57]. Although several studies assessing the effectiveness of ICT-based interventions on diabetes outcomes have reported small but significant effect-sizes [18-22,58], very few have assessed cost-effectiveness. Cost-effectiveness is especially relevant for the assessment of ICT-based interventions aimed at prevalent chronic diseases, given that the highest costs of the interventions correspond to the development of ICT applications whose effectiveness will become blurred over time as well as with their use by thousands of patients and physicians. In the current times of financial crisis, interventions not only have to prove effectiveness but also cost-effectiveness to reduce uncertainty in healthcare policy decision-making to contribute to the economic sustainability of public healthcare services. Consequently, while much is promised by electronic communications and tele-health interventions, there is a lack of robust information to support decisions at patient, clinician, and healthcare policy decision-maker level.

The current worldwide availability of mobile phones and internet use across socio-economic, gender, and age groups, combined with their unique ability to process and communicate data in real-time, make them an ideal platform to create simple, effective, and real-time diabetes management programs that can be used for large groups of patients. Few previous studies of electronic communication interventions for T2DM are randomized, include a control group, or involve more than one treatment group to evaluate complex or multicomponent interventions for all actors involved, not only from the effectiveness perspective but also the assessment of cost-effectiveness. This approach will improve transferability by extending the usefulness of the expected results beyond patients and clinicians in primary care to healthcare policy decision-makers.

Abbreviations

BMI: Body mass index; CIHS: Canary Islands Health Service; CPG: Clinical practice guidelines; CT: Clinical test; DM: Diabetes mellitus; DST: Decision support tool; eGFR: Estimated glomerular filtration rate; ECR: Electronic clinical records; F to F: Face-to-face interview; FCU: Family Care Unit; HbA1c: Glycated hemoglobin; HRQoL: Health-related quality of life; ICER: Incremental cost-effectiveness ratio; ICT: Information and

communication technology; M: Month; OCT: Optical coherence tomography; PHCP: Primary healthcare practices; QALY: Quality-adjusted life year; RCT: Randomized controlled trial; SMS: Short message service; SRI: Self-reported interview; T2DM: Type 2 diabetes mellitus.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PSA is the principle investigator and conceptualized and designed the INDICA study with other investigators: YRF, LGP, ICR, LPP, AW, PPV, ACD, MBC, LVT, APR, ACL, AGQ, DAM, EEP, FMA, FHD, GMM, JAP, LRR, LSM, MRF, ORA, PPA, RAG, and VLS. YRF made the project coordination. PSA and YRF wrote the first draft of this publication, with contributions from LPP, AW, MER, MSF, LGP, ICR (the 'Interventions' section) and LVT (the 'Cost-effectiveness analysis' section). LRR, APDR, APC, MBSS, JFJ, and HRM have a continuing role in monitoring the trial. AW, PPV, ACD, MBC, PPM IGP, ACF, APR, AGQ, AGP, CRA, DHC, EFM, FMA, ILG, JAS, JCW, RCS, RTA, and LMH provided clinical expertise and participated in the reviews of literature for the design of interventions. YRF, LGP, AW, ACD, AGP, CSP, CMA, CDA, CGM, CPP, DAM, EEP, EFM, GMM, HRM, JAP, JCW, LRR, MRR, PPA, and SKG developed the educational intervention for patients, and CSP, CDA, CGM, GMM, MRR, and SKG applied this intervention. YRF, LGP, ICR, LRR, ACD, EPP, JAP, MRF, RMF, and SKG developed the ICT intervention for patients. LPP, JPV, EEP, and RVL developed the educational intervention for professionals, and GGT, JPV, MMG, and RVL applied the intervention. YRF, LGP, PPV, MER, PPM, IGP, and MRF developed the TIC intervention to professionals. The following authors contributed considerably to the acquisition of data and critically reviewed the article: ASP, APC, BHD, CLS, CSV, DHO, DCP, EPD, FHG, FBA, FCL, GRMM, GR, IGC, JFAP, JGD, JSH, JRMS, JBH, JBS, LMM, MGP, IVM, PAM, MRR, MTS, MLM, MPP, NPD, RBT, RSD, and SAG. All authors contributed to revisions of the manuscript and read and approved the final manuscript.

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Publicación 2.

Original Paper

Effectiveness of Internet-Based Multicomponent Interventions for Patients and Health Care Professionals to Improve Clinical Outcomes in Type 2 Diabetes Evaluated Through the INDICA Study: Multiarm Cluster Randomized Controlled Trial

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic disease in which health outcomes are related to decision making by patients and health care professionals.

Objective: This study aims to assess the effectiveness of internet-based multicomponent interventions to support decision making of all actors involved in the care of patients with T2DM in primary care.

Methods: The INDICA study is an open, community-based, multicenter trial with random allocation to usual care or the intervention for patients, the intervention for health care professionals in primary care, or the combined intervention for both. In the intervention for patients, participants received an educational group program and were monitored and supported by logs, a web-based platform, and automated SMS. Those in the intervention for professionals also received an educational program, a decision support tool embedded in the electronic clinical record, and periodic feedback about patients' results. A total of 2334 people with T2DM, regardless of glycated hemoglobin (HbA_{1c}) levels and without diabetes-related complications, were included. The primary end point was change in HbA_{1c} level. The main analysis was performed using multilevel mixed models.

Results: For the overall sample, the intervention for patients attained a significant mean reduction in HbA_{1c} levels of 0.27 (95% CI 0.45 to 0.10) at month 3 and 0.26 (95% CI 0.44 to 0.08) at month 6 compared with usual care, which remained marginally significant at month 12. A clinically relevant reduction in HbA_{1c} level was observed in 35.6% (191/537) of patients in the intervention for patients and 26.0% (152/586) of those in usual care at month 12 (P=.006). In the combined intervention, HbA_{1c}

reduction was significant until month 18 (181/557, 32.6% vs 140/586, 23.9%; *P*=.009). Considering the subgroup of patients uncontrolled at baseline, all interventions produced significant reductions in HbA_{1c} levels across the entire study period: 0.49 (95% CI 0.70 to 0.27) for the intervention for patients, 0.35 (95% CI 0.59 to 0.14) for the intervention for professionals, and 0.35 (95% CI 0.57 to 0.13) for the combined intervention. Differences in HbA_{1c} for the area under the curve considering the entire period were significant for the intervention for patients and the combined intervention compared with usual care (*P*=.03 for both). Compared with usual care, the intervention for professionals and the combined intervention had significant longer-term reductions in systolic and diastolic blood pressure.

Conclusions: In uncontrolled patients, the intervention for patients at baseline provided clinically relevant and significant longer-term reductions of HbA_{1c} levels. The intervention for professionals and combined intervention also improved the cardiovascular risk profile of patients.

Trial Registration: ClinicalTrials.gov NCT01657227; https://clinicaltrials.gov/ct2/show/NCT01657227

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KEYWORDS

behavior modification; primary care; type 2 diabetes mellitus; patients adherence; eHealth

Introduction

Background

Type 2 diabetes mellitus (T2DM) is a chronic condition in which long-term health outcomes are related to patients' adherence to lifestyle modifications and pharmacologic treatments. Other stakeholders, such as relatives and primary health care professionals, are also involved in guiding patients' decisions.

Although the prevalence of T2DM in the Canary Islands is slightly higher than the average in Spain [1], the incidence of chronic diabetes-related complications [2,3] and mortality [4] is much greater. This occurs despite a continuous increase in diabetes-related public expenditure [5].

Regardless of the widespread availability of evidence-based clinical practice guidelines (CPGs) to care for T2DM, patients' access to effective educational interventions [6] and adherence to self-management activities remains limited internationally [7].

To address these unmet needs, many publications have reported on the effectiveness of using information and communications technology (ICT) applications to support decision making by patients and professionals [8-12], reporting favorable short-term effects on blood glucose control [11,12]. The effectiveness of other biological, cognitive, behavioral, or emotional outcome measures remains controversial [11]. Few large randomized controlled trials (RCTs) have assessed the long-term effectiveness of multicomponent ICT-based interventions, not only for patients but also for all stakeholders involved in diabetes management.

Objectives

The INDICA study is a cluster RCT conducted in the Canary Islands that assesses the effectiveness and cost-effectiveness of multicomponent interventions to support decision making for the main actors involved in the management of T2DM (patients, relatives, and primary health care professionals) in a large number of primary health care practices (PHCPs) [13]. We hypothesized that combining conventional educational activities with different ICT-based decision support tools would efficiently improve health outcomes in patients with T2DM. The main purpose of this study is to evaluate the long-term clinical effectiveness (24 months) of these multicomponent interventions compared with usual care on glycated hemoglobin (HbA_{1c}).

Methods

Study Design

The INDICA study is an open, community-based pragmatic, multicenter, clinical controlled trial with random allocation by clusters to usual care or to one of the following 3 interventions of knowledge transfer and behavior modification:

- Group 1 included interventions for patients and a family member (intervention for patients)
- Group 2 included interventions for health care professionals (physicians and nurses) at primary care (intervention for professionals)
- Group 3 combined the interventions for patients and professionals (combined intervention)

In the usual care or control group, neither patients or families nor physicians or nurses received any additional educational or supporting activities beyond the usual activities provided by the PHCP. The full study protocol has been reported elsewhere [13].

Study Participants

The INDICA study included patients with T2DM aged between 18 and 65 years, diagnosed at least 1 year before study enrollment, without diabetes-related complications, and who regularly used a mobile phone (Textbox 1 provides more details).

Textbox 1. Patients' inclusion and exclusion criteria.

Patient inclusion criteria:

- Patients with type 2 diabetes mellitus diagnosed at least 1 year before study enrollment
- Aged between 18 and 65 years
- Formal consent to participate in the study
- Regular usage of mobile phone

Patient exclusion criteria:

- Chronic kidney disease ≥ stage 3b, as defined by the National Kidney Foundation's Kidney Disease Outcomes and Quality Improvement Initiative, urinary albumin to creatinine ratio ≥ 300 mg/g, or urinary protein excretion ≥ 300 mg/24 hours
- Acute coronary syndrome (documented angina or myocardial infarction) or stroke in the last 6 months or class III or IV heart failure, according to the New York Heart Association
- Proliferative diabetic retinopathy or clinically significant diabetic macular edema requiring previous treatment with retinal photocoagulation, vitrectomy, or intravitreal injections of antivascular endothelial growth factor or triamcinolone acetonide 6 months before study inclusion
- Uncorrected severe hearing or visual impairment or corrected visual acuity ≤ 20/40 by any cause
- Diabetic foot with ulcers ≥ 2 according to the Wagner scale
- Liver cirrhosis
- Cancer, unless disease free 5 years after diagnosis
- Other terminal illnesses
- Intellectual retardation, dementia, and psychotic diseases
- Active substance abuse, alcohol, or drugs (must be sober for 1 year)
- Pregnancy
- Insufficient (Spanish) language skills
- Physical disability limiting participation in group education activities
- Concurrent participation in another clinical trial or any other investigational study

The family care unit (FCU) in each PHCP, comprising a family physician and a nurse responsible for the same set of patients, was the unit of recruitment. FCUs either planning or awaiting placement changes among PHCP in the first 6 months after project initiation were excluded.

All PHCPs included had to have at least eight FCUs and the availability of appropriate places to provide educational group sessions.

Setting and Recruitment

PHCPs were recruited in 4 Canary Islands (Tenerife, Gran Canaria, Lanzarote, and La Palma). FCUs were randomly selected from all consenting FCUs at each PHCP. The electronic clinical records (ECRs) of all potentially eligible patients in all selected FCUs were screened to verify inclusion and exclusion criteria. Finally, eligible patients were randomly selected per FCU.

Random Assignment

Randomization was performed at different levels. First, 3 different strata were created according to the geographical areas in the more populated islands (Tenerife and Gran Canaria). Second, 4 PHCP (clusters) were randomly allocated to every geographical stratum, and block permutation was used to assign PHCPs to the study arms (in total 12 PHCPs for each island), with PHCP as the sampling unit. La Palma and Lanzarote (less populated islands) were geographically divided into 4 zones with only 1 eligible PHCP available in each zone, which was randomly assigned to one of the study arms. On every island, all arms were equally distributed. A total of 6 FCUs were randomly selected from all those consenting to participate in each PHCP. Furthermore, 15 patients were randomly selected from all patients fulfilling the inclusion criteria and consenting to participate in each FCU. Exceptionally, more than 6 FCUs or more than 15 patients per FCU were selected to recruit 90 patients at every PHCP.

FCU and patient randomizations were performed by simple generation from a list of random numbers.

Cluster allocation avoids contamination bias among participants, also facilitating logistics in group interventions.

Interventions

Patient Interventions

Patients recruited to the intervention for patients and combined intervention groups received a complex intervention of knowledge transfer and behavior modification, informed by conceptual frameworks of behavioral change [14]. Key determinants of behavior change suggested by Michie et al [14] were considered for intervention design and implementation, including social and professional role and identity, knowledge, skills, beliefs about capabilities, beliefs about consequences,

motivation and goals, memory, attention and decision processes, environmental context and resources, social influences, emotion, and action planning. Linked to these construct domains, interventions included all techniques judged as effective by the same authors [14], combining (1) a conventional group educational program with a set of 8 quarterly 3-hour group sessions; (2) monitoring of physical activity, diet, drug adherence, mood, blood pressure, and blood glucose readings by daily usage of paper workbooks, complemented by weekly access to a website to download paper workbook data (Multimedia Appendix 1); and (3) continuous personalized feedback by semiautomated mobile phone messages based on the results from the website.

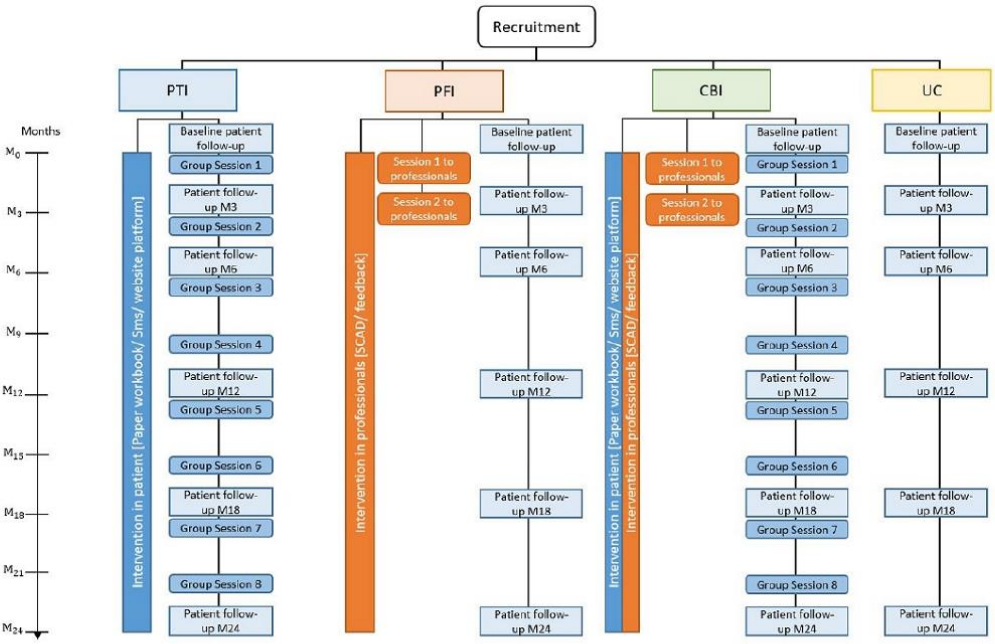
Interventions for Primary Care Professionals

Primary care professionals recruited to the intervention for professionals and combined intervention groups received a complex intervention of knowledge transfer and decision support, partially addressing the determinants of behavior change suggested by Michie et al [14] for its design and implementation, including only techniques to improve skills, environmental changes, prompts and cues by means of electronic clinical guidelines linked to the ECR, processes for encouraging and supporting doctors and nurses, persuasive communication, and periodic feedback on outcomes compared with other colleagues. The interventions combined (1) an educational and interactive group program of 2 sessions to update clinical management and promote patient-centered care; (2) an automated decision aid tool based on a CPG for T2DM, embedded into the ECR (Multimedia Appendix 2); and (3) monthly computerized graphic feedback, displaying a set of processes and outcome indicators for all patients with T2DM of the corresponding FCU.

To maintain the fidelity of interventions, a manual was developed for each intervention. Furthermore, all group sessions were recorded and reviewed.

Both interventions were applied during the 2 years of follow-up (Figure 1).

Figure 1. Arm's intervention timeline and follow-up points.



Duration of Fieldwork

Fieldwork took place between February 2013 and October 2016. The first year was devoted to the recruitment of patients and health care providers and the following 2 years to the intervention and follow-up. As interventions were maintained over time, the intervention and follow-up periods overlapped.

Outcomes

Primary End Point

The primary outcome was the mean change in HbA_{1c} levels from baseline to 24 months of follow-up. HbA_{1c} was also measured at 3, 6, 12, and 18 months. We considered a change in HbA_{1c} of 0.4% as clinically significant [15], just between the thresholds of 0.3% reported by National Institute for Health and Care Excellence [16] and 0.5% by the United Kingdom Prospective Diabetes Study [17].

Secondary End Points

BMI, weight, waist circumference, waist-to-hip ratio, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were also assessed at baseline and after 3, 6, 12, 18, and 24 months. Total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting serum glucose were assessed at baseline and after 6, 12, and 24 months. Serum creatinine and glomerular filtration rate were measured at baseline and at 12 and 24 months. Demographic data and disease history were recorded at baseline. Health status and current medications were also recorded at each follow-up.

Statistical Analysis

The main analysis for primary and secondary end points were multilevel mixed models including the baseline value of the dependent variable and the time elapsed since diagnosis (in years) as covariates. The null hypothesis for each end point is that the mean change with regard to the usual care arm and the interactions between each arm and time (follow-up) are the same across arms and equal to zero. The alternative hypothesis is that the changes are not equal to zero. First-level variables are those corresponding to each measurement along follow-up (repeated time measurements), the second level includes patients' variables, and third-level variables correspond to PHCPs. The mean change was estimated at the observation level. The effect that identifies the intervention arm was considered fixed for the PHCPs, whereas the intercept was considered random. The model also included an interaction term between arm and month, allowing for differences in the intervention effect between follow-up assessments [18]. In addition, to summarize the global treatment effect throughout the whole study period, differences were also calculated for the area under the curve (AUC) of HbA_{1c} and other continuous variables between the different interventions and the usual care group. Furthermore, we examined whether the most intensive intervention, the combined intervention group (intervention for patients plus intervention for professionals), was better than the intervention for patients and intervention for professionals groups on their own.

The adjusted estimated mean was calculated for each moment of follow-up compared with baseline, and its significance was calculated using the model already set out.

A post hoc analysis was performed for the primary end point, HbA_{1c}, considering the patient subsample with baseline HbA_{1c} higher than 7%.

To accommodate missing values in the effect analyses, the multiple imputation procedure in Stata 15.0 software (Stata Corporation) was used [19], with results based on 100 imputed data sets. This procedure saves cases for the analysis and can be considered an intention-to-treat analysis. Analysis under multiple imputation is valid for randomly missed data [20]. The model of imputation used and further details on data analysis are outlined in Multimedia Appendix 3. A threshold of .05 was used to define the statistical significance of those tests.

Sample Size Calculation

We estimated the sample size requirement of 448 patients per study arm to detect an absolute difference in HbA_{1c} of 0.4%, assuming a common standard deviation of 1.4% [15], a two-tailed power of 90%, an alpha of .05, and an adjustment for clustering of patients within the FCU by the design effect [21], 15 patients per FCU, and an intraclass correlation coefficient (ICC) of 0.01 (interquartile range 0-0.032) [22]. The intraclass correlation within PHCPs was insignificant as they are formed of several FCUs sharing administrative management and some additional services whose potential effects were already controlled by means of the stratification. Despite this consideration, the sample size was increased by an additional 30% to accommodate for expected losses to follow-up and to warrant the presence of each study arm in all islands. Hence, we aimed to obtain a total sample size of 2330.

Ethics Approval and Consent to Participate

All participants provided written informed consent. The scientific and ethics committees of both the University Hospital of Canarias and the University Hospital Nuestra Señora de la Candelaria approved the study protocol. The study was performed in accordance with Good Clinical Practice standards, applicable local regulatory requirements, and the recommendations of the Declaration of Helsinki.

Results

Study Participants

A total of 32 PHCPs with a mean of 6.6 (SD 0.9) FCUs were included (211 professionals), with 8 PHCPs allocated to each of the 4 study arms. Every PHCP enrolled a mean of 72.9 (SD 14.1) patients (12 patients per FCU), totaling 2334 patients. Figure 2 shows the flowchart for the patients taking part.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

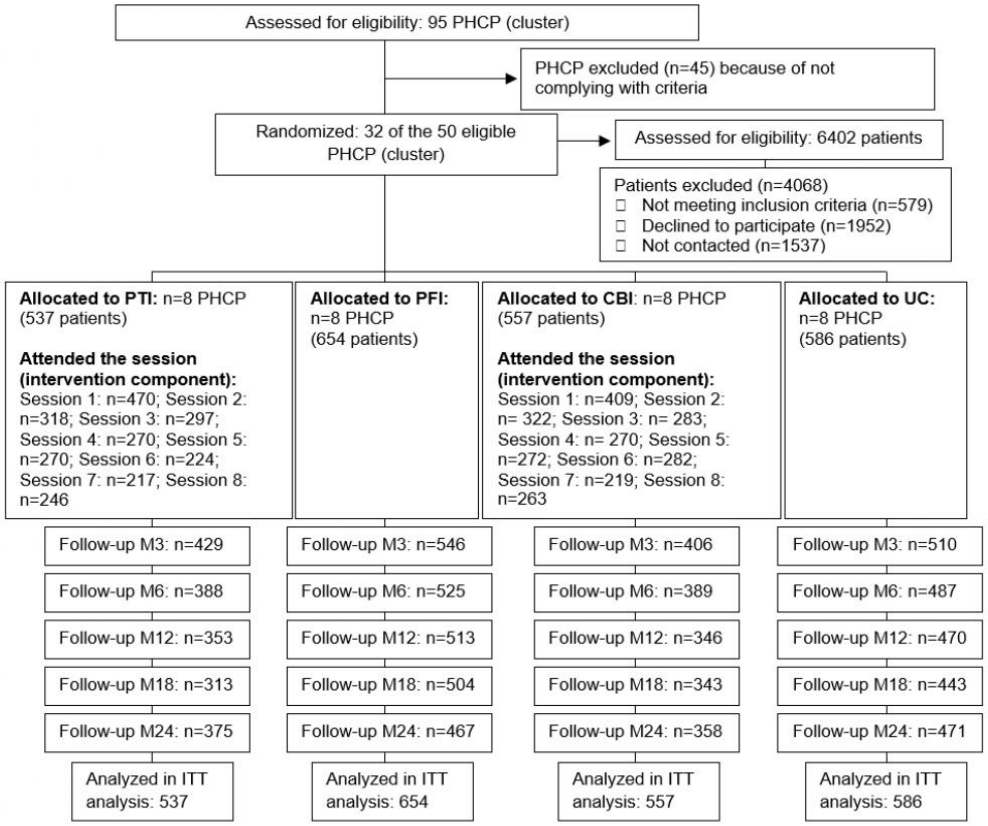


Table 1 shows the patients' baseline characteristics according to the intervention assignment. The mean age of the whole population was 55.7 (SD 7.1) years, with 51.9% (1212/2334) being women. The mean basal HbA_{1c} value was 7.3% (SD 1.5). Overall, 53.4% (1246/2334) of patients had HbA_{1c} levels within the accepted therapeutic goal (≤7%). There were no statistically significant differences among the groups in terms of their baseline characteristics.

Table 1. Baseline characteristics of patients.

Characteristics	PTI[a] (n=537)	PFI[b] (n=654)	CBI[c] (n=557)	UC[d] (n=586)
Age (years), mean (SD)	55.9 (7.0)	56.2 (7.0)	55.5 (7.1)	55.2 (7.3)
Gender (male), n (%)	284 (52.9)	288 (44.0)	264 (47.4)	286 (48.8)
Smoking status, n (%)				
Current smokers	114 (21.2)	156 (23.9)	109 (19.6)	145 (24.7)
Former smokers	223 (41.5)	280 (42.8)	225 (40.4)	240 (41.0)
Nonsmoker	200 (37.2)	218 (33.3)	223 (40.0)	201 (34.3)
Education, n (%)				
Primary or less	323 (60.2)	409 (62.5)	347 (62.3)	379 (64.7)
High school	159 (29.6)	176 (26.9)	147 (26.4)	157 (26.8)
Bachelor's degree or higher	55 (10.2)	69 (10.6)	63 (11.3)	50 (8.5)
Income per person in the household per month, n (%)				
<€250 (US $325)	118 (21.9)	139 (21.2)	121 (21.7)	146 (24.9)
€250-€499 (US $325-$649)	229 (42.7)	323 (49.4)	272 (48.8)	264 (45.1)
€500-€649 (US $650-$844)	86 (16.0)	99 (15.2)	122 (14.2)	96 (16.3)
>€750 (US $975)	104 (19.4)	93 (14.2)	64 (15.3)	80 (13.7)
BMI categories, n (%)				
Normal or underweight (<25)	52 (9.7)	58 (8.9)	45 (8.1)	44 (7.5)
Preobese (<30)	164 (30.5)	183 (28.0)	181 (32.5)	197 (33.6)
Obese class 1 (<35)	200 (37.2)	227 (34.7)	175 (31.4)	195 (33.3)
Obese class 2 (<40)	77 (14.3)	122 (18.7)	103 (18.5)	99 (16.9)
Obese class 3 or 4 (≥40)	44 (8.2)	64 (9.8)	53 (9.5)	51 (8.7)
BMI (kg/m^2), mean (SD)	31.6 (5.7)	32.4 (6.0)	32.1 (5.8)	32.1 (6.0)
Duration of diabetes (years), mean (SD)	8.4 (6.8)	8.2 (6.1)	8.9 (6.3)	8.6 (6.8)
Diabetes treatment, n (%)				
Only lifestyle	40 (7.5)	60 (9.2)	26 (4.7)	53 (9.0)
Oral	394 (73.4)	445 (68.0)	413 (74.1)	395 (67.4)
Injectable (insulin or GLP-1[e])	12 (2.2)	17 (2.6)	17 (3.1)	25 (4.3)
Oral+injectable	85 (15.8)	114 (17.4)	98 (17.6)	98 (16.7)
Do not know/not answered	6 (1.1)	18 (2.8)	3 (0.5)	15 (2.6)
HbA_{1c}[f] categories, n (%)				
<7%	258 (48.0)	351 (53.7)	241 (43.3)	304 (51.9)
7.0%-8.0%	146 (27.2)	165 (25.2)	165 (29.6)	141 (24.1)
8.1%-9.0%	66 (12.3)	75 (11.5)	82 (14.7)	67 (11.4)
>9.0%	67 (12.5)	63 (9.6)	69 (12.4)	74 (12.6)
HbA_{1c} (%), mean (SD)	7.3 (1.5)	7.2 (1.4)	7.4 (1.5)	7.3 (1.5)
Comorbidities, n (%)				
Hypertension	323 (60.3)	434 (66.4)	363 (65.2)	382 (67.1)
Hypercholesterolemia	353 (65.7)	448 (68.0)	349 (62.7)	367 (64.0)
Coronary artery disease	32 (6.0)	39 (6.0)	26 (4.67)	27 (3.9)
Ictus	12 (2.2)	5 (0.8)	13 (2.3)	14 (2.1)
Thyroid gland disorders	68 (12.7)	76 (11.6)	57 (9.7)	57 (11.8)

[a]PTI: intervention only for patients and family members.

[b]PFI: intervention only for health care professionals at primary care.

[c]CBI: combined intervention for patients and professionals.

[d]UC: usual care or control group.

[e]GLP-1: glucagon-like peptide-1.

[f]HbA_{1c}: glycated hemoglobin.

The rate of attendance at educational sessions is also shown in Figure 2. The mean number of sessions attended by patients in the intervention for patients and combined intervention groups was 4.3 (SD 2.7) and 4.2 (SD 2.8), respectively. Overall, 87.5% (470/537) of the patients assigned to the intervention for patients group attended the first of the 8 educational sessions, which decreased to 59.2% (318/537) in the second session and to 45.8% (246/537) in the last session. In the combined intervention group, attendance rates were 73.4% (409/557), 57.8% (322/557), and 47.2% (263/557), respectively. All patients in the intervention groups received SMS during the 2 years of follow-up and had access to the web platform that contained the video recordings of all group sessions in addition to other educational materials. The average number of web-based questionnaires filled in by each patient was 16.3 (SD 29.4) in the intervention for patients group and 9.9 (SD 23.1) in the combined intervention group. These differences were statistically significant (P<.001) at the 2-year follow-up.

Primary End Point: HbA1c

Multimedia Appendix 4 shows the adjusted differences in the mean HbA_{1c} levels at each follow-up evaluation and the adjusted differences in AUCs of HbA_{1c} throughout the whole study for each intervention group, in comparison with the usual care group. Compared with usual care, intervention for patients achieved a significant mean HbA_{1c} reduction of 0.27 (95% CI 0.45 to 0.10) at month 3 and 0.26 (95% CI 0.44 to 0.08) at month 6. Differences between intervention for patients and usual care groups were marginally significant at 12 months (P=.07). There were no statistically significant differences in mean HbA_{1c} levels in the intervention for professionals and combined intervention groups, when compared with the usual care group. With regard to the AUC of HbA_{1c}, the effect of intervention for patients was marginally significant compared with usual care (P=.06), considering all the follow-up sessions.

The mean levels of HbA_{1c} across the study and their adjusted differences with regard to baseline values are shown in Multimedia Appendix 5 by the study arm. Mean HbA_{1c} levels of the intervention for patients group significantly improved during the first 12 months of follow-up, showing a maximal reduction at month 3 (0.35; 95% CI 0.48 to 0.22). The differences gradually diminished over time until they disappeared at months 18 and 24.

At month 3, a clinically relevant reduction in HbA_{1c} (at least 0.4%) was observed in 38.6% (207/537) of participants in the intervention for patients group and only in 20.3% (119/586) of patients with usual care (P<.001; Multimedia Appendix 6). Differences between both groups in the proportion of subjects with a clinically significant decrease in HbA_{1c} remained statistically significant until month 12 (191/537, 35.6% vs 152/586, 26.0%; P=.006) and marginally significant until month 18. The percentage of patients with clinically relevant decrease in HbA_{1c} was also significantly greater in the combined intervention group than in the usual care group at months 3, 6, and 18.

The results of the interventions were also analyzed in the relevant subgroup of uncontrolled patients with baseline HbA_{1c} >7%. As shown in Multimedia Appendix 7, for this subgroup, the differences in the HbA_{1c} reduction between the intervention for patients and usual care groups were statistically significant, favoring the intervention for patients group from months 3 to 12. The differences in HbA_{1c} AUC between the intervention groups and the usual care group considering the entire period were statistically significant for the intervention for patients and combined intervention: 0.26 (95% CI 0.48 to 0.04) and 0.25 (95% CI 0.47 to 0.03), respectively. For the intervention for professionals group, the differences were marginally statistically significant (P=.09).

All interventions led to a significant reduction in HbA_{1c} among subjects with baseline HbA_{1c} levels >7% across the entire study period (Multimedia Appendix 8). The differences at 24 months were 0.49 (95% CI 0.70 to 0.27) for intervention for patients, 0.35 (95% CI 0.59 to 0.14) for intervention for professionals, and 0.35 (95% CI 0.57 to 0.13) for combined intervention (Multimedia Appendix 8). Patients with usual care showed significant decreases in HbA_{1c} at months 12, 18, and 24.

Finally, in the subgroup with baseline HbA_{1c} levels >7%, the proportion of subjects with clinically significant reductions in HbA_{1c} (≥0.4%) was greater in the intervention for patients group than in the usual care group until month 12 (140/263, 53.1% vs 116/269, 43.2%; P=.049). The differences between the combined intervention and the usual care groups were significant at month 3 (Multimedia Appendix 6).

Secondary End Points

Compared with usual care, the intervention for professionals group had significantly lower SBP at months 3 and 18 and the combined intervention group had significantly lower SBP at month 24 (Multimedia Appendix 4). Compared with their respective baseline values, mean SBP fell significantly in all study groups, but the difference was greatest for the combined intervention group at 24 months (7.5 mm Hg; 95% CI 9.8 to 5.2; Multimedia Appendix 5). For DBP, compared with usual care, we found significant reductions at months 3 and 24 for intervention for professionals and at months 12 and 24 for combined intervention (Multimedia Appendix 4). When compared with baseline, all groups improved; the maximum reduction was at 24 months for the combined intervention group, with a fall of 6.7 mm Hg (95% CI 8.2 to 5.3; Multimedia

Appendix 5). The intervention for patients did not lead to a significant decrease in blood pressure compared with usual care (Multimedia Appendix 4).

Comparisons in BMI between the intervention for patients and usual care groups only attained statistically significant differences at month 3. None of the other interventions achieved greater BMI reductions than those observed for usual care (Multimedia Appendix 4). Compared with the baseline values, the mean values of BMI decreased in the intervention for professionals group throughout the follow-up and in the usual care group at months 3 and 24. The intervention for patients group experienced the greatest improvement and showed a statistically significant reduction at month 24: 0.78 kg/m^2 (95% CI 1.0 to 0.6; Multimedia Appendix 5).

Multimedia Appendices 4 and 5 contain detailed biochemical, clinical, and anthropometric data for the whole sample. Multimedia Appendices 7 and 8 contain these data for the subgroup with basal HbA_{1c} >7%.

All 4 groups showed statistically significant improvements in total and LDL cholesterol levels at the end of follow-up. The differences between the intervention and usual care groups were not statistically significant. HDL cholesterol and triglyceride levels did not reveal clinically relevant changes.

We did not detect statistically significant differences in the comparison of intervention for patients and intervention for professionals groups in relation to the most intensive intervention in the combined intervention group regarding the primary or secondary outcomes in the AUC over the follow-up period, except for BMI, which had a difference in area of −0.29 (95% CI −0.57 to 0.01) kg/m^2 in favor of the intervention for patients group.

For most clinical results, ICC values were low in every PHCP. Variance homogeneity was verified and thus reflected a very small effect associated with PHCP for intervention and control groups (similar clinical results among PHCP in every study arm). The ICC at the patient level was broad, accounting for considerable variations among individuals. Considering both ICC values, the results from the INDICA study appear to have good external validity.

Discussion

Principal Findings

The INDICA study assessed the effectiveness of multicomponent interventions to support decision making for the main actors involved in the management of T2DM (patients, relatives, and primary health care professionals) in many PHCPs [13]. We hypothesized that combining conventional educational activities with different ICT-based decision support tools would improve HbA_{1c} at long term (24 months) compared with usual care.

This study revealed that the intervention for patients group achieved a significant but temporary reduction of HbA_{1c}, compared with the usual care group, which lasted for 6 months, with a gradual dilution effect from then onward. Interventions focused on health care professionals and on both patients and health care professionals did not translate into a significant lowering of HbA_{1c}, in comparison with usual care, when evaluated in the whole study population. Even so, more than 30% of the participants belonging to the intervention for patients and combined intervention groups attained statistically and clinically relevant reductions in HbA_{1c} (>0.4%). These percentages were significantly greater than those observed in the control group at 12 months (for the intervention for patients group) and 18 months (for the combined intervention group).

It must be noted that, with the intention of assessing the effectiveness of the intervention for all patients with T2DM, the INDICA study did not limit inclusion of participants by their HbA_{1c} level. Therefore, the study's power to find clinically relevant differences for the main outcome measures could have been insufficient, according to Jackson et al [23], as only 50.6% (1180/2334) of all participants had baseline HbA_{1c} concentrations >7% (mean 7.3%, SD 1.5). Nonetheless, the study's sample size provided statistical power to examine the results of patients with worse metabolic control, allowing the comparison with other studies that limited recruitment to patients with poor metabolic control.

As expected, the magnitude and duration of the intervention effect was greater among patients with baseline HbA_{1c} >7%, mainly for the intervention for patients group, which showed a statistically significant reduction in HbA_{1c}, in comparison with usual care, although the difference disappeared at 18 months. Moreover, considering the differences in the AUC values of HbA_{1c}, our results provide evidence of effectiveness for both the intervention for patients and the combined intervention throughout the study period. These results support previous findings reporting greater effects for interventions on patients with higher baseline HbA_{1c} levels [24,25]. Similarly, the effectiveness of quality improvement strategies exclusively focused on health care providers seems to be beneficial only among patients with HbA_{1c} levels >8% [26].

The Mobile Diabetes Intervention Study (MDIS) published by Quinn et al [27] also reported a higher reduction in HbA_{1c} over 1 year among patients with T2DM (with baseline HbA_{1c}=9.1%) by means of a multicomponent behavioral intervention exclusively for patients, without detecting effects on other relevant outcomes such as blood pressure or lipid levels.

Although MDIS provided evidence of sustained 12-month treatment difference in HbA_{1c}, rather than *regression to the mean*, the INDICA results, for the whole sample, show a progressive effect reduction close to the baseline HbA_{1c} values. Similar to MDIS, the observed reduction in HbA_{1c} in the INDICA subgroup with baseline HbA_{1c}>7% remained stable over the long term. However, evidence of long-term effectiveness of these complex interventions is not well stated yet because of the reduced number of studies providing results at 12 months of follow-up and beyond [28,29].

Several systematic reviews found that interventions based on ICTs led to significant improvements of 4% to 5% in HbA_{1c}

compared with usual care [12,28,30,31], with effect differences according to the type of ICT used (internet, automated SMS, and apps) [11,12,32]. In contrast, smaller effects than those reported in our study for the intervention for patients and combined intervention groups were published for individual and group education among patients with HbA_{1c} levels >8% [33,34].

Beyond the reported effects on HbA_{1c}, we also found an improvement in blood pressure monitoring for patients included in the 2 groups with intervening health professionals. Long-term reductions compared with the baseline were observed in SBP and DBP, with statistically significant differences in relation to usual care. These combined effects on HbA_{1c}, SBP, and DBP, together with the improvement observed for BMI, might contribute to enhanced cardiovascular risk [35,36], suggesting the overall value of these comprehensive approach strategies addressing multiple components and actors involved in T2DM management [37]. Although some outcomes, such as the improvement of blood pressure, might require the involvement of health care providers, others, such as the reduction in HbA_{1c}, will depend largely on the patients' intervention. Thus, our findings provide long-term evidence on the effectiveness of multicomponent interventions to empower patients and support clinical decision making to improve T2DM outcomes beyond that published by Taylor et al [29] in their systematic review for self-management interventions for patients with chronic conditions. The potential expected clinical benefits, associated with the overall metabolic and cardiovascular risk improvement provided by INDICA over 2 years, could be estimated in the longer-term follow-up on both microvascular and macrovascular complications and mortality [38].

Conceptual Frameworks

The assessed interventions were informed by conceptual frameworks of behavioral change [14] and applied to a large and heterogeneous sample of patients, caregivers, and professionals. The INDICA intervention characteristics were planned to increase the validity of the obtained data and the transferability of the interventions assessed. The key determinants of behavior change suggested by Michie et al [14] were considered for the INDICA interventions, with a higher degree of adherence in their design and implementation in the case of interventions for patients than for professionals, which could help explain the magnitude of the effect observed for HbA_{1c} among intervention groups. Furthermore, time constraints, staff turnover, and self-perception of work overload among health professionals limited the possibility of going deeper into the following dimensions: professional role, motivation and goals, social and professional influences, emotions, and action planning. A detailed description of the complex behavior change interventions applied was reported elsewhere [13] to promote replication at other sites. Other potential explanations for the unexpected differences between the intervention for patients and combined intervention groups were the higher attendance rate of patient and family members in the educational group sessions and a significantly higher rate of web questionnaire completion observed in the intervention for patients group. This higher rate of questionnaire completion was key to adjusting the individualized components of SMS messages, providing an extended exposure to web-based educational material. The high turnover among health care professionals in most PHCPs included in the study, as occurs in the real world, could also account for the lesser effect of the intervention for professionals and the combined intervention.

To maximize effectiveness, the INDICA interventions incorporated all the components of a technology-enabled self-management feedback cycle, connecting patients and the research team by using bidirectional communication, analyzing patient-provided behavior and health data, tailoring education, and personalizing feedback according to the eHealth Enhanced Chronic Care Model [24,39,40].

Strengths and Limitations

This study has some limitations. First, it was difficult to obtain a full data set because of the high number of control visits and the duration of follow-up for many patients. Robust imputation techniques [19] were used to minimize the impact of missing data. Second, as previously mentioned, the high turnover among primary care professionals included in the study could explain the smaller than expected impact of the intervention for professionals and the combined intervention. Third, the fact that around 49.4% (1154/2334) of the whole patient sample had baseline HbA_{1c} <7% and only around 23.0% (536/2334) had basal HbA_{1c} levels ≥8% clearly limits the ability of interventions to reduce HbA_{1c}. Fortunately, the available sample size was sufficient to find valid evidence. Fourth, similar to other reported findings [23,26,41], our usual care group was not a proper control group; it was subject to repetitive and intensive follow-up activities, including 6 different follow-up visits over the study to apply all prespecified questionnaires, in addition to clinical and laboratory tests. This intense follow-up activity could act as an intervention in itself, as patients might focus on important topics on which they had to pay attention. Fifth, INDICA interventions were not fully theory-based, making it more difficult to understand as to what works across contexts, populations, and behaviors. Finally, the INDICA study was not designed to test the efficacy of every component of the complex interventions assessed.

The strengths of the INDICA study include the pragmatic character of the trial and its wide sample size; the random assignment by clusters; the engagement, as research subjects, of all actors involved in management decisions; and the follow-up duration. Moreover, all educational group sessions and coaching activities by SMS were recorded to monitor and assess homogeneity, educator fidelity to interventions, and quality delivery. Educational workshops and periodic feedback to health care professionals were equally delivered to all participants in the intervention for professionals and the combined intervention.

The INDICA findings highlight the importance of conducting trials with long follow-up periods and sufficient statistical power to assess interventions of limited expected effect sizes but of high potential efficiency. ICT-supported interventions enable its extended and continuous usage by thousands of people in need to complement and spread interventions beyond the limited

capacity of the health care systems to deliver usual care. We should be careful, however, to generalize the findings of INDICA. Interventions took place through PHCPs and were largely implemented through electronic communications. Health and digital literacy levels of the assessed population might vary with regard to other settings. Moreover, health care professionals were subject to differences in workload, interest and training in ICT used to support patients, access to CPG, and specialist support.

The potential effects of all these factors on the different study arms were minimized by randomization.

Future Research

Future research on the effectiveness of these complex interventions should be complemented by the analysis of patients' self-reported outcomes and intervention cost-effectiveness to fully inform clinical and health policy decision making. The effectiveness of these interventions should also be assessed after longer follow-up periods to allow the measurement of relevant clinical (micro and macrovascular) outcomes, together with the assessment of potential longer-term reinforcement of the most cost-effective interventions in the short term. The use of real-world data will efficiently help to provide this valuable information. Effectiveness and cost-effectiveness assessment according to patients' clinical risk and health literacy levels are also highly relevant. Additional evidence on cost-effectiveness and budget impact analysis is needed to support health policy decision making in cases of limited funding to support all assessed interventions.

Theory-based research on complex interventions to promote behavior change is also needed, rather than theory-inspired research, if we are to achieve a sound scientific basis for the development and reporting of such interventions. Comparative effectiveness assessment among components of complex interventions is also of interest, although it will require additional funding.

Finally, qualitative research is also needed to better understand the relationships between patient and professional characteristics, their engagement, and the observed results.

Conclusions

We found that INDICA interventions improved long-term metabolic control in patients with T2DM with uncontrolled basal HbA_{1c} values compared with the usual care group. We also found moderate but clinically and statistically significant effects on blood pressure reduction, contributing to reduced overall cardiovascular risk. The increasing access to computers, internet, and mobile phones, together with improvements in digital literacy, regardless of social status, sex, and age, make these complex interventions appropriate instruments to improve patient empowerment in the continuous management of their chronic diseases by tailoring interventions to individual needs and extending patient support beyond the limited capacities of conventional office-based care.

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Authors' Contributions

The INDICA team included the following members: Abraham Pérez de la Rosa (Canary Islands Health Research Institute Foundation, FIISC), Alicia Pareja Ríos (University Hospital of Canary Island), Andrés Sifre Perello (Molina Orosa Hospital), Ángela Trinidad Gutiérrez Pérez (Primary Care of Gran Canaria), Antonio Cabrera de León (Ntra Sra de la Candelaria University Hospital), Antonio García Quintana (Dr. Negrín University Hospital), Armando Carrillo Domínguez (Insular University Hospital), Bernardo Eusebio Herrera Domínguez (General de La Palma Hospital), Carlos Sedeño Pérez (Primary Care of Tenerife), Carlos Ramírez Álamo (Primary Care of Gran Canaria), Carmen Daranas Aguilar (Canary Islands Health Research Institute Foundation, FIISC), Carolina Guerra Marrero (Canary Islands Health Research Institute Foundation, FIISC), Cecilia Lobos Soto (Insular University Hospital), Cristina Padrón Pérez (Canary Islands Health Research Institute Foundation, FIISC), Dácil Alvarado Martel (Dr. Negrín University Hospital), Daniel Hernández Obregón (Dr. Negrín University Hospital), Dulce N. Hernández Correa (Primary Care of Gran Canaria), Elsa Espinosa Pozuelo (Diabetes Patient´ association of Tenerife), Elsa Florido Mayor (Canary Islands Health Research Institute Foundation, FIISC), Engracia Pinilla Domínguez (Ntra Sra de la Candelaria University Hospital), Fátima Herrera García (University Hospital of Canary Island), Félix Bonilla Aguiar (Dr. José Molina Hospital), Fernando Montón Álvarez (Ntra Sra de la Candelaria University Hospital), Francisco Cabrera López (Insular University Hospital), Gloria Guerra de la Torre (Primary Care of Gran Canaria), Gregorio Muelas Martín (Dr. Negrín University Hospital), Guillermo Monzón Monzón (Primary Care of Gran Canaria), Héctor de la Rosa Merino (Canary Islands Health Research Institute Foundation, FIISC), Ignacio García Puente (Dr. Negrín University Hospital), Isabel García Calcerrada (Ntra Sra de la Candelaria University Hospital), Iván Castilla Rodríguez (Canary Islands Health Research Institute Foundation, FIISC), Jacqueline Álvarez Pérez (Canary Islands Health Research Institute Foundation, FIISC), Jorge Federico Aldunate Page (Insular University Hospital), Jose Antonio García Dopico (University Hospital of Canary Island), Juan Andrés Báez Hernández (Primary Care of La Palma), Juan José Pérez

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Screenshots of patients' website.
[DOC File , 779 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Representative screenshots of automated decision aid tool embedded into the electronic clinical record.
[DOC File , 491 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Multiple imputation model.
[DOC File , 525 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Adjusted difference in means and area under the curve of each group compared with the usual care group for the whole sample.
[DOC File , 176 KB-Multimedia Appendix 4]

Multimedia Appendix 5

Adjusted means for each group and intragroup differences compared with the baseline measurement for the whole sample.
[DOC File , 201 KB-Multimedia Appendix 5]

Multimedia Appendix 6

Patients with clinically relevant changes in glycated hemoglobin and comparison with the usual care group.
[DOC File , 57 KB-Multimedia Appendix 6]

Multimedia Appendix 7

Adjusted difference in means and area under the curve of each group compared with the usual care group for patients with a baseline glycated hemoglobin level >7%.
[DOC File , 143 KB-Multimedia Appendix 7]

Multimedia Appendix 8

Adjusted means for each group and intragroup differences compared with the baseline measurement for patients with a baseline glycated hemoglobin level >7 %.
[DOCX File , 61 KB-Multimedia Appendix 8]

Multimedia Appendix 9

CONSORT-EHEALTH checklist (V 1.6.1).

[PDF File (Adobe PDF File), 1620 KB-Multimedia Appendix 9]

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Abbreviations

AUC: area under the curve
CPG: clinical practice guideline
DBP: diastolic blood pressure
ECR: electronic clinical record
FCU: family care unit
HbA1c: glycated hemoglobin
HDL: high-density lipoprotein
ICC: intraclass correlation coefficient
ICT: information and communications technology
LDL: low-density lipoprotein
MDIS: Mobile Diabetes Intervention Study
PHCP: primary health care practice
RCT: randomized controlled trial
SBP: systolic blood pressure
T2DM: type 2 diabetes mellitus

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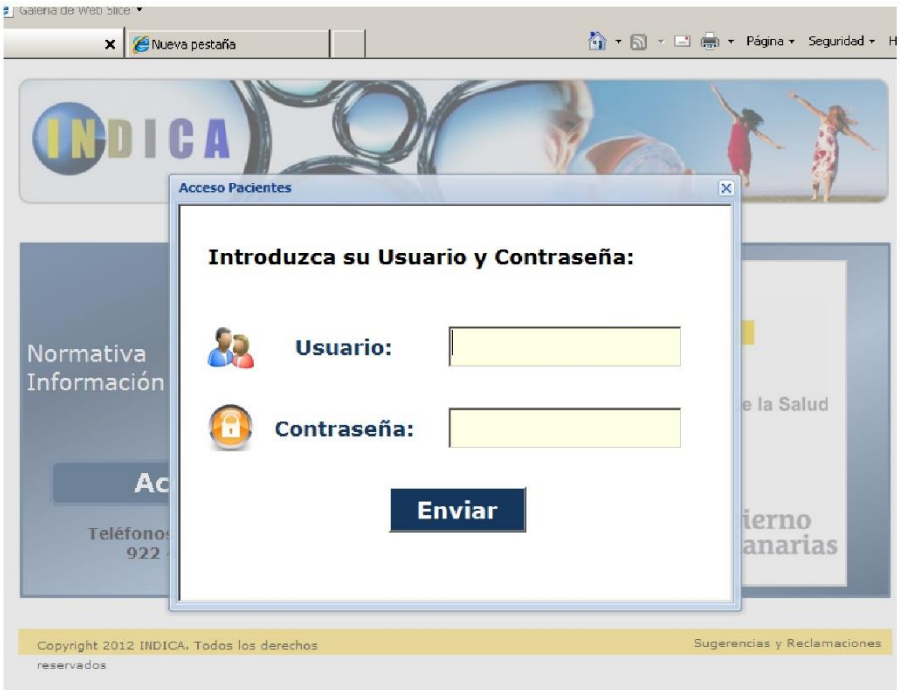
Multimedia Appendix 1.

Screenshots of patients' website



Estás en: Inicio **Datos Autoseguimiento**

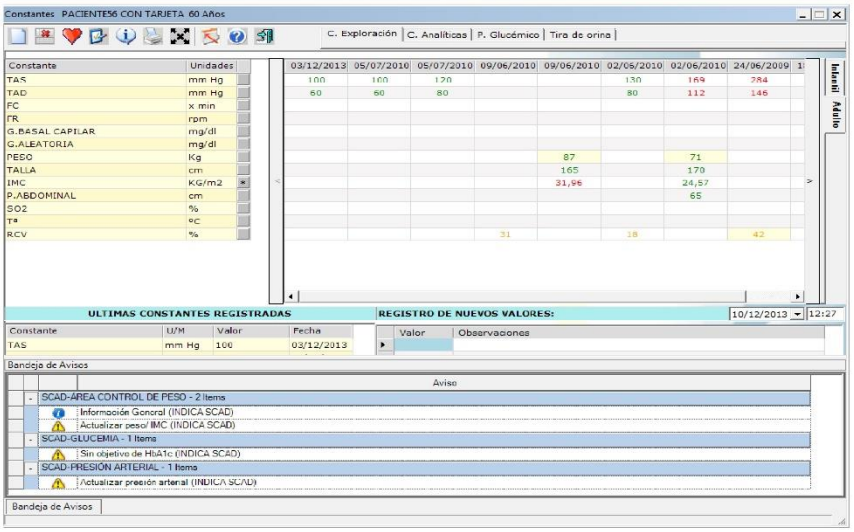
P1. ¿Con qué frecuencia ha consumido los siguientes alimentos durante la semana pasada?

	No lo he consumido la semana pasada (Nunca)	Una vez por semana (Semanal)	2-4 veces por semana (Frecuente)	Casi diario o a diario (Diario)	Dos o más veces al día (+ 1 vez día)
Verduras y hortalizas: col, calabacín, calabaza, lechuga, zanahoria..	Nunca	Semanal	Frecuente	Diario	+ 1 vez/día
Farináceos: pan, papas, pasta, arroz, fideos, gofio, batatas, cereales,..	Nunca	Semanal	Frecuente	Diario	+ 1 vez/día
Carne de vaca, pollo, cerdo, pavo, cordero, conejo,...	Nunca	Semanal	Frecuente	Diario	+ 1 vez/día
Pescados o mariscos	Nunca	Semanal	Frecuente	Diario	+ 1 vez/día
Fruta	Nunca	Semanal	Frecuente	Diario	+ 1 vez/día
Dulces o bollería industrial: donuts, galletas, cruasanes, chocolate, golosinas,...	Nunca	Semanal	Frecuente	Diario	+ 1 vez/día

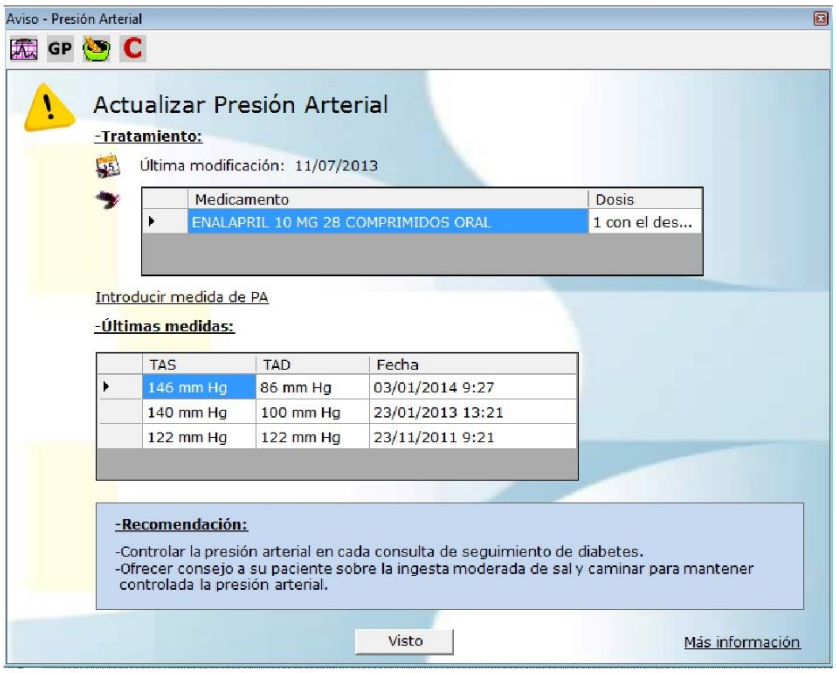
Guardar y pasar a siguiente

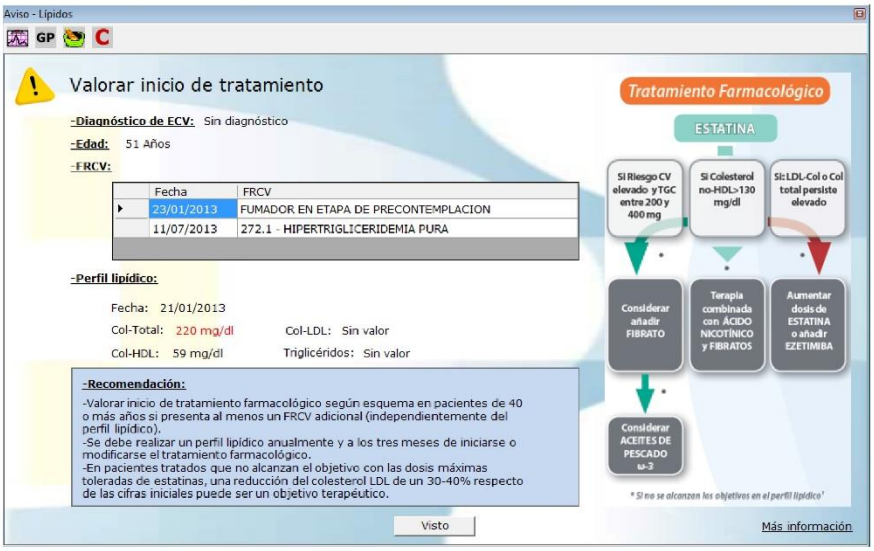
Multimedia Appendix 2.

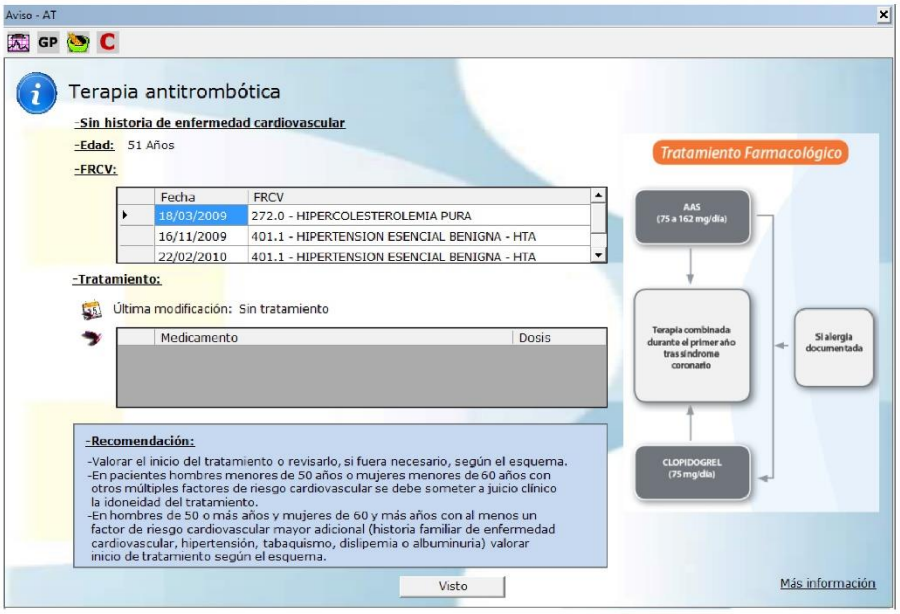
Representative screenshots of automated decision aid tool embedded into the electronic clinical record.



Message that include the evaluation of the patient's health and recommendations based on the specific needs of every patient.




Aviso - Lípidos
GP
Valorar inicio de tratamiento
-Diagnóstico de ECV: Sin diagnóstico
-Edad: 51 Años
-FRCV:
Fecha
FRCV
23/01/2013
FUMADOR EN ETAPA DE PRECONTEMPLACION
11/07/2013
272.1 - HIPERTRIGLICERIDEMIA PURA
-Perfil lipídico:
Fecha: 21/01/2013
Col-Total: 220 mg/dl
Col-LDL: Sin valor
Col-HDL: 59 mg/dl
Triglicéridos: Sin valor
-Recomendación:
-Valorar inicio de tratamiento farmacológico según esquema en pacientes de 40 o más años si presenta al menos un FRCV adicional (independientemente del perfil lipídico).
-Se debe realizar un perfil lipídico anualmente y a los tres meses de iniciarse o modificarse el tratamiento farmacológico.
-En pacientes tratados que no alcanzan el objetivo con las dosis máximas toleradas de estatinas, una reducción del colesterol LDL de un 30-40% respecto de las cifras iniciales puede ser un objetivo terapéutico.
Visto
Tratamiento Farmacológico
ESTATINA
Si Riesgo CV elevado y TGC entre 200 y 400 mg
Si Colesterol no-HDL>130 mg/dl
Si: LDL-Col o Col total persiste elevado
Considerar añadir FIBRATO
Terapia combinada con ÁCIDO NICOTÍNICO y FIBRATOS
Aumentar dosis de ESTATINA o añadir EZETIMIBA
Considerar ACEITES DE PESCADO ω-3
* Si no se alcanzan los objetivos en el perfil lipídico'
Más información


Aviso - AT
GP
Terapia antitrombótica
-Sin historia de enfermedad cardiovascular
-Edad: 51 Años
-FRCV:
Fecha
FRCV
18/03/2009
272.0 - HIPERCOLESTEROLEMIA PURA
16/11/2009
401.1 - HIPERTENSION ESENCIAL BENIGNA - HTA
22/02/2010
401.1 - HIPERTENSION ESENCIAL BENIGNA - HTA
-Tratamiento:
Última modificación: Sin tratamiento
Medicamento
Dosis
-Recomendación:
-Valorar el inicio del tratamiento o revisarlo, si fuera necesario, según el esquema.
-En pacientes hombres menores de 50 años o mujeres menores de 60 años con otros múltiples factores de riesgo cardiovascular se debe someter a juicio clínico la idoneidad del tratamiento.
-En hombres de 50 o más años y mujeres de 60 y más años con al menos un factor de riesgo cardiovascular mayor adicional (historia familiar de enfermedad cardiovascular, hipertensión, tabaquismo, dislipemia o albuminuria) valorar inicio de tratamiento según el esquema.
Visto
Tratamiento Farmacológico
AAS (75 a 162 mg/día)
Terapia combinada durante el primer año tras síndrome coronario
Si alergia documentada
CLOPIDOGREL (75 mg/día)
Más información

Multimedia Appendix 3.

Multiple imputation model.

Description of Missing data

Percentage of missing data in primary endpoint, across observations

The percentage of missing data is maximum at 18 months, and decline a little at 24 months. The percentage is always less than 40%. There are a 4.5% (105/2,334) of patients with missing data in all the observations at follow-up (except in baseline).

	n (%)
HbA1c, baseline	
Non missing data	2250 (96.4)
Missing data	84 (3.6)
HbA1c, 3 months	
Non missing data	1794 (76.9)
Missing data	540 (23.1)
HbA1c, 6 months	
Non missing data	1641 (70.3)
Missing data	693 (29.7)
HbA1c, 12 months	
Non missing data	1662 (71.2)
Missing data	672 (28.8)
HbA1c, 18 months	
Non missing data	1562 (66.9)
Missing data	772 (33.1)
HbA1c, 24 months	
Non missing data	1590 (68.1)
Missing data	744 (31.9)

Mechanisms causing missing data

Rubin [1] classified missing data problems into three categories. In his theory every data point has some likelihood of being missing. The process that governs these probabilities is called the missing data mechanism or response mechanism.
There are three typical mechanism causing missing data: missing completely at random (**MCAR**), missing at random (**MAR**) and missing not at random (**MNAR**).

The data are said to be MCAR if the probability of being missing data depends only on the overall probability of being missing: the probability is the same for all cases and is unrelated to the data. When the mechanism is MCAR this causes enlarged standard errors due the reduced sample size, but does not cause bias. In this situation we can analyze the

incomplete datasets. While it would be convenient, MCAR is often unrealistic. If the mechanism of missing data depends on observed data, we would have to reject MCAR and if we analyze the incomplete sample we would be assuming important bias effects.

The data are MAR if the missingness probability depends on observed information, including any design factors. If only depends on the observed data, then the missing data are missing at random given the observed data. MAR is more realistic than MCAR. In the presence of MAR, methods such as multiple imputation of full information direct maximum likelihood may lead to unbiased results. But nevertheless, methods such as listwise delection, mean imputation or last observation carried forward should be avoided.

Finally, the data are MNAR if the missingness probability depends on unobserved information, including the value missing itself. MNAR implies that the probability of being missing varies for reason that are unknown to us. MNAR is difficult to detect because in practice it´s impossible discard the existence of MNAR, since we would not have observations related with missing data.

Evaluating if missing data is MCAR in INDICA dataset.

The mechanism is not MCAR if the missing data depending on observed variables. For data to be missing completely at random, the probability that Xi is missing is unrelated to the value of other variables in the analysis.
So, we checked if the probabily of missing observations depends on observable variables:

1) Hba1c across observations depending on missing data at baseline for Hba1c.
Those patients that not have HbA1c at baseline, have worse levels at month 24 (*P*=.03). In the rest of the follow-ups no differences are find.

Variables	Non missing data at baseline (N=2250)	Missing data at baseline (N=84)	*P*
	Mean (SD)	Mean (SD)	
HbA1c, 3 months (N1=1721 y N2=73)	7.11 (1.33)	7.3 (1.33)	.24
HbA1c, 6 months (N1=1590 y N2=51)	7.17 (1.33)	7.45 (1.25)	.13
HbA1c, 12 months (N1=1610 y N2=52)	7.24 (1.39)	7.26 (1.30)	.90
HbA1c, 18 months (N1=1510 y N2=52)	7.28 (1.39)	7.74 (1.81)	.08
HbA1c, 24 months (N1=1534 y N2=56)	7.29 (1.36)	7.68 (1.28)	.03

N1: total number of patients with non missing data at each variable and with non missing data at baseline.
N2: total number of patients with non missing data at each variable and with missing data at baseline.

2) Hba1c across observations depending on missing data at month 24 for Hba1c.
Those patients that not have HbA1c at month 24, have worse levels at baseline (*P*=.006), month 3 (*P*=.02), month 12 (*P*=.016) and month 24 (*P*=.007).

Variables	Non missing	Missing data at	*P*

	data at month 24 (N=1590)	month 24 (N=744)	
	Mean (SD)	Mean (SD)	
HbA1c, baseline (N1=1534 y N2=716)	7.21 (1.4)	7.41 (1.61)	.006
HbA1c, 3 months (N1=1313 y N2=481)	7.07 (1.28)	7.25 (1.43)	.02
HbA1c, 6 months (N1=1262 y N2=379)	7.18 (1.32)	7.17 (1.36)	.91
HbA1c, 12 months (N1=1292 y N2=370)	7.19 (1.33)	7.4 (1.54)	.016
HbA1c, 18 months (N1=1238 y N2=324)	7.24 (1.35)	7.51 (1.6)	.007

N1: total number of patients with non missing data at each variable and with non missing data at month 24. N2: total number of patients with non missing data at each variable and with missing data at month 24.

3) Missing data across Hba1c depending on age.

Those patients with missing data in Hba1c are younger that patients with non missing data at baseline and 24 months.

Variables	Non missing data at baseline (N=2250)	Missing data at baseline (N=84)	*P*
Age, mean (SD)	55.81 (7.07)	52.69 (8.24)	<.001
	Non missing at month 24 (N=1590)	**Missing at month 24 (N=744)**	
Age, mean (SD)	56.09 (6.82)	54.86 (7.73)	<.001

4) Missing data across Hba1c depending on smoker at baseline.

Smokers at baseline have more missing data in Hba1c at month 6, 12, 18 and 24.

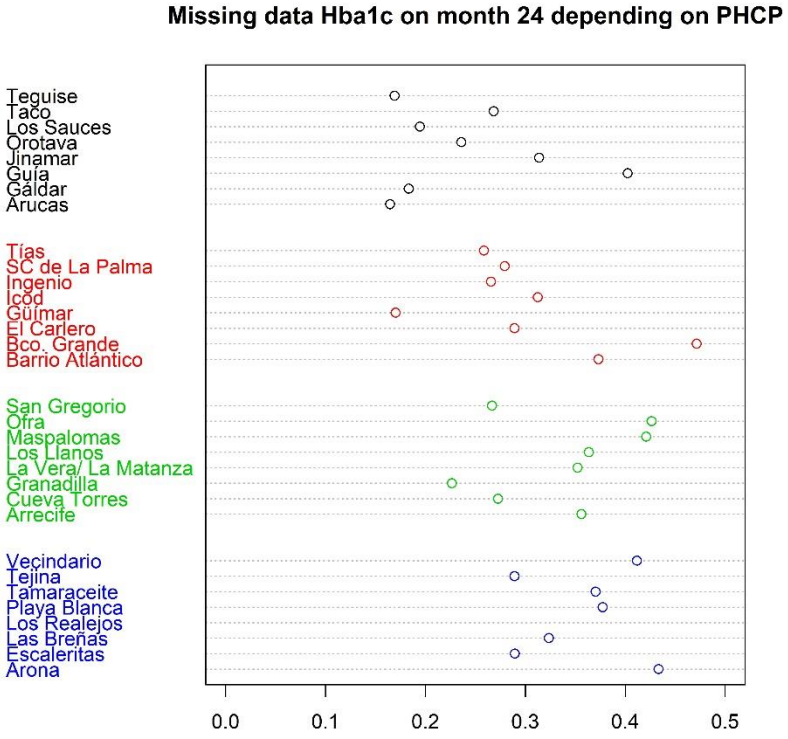
Variables	Non missing data at baseline (N=2250)	Missing data at baseline (N=84)	*P*
	n(%)	n(%)	
Smoker Vs Non smoker at baseline			.077
Non smoker, N=1810	1752(96.8)	58(3.2)	
Smoker, N=524	498(95)	26(5)	
	Non missing data at month 3 (N=1794)	**Missing data at month 3 (N=540)**	
	n(%)	n(%)	
Smoker Vs Non smoker at month 3			.227
Non smoker, N=1810	1402(77.5)	408(22.5)	
Smoker, N=524	392(74.8)	132(25.2)	
	Non missing data at month 6 (N=1641)	**Missing data at month 6 (N=693)**	
	n(%)	n(%)	

Smoker Vs Non smoker at month 6			<.001
Non smoker, N=1810	1312(72.5)	498(27.5)	
Smoker, N=524	329(62.8)	195(37.2)	
	Non missing data at month 12 (N=1662)	**Missing data at month 12 (N=672)**	
	n(%)	n(%)	
Smoker Vs Non smoker at month 12			<.001
Non smoker, N=1810	1326(73.3)	484(26.7)	
Smoker, N=524	336(64.1)	188(35.9)	
	Non missing data at month 18 (N=1562)	**Missing data at month 18 (N=772)**	
	n(%)	n(%)	
Smoker Vs Non smoker at month 18			<.001
Non smoker, N=1810	1259(69.6)	551(30.4)	
Smoker, N=524	303(57.8)	221(42.2)	
	Non missing data at month 24 (N=1590)	**Missing data at month 24 (N=744)**	
	n(%)	n(%)	
Smoker Vs Non smoker at month 24			<.001
Non smoker, N=1810	1266(69.9)	544(30.1)	
Smoker, N=524	324(61.8)	200(38.2)	

5) Missing data at Hba1c in month 24 depending on smoker at PHCP.

The percentage of missing data depends on PHCP in a 3.64% (Figure 1). There are some PHCP with almost 50% of missing data.

Figure 1. Percentage of missing data at 24 months in Hba1c.


Missing data Hba1c on month 24 depending on PHCP
Teguise
Taco
Los Sauces
Orotava
Jinamar
Guía
Gáldar
Arucas
Tías
SC de La Palma
Ingenio
Icod
Güímar
El Carlero
Bco. Grande
Barrio Atlántico
San Gregorio
Ofra
Maspalomas
Los Llanos
La Vera/ La Matanza
Granadilla
Cueva Torres
Arrecife
Vecindario
Tejina
Tamaraceite
Playa Blanca
Los Realejos
Las Breñas
Escaleritas
Arona
0.0
0.1
0.2
0.3
0.4
0.5

6) Hba1c at month 24 depending on several variables.

The missing datra of Hba1c at month 24 can be partially explained by a multilevel logistic model, using Hba1c baseline, age, smoker and sex as covariates.

	OR	B	Std. Error	z value	Pr(>|z|)
(Intercept)	0.92	-0.082	0.449	-0.183	.86
HbA1c baseline	1.0715	0.069	0.031	2.223	.03
Age, years	0.978	-0.022	0.007	-3.382	.001
Smoker at baseline	1.418	0.349	0.11	3.166	.002
Women	0.869	-0.14	0.094	-1.481	.14

ICC PHCP = 3.7%

Conclusion about mechanism

As our missing data are related to observable data, MCAR is not a mechanism plausible in our study. Since we have a lot of observed variables related with missing, the mechanism Missing not at Random (MNAR) is not plausible either. When the likelihood of missing data is related to observed variables, but not to unobserved variables, the missing data mechanism is referred to as missing at random (MAR) and this is the pattern in our missing data. Nevertheless, we cannot determinate if the mechanism is MNAR, because by definition the missing data are unknown and it can therefore not be assessed if the observed data can predict the unknown data.

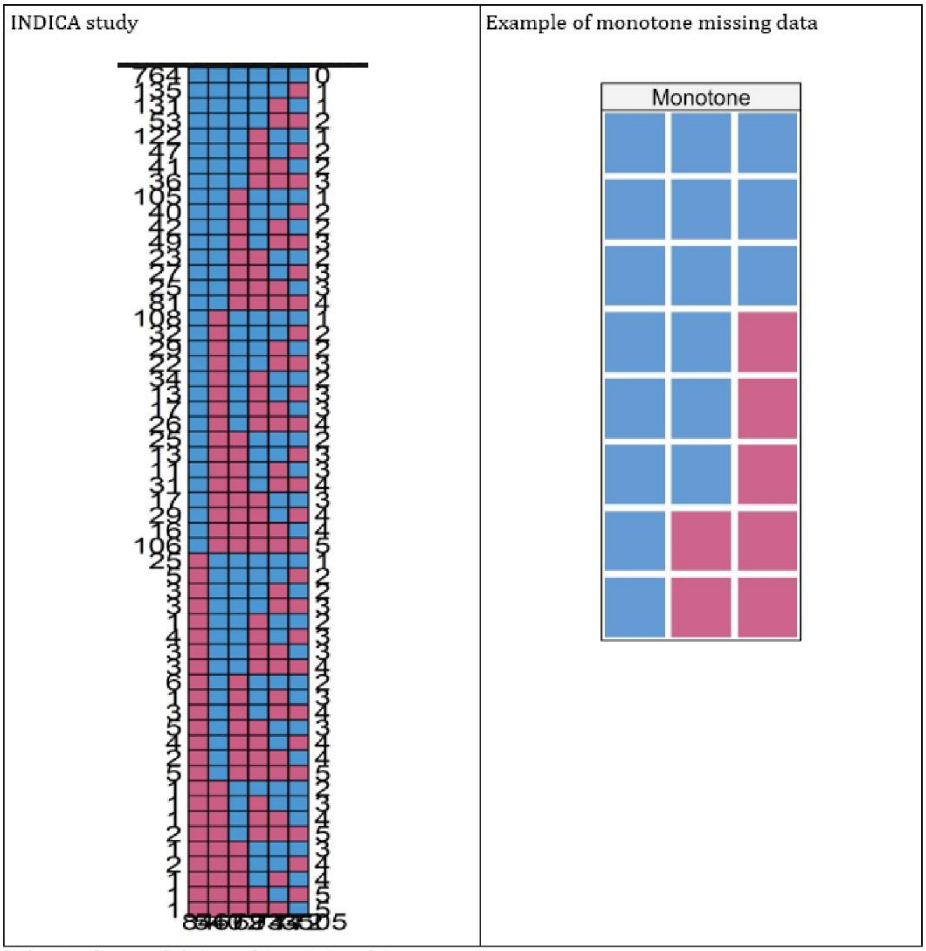
When the likelihood of missing data is related to observed variables, but not to unobserved variables, the missing data mechanism is referred to as missing at random (MAR). Since we have a lot of observed variables related with missing, the mechanism Missing not at Random (MNAR) is not plausible. Nevertheless, we cannot determinate if the mechanism is MAR or MNAR, because by definition the missing data are unknown and it can therefore not be assessed if the observed data can predict the unknown data.

Evaluating if missing data is monotone

The missing data is monotone if its columns can be reordered such that for any patient (a) if a data is missing all data after this value are also missing, and (b) if a data is observed all data before of this value are also are observed. In the presence of MAR, methods such as multiple imputation or full information direct maximum likelihood may lead to unbiased results. If missing data is not monotone, to avoid bias, a multiple imputation should be conducted using the chained equations or the MCMC method.

The missing data in INDICA is not Monotone because there are a total of 1159 patients with observations after at least one missing data. For this reason we used the chained equation method which is the most appropriate.

Figure 2. Monotone missing data



*Blue is observed data, red is missing data.

References

1. Rubin D. 1976. Inference and Missing Data. Biometrika 63 (3): 581–592. doi:10.2307/2335739

Description of mechanism for imputation of missed data.

Multiple imputation was performed by means of *mi impute chained* using the software Stata 15.0. Imputations were performed in a differentiated way for each of the four treatment groups. The following variables were considered regular and used as predictors to perform imputations: age of onset of the study, sex, baseline smoker status, oral anti-diabetics and basic health area. A total of 136 variables were imputed. Imputation of variables was organized starting from those that had less data lost (e.g. age of onset of the diabetes or level of studies). Each variable was imputed in

chronological order: baseline first and afterwards 3, 6, 12, 18 and 24 months. As a general rule, the latest available information of the variable to impute was used. When information from other variables was used the information from the same time moment was used. The imputation was not performed using secondary variables as random effects without fixed effects being used. A total of 100 imputations was performed for every missed data. For some variables the variable ZBS was not used as predictor due to convergence problems because of problems of full separation in the logistic or ordinal models.

The following table shows the order of imputation of the variables, the variables used in the imputation, the prediction model and the number of lost data for this variable.

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
1	Duration of Diabetes (years)	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline	Pmm, knn(3)	6
2	Education	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes	Ologit	24
3	Laboral Status	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes	Logit	43
4	BMI, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline	Pmm, knn(3)	5
5	BMI, 3 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 3 months, Duration of Diabetes, Laboral Status baseline, BMI baseline	Pmm, knn(3)	478
6	BMI, 6 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, BMI 3 months	Pmm, knn(3)	567
7	BMI, 12 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, BMI 6 months	Pmm, knn(3)	669
8	BMI, 18 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 18 months, Duration of Diabetes, Laboral Status baseline, BMI 12 months	Pmm, knn(3)	744
9	BMI, 24 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, BMI 18 months	Pmm, knn(3)	667
10	Waist circumference, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, BMI baseline	Pmm, knn(3)	65
11	Waist circumference, 3 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 3 months, Duration of Diabetes, Laboral Status baseline, BMI 3 months, Waist Circumference baseline	Pmm, knn(3)	485
12	Waist circumference,	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 6 months, Duration of Diabetes, Laboral	Pmm, knn(3)	574

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
	6 months	Status baseline, BMI 6 months, Waist Circumference 3 months		
13	Waist circumference, 12 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, BMI 12 months, Waist Circumference 6 months	Pmm, knn(3)	665
14	Waist circumference, 18 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 18 months, Duration of Diabetes, Laboral Status baseline, BMI 18 months, Waist Circumference 12 months	Pmm, knn(3)	747
15	Waist circumference, 24 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, BMI 24 months, Waist Circumference 18 months	Pmm, knn(3)	666
16	Waist to hip ratio, Baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, BMI baseline, Waist Circumference baseline	Pmm, knn(3)	66
17	Waist to hip ratio, 3 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 3 months, Duration of Diabetes, Laboral Status baseline, BMI 3 months, waist circumference 3 months, Waist to Hip Ratio baseline	Pmm, knn(3)	485
18	Waist to hip ratio, 6 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, BMI 6 months, waist circumference 6 months, Waist to Hip Ratio 3 months	Pmm, knn(3)	575
19	Waist to hip ratio, 12 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, BMI 12 months, waist circumference 12 months, Waist to Hip Ratio 6 months	Pmm, knn(3)	669
20	Waist to hip ratio, 18 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 18 months, Duration of Diabetes, Laboral Status baseline, BMI 18 months, waist circumference 18 months, Waist to Hip Ratio 12 months	Pmm, knn(3)	747
21	Waist to hip ratio, 24 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, BMI 24 months, waist circumference 24 months, Waist to Hip Ratio 18 months	Pmm, knn(3)	667
22	Systolic blood pressure, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, BMI baseline	Pmm, knn(3)	68
23	Systolic blood pressure, 3 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 3 months, Duration of Diabetes, Laboral Status baseline, BMI 3 months, SBP baseline	Pmm, knn(3)	467

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
24	Systolic blood pressure, 6 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, BMI 6 months, SBP 3 months	Pmm, knn(3)	567
25	Systolic blood pressure, 12 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, BMI 12 months, SBP 6 months	Pmm, knn(3)	665
26	Systolic blood pressure, 18 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 18 months, Duration of Diabetes, Laboral Status baseline, BMI 18 months, SBP 12 months	Pmm, knn(3)	746
27	Systolic blood pressure, 24 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, BMI 24 months, SBP 18 months	Pmm, knn(3)	663
28	Diastolic blood pressure, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, BMI baseline, SBP baseline	Pmm, knn(3)	68
29	Diastolic blood pressure, 3 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 3 months, Duration of Diabetes, Laboral Status baseline, BMI 3 months, SBP 3 months, DBP baseline	Pmm, knn(3)	467
30	Diastolic blood pressure, 6 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, BMI 6 months, SBP 6 months, DBP 3 months	Pmm, knn(3)	567
31	Diastolic blood pressure, 12 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, BMI 12 months, SBP 12 months, DBP 6 months	Pmm, knn(3)	665
32	Diastolic blood pressure, 18 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 18 months, Duration of Diabetes, Laboral Status baseline, BMI 18 months, SBP 18 months, DBP 12 months	Pmm, knn(3)	745
33	Diastolic blood pressure, 24 months	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, BMI 24 months, SBP 24 months, DBP 18 months	Pmm, knn(3)	663
34	Hba1c, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline	Pmm, knn(3)	84
35	Hba1C, 3 months	PHCP, Age, Sex, Smoking status 3 months, Diabetes treatment 3 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 3 months, SBP 3 months, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline	Pmm, knn(3)	538

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
36	Hba1C, 6 months	PHCP, Age, Sex, Smoking status 6 months, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 6 months, SBP 6 months, Morisky Scale 6 months, ADDQoL 6 months, HbA1c 3 months	Pmm, knn(3)	689
37	Hba1C, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 6 months	Pmm, knn(3)	665
38	Hba1C, 18 months	PHCP, Age, Sex, Smoking status 18 months, Diabetes treatment 18 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 18 months, SBP 18 months, Morisky Scale 18 months, ADDQoL 18 months, HbA1c 12 months	Pmm, knn(3)	768
39	Hba1C, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 18 months	Pmm, knn(3)	737
40	Fasting serum glucose, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline	Pmm, knn(3)	44
41	Fasting serum glucose, 6 months	PHCP, Age, Sex, Smoking status 6 months, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 6 months, SBP 6 months, Morisky Scale 6 months, ADDQoL 6 months, HbA1c 6 months, Fasting serum glucose baseline	Pmm, knn(3)	667
42	Fasting serum glucose, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 6 months	Pmm, knn(3)	446
43	Fasting serum glucose, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 12	Pmm, knn(3)	705

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
		months		
44	Total cholesterol, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline, Fasting serum glucose baseline	Pmm, knn(3)	46
45	Total cholesterol, 6 months	PHCP, Age, Sex, Smoking status 6 months, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 6 months, SBP 6 months, Morisky Scale 6 months, ADDQoL 6 months, HbA1c 6 months, Fasting serum glucose 6 months, Total colesterol baseline	Pmm, knn(3)	676
46	Total cholesterol, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 12 months, Total colesterol 6 months	Pmm, knn(3)	460
47	Total cholesterol, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 24 months, Total colesterol 12 months	Pmm, knn(3)	705
48	LDL, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline, Fasting serum glucose baseline, Total colesterol baseline	Pmm, knn(3)	102
49	LDL, 6 months	PHCP, Age, Sex, Smoking status 6 months, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 6 months, SBP 6 months, Morisky Scale 6 months, ADDQoL 6 months, HbA1c 6 months, Fasting serum glucose 6 months, Total colesterol 6 months, LDL baseline	Pmm, knn(3)	736
50	LDL, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 12 months, Total colesterol 12 months, LDL 6 months	Pmm, knn(3)	550
51	LDL, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 24	Pmm, knn(3)	765

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
		months, Total colesterol 24 months, LDL 12 months		
52	HDL, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline, Fasting serum glucose baseline, Total colesterol baseline, LDL baseline, Waist to hip ratio baseline, Waist circumference baseline	Pmm, knn(3)	55
53	HDL, 6 months	PHCP, Age, Sex, Smoking status 6 months, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 6 months, SBP 6 months, Morisky Scale 6 months, ADDQoL 6 months, HbA1c 6 months, Fasting serum glucose 6 months, Total colesterol 6 months, LDL 6 months, Waist to hip ratio 6 months, Waist circumference 6 months, HDL baseline	Pmm, knn(3)	701
54	HDL, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 12 months, Total colesterol 12 months, LDL 12 months, Waist to hip ratio 12 months, Waist circumference 12 months, HDL 6 months	Pmm, knn(3)	493
55	HDL, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 24 months, Total colesterol 24 months, LDL 24 months, Waist to hip ratio 24 months, Waist circumference 24 months, HDL 12 months	Pmm, knn(3)	720
56	Triglycerides, Baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline, Fasting serum glucose baseline, Total colesterol baseline, LDL baseline, Waist to hip ratio baseline, Waist circumference baseline, HDL baseline	Pmm, knn(3)	49
57	Triglycerides, 6 months	PHCP, Age, Sex, Smoking status 6 months, Diabetes treatment 6 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 6 months, SBP 6 months, Morisky Scale 6 months, ADDQoL 6 months, HbA1c 6 months, Fasting serum glucose 6 months, Total colesterol 6 months, LDL 6 months, Waist to hip ratio 6 months, Waist circumference 6 months, HDL 6 months, Triglycerides baseline	Pmm, knn(3)	681

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
58	Triglycerides, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 12 months, Total colesterol 12 months, LDL 12 months, Waist to hip ratio 12 months, Waist circumference 12 months, HDL 12 months, Triglycerides 6 months	Pmm, knn(3)	461
59	Triglycerides, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 24 months, Total colesterol 24 months, LDL 24 months, Waist to hip ratio 24 months, Waist circumference 24 months, HDL 24 months, Triglycerides 12 months	Pmm, knn(3)	700
60	Serum Creatinine, baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline, Fasting serum glucose baseline, Total colesterol baseline, LDL baseline, Triglycerides baseline	Pmm, knn(3)	55
61	Serum Creatinine, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 12 months, Total colesterol 12 months, LDL 12 months, Triglycerides 12 months, Serum Creatinine baseline	Pmm, knn(3)	467
62	Serum Creatinine, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 24 months, Total colesterol 24 months, LDL 24 months, Triglycerides 24 months, Serum Creatinine 12 months	Pmm, knn(3)	699
63	Glomerular filtration rate, Baseline	PHCP, Age, Sex, Smoking status baseline, Diabetes treatment baseline, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI baseline, SBP baseline, Morisky Scale baseline, ADDQoL baseline, HbA1c baseline, Fasting serum glucose baseline, Total colesterol baseline, LDL baseline, Triglycerides baseline, Serum Creatinine baseline	Pmm, knn(3)	55

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
64	Glomerular filtration rate, 12 months	PHCP, Age, Sex, Smoking status 12 months, Diabetes treatment 12 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 12 months, SBP 12 months, Morisky Scale 12 months, ADDQoL 12 months, HbA1c 12 months, Fasting serum glucose 12 months, Total colesterol 12 months, LDL 12 months, Triglycerides 12 months, Serum Creatinine baseline, Glomerular filtration rate baseline	Pmm, knn(3)	468
65	Glomerular filtration rate, 24 months	PHCP, Age, Sex, Smoking status 24 months, Diabetes treatment 24 months, Duration of Diabetes, Laboral Status baseline, Education baseline, BMI 24 months, SBP 24 months, Morisky Scale 24 months, ADDQoL 24 months, HbA1c 24 months, Fasting serum glucose 24 months, Total colesterol 24 months, LDL 24 months, Triglycerides 24 months, Serum Creatinine 24 months, Glomerular filtration rate 12 months	Pmm, knn(3)	705

Adjusted difference in means and area under the curve of each group compared with the usual care group for the whole sample

	Adjusted difference in means compared to the UC[a] group: Mean (95%CI)										Difference in AUC[b] compared to the UC group (95%CI)	
	3M[c]	***P***	**6M**	***P***	**12M**	***P***	**18M**	***P***	**24M**	***P***	**3M to 24M**	***P***
HbA_{1c}[d] (%): F=99.9: *P*<.001; ICC[e] PHCP[f]=0.01; ICC subject|PHCP=0.39												
PTI[g]	-0.27 (-0.45, -0.10)	.002	-0.26 (-0.44, -0.08)	.005	-0.17 (-0.37, 0.01)	.07	-0.06 (-0.25, 0.13)	.52	-0.04 (-0.23, 0.15)	.70	-0.15 (-0.30, 0.004)	.06
PFI[h]	-0.11 (-0.28, 0.07)	.23	-0.17 (-0.34, 0.01)	.06	0.07 (-0.10, 0.25)	.42	-0.17 (-0.35, 0.02)	.07	0.03 (-0.15, 0.21)	.77	-0.07 (-0.21, 0.08)	.38
CBI[i]	-0.10 (-0.28, 0.07)	.26	-0.15 (-0.33, 0.03)	.09	-0.10 (-0.28, 0.08)	.28	-0.16 (-0.35, 0.03)	.10	0.05 (-0.14, 0.24)	.61	-0.11 (-0.26, 0.04)	.17
BMI (kg/m^2): F=732.9 *P*<.001; ICC PHCP = 0.01; ICC subject|PHCP=0.59												
PTI	-0.34 (-0.65, -0.03)	.03	-0.28 (-0.60, 0.04)	.08	-0.06 (-0.39, 0.27)	.71	-0.26 (-0.59, 0.08)	.14	-0.15 (-0.49, 0.18)	.37	-0.20 (-0.48, 0.09)	.17
PFI	-0.05 (-0.35, 0.24)	.72	-0.06 (-0.35, 0.24)	.71	0.08 (-0.22, 0.38)	.61	-0.29 (-0.59, 0.02)	.07	-0.12 (-0.43, 0.19)	.45	-0.09 (-0.35, 0.17)	.49
CBI	-0.09 (-0.40, 0.22)	.57	0.04 (-0.27, 0.35)	.80	0.27 (-0.05, 0.59)	.09	0.05 (-0.28, 0.38)	.76	0.11 (-0.22, 0.44)	.52	0.11 (-0.17, 0.39)	.44
Systolic blood pressure (mm Hg): F=60.18 *P*<.001; ICC PHCP =0.01 ICC; subject|PHCP=0.28												
PTI	-2.06 (-4.66, 0.55)	.12	0.06 (-2.61, 2.73)	.96	-1.96 (-4.60, 0.68)	.15	-1.76 (-4.53, 1.02)	.21	-2.10 (-4.80, 0.61)	.13	-1.49 (-3.62, 0.63)	.17
PFI	-5.30 (-7.77, -2.82)	<.001	-0.85 (-3.45, 1.66)	.51	-1.92 (-4.41, 0.58)	.13	-3.77 (-6.29, -1.26)	.003	-1.87 (-4.40, 0.66)	.15	-2.45 (-4.46, -0.44)	.02
CBI	-1.50 (-4.13, 1.14)	.27	0.81 (-1.88, 3.49)	.6	-2.17 -4.88, 0.54)	.12	-2.29 (-4.97, 0.38)	.09	-4.43 (-7.30, -1.56)	.003	-1.84 (-3.95, 0.27)	.09
Diastolic blood pressure (mm Hg): F=48.8 *P*<.001; ICC PHCP =0.02 ICC; subject|PHCP=0.25												
PTI	-1.62 (-3.50, 0.25)	.09	-1.19 (-3.10, 0.70)	.22	-1.10 (-3.01, 0.81)	.26	0.40 (-1.53, 2.33)	.68	-1.75 (-3.63, 0.13)	.07	-0.82 (-2.43, 0.79)	.32
PFI	-2.48 (-4.29, -0.66)	.008	-1.44 (-3.27, 0.40)	.13	-1.65 (-3.45, 0.16)	.07	-1.37 (-3.21, 0.47)	.14	-2.59 (-4.41, -0.77)	.005	-1.72 (-3.29, -0.15)	.03
CBI	-0.37 (-2.26, 1.53)	.71	-1.80 (-3.70, 0.10)	.06	-1.97 (-3.87, -0.07)	.04	-1.38 (-3.28, 0.51)	.15	-4.50 (-6.43, -2.59)	<.001	-2.01 (-3.63, -0.39)	.01

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Waist circumference (cm): *F=331.7 P<.001; ICC PHCP =0.02; ICC subject|PHCP=0.49*												
PTI	-0.56 (-1.85, 0.73)	.40	0.07 (-1.28, 1.42)	.92	-0.58 (-1.92, 0.76)	.40	-0.52 (-1.85, 0.82)	.45	-0.69 (-2.03, 0.65)	.31	-0.44 (-1.62, 0.75)	.47
PFI	-0.17 (-1.42, 1.08)	.79	-2 (-3.27, -0.72)	.002	0.08 (-1.19, 1.35)	.90	-0.51 (-1.79, 0.76)	.43	-1.2 (-2.5, 0.1)	.07	-0.73 (-1.88, 0.41)	.21
CBI	-0.6 (-1.88, 0.68)	.36	-0.71 (-2.04, 0.63)	.30	-0.15 (-1.49, 1.19)	.83	-0.98 (-2.31, 0.35)	.15	-0.56 (-1.91, 0.78)	.41	-0.6 (-1.79, 0.59)	.32
Weight (kg): *F=977.2 P<.001; ICC PHCP =0.01; ICC subject|PHCP=0.59*												
PTI	-0.98 (-1.8, -0.14)	.02	-0.83 (-1.7, 0.01)	.05	-0.19 (-1.1, 0.69)	.68	-0.67 (-1.6, 0.23)	.15	-0.42 (-1.3, 0.48)	.36	-0.55 (-1.3, 0.2)	.15
PFI	-0.33 (-1.1, 0.46)	.42	-0.35 (-1.2, 0.44)	.38	0.03 (-0.78, 0.84)	.94	-0.92 (-1.7, -0.1)	.03	-0.49 (-1.3, 0.34)	.25	-0.42 (-1.1, 0.28)	.24
CBI	-0.31 (-1.13, 0.51)	.45	-0.002 (-0.84, 0.84)	.99	0.64 (-0.21, 1.5)	.14	0.06 (-0.83, 0.95)	0.90	0.24 (-0.66, 1.14)	.61	0.21 (-0.54, 0.96)	.58
Waist-to-hip ratio: *F=92.1 P<.001; ICC PHCP =0.02; ICC subject|PHCP=0.44*												
PTI	0.001 (-0.01, 0.01)	.85	0.004 (-0.01, 0.01)	.46	0.005 (-0.01, 0.01)	.35	0.008 (0, 0.02)	.12	0.005 (-0.01, 0.02)	.34	0.01 (0, 0.01)	.24
PFI	0.005 (0, 0.02)	.28	0.006 (0, 0.02)	.22	0.01 (0, 0.02)	.05	0.005 (-0.01, 0.01)	.35	0.011 (0, 0.02)	.03	0.01 (0, 0.02)	.09
CBI	0.004 (-0.01, 0.01)	.48	0.008 (0, 0.02)	.14	0.01 (0, 0.02)	.049	0.007 (0, 0.02)	.19	0.008 (0, 0.02)	.14	0.01 (0, 0.02)	.08
			6M	***P***	**12M**	***P***			**24M**	***P***	**6M to 24M**	***P***
Total cholesterol (mg/dL): F= 101.3 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.35												
PTI			-0.40 (-6.1, 5.3)	.89	3.5 (-2.1, 9.0)	.22			2.8 (-2.1, 8.4)	.32	2.6 (-2.1, 7.4)	.28
PFI			-2.2 (-7.6, 3.2)	.42	2.1 (-3.1, 7.3)	.43			-2.9 (-8.3, 2.6)	.30	-0.28 (-4.9, 4.3)	.91
CBI			-2.5 (-8.1, 3.1)	.38	1.7 (-3.8, 7.3)	.54			-2.9 (-8.4, 2.7)	.31	-0.51 (-5.2, 4.2)	.83
LDL[k] (mg/dL): F=108.8 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.34												
PTI			2.8 (-1.8, 7.5)	.24	3.0 (-1.6, 7.7)	.20			2.0 (-2.6, 6.7)	.39	2.7 (-1.2, 6.5)	.18
PFI			-3.5 (-7.8, 0.87)	.12	2.3 (-1.9, 6.6)	.28			-2.8 (-7.3, 1.7)	.22	-0.34 (-4.0, 3.4)	.86
CBI			-1.2	.59	3.7	.12			-1.4	.56	1.2 (-2.7, 5.1)	.56

	(-5.8, 3.3)		(-0.96, 8.3)		(-6.1, 3.3)			
HDL[1] (mg/dL): F=302.91 *P*<.001; ICC PHCP =0.03; ICC subject|PHCP=0.43								
PTI	1.1 (-0.56, 2.8)	.19	0.70 (-0.97, 2.4)	.41	1.2 (-0.55, 2.8)	.18	0.92 (-0.62, 2.5)	.24
PFI	0.91 (-0.71, 2.5)	.27	0.15 (-1.5, 1.8)	.85	1.9 (0.28, 3.6)	.02	0.87 (-0.63, 2.4)	.26
CBI	0.82 (-0.82, 2.5)	.33	-0.80 (-2.5, 0.86)	.35	-0.24 (-1.9, 1.5)	.78	-0.34 (-1.9, 1.2)	.66
Triglycerides (mg/dL): F=46.4 *P*<.001; ICC PHCP =0.003; ICC subject|PHCP=0.41								
PTI	-14.7 (-29.9, 0.46)	.05	-2.6 (-16.9, 11.8)	.73	-7.3 (-22.2, 7.5)	.33	-6.2 (-18.2, 5.8)	.31
PFI	7.2 (-7.8, 22.2)	.35	-1.1 (-14.6, 12.3)	.87	-10.9 (-24.8, 2.9)	.12	-3.0 (-14.4, 8.4)	.61
CBI	-1.6 (-16.2, 12.9)	.83	-2.0 (-16.0, 12.1)	.79	3.3 (-11.5, 18.2)	.66	-0.14 (-12.0, 11.7)	.98
Fasting serum glucose (mg/dL): F=87.1 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.31								
PTI	-5.6 (-12.2, 1.0)	.099	-1.6 (-8.2, 5.0)	.63	0.83 (-6.1, 7.8)	.82	-1.5 (-7.0, 4.0)	.60
PFI	-9.4 (-15.7, -3.1)	.004	-1.9 (-8.1, 4.3)	.56	3.5 (-3.0, 10.0)	.29	-1.3 (-6.6, 3.9)	.62
CBI	-6.3 (-12.7, 0.2)	.05	-4.9 (-11.4, 1.6)	.14	4.1 (-2.9, 11.1)	.25	-2.1 (-7.6, 3.3)	.44
			12M	***P***	**24M**	***P***	**12M to 24M**	***P***
Serum Creatinine (mg/dL): F=407.1 *P*<.001; ICC PHCP =0.21; ICC subject|PHCP=0.53								
PTI			-0.01 (-0.07, 0.05)	.74	-0.04 (-0.1, 0.03)	.25	-0.02 (-0.09, 0.04)	.45
PFI			-0.02 (-0.09, 0.04)	.46	-0.04 (-0.10, 0.02)	.21	-0.03 (-0.09, 0.03)	.32
CBI			0.02 (-0.04, 0.09)	.44	0.002 (-0.06, 0.06)	.96	0.01 (-0.05, 0.08)	.68
Glomerular filtration rate (mL/min): F=297.6 *P*<.001; ICC PHCP =0.24; ICC subject|PHCP=0.56								
PTI			1.2 (-6.9, 9.3)	.78	4.7 (-3.4, 12.8)	.26	2.9 (-5.1, 11)	.47
PFI			2.4 (-5.7, 10.4)	.57	5.5 (-2.6, 13.6)	.19	3.9 (-4.1, 11.9)	.34

CBI	-4.0 (-12.1, 4.1)	.34	0.54 (-7.6, 8.7)	.90	-1.7 (-9.8, 6.3)	.68

[a]UC: usual care or control group.

[b]AUC: area under the curve.

[c]M: months.

[d]HbA_{1c}: glycated hemoglobin

[e]ICC: Intraclass correlation coefficient.

[f]PHCP: Primary Care Health Practices.

[g]PTI is an intervention only for patients and family members.

[h]PFI is an intervention only for health care professionals at primary care.

[i]CBI is a combined intervention for patients and professionals.

[j]LDL: low-density lipoprotein.

[k]HDL: high-density lipoprotein.

Adjusted means for each group and intragroup differences compared with the baseline measurement for the whole sample

	Adjusted means in each group (95%CI)						Difference in intragroup of adjusted means compared to baseline (95%CI)				
	B[d]	3M[e]	6M	12M	18M	24M	3M-B	6M-B	12M-B	18M-B	24M-B
HbA_{1c}[f] (%)											
PTI[g]	7.3 (7.3, 7.4)	7.0 (6.8, 7.1)	7.1 (7.0, 7.2)	7.1 (7.0, 7.3)	7.4 (7.2, 7.5)	7.3 (7.2, 7.4)	-0.35 (-0.5, -0.2)[a]	-0.24 (-0.4, -0.1)[b]	-0.20 (-0.3, -0.07)[b]	0.05 (-0.09, 0.2)	-0.03 (-0.2, 0.1)
PFI[h]	7.2 (7.1, 7.3)	7.1 (7.0, 7.3)	7.2 (7.1, 7.3)	7.4 (7.2, 7.5)	7.3 (7.1, 7.4)	7.4 (7.2, 7.5)	-0.02 (-0.1, -0.1)[b]	0.02 (-0.1, 0.1)	0.21 (0.08, 0.3)[b]	0.11 (-0.02, 0.2)[c]	0.20 (0.07, 0.3)[b]
CBI[i]	7.4 (7.3, 7.4)	7.1 (7.0, 7.3)	7.2 (7.1, 7.3)	7.2 (7.1, 7.3)	7.3 (7.1, 7.4)	7.4 (7.2, 7.5)	-0.22 (-0.4, -0.09)[b]	-0.17 (-0.3, -0.04)[b]	-0.17 (-0.3, -0.04)[b]	-0.09 (-0.2, 0.05)	0.01 (-0.1, 0.2)
UC[j]	7.3 (7.2, 7.3)	7.2 (7.1, 7.4)	7.4 (7.2, 7.5)	7.3 (7.2, 7.4)	7.4 (7.3, 7.6)	7.3 (7.2, 7.5)	-0.02 (-0.1, 0.1)	0.08 (-0.04, 0.2)	0.03 (-0.09, 0.2)	0.17 (0.04, 0.3)[b]	0.07 (-0.06, 0.2)
BMI (kg/m^2)											
PTI	31.6 (31.4, 31.8)	31.7 (31.5, 31.9)	31.8 (31.5, 32.0)	31.7 (31.4, 31.9)	31.7 (31.5, 32.0)	31.6 (31.3, 31.9)	-0.09 (-0.1, 0.3)	0.14 (-0.1, 0.4)	0.06 (-0.2, 0.3)	0.10 (-0.2, 0.4)	-0.02 (-0.3, 0.6)
PFI	32.4 (32.2, 32.6)	32.0 (31.8, 32.2)	32.0 (31.8, 32.2)	31.8 (31.6, 32.0)	31.7 (31.5, 31.9)	31.6 (31.4, 31.9)	-0.42 (-0.6, -0.2)[a]	-0.43 (-0.6, -0.2)[a]	-0.59 (-0.8, -0.4)[a]	-0.73 (-0.9, -0.5)[a]	-0.78 (-1.0, -0.6)[a]
CBI	32.1 (31.9, 32.3)	32.0 (31.7, 32.2)	32.1 (31.9, 32.3)	32.0 (31.8, 32.3)	32.0 (31.8, 32.3)	31.9 (31.6, 32.1)	-0.11 (-0.3, 0.1)	0.02 (-0.2, 0.3)	-0.05 (-0.3, 0.2)	-0.04 (-0.3, 0.2)	-0.20 (-0.4, 0.05)
UC	32.1 (31.9, 32.3)	32.1 (31.8, 32.3)	32.1 (31.8, 32.3)	31.8 (31.5, 32.0)	32.0 (31.8, 32.2)	31.8 (31.5, 32.0)	-0.02 (-0.2, 0.2)	-0.03 (-0.2, 0.2)	-0.32 (-0.5, -0.1)[b]	-0.09 (-0.3, 0.1)	-0.31 (-0.5, -0.09)[b]
Systolic blood pressure (mm Hg)											
PTI	132.8 (132.1, 133.6)	128.4 (126.5, 130.3)	131.4 (129.5, 133.3)	129.2 (127.3, 131.1)	130.8 (128.7, 132.8)	127.6 (125.7, 129.6)	-4.4 (-6.3, -2.5)[a]	-1.5 (-3.4, 0.5)	-3.7 (-5.6, -1.8)[a]	-2.1 (-4.1, -0.03)[b]	-5.2 (-7.2, -3.2)[a]
PFI	133.4 (132.7, 134.0)	125.2 (123.5, 126.9)	130.5 (128.8, 132.2)	129.2 (127.5, 130.9)	128.8 (127.0, 130.5)	127.9 (126.1, 129.7)	-8.2 (-9.9, -6.5)[a]	-2.9 (-4.6, -1.2)[b]	-4.2 (-5.9, -2.4)[a]	-4.6 (-6.3, -2.9)[a]	-5.5 (-7.3, -3.7)[a]
CBI	132.8 (131.9, 133.6)	129.0 (127.1, 130.9)	132.1 (130.3, 134.0)	129.0 (127.0, 130.9)	130.2 (128.3, 132.2)	125.3 (123.0, 127.6)	-3.8 (-5.7, -1.9)[a]	-0.64 (-2.5, 1.2)	-3.8 (-5.8, -1.9)[a]	-2.5 (-4.5, -0.6)[b]	-7.5 (-9.8, -5.2)[a]
UC	132.6 (131.9, 133.3)	130.5 (128.7, 132.3)	131.3 (129.5, 133.2)	131.1 (129.3, 132.9)	132.5 (130.7, 134.4)	129.7 (127.9, 131.5)	-2.1 (-3.9, -.3)[b]	-1.3 (-3.1, 0.6)	-1.5 (-3.3, 0.3)	-0.08 (-1.9, 1.8)	-2.9 (-4.7, -1.1)[b]
Diastolic blood pressure (mm Hg)											

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PTI	84.2 (83.7, 84.6)	80.8 (79.4, 82.1)	83.0 (81.6, 84.3)	82.2 (80.8, 83.6)	83.2 (81.8, 84.6)	80.7 (79.4, 82.1)	-3.4 (-4.7, -2.0)[a]	-1.2 (-2.5, 0.2)[c]	-2.0 (-3.3, -0.6)[b]	-0.95 (-2.3, 0.4)	-3.4 (-4.8, -2.1)[a]
PFI	84.5 (84.1, 84.9)	79.9 (78.6, 81.2)	82.7 (81.5, 84.0)	81.7 (80.4, 82.9)	81.4 (80.1, 82.7)	79.9 (78.6, 81.2)	-4.6 (-5.9, -3.3)[a]	-1.8 (-3.1, -0.5)[b]	-2.8 (-4.1, -1.6)[a]	-3.1 (-4.4, -1.8)[a]	-4.6 (-5.9, -3.3)[a]
CBI	84.7 (84.2, 85.2)	82.0 (80.6, 83.4)	82.4 (81.0, 83.7)	81.3 (80.0, 82.7)	81.4 (80.0, 82.8)	78.0 (76.5, 79.4)	-2.7 (-4.1, -1.3)[a]	-2.3 (-3.7, -1.0)[b]	-3.4 (-4.7, -2.0)[a]	-3.3 (-4.7, -1.9)[a]	-6.7 (-8.2, -5.3)[a]
UC	83.8 (83.4, 84.1)	82.4 (81.1, 83.7)	84.2 (82.8, 85.5)	83.3 (82.0, 84.6)	82.8 (81.5, 84.1)	82.5 (81.2, 83.8)	-1.4 (-2.7, -0.08)[b]	-0.40 (-0.9, 1.7)	-0.47 (-1.8, 0.8)	-1.0 (-2.3, 0.3)	-1.3 (-2.6, -0.004)[b]
Waist circumference (cm)											
PTI	104.8 (104.3, 105,3)	105.4 (104.4, 106.3)	106.1 (105.1, 107.1)	105 (104, 106)	105.4 (104.5, 106.4)	105.1 (104.2, 106.1)	0.58 (-0.34, 1.51)	1.33 (0.35, 2.3)[b]	0.21 (-0.75, 1.2)	0.66 (-0.32, 1.6)	0.37 (-0.61, 1.4)
PFI	106.7 (106.2, 107.1)	105.7 (104.9, 106.6)	104 (103.1, 104.9)	105.6 (104.7, 106.5)	105.4 (104.5, 106.3)	104.6 (103.7, 105.5)	-0.91 (-1.8, -0.04)[b]	-2.63 (-3.5, -1.7)[a]	-1.01 (-1.9, -0.11)[b]	-1.23 (-2.2, -0.33)[b]	-2.02 (-2.9, -1.1)[a]
CBI	105.4 (104.9, 105.9)	105.3 (104.4, 106.2)	105.3 (104.4, 106.3)	105.4 (104.4, 106.4)	105 (104, 105.9)	105.3 (104.3, 106.2)	-0.12 (-1.04, 0.8)	-0.12 (-1.08, 0.85)	-0.02 (-1, 0.95)	-0.48 (-1.4, 0.48)	-0.17 (-1.1, 0.81)
UC	105.8 (105.3, 106.2)	105.9 (105, 106.8)	106 (105.1, 106.9)	105.6 (104.6, 106.5)	105.9 (105, 106.9)	105.8 (104.9, 106.8)	0.13 (-0.76, 1.03)	0.25 (-0.66, 1.2)	-0.22 (-1.1, 0.7)	0.16 (-0.75, 1.1)	0.05 (-0.87, 0.98)
Weight (kg)											
PTI	86 (84.5, 87.5)	85.8 (85.2, 86.4)	85.9 (85.3, 86.6)	85.8 (85.1, 86.4)	85.9 (85.2, 86.6)	85.5 (84.8, 86.2)	-0.94 (-1.6, -0.33)[b]	-0.78 (-1.4, -0.16)[b]	-0.95 (-1.6, -0.29)[b]	-0.84 (-1.5, -0.14)[b]	-1.2 (-1.9, -0.46)[b]
PFI	87 (85.7, 88.4)	86.4 (85.9, 87)	86.4 (85.8, 87)	86 (85.4, 86.5)	85.6 (85, 86.2)	85.5 (84.9, 86.1)	-0.29 (-0.84, 0.26)	-0.3 (-0.86, 0.25)	-0.74 (-1.3, -0.17)[b]	-1.1 (-1.7, -0.52)[a]	-1.2 (-1.8, -0.65)[a]
CBI	86.8 (85.4, 88.2)	86.4 (85.8, 87)	86.8 (86.1, 87.4)	86.6 (86, 87.2)	86.6 (85.9, 87.3)	86.2 (85.5, 86.9)	-0.27 (-0.86, 0.31)	0.05 (-0.56, 0.66)	-0.13 (-0.75, 0.5)	-0.11 (-0.77, 0.54)	-0.51 (-1.2, 0.16)
UC	86.9 (85.5, 88.4)	86.7 (86.2, 87.3)	86.8 (86.2, 87.3)	85.9 (85.4, 86.5)	86.5 (85.9, 87.1)	86.0 (85.4, 86.6)	0.04 (-0.53, 0.61)	0.05 (-0.52, 0.62)	-0.76 (-1.35, -0.18)[b]	-0.17 (-0.76, 0.43)	-0.74 (-1.34, -0.15)[b]
Waist-to-hip ratio											
PTI	0.99 (0.98, 0.99)	0.98 (0.97, 0.98)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)	0.99 (0.98, 1)	0.99 (0.98, 0.99)	-0.01 (-0.02, -0.001)[b]	-0.01 (-0.01, 0.002)	-0.003 (-0.01, 0.004)	0.005 (0, 0.01)	0.001 (-0.01, 0.01)
PFI	0.97 (0.97, 0.98)	0.98 (0.98, 0.99)	0.98 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1)	0.01 (0.001, 0.01)[b]	0.01 (0.002, 0.02)[b]	0.01 (0.01, 0.02)[a]	0.01 (0.01, 0.02)[a]	0.02 (0.01, 0.03)[a]
CBI	0.98 (0.98, 0.98)	0.98 (0.97, 0.99)	0.98 (0.98, 0.99)	0.99 (0.98, 1)	0.99 (0.98, 1)	0.99 (0.98, 1)	0.001 (-0.01, 0.01)	0.005 (0, 0.01)	0.01 (0, 0.02)[b]	0.01 (0, 0.02)[b]	0.01 (0, 0.02)[b]
UC	0.99 (0.99, 0.99)	0.98 (0.97, 0.98)	0.98 (0.97, 0.98)	0.98 (0.97, 0.98)	0.98 (0.98, 0.99)	0.98 (0.97, 0.99)	-0.01 (-0.02, -0.01)[a]	-0.01 (-0.02, -0.01)[a]	-0.01 (-0.02, -0.01)[a]	-0.01 (-0.02, -0.002)[b]	-0.01 (-0.02, -0.003)[b]
	B		**6M**	**12M**		**24M**		**6M-B**	**12M-B**		**24M-B**

Total cholesterol (mg/dL)							
PTI	189.6 (188.1, 191.1)	186.5 (182.3, 190.7)	187.1 (183.1, 191.2)	185.2 (181.1, 189.3)	-3.1 (-7.3, 1)	-2.5 (-6.5, 1.6)	-4.4 (-8.6, -0.28)[b]
PFI	188.7 (187.3, 190.1)	184.7 (181, 188.4)	185.7 (182.1, 189.4)	179.5 (175.7, 183.3)	-4 (-7.7, -0.30)[b]	-3 (-6.6, 0.66)	-9.2 (-13, -5.4)[a]
CBI	189.5 (187.9, 191.1)	184.4 (180.4, 188.3)	185.4 (181.3, 189.4)	179.5 (175.4, 183.5)	-5.1 (-9.1, -1.2)[b]	-4.1 (-8.1, -0.07)[b]	-10 (-14.1, -6.0)[a]
UC	186.6 (185.2, 188.1)	186.9 (182.9, 190.8)	183.6 (179.9, 187.4)	182.4 (178.5, 186.2)	0.3 (-3.7, 4.2)	-3 (-6.7, 0.77)	-4.3 (-8.2, -0.39)[b]
LDL[k] (mg/dL)							
PTI	109.1 (107.8, 110.5)	110.2 (106.8, 113.6)	106.3 (103, 109.7)	105.8 (102.4, 109.2)	1 (-2.4, 4.5)	-2.8 (-6.2, 0.5)	-3.4 (-6.8, 0)[c]
PFI	108.9 (107.7, 110.2)	103.9 (100.9, 107)	105.7 (102.7, 108.6)	100.9 (97.8, 104)	-5 (-8.1, -2)[b]	-3.3 (-6.3, -0.3)[b]	-8 (-11.1, -4.9)[a]
CBI	107.8 (106.4, 109.3)	106.1 (102.9, 109.4)	107 (103.6, 110.4)	102.3 (98.9, 105.8)	-1.7 (-5, 1.6)	-0.9 (-4.2, 2.5)	-5.5 (-9, -2.1)[b]
UC	108.4 (107.1, 109.8)	107.4 (104.2, 110.5)	103.3 (100.2, 106.4)	103.7 (100.5, 106.9)	-1.1 (-4.2, 2.1)	-5.1 (-8.2, -2)[b]	-4.7 (-7.9, -1.5)[b]
HDL[l] (mg/dL)							
PTI	49.2 (48.7, 49.6)	49.2 (48, 50.5)	49.1 (47.9, 50.4)	48.3 (47.1, 49.6)	0.05 (-1.19, 1.3)	-0.03 (-1.3, 1.2)	-0.82 (-2.0, 0.41)
PFI	48.6 (48.1, 49)	49 (47.8, 50.1)	48.6 (47.5, 49.7)	49.1 (48, 50.3)	0.40 (-0.73, 1.5)	0.01 (-1.1, 1.1)	0.54 (-0.62, 1.7)
CBI	49.2 (48.7, 49.7)	48.9 (47.7, 50.1)	47.6 (46.4, 48.9)	47 (45.7, 48.2)	-0.30 (-1.5, 0.89)	-1.6 (-2.8, -0.34)[b]	-2.2 (-3.5, -1.0)[a]
UC	47.6 (47.1, 48.1)	48.1 (46.9, 49.2)	48.4 (47.3, 49.6)	47.2 (46, 48.4)	0.46 (-0.69, 1.6)	0.82 (-0.32, 2.0)	-0.42 (-1.6, 0.75)
Triglycerides (mg/dL)							
PTI	166.9 (162.2, 171.7)	150.6 (139.8, 161.4)	164.9 (153.2, 174.7)	157.4 (146.6, 168.2)	-16.3 (-27.1, -5.5)[b]	-3 (-13.8, 7.8)	-9.6 (-20.4, 1.2)[c]
PFI	160.1 (156.8, 163.3)	172.5 (162.1, 183)	165.4 (156.1, 174.7)	153.8 (144.2, 163.3)	12.5 (2.1, 22.9)[b]	5.4 (-4, 14.7)	-6.3 (-15.8, 3.2)
CBI	165.5 (161.4, 169.6)	163.7 (153.5, 173.8)	164.6 (154.3, 174.8)	168 (157.3, 178.7)	-1.8 (-12, 8.3)	-0.9 (-11.2, 9.3)	2.5 (-8.2, 13.2)
UC	158.4 (154.5, 162.3)	165.3 (154.7, 176)	166.5 (156.8, 176.2)	164.7 (154.6, 174.8)	6.9 (-3.7, 17.6)	8.1 (-1.6, 17.8)	6.3 (-3.8, 16.4)

Fasting serum glucose (mg/dL)							
PTI	153.7 (151.8, 155.7)	150.8 (146, 155.6)	151.8 (146.9, 156.7)	151.5 (146.4, 156.5)	-2.9 (-7.8, 1.8)	-1.9 (-6.8, 3.0)	-2.3 (-7.3, 2.7)
PFI	148.6 (147, 150.3)	147 (142.6, 151.3)	151.6 (147.3, 155.9)	154.1 (149.6, 158.6)	-1.7 (-6.0, 2.7)	2.9 (-1.3, 7.3)	5.5 (1.0, 10.0)[b]
CBI	154 (152, 156.1)	150.1 (145.4, 154.8)	148.5 (143.8, 153.2)	154.7 (149.6, 159.8)	-3.9 (-8.6, 0.75)	-5.5 (-10.2, -0.78)[b]	0.7 (-4.4, 5.8)
UC	152.1 (150.3, 154)	156.4 (151.8, 160.9)	153.5 (149, 157.9)	150.6 (145.9, 155.3)	4.2 (-0.31, 8.8)[c]	1.3 (-3.1, 5.8)	-1.5 (-6.2, 3.2)
	B		**12M**	**24M**		**12M-B**	**24M-B**
Serum Creatinine (mg/dL)							
PTI	0.82 (0.81, 0.83)		0.78 (0.74, 0.83)	0.78 (0.73, 0.82)		-0.04 (-0.08, 0.01)	-0.04 (-0.08, 0.00)[c]
PFI	0.81 (0.8, 0.82)		0.77 (0.73, 0.81)	0.78 (0.73, 0.82)		-0.04 (-0.08, 0)[c]	-0.03 (-0.08, 0.01)
CBI	0.78 (0.77, 0.79)		0.82 (0.77, 0.86)	0.82 (0.77, 0.86)		0.04 (-0.01, 0.08)[c]	0.04 (-0.01, 0.08)
UC	0.78 (0.77, 0.79)		0.79 (0.75, 0.84)	0.82 (0.77, 0.86)		0.01 (-0.03, 0.06)	0.03 (-0.01, 0.08)
Glomerular filtration rate (mL/min)							
PTI	90.0 (89.2, 90.9)		93.4 (87.7, 99.2)	92.9 (87.2, 98.7)		3.4 (-2.4, 9.1)	2.9 (-2.8, 8.7)
PFI	88.6 (87.8, 89.3)		94.6 (88.9,100.3)	93.8 (88.0, 99.5)		6.1 (0.36, 11.8)[b]	5.2 (-0.52, 10.9)[c]
CBI	93.5 (92.7, 94.4)		88.3 (82.5, 94.0)	88.8 (83.0, 94.6)		-5.2 (-10.9, 0.54)[c]	-4.7 (-10.5, 1.1)
UC	93.9 (93.1, 94.7)		92.3 (86.5, 97.9)	88.3 (82.5, 94.0)		-1.6 (-7.4, 4.1)	-5.6 (-11.4, 0.11)[c]

[a]: $P<.001$.

[b]: $P<.05$.

[c]: $P<.1$.

[d]B: baseline.

[e]M: months.

[f]HbA_{1c}: glycated hemoglobin.

[g]PTI is an intervention only for patients and family members.

[h]PFI is an intervention only for health care professionals at primary care.

[i]CBI is a combined intervention for patients and professionals.

[j]UC: usual care or control group.

[k]LDL: low-density lipoprotein.

[l]HDL: high-density lipoprotein.

Patients with clinically relevant changes in HbA_{1c} and comparison with the usual care group. HbA_{1c}: glycated hemoglobin.

All the sample										
	3M[a]	*P*	6M	*P*	12M	*P*	18M	*P*	24M	*P*
PTI[b]	38.6%	<.001	33.1%	.005	35.6%	.006	29.2%	.10	30.2%	.21
PFI[c]	24.4%	.20	26.7%	.16	22.8%	.27	27.5%	.24	26.1%	.99
CBI[d]	27.8%	.03	30.5%	.02	31.6%	.09	32.6%	.009	30.8%	.14
UC[e]	20.3%		21.4%		26.0%		23.9%		26.2%	
HbA_{1c}[f] baseline > 7%										
	3M	*P*	6M	*P*	12M	*P*	18M	*P*	24M	*P*
PTI	57.3%	<.001	51.8%	.01	53.1%	.049	46.0%	.41	48.7%	.46
PFI	42.2%	.02	46.1%	.08	40.5%	.57	46.3%	.35	47.7%	.59
CBI	42.6%	.02	45.6%	.10	47.2%	.41	48.8%	.16	48.0%	.54
UC	31.7%		36.4%		43.2%		41.8%		45.1%	

[a]M: months.

[b]PTI is an intervention only for patients and family members.

[c]PFI is an intervention only for health care professionals at primary care.

[d]CBI is a combined intervention for patients and professionals.

[e]UC: usual care or control group.

[f]HbA_{1c}: glycated hemoglobin.

Clinically relevant changes are differences in HbA_{1c} >= 0.4%.

Adjusted difference in means and area under the curve of each group compared with the usual care group for patients with a baseline HbA_{1c} >7. HbA_{1c}: glycated hemoglobin.

	Adjusted difference in intragroup means compared to the UC[a] group: Mean (95%CI)										Difference in AUC[b] compared to the UC group (95%CI)	
	3M[c]	*P*	6M	*P*	12M	*P*	18M	*P*	24M	*P*	3M to 24M	*P*
HbA_{1c}[d] (%): F=17.0: *P*<.001; ICC[e] PHCP[f] = 0.01; ICC subject|PHCP=0.37												
PTI[g]	-0.53 (-0.80, -0.25)	<.001	-0.49 (-0.77, -0.20)	.001	-0.29 (-0.59, 0.01)	.05	-0.06 (-0.36, 0.24)	.68	-0.10 (-0.40, 0.19)	.49	-0.26 (-0.48, -0.04)	.03
PFI[h]	-0.30 (-0.57, -0.02)	.03	-0.36 (-0.63, -0.08)	.01	-0.05 (-0.32, 0.23)	.74	-0.24 (-0.53, 0.04)	.09	-0.07 (-0.36, 0.22)	.63	-0.19 (-0.41, 0.03)	.09
CBI[i]	-0.29 (-0.56, -0.02)	.04	-0.33 (-0.60, -0.05)	.02	-0.26 (-0.55, 0.02)	.07	-0.27 (-0.56, 0.02)	.07	-0.04 (-0.34, 0.25)	.79	-0.25 (-0.47, -0.03)	.03
BMI (kg/m2): F=342.2 *P*<.001; ICC PHCP = 0.01; ICC subject|PHCP=0.59												
PTI	-0.24 (-0.62, 0.15)	.23	-0.18 (-0.57, 0.20)	.35	-0.01 (-0.42, 0.40)	.96	-0.4 (-0.83, 0.02)	.06	-0.21 (-0.64, 0.22)	.35	-0.2 (-0.54, 0.13)	.23
PFI	-0.05 (-0.42, 0.32)	.78	-0.02 (-0.39, 0.35)	.91	-0.01 (-0.39, 0.36)	.94	-0.45 (-0.85, -0.06)	.03	-0.36 (-0.77, 0.04)	.08	-0.19 (-0.51, 0.12)	.23
CBI	-0.003 (-0.37, 0.36)	.99	0.08 (-0.29, 0.46)	.66	0.26 (-0.12, 0.64)	.18	-0.01 (-0.41, 0.38)	.96	0.02 (-0.38, 0.42)	.92	0.09 (-0.22, 0.41)	.57
Systolic blood pressure (mm Hg): F=26.9 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.28												
PTI	-1.7 (-5.2, 1.8)	.33	-0.63 (-4.2, 3)	.73	-1.8 (-5.3, 1.8)	.32	-2.2 (-5.9, 1.4)	.24	-3.2 (-6.8, 0.39)	.08	-1.9 (-4.5, 0.82)	.17
PFI	-5.4 (-8.8, -2)	.002	0.06 (-3.4, 3.5)	.97	-0.93 (-4.4, 2.5)	.60	-3.2 (-6.7, 0.24)	.07	-2.0 (-5.5, 1.5)	.26	-1.8 (-4.4, 0.73)	.16
CBI	-1.6 (-5.0, 1.8)	.36	1.1 (-2.4, 4.7)	.53	-1.7 (-5.2, 1.9)	.35	-2.6 (-6.1, 0.93)	.15	-5.2 (-9.0, -1.5)	.007	-1.8 (-4.4, 0.76)	.17
Diastolic blood pressure (mm Hg): F=22.1 *P*<.001; ICC PHCP =0.02; ICC subject|PHCP=0.23												
PTI	-1.1 (-3.5, 1.3)	.37	-1.5 (-3.9, 0.9)	.22	-1.3 (-3.7, 1.1)	.29	0.91 (-1.5, 3.3)	.46	-1.4 (-3.8, 0.9)	.23	-0.71 (-2.6, 1.2)	.46
PFI	-2.5 (-4.8, -0.25)	.03	-1.3 (-3.6, 1.1)	.29	-1.3 (-3.6, 1)	.27	-0.71 (-3, 1.6)	.55	-1.8 (-4.1, 0.52)	.13	-1.3 (-3.1, 0.56)	.17
CBI	-0.03 (-2.4, 2.3)	.98	-1.9 (-4.3, 0.43)	.11	-2.4 (-4.8, -0.06)	.04	-0.99 (-3.3, 1.3)	.41	-3.8 (-6.1, -1.4)	.002	-1.9 (-3.8, -0.07)	.04

Waist circumference (cm): *F=175.5 P<.001; ICC PHCP =0.02; ICC subject|PHCP=0.44*												
PTI	-0.28 (-1.7, 1.2)	.71	0.33 (-1.2, 1.9)	.68	-0.18 (-1.7, 1.4)	.82	0.27 (-1.3, 1.8)	.73	-0.31 (-1.9, 1.2)	.69	0.03 (-1.2, 1.3)	.96
PFI	-0.13 (-1.56, 1.3)	.86	-2.03 (-3.52, -0.55)	.007	-0.05 (-1.52, 1.41)	.94	-0.37 (-1.85, 1.1)	.62	-1.44 (-2.98, 0.1)	.07	-0.77 (-2.0, 0.44)	.21
CBI	-0.84 (-2.2, 0.56)	.24	-0.78 (-2.3, 0.71)	.31	-0.43 (-1.9, 1.1)	.57	-0.49 (-1.9, 0.99)	.52	-0.6 (-2.1, 0.91)	.44	-0.58 (-1.8, 0.66)	.36
Weight (kg): *F=484.2 P<.001; ICC PHCP =0.01; ICC subject|PHCP=0.57*												
PTI	-0.72 (-1.74, 0.3)	.17	-0.53 (-1.57, 0.5)	.31	-0.03 (-1.13, 1.08)	.96	-1 (-2.14, 0.15)	.09	-0.52 (-1.69, 0.65)	.38	-0.53 (-1.4, 0.37)	.25
PFI	-0.33 (-1.32, 0.66)	.0.56	-0.23 (-1.22, 0.76)	.65	-0.14 (-1.15, 0.87)	.78	-1.24 (-2.31, 0.18)	.02	-1.07 (-2.15, 0.02)	.05	-0.62 (-1.5, 0.22)	.15
CBI	-0.1 (-1.07, 0.88)	.85	0.16 (-0.83, 1.16)	.75	0.71 (-0.32, 1.73)	.18	0.02 (-1.05, 1.09)	.97	0.08 (-1, 1.16)	.88	0.25 (-0.61, 1.1)	.57
Waist-to-hip ratio: *F=42.2 P<.001; ICC PHCP =0.02; ICC subject|PHCP=0.42*												
PTI	0 (-0.01, 0.01)	.98	0 (-0.01, 0.01)	.98	0.005 (-0.01, 0.02)	.39	0.009 (-0.004, 0.02)	.18	0.005 (-0.01, 0.02)	.41	0.005 (-0.01, 0.01)	.37
PFI	0.004 (-0.01, 0.02)	.54	0.007 (-0.005, 0.02)	.27	0.009 (-0.003, 0.02)	.16	0.008 (-0.004, 0.02)	.21	0.009 (-0.003, 0.02)	.14	0.008 (-0.002, 0.02)	.13
CBI	0.002 (-0.01, 0.01)	.74	0.005 (-0.007, 0.02)	.40	0.011 (-0.002, 0.02)	.098	0.009 (-0.003, 0.02)	.14	0.009 (-0.003, 0.02)	.16	0.008 (-0.002, 0.02)	.12
			6M	***P***	**12M**	***P***			**24M**	***P***	**3M to 24M**	***P***
Total cholesterol (mg/dL): F= 43.0 p<.001; ICC PHCP =0.01; ICC subject|PHCP=0.37												
PTI			-1.1 (-9.1, 6.8)	.78	4.8 (-2.8, 12.4)	.21			1.7 (-6.2, 9.6)	.67	2.4 (-1.6, 6.4)	.24
PFI			-1.3 (-8.9, 6.2)	.73	2.8 (-4.3, 9.96)	.44			-4.5 (-12.2, 3.2)	.25	0.8 (-3, 4.5)	.69
CBI			-2.4 (-9.9, 5.2)	.53	3.6 (-3.8, 11)	.34			-2.9 (-10.5, 4.6)	.44	0.9 (-2.9, 4.7)	.65
LDL[j] (mg/dL): F=46.4 p<.001; ICC PHCP =0.01; ICC subject|PHCP=0.35												
PTI			3.5 (-2.9, 10)	.28	3.9 (-2.5, 10.2)	.23			2.0 (-4.6, 8.6)	.56	3.3 (0.1, 6.6)	.04
PFI			-4 (-10.1, 2.1)	.20	2.6 (-3.3, 8.6)	.40			-3.6 (-10, 2.9)	.28	-1.1 (-4.2, 1.9)	.47

CBI	-1.7 (-7.9, 4.5)	.60	3.9 (-2.4, 10.1)	.22	-2.3 (-8.8, 4.2)	.49	-0.83 (-3.9, 2.3)	.60
HDL[k] (mg/dL): F=122.6 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.44								
PTI	0.5 (-1.4, 2.3)	.62	0.1 (-1.7, 2)	.88	0.6 (-1.3, 2.4)	.55	0.66 (-0.3, 1.6)	.16
PFI	1.7 (-0.1, 3.4)	.06	0.1 (-1.6, 1.9)	.88	1.7 (-0.1, 3.5)	.07	0.95 (0.1, 1.8)	.03
CBI	1.5 (-0.2, 3.2)	.09	-0.7 (-2.4, 1)	.43	0.5 (-1.3, 2.4)	.57	1.17 (0.3, 2.0)	.008
Triglycerides (mg/dL): F=18.0 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.45								
PTI	-14.3 (-29.3, 0.7)	.06	-2.2 (-16.9, 12.6)	.77	-6.8 (-21.7, 8.06)	.37	2.3 (-5.2, 9.8)	.55
PFI	7.6 (-7.6, 22.8)	.33	-1.1 (-14.8, 12.7)	.88	-10.7 (-24.6, 3.2)	.13	7.64 (0.04, 15.2)	.049
CBI	-1.3 (-16.1, 13.4)	.86	-1.2 (-15.6, 13.1)	.87	4.3 (-10.9, 19.4)	.58	8.1 (0.7, 15.4)	.03
Fasting serum glucose (mg/dL): F=21.2 *P*<.001; ICC PHCP =0.01; ICC subject|PHCP=0.28								
PTI	-9.6 (-20.2, 0.95)	.07	-2.8 (-13.3, 7.8)	.6	-0.55 (-11.7, 10.6)	.92	-4.4 (-9.7, 0.9)	.104
PFI	-15.7 (-25.8, -5.6)	.002	-5.9 (-15.8, 4.0)	.24	-0.55 (-11.1, 10.0)	.92	-9.8 (-14.9, -4.7)	<.001
CBI	-13.0 (-23, -2.9)	.01	-7.2 (-17.2, 2.9)	.17	-1.4 (-12.2, 9.4)	.80	-7.2 (-12.2, -2.16)	.005
			12M	***P***	**24M**	***P***	**12M to 24M**	***P***
Serum Creatinine (mg/dL): F=164.6 *P*<.001; ICC PHCP =0.17; ICC subject|PHCP=0.48								
PTI			-0.02 (-0.08, 0.05)	.66	-0.04 (-0.1, 0.03)	.25	-0.03 (-0.09, 0.04)	.42
PFI			-0.03 (-0.1, 0.03)	.33	-0.04 (-0.1, 0.02)	.21	-0.04 (-0.1, 0.03)	.26
CBI			0.02 (-0.04, 0.09)	.53	0.002 (-0.06, 0.07)	.96	0.01 (-0.05, 0.08)	.73
Glomerular filtration rate (mL/min): F=128.6 *P*<.001; ICC PHCP =0.21; ICC subject|PHCP=0.54								
PTI			1.2 (-7.2, 9.5)	.78	4.7 (-3.7, 13.1)	.27	3.0 (-5.2, 11.1)	.48
PFI			2.9	.49	5.7	.18	4.3	.30

	(-5.4, 11.2)			(-2.7, 14.1)		(-3.9, 12.5)	
CBI	-4.3 (-12.6, 4.0)	.31		0.19 (-8.2, 8.6)	.96	-2.0 (-10.3, 6.2)	.63

[a]UC: usual care or control group.

[b]AUC: area under the curve.

[c]M: months.

[d]HbA_{1c}: glycated hemoglobin.

[e]ICC: Intraclass correlation coefficient.

[f]PHCP: Primary Care Health Practices.

[g]PTI is an intervention only for patients and family members.

[h]PFI is an intervention only for health care professionals at primary care.

[i]CBI is a combined intervention for patients and professionals.

[j]LDL: low-density lipoprotein.

[k]HDL: high-density lipoprotein.

Adjusted means for each group and intragroup differences compared with the baseline measurement for patients with a baseline HbA_{1c} >7. HbA_{1c}: glycated hemoglobin.

	Adjusted means in each group (95%CI)						Difference in intragroup adjusted means compared to baseline (95%CI)				
	B[d]	3M[e]	6M	12M	18M	24M	3M-B	6M-B	12M-B	18M-B	24M-B
HbA_{1c}[f] (%)											
PTI[g]	8.4 (8.3, 8.5)	7.7 (7.5, 8.0)	7.8 (7.6, 8.0)	7.9 (7.7, 8.1)	8.1 (7.9, 8.4)	8.0 (7.7, 8.2)	-0.69 (-0.9, -0.5)[a]	-0.61 (-0.8, -0.4)[a]	-0.56 (-0.8, -0.3)[a]	-0.30 (-0.5, -0.08)[b]	-0.49 (-0.7, -0.3)[a]
PFI[h]	8.3 (8.3, 8.4)	8.0 (7.8, 8.2)	8.0 (7.7, 8.2)	8.1 (7.9, 8.3)	8.0 (7.8, 8.2)	8.0 (7.8, 8.2)	-0.36 (-0.6, -0.2)[b]	-0.38 (-0.6, -0.2)[a]	-0.21 (-0.4,-0.002)[b]	-0.38 (-0.6, -0.2)[a]	-0.35 (-0.6, -0.4)[b]
CBI[i]	8.4 (8.3, 8.6)	8.0 (7.8, 8.2)	8.0 (7.8, 8.2)	7.9 (7.7, 8.1)	8.0 (7.7, 8.1)	8.0 (7.8, 8.2)	-0.38 (-0.6, -0.2)[a]	-0.38 (-0.6, -0.2)[a]	-0.45 (-0.7, -0.3)[a]	-0.43 (-0.7, -0.2)[a]	-0.35 (-0.6, -0.1)[b]
UC[j]	8.5 (8.4, 8.6)	8.3 (8.1, 8.5)	8.3 (8.1, 8.5)	8.2 (8.0, 8.4)	8.2 (8.0, 8.4)	8.1 (7.8, 8.3)	-0.20 (-0.4, 0.003)[c]	-0.16 (-0.4, 0.05)	-0.30 (-0.5, -0.08)[b]	-0.27 (-0.5, -0.05)[b]	-0.41 (-0.6, -0.2)[a]
BMI (Kg/m^2)											
PTI	32.2 (31.9, 32.5)	32 (31.7, 32.3)	32 (31.7, 32.3)	31.9 (31.6, 32.3)	31.9 (31.5, 32.2)	31.8 (31.5, 32.2)	-0.21 (-0.49, 0.07)	-0.16 (-0.45, 0.12)	-0.24 (-0.56, 0.07)	-0.33 (-0.65, 0)[b]	-0.38 (-0.73, -0.04)[b]
PFI	32.9 (32.6, 33.2)	32.2 (31.9, 32.4)	32.2 (31.9, 32.5)	31.9 (31.7, 32.2)	31.8 (31.5, 32.1)	31.7 (31.4, 31.9)	-0.76 (-1.02, -0.5)[a]	-0.74 (-1, -0.48)[a]	-0.99 (-1.25, -0.72)[a]	-1.12 (-1.4, -0.83)[a]	-1.28 (-1.57, -0.99)[a]
CBI	32 (31.7, 32.3)	32.2 (32, 32.5)	32.3 (32, 32.6)	32.2 (31.9, 32.5)	32.3 (32, 32.5)	32 (31.7, 32.3)	0.23 (-0.03, 0.48)[c]	0.3 (0.04, 0.57)[b]	0.23 (-0.05, 0.5)	0.27 (-0.02, 0.55)c	0.04 (-0.25, 0.34)[b]
UC	32.1 (31.7, 32.4)	32.2 (32, 32.5)	32.2 (32, 32.5)	32 (31.7, 32.2)	32.3 (32, 32.6)	32 (31.7, 32.3)	0.14 (-0.12, 0.4)	0.13 (-0.13, 0.39)	-0.12 (-0.39, 0.15)	0.19 (-0.09, 0.47)	-0.06 (-0.34, 0.21)
Systolic blood pressure (mm Hg)											
PTI	135.1 (134.1, 136.1)	130.8 (128.2, 133.3)	132.8 (130.2, 135.4)	130.6 (128, 133.2)	132 (129.3, 134.7)	128.7 (126, 131.3)	-4.3 (-6.8, -1.8)[b]	-2.3 (-4.9, 0.28)[c]	-4.5 (-7.1, -1.9)[b]	-3.1 (-5.8, -0.42)[b]	-6.4 (-9, -3.8)[a]
PFI	136.5 (135.6, 137.5)	127.1 (124.7, 129.5)	133.5 (131.1, 135.8)	131.4 (129.1, 133.8)	131 (128.6, 133.4)	129.9 (127.4, 132.4)	-9.4 (-11.8, -7.0)[a]	-3.1 (-5.4, -0.68)[b]	-5.1 (-7.5, -2.7)[a]	-5.5 (-7.9, -3.2)[a]	-6.6 (-9.1, -4.2)[a]
CBI	135.5 (134.3, 136.6)	130.9 (128.5, 133.3)	134.6 (132.1, 137)	130.7 (128.2, 133.2)	131.6 (129.2, 134.1)	126.7 (123.7, 129.7)	-4.6 (-7, -2.2)[a]	-0.9 (-3.4, 1.47)	-4.8 (-7.3, -2.3)[a]	-3.9 (-6.3, -1.4)[b]	-8.8 (-11.8, -5.8)[a]
UC	134.4 (133.4, 135.4)	132.5 (130.1, 134.9)	133.4 (130.9, 135.9)	132.4 (129.9, 134.8)	134.2 (131.7, 136.7)	131.9 (129.5, 134.3)	-1.9 (-4.3, 0.49)	-1 (-3.5, 1.49)	-2 (-4.5, 0.41)	-0.2 (-2.7, 2.26)	-2.5 (-4.9, -0.13)[b]
Diastolic blood pressure (mm Hg)											
PTI	85.2 (84.7, 85.8)	82 (80.3, 83.7)	83.5 (81.9, 85.2)	81.7 (80.1, 83.4)	83.8 (82, 85.5)	81.3 (79.6, 83)	-3.3 (-5, -1.6)[a]	-1.7 (-3.4, 0)[c]	-2.4 (-4.1, -0.63)[b]	-1.5 (-3.2, 0.24)[c]	-4 (-5.7, -2.3)[a]

PFI	85.4 (84.8, 85.9)	80.5 (78.9, 82.1)	83.8 (82.1, 85.4)	82.9 (81.2, 84.5)	82.1 (80.5, 83.8)	80.9 (79.2, 82.6)	-4.9 (-6.5, -3.2)[a]	-1.6 (-3.2, 0.04)[c]	-2.5 (-4.1, -0.87)[b]	-3.2 (-4.9, -1.6)[a]	-4.4 (-6.1, -2.7)[a]
CBI	86.2 (85.5, 86.8)	83 (81.3, 84.7)	83.1 (81.5, 84.7)	82.9 (81.2, 84.6)	81.9 (80.2, 83.5)	78.9 (77.2, 80.6)	-3.2 (-4.9, -1.5)[a]	-3.1 (-4.7, -1.4)[a]	-4.4 (-6.1, -2.79)[a]	-4.3 (-6, -2.67)[a]	-7.3 (-9, -5.57)[a]
UC	84 (83.5, 84.6)	83 (81.4, 84.7)	85 (83.4, 86.7)	84.2 (82.5, 85.8)	82.8 (81.2, 84.5)	82.7 (81.1, 84.3)	-1 (-2.6, 0.63)	1 (-0.7, 2.65)	0.1 (-1.5, 1.76)	-1.2 (-2.8, 0.46)	-1.3 (-2.9, 0.28)
Waist circumference (cm)											
PTI	106.8 (106.1, 107.5)	107 (105.9, 108)	107.5 (106.4, 108.7)	106.7 (105.6, 107.8)	106.9 (105.8, 108)	106.4 (105.2, 107.6)	0.18 (-0.87, 1.23)	0.76 (-0.38, 1.89)	-0.07 (-1.2, 1.06)	0.14 (-0.99, 1.27)	-0.38 (-1.55, 0.8)
PFI	109 (108.4, 109.7)	107.1 (106.1, 108.1)	105.2 (104.1, 106.2)	106.8 (105.8, 107.9)	106.3 (105.2, 107.3)	105.3 (104.2, 106.4)	-1.91 (-2.92, -0.9)[a]	-3.85 (-4.91, -2.8)[a]	-2.19 (-3.23, -1.14)[a]	-2.74 (-3.8, -1.68)[a]	-3.74 (-4.84, -2.64)[a]
CBI	106.2 (105.6, 106.9)	106.4 (105.4, 107.4)	106.4 (105.4, 107.5)	106.4 (105.4, 107.5)	106.2 (105.1, 107.2)	106.1 (105, 107.2)	0.18 (-0.81, 1.17)	0.2 (-0.85, 1.25)	0.23 (-0.83, 1.3)	-0.05 (-1.1, 1)	-0.1 (-1.19, 0.99)
UC	106.4 (105.7, 107.1)	107.2 (106.2, 108.2)	107.2 (106.2, 108.2)	106.9 (105.8, 107.9)	106.6 (105.6, 107.7)	106.7 (105.7, 107.8)	0.84 (-0.17, 1.85)	0.81 (-0.24, 1.85)	0.49 (-0.55, 1.53)	0.26 (-0.78, 1.3)	0.32 (-0.73, 1.37)
Weight (kg)											
PTI	88.5 (86.4, 90.5)	87.1 (86.4, 87.9)	87.3 (86.5, 88)	87 (86.2, 87.9)	86.8 (85.9, 87.7)	86.7 (85.7, 87.6)	-0.83 (-1.58, -0.08)[b]	-0.69 (-1.46, 0.08)[c]	-0.91 (-1.78, -0.05)[b]	-1.12 (-2.01, -0.24)[b]	-1.28 (-2.22, -0.34)[b]
PFI	89.4 (87.4, 91.3)	87.5 (86.8, 88.2)	87.6 (86.8, 88.3)	86.9 (86.2, 87.6)	86.6 (85.8, 87.3)	86.1 (85.3, 86.9)	-0.44 (-1.13, 0.25)	-0.38 (-1.09, 0.33)	-1.03 (-1.75, -0.31)[b]	-1.37 (-2.14, -0.61)[a]	-1.83 (-2.61, -1.04)[a]
CBI	87.3 (85.4, 89.2)	87.7 (87.1, 88.4)	88 (87.2, 88.7)	87.8 (87, 88.5)	87.8 (87, 88.6)	87.3 (86.5, 88.1)	-0.2 (-0.89, 0.48)	0.01 (-0.7, 0.72)	-0.18 (-0.92, 0.56)	-0.11 (-0.89, 0.67)	-0.68 (-1.47, 0.11)[c]
UC	86.6 (84.5, 88.8)	87.8 (87.1, 88.5)	87.8 (87.1, 88.5)	87.1 (86.3, 87.8)	87.8 (87, 88.6)	87.2 (86.4, 87.9)	-0.11 (-0.81, 0.59)	-0.15 (-0.85, 0.55)	-0.89 (-1.61, -0.17)[b]	-0.13 (-0.89, 0.63)	-0.76 (-1.51, -0.01)[b]
Waist-to-hip ratio											
PTI	1 (0.99, 1)	0.99 (0.98, 1)	0.99 (0.98, 1)	0.99 (0.98, 1)	1 (0.99, 1.01)	1 (0.99, 1)	-0.009 (-0.02, 0)	-0.008 (-0.02, 0)	-0.002 (-0.01, 0.01)	0.003 (-0.006, 0.01)	0 (-0.009, 0.01)
PFI	0.99 (0.98, 0.99)	0.99 (0.98, 1)	0.99 (0.99, 1)	1 (0.99, 1.01)	1 (0.99, 1.01)	1 (0.99, 1.01)	0.004 (-0.004, 0.01)	0.008 (0, 0.02)	0.011 (0.002, 0.02)	0.011 (0.003, 0.02)	0.013 (0.004, 0.02)
CBI	0.99 (0.99, 0.99)	0.99 (0.98, 1)	0.99 (0.98, 1)	1 (0.99, 1.01)	1 (0.99, 1.01)	1 (0.99, 1.01)	0 (-0.009, 0.01)	0.004 (-0.005, 0.01)	0.01 (0.001, 0.02)	0.01 (0.001, 0.02)	0.01 (0.001, 0.02)
UC	1 (1, 1.01)	0.99 (0.98, 0.99)	0.99 (0.98, 1)	0.99 (0.98, 1)	0.99 (0.98, 1)	0.99 (0.98, 1)	-0.02 (-0.02, -0.01)	-0.01 (-0.02, -0.01)	-0.01 (-0.02, -0.01)	-0.01 (-0.02, 0)	-0.01 (-0.02, 0)
	B		**6M**	**12M**		**24M**		**6M-B**	**12M-B**		**24M-B**
Total cholesterol (mg/dL)											
PTI	192 (189.7, 194.2)		184.9 (179.2, 190.7)	187.2 (181.7, 192.7)		183.6 (177.9, 189.3)		-7.1 (-12.8, -1.3)[b]	-4.8 (-10.3, 0.71)[c]		-8.4 (-14.1, -2.65)[b]
PFI	188.9 (186.6, 191.3)		184.7 (179.5, 190)	185.2 (180.2, 190.2)		177.4 (172.1, 182.7)		-4.2 (-9.5, 1.08)	-3.7 (-8.7, 1.24)		-11.6 (-16.9, -6.25)[a]

CBI	190.2 (187.9, 192.6)	183.7 (178.4, 188.9)	186 (180.7, 191.3)	178.9 (173.5, 184.4)	-6.5 (-11.8, -1.31)[b]	-4.2 (-9.5, 1.06)	-11.3 (-16.7, -5.85)[a]
UC	186.1 (183.8, 188.4)	186.1 (180.6, 191.5)	182.4 (177.2, 187.5)	181.9 (176.5, 187.3)	-0.01 (-5.5, 5.45)	-3.7 (-8.8, 1.42)	-4.2 (-9.6, 1.17)
LDL[k] (mg/dL)							
PTI	110.5 (108.5, 112.6)	46.6 (45.2, 47.9)	105.9 (101.3, 110.4)	104.7 (99.9, 109.4)	-0.17 (-4.8, 4.48)	-4.7 (-9.2, -0.1)[b]	-5.9 (-10.6, -1.12)[b]
PFI	109.2 (107.1, 111.3)	47.8 (46.6, 49)	104.6 (100.5, 108.8)	99.1 (94.7, 103.6)	-6.3 (-10.6, -2)[b]	-4.5 (-8.7, -0.35)[b]	-10.0 (-14.4, -5.61)[a]
CBI	107.5 (105.4, 109.6)	47.6 (46.4, 48.9)	105.9 (101.4, 110.3)	100.4 (95.8, 105.1)	-2.3 (-6.7, 2.06)	-1.6 (-6, 2.88)	-7.0 (-11.7, -2.36)[b]
UC	107.5 (105.4, 109.5)	46.1 (44.9, 47.4)	102 (97.7, 106.4)	102.7 (98.2, 107.2)	-0.64 (-5, 3.76)	-5.4 (-9.8, -1.1)[b]	-4.8 (-9.3, -0.24)[b]
HDL[l] (mg/dL)							
PTI	47.3 (46.7, 48)	46.6 (45.2, 47.9)	47 (45.7, 48.3)	46.3 (45, 47.7)	-0.73 (-2.1, 0.61)	-0.34 (-1.7, 0.99)	-0.99 (-2.4, 0.37)
PFI	46.7 (46, 47.4)	47.8 (46.6, 49)	47 (45.8, 48.2)	47.5 (46.2, 48.7)	1.1 (-0.1, 2.4)[c]	0.28 (-0.9, 1.5)	0.77 (-0.5, 2.05)
CBI	47.3 (46.6, 47.9)	47.6 (46.4, 48.9)	46.1 (44.9, 47.4)	46.3 (45, 47.6)	0.36 (-0.9, 1.6)	-1.2 (-2.4, 0.11)[c]	-0.98 (-2.3, 0.31)
UC	46.5 (45.8, 47.1)	46.1 (44.9, 47.4)	46.8 (45.6, 48.1)	45.8 (44.5, 47)	-0.32 (-1.6, 0.92)	0.38 (-0.9, 1.6)	-0.69 (-2, 0.59)
Triglycerides (mg/dL)							
PTI	185.7 (178.2, 193.1)	161.4 (143.1, 179.7)	183.4 (165.6, 201.2)	166 (148.4, 183.5)	-24.3 (-42.6, -5.97)[b]	-2.3 (-20.1, 15.47)	-19.7 (-37.3, -2.19)[b]
PFI	174.5 (168.6, 180.5)	185.2 (166.8, 203.5)	178.6 (162.4, 194.8)	165.8 (149.2, 182.3)	10.7 (-7.7, 29.02)	4.1 (-12.1, 20.3)	-8.8 (-25.4, 7.83)
CBI	184.3 (177.8, 190.7)	176.7 (160.5, 192.9)	182.2 (166, 198.3)	179.1 (161.9, 196.4)	-7.5 (-23.7, 8.67)	-2.1 (-18.3, 14.05)	-5.1 (-22.3, 12.09)
UC	166.8 (159.9, 173.7)	177.5 (159.6, 195.4)	173.6 (156.9, 190.3)	171.8 (154.9, 188.7)	10.7 (-7.2, 28.55)	6.8 (-10, 23.49)	5.0 (-11.9, 21.88)
Fasting serum glucose (mg/dL)							
PTI	182.1 (179, 185.2)	173.8 (166.2, 181.4)	173 (165.2, 180.7)	170.1 (162.1, 178.2)	-8.3 (-15.9, -0.69)[b]	-9.1 (-16.8, -1.34)[b]	-11.9 (-20, -3.91)[b]
PFI	177.3 (174.4, 180.2)	167.7 (160.6, 174.8)	169.9 (163, 176.8)	170.1 (162.7, 177.5)	-9.6 (-16.7, -2.5)[b]	-7.5 (-14.3, -0.54)[b]	-7.2 (-14.6, 0.22)[c]
CBI	179.8 (176.7, 182.9)	170.5 (163.4, 177.5)	168.6 (161.6, 175.6)	169.3 (161.7, 176.8)	-9.3 (-16.4, -2.26)[b]	-11.2 (-18.2, -4.17)[b]	-10.5 (-18.1, -2.94)[b]
UC	181.2 (178.1, 184.3)	183.4 (176.1, 190.7)	175.8 (168.6, 182.9)	170.7 (163.2, 178.2)	2.2 (-5.1, 9.53)	-5.5 (-12.6, 1.71)	-10.5 (-18, -3.04)[b]

	B	12M	24M	12M-B	24M-B
Serum Creatinine (mg/dL)					
PTI	0.81 (0.8, 0.82)	0.78 (0.73, 0.82)	0.78 (0.73, 0.82)	-0.03 (-0.1, 0.01)	-0.04 (-0.1, 0.01)
PFI	0.8 (0.79, 0.81)	0.76 (0.71, 0.81)	0.77 (0.73, 0.82)	-0.04 (-0.1, 0.01)[c]	-0.03 (-0.1, 0.02)
CBI	0.77 (0.76, 0.78)	0.81 (0.77, 0.86)	0.82 (0.77, 0.86)	0.04 (0, 0.09)[c]	0.04 (0, 0.09)[c]
UC	0.76 (0.75, 0.77)	0.79 (0.75, 0.84)	0.81 (0.77, 0.86)	0.03 (0, 0.08)	0.05 (0, 0.1)[b]
Glomerular filtration rate (mL/min)					
PTI	92.1 (90.8, 93.4)	95.4 (89.5, 101.3)	94.5 (88.6, 100.4)	3.3 (-2.6, 9.2)	2.4 (-3.5, 8.3)
PFI	90.3 (89.1, 91.5)	97.1 (91.3, 103)	95.5 (89.6, 101.4)	6.8 (1, 12.7)[b]	5.2 (-0.7, 11.1)[c]
CBI	95.6 (94.5, 96.8)	89.9 (84, 95.8)	90.0 (84.1, 96)	-5.8 (-11.7, 0.16)[c]	-5.6 (-11.6, 0.31)[c]
UC	97.2 (95.8, 98.5)	94.2 (88.3, 100.1)	89.8 (83.9, 95.8)	-3 (-8.9, 3)	-7.3 (-13.3, -1.4)[b]

[a]: $P<.001$.

[b]: $P<.05$.

[c]: $P<.1$.

[d]B: baseline.

[e]M: months.

[f]HbA_{1c}: glycated hemoglobin.

[g]PTI is an intervention only for patients and family members.

[h]PFI is an intervention only for health care professionals at primary care.

[i]CBI is a combined intervention for patients and professionals.

[j]UC: usual care or control group.

[k]LDL: low-density lipoprotein.

[l]HDL: high-density lipoprotein.

Publicación 3.

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Patient-reported outcome measures for knowledge transfer and behaviour modification interventions in type 2 diabetes—the INDICA study: a multiarm cluster randomised controlled trial

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ABSTRACT

Objective This study assesses the effectiveness of different interventions of knowledge transfer and behaviour modification to improve type 2 diabetes mellitus patients' (T2DM) reported outcomes measures (PROMs) in the long-term. *Design*: open, community-based pragmatic, multicentre, controlled trial with random allocation by clusters to usual care (UC) or to one of the three interventions.

Participants A total of 2334 patients with uncomplicated T2DM and 211 healthcare professionals were included of 32 primary care centres.

Setting Primary Care Centers in Canary Islands (Spain).

Intervention The intervention for patients (PTI) included an educational group programme, logs and a web-based platform for monitoring and automated short message service (SMS). The intervention for professionals (PFI) included an educational programme, a decision support tool embedded into the electronic clinical record and periodic feedback about patients' results. A third group received both PTI and PFI (combined intervention, CBI).

Outcome measure Cognitive-attitudinal, behavioural, affective and health-related quality of life (HQoL) variables.

Results Compared with UC at 24 months, the PTI group significantly improved knowledge (p=0.005), self-empowerment (p=0.002), adherence to dietary recommendations (p<0.001) and distress (p=0.01). The PFI group improved at 24 months in distress (p=0.03) and at 12 months there were improvements in depression (p=0.003), anxiety (p=0.05), HQoL (p=0.005) and self-empowerment (p<0.001). The CBI group improved at 24 months in self-empowerment (p=0.008) and adherence to dietary recommendations (p=0.004) and at 12 months in knowledge (p=0.008), depression (p=0.006), anxiety (p=0.003), distress (p=0.01), HQoL (p<0.001) and neuropathic symptoms (p=0.02). Statistically significant improvements were also observed at 24 months in the proportion of patients who quit smoking for PTI and CBI (41.5% in PTI and 42.3% in CBI vs 21.2% in the UC group).

Conclusions Assessed interventions to improve PROMs in T2DM attain effectiveness for knowledge, self-empowerment, distress, diet adherence and tobacco cessation. PTI produced the most lasting benefits.

Trial registration number ClinicalTrials.gov NCT01657227 (6 August 2012) https://clinicaltrials.gov/ct2/show/NCT01657227.

Strengths and limitations of this study

- ► The INDICA study provides randomised evidence on the effectiveness of complex interventions to improve outcomes in patients with type 2 diabetes mellitus, with a longer follow-up than previous studies.
- ► All relevant stakeholders in the community are involved in the INDICA study (patients and family caregivers and primary care professionals).
- ► The trial included a large sample of patients with type 2 diabetes regardless of their baseline HbA1c level, reinforcing the external validity of the results.
- ► The INDICA interventions with information and communication technology-based components favour applicability and access, in a cost-effective manner, to a growing number of patients.
- ► A limitation in the use of patient-reported outcome measures is the absence of well-established empirically derived minimum clinically significant differences

INTRODUCTION

Many patients with type 2 diabetes mellitus (T2DM) do not achieve the recommended treatment goals for glycaemic control.[1] This might be due to inappropriate healthcare access and/or clinical management. Moreover, psychological and emotional aspects, such as knowledge of the disease or diabetes-related distress, are also important issues for an appropriate self-management and glycaemic control.[2 3] Previous research has shown the value of patient-reported outcome measures (PROMs) to monitor these variables in diabetes,[4] which contribute to patient empowerment and patient-centred care.[5] PROMs are generally assessed with standardised, validated questionnaires aimed to measure patients' perception of their health status, perceived level of impairment, disability or health-related quality of life.[6]

Interventions that aim to empower people with chronic illnesses and specifically diabetes have included distinct strategies such as educational programmes, websites, support phone calls, text messages and other technological resources,[4 7–10] in order to improve patients' diabetes knowledge, self-management, psychological outcomes and health status. However, the results obtained have been mixed, with a considerable number of studies showing no effect of the interventions.[8–11] The INDICA study is a pragmatic, cluster-randomised controlled trial with 2 years follow-up that assesses the effectiveness and cost-effectiveness of multicomponent interventions for knowledge transfer and behaviour modification of patients with T2DM, their families and healthcare professionals (physicians and nurses) in a large number of Primary Care Health Practices (PHCP). These interventions combine conventional group educational and training activities with different information and communication technology (ICT)-based interventions to guide the decisions of the main actors involved in the management of T2DM.[12] The intervention for patients (PTI) included an educational group programme led by trained nurses, consisting of eight face-to-face sessions (one every 3 months over 2 years); continuous self-monitoring by means of logs and a web-based platform; and tailored automated SMS to provide continuous support to patients and to reinforce self-care and lifestyle changes. The intervention for professionals (PFI) included an educational programme to update their diabetes knowledge, a decision support tool embedded into the electronic clinical record (ECR) with recommendations based on the best available scientific knowledge, adapted to the specific needs of every patient, and periodic feedback about patients' results.

The results on the effectiveness of these interventions on clinical outcomes can be seen in Ramallo-Fariña *et al*.[13] and the cost-effectiveness evaluation can be reviewed in García-Pérez *et al*.[14] The aim of this article is to report the effect of the INDICA interventions on a set of PROMs assessed in the trial: cognitive-attitudinal (knowledge, empowerment), behavioural (adherence to the dietary recommendation, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. These outcomes are commonly targeted for most diabetes interventions because of their association with critical, longer term outcomes, such as functional capacity,[15] complications,[16–18] mortality,[19] healthcare costs[20] and quality of life.[21]

METHODS

Trial design

The INDICA study is an open, community-based pragmatic, multicentre, controlled trial with random allocation by clusters to usual care (UC) or one of three multicomponent interventions of knowledge transfer and behaviour modification. One intervention was aimed at patient and family members (PTI); another intervention was aimed at primary care healthcare professionals (physicians and nurses) (PFI) and the third intervention combined the other two (CBI). In the control group, both patients/families and physicians/nurses received the usual activities provided by the PHCP. The full study protocol has been published before.[12]

Study participants

The INDICA study included adults aged 18–65 years who had been diagnosed with T2DM at least 1 year before, did not have any diabetes-related complications, and used a mobile phone regularly.[12] Family Care Units (FCU) in each PHCP, comprised of a family physician and a nurse, were the recruitment unit. All PHCPs included had to have at least eight FCUs and the availability of appropriate facilities to provide educational group sessions. FCUs planning or awaiting placement changes among PHCP in the first 6 months after the project began were excluded.

Setting and recruitment

PHCPs were randomly selected in the islands of Tenerife, Gran Canaria, Lanzarote, and La Palma (Canary Islands, Spain). Moreover, FCUs were randomly selected from all consenting FCUs at each PHCP. The ECRs of all potentially eligible patients in selected FCUs were screened to verify inclusion and exclusion criteria.

Patient and public involvement

Patients were actively involved in the design of the trial. Two associations of patients with T2DM in the Canary Islands were included from the beginning of the study as part of the research team, with an active participation in the design of the interventions and selection of the outcomes measured. In the same way, primary care professionals and clinical management staff participated in the elaboration of the protocol. The patients and professionals included in the study could express their satisfaction with the interventions through a questionnaire, as well as through focus groups and in-depth interviews that will be the objective of another publication. Finally, we established a commitment with patients and

healthcare professionals to share the results with them in an easy-to-understand way.

Random assignment

Randomisation was applied at different levels. First, three different strata were created according to the geographic areas in the more populated islands (Tenerife and Gran Canaria). Second, four PHCP (clusters) were randomly allocated to every geographical stratum and block permutation was used to assign PHCPs to the study arms; the PHCP being the sampling unit. La Palma and Lanzarote (less populated islands) were geographically divided into four zones with only one eligible PHCP available in each zone randomly assigned to one of the study arms. In every island, all arms were equally distributed. Six FCUs were randomly selected, from all those consenting to participate in each PHCP. From all patients fulfilling inclusion criteria and consenting to participate in each PHCP, 15 were randomly selected per FCU. Exceptionally, more than six FCUs or more than 15 patients per FCU were selected, to try to recruit 90 patients in every PHCP. However, it was not possible to attain this objective of 90 patients in all PHCPs as there were insufficient patients in all FCU selected that complied with the inclusion and exclusion criteria.

FCU and patient randomisation were performed by simple generation from a list of random numbers.

Interventions

Patient interventions

Patients recruited to the PTI and CBI groups received a complex intervention of knowledge transfer and behaviour modification, informed by conceptual frameworks of behavioural change.[16] The intervention combined: (1) an eight-session, conventional, group educational programme given by a nurse specialised in diabetes; (2) monitoring of physical activity, diet, drug adherence, mood, blood pressure and blood glucose readings by daily use of paper workbooks, complemented by weekly access to a website platform to upload paper workbook data; and (3) continuous, personalised feedback by semiautomated mobile phone messages (SMS), modified according to the website information.

Interventions for primary care professionals

Primary care professionals recruited to the PFI and CBI groups received a complex intervention of knowledge transfer and decision support, informed by the determinants of behaviour change suggested by Michie *et al*[22] for its design and implementation. The intervention included: (1) an educational and interactive group programme of two sessions to update clinical management information and promote patient-centred care; (2) an automated decision aid tool, based on a Clinical Practice Guide (CPG) for T2DM embedded into the ECR; and (3) monthly computerised graphic feedback, which displayed a set of processes and outcome indicators for all patients with T2DM of the corresponding FCU compared with other FCU in their setting and the FCU with the best results. Both interventions were applied during the 2 years follow-up.

Duration of fieldwork

Fieldwork took place between February 2013 and October 2016. The first year and the following 2 years were devoted to recruitment of patients and healthcare providers, and intervention and follow-up, respectively. As interventions were maintained over time, intervention and follow-up periods overlapped.

Outcomes

Cognitive-attitudinal outcomes

To assess potential changes in patient knowledge about T2DM and its self-management, we developed a specific instrument created in the context of this project, Diabetes Knowledge Test (DIATEK), which consisted of 30 questions. Each item has four response options and only one correct answer. Items examined risk factors for disease development and deterioration, objective values for biochemical parameters; recommendations on nutrition, physical activity, drug use and self-management. The total score, obtained by adding all correct responses, and ranging from 0 to 30, was later rescaled from 0 to 10.

The Diabetes Empowerment Scale-Short Form (DES-SF)[23] is a validated questionnaire designed to evaluate psychosocial self-efficacy in diabetes. DES-SF is the short form of the original DES, which includes eight items (need for change, developing a plan, overcoming barriers, asking for support, supporting oneself, coping with emotion, motivating oneself and making diabetes care choices appropriate for one's priorities and circumstances) with responses on a five-point Likert scale and an overall range from eight to 40, according to increasing patient empowerment.

Behavioural outcomes

The Mediterranean Diet Adherence Screener (MEDAS)[24] is a validated questionnaire to assess dietary recommendation adherence, which consists of 14 targets for food consumption, rated with one point for each target attained. According to the final score, patients are classified as having low (0–6 points), moderate (7–10) or high adherence (11–14 points) to the Mediterranean diet.

The Morisky Medication Adherence Scale (MGLS)[25] assesses drug-treatment adherence, by means of a validated four-item self-report instrument and a final score ranging from 0 to 4. Patients are considered adherent, only if they obtain four points.

Smoking status was monitored from baseline and during follow-up, to check for potential cessation throughout the study.

Affective outcomes

The State Trait Anxiety Inventory (STAI-S)[26] is a validated patient-reporting questionnaire that includes two non-dependent scales; the applied state-anxiety scale (STAI State) and the trait-anxiety scale (STAI Trait). It assesses

transient emotional state or condition as characterised by subjective feelings of tension and apprehension that can fluctuate in time and intensity. The STAI-S includes 20 items, with each item scored on a four-point Likert scale. Anxiety is defined by a cut-off point≥30.

The Beck Depression Inventory II (BDI-II)[27] consists of 21 items scored on a four-point scale from 0 ('not at all') to 3 ('most of the time'). The items assess depression symptoms in the last 2 weeks. All item scores are added to a maximum score of 63. A BDI-II score of ≥14 indicates mild depressive symptoms.

The Diabetes Distress Scale (DDS2)[28] is a validated two-item diabetes distress-screening instrument that asks respondents to rate, on a six-point scale, the degree of distress caused by the two following items: (1) feeling overwhelmed by the demands of living with diabetes and (2) feeling that I am often failing with my diabetes regimen. High diabetes distress can be identified by an average score ≥3 or more, low distress by scores under 2, and moderate distress by the scores in between.

Health-related quality of life and symptoms

The Audit of Diabetes-Dependent Quality of life (ADDQoL-19)[29] is a specific health-related quality of life (HRQoL) questionnaire for diabetes. It assesses 19 domains, each with its impact and importance index to provide an integrated score for each domain. The sum of the score in each domain forms the global score (range: −9 to 3). The lower the score, the worse the quality of life.

The Michigan Neuropathy Screening Instrument (MNSI)[30] is an instrument that measures the incidence of distal diabetic peripheral polyneuropathy. It is composed of 15 self-administered items, in which the abnormal responses are added. A score of seven or more is considered abnormal.

Satisfaction

An ad-hoc self-completed questionnaire *Patient Satisfaction with INDICA* (INDICA-SATP) was developed to measure satisfaction with each component of the interventions in PTI and CBI groups. It was measured in the 24-month follow-up in patients who, having attended the group educational programme, also used the web platform or received the semiautomated mobile phone messages. Satisfaction with each component was valued from 0 to 10 points, with 10 reflecting maximum satisfaction.

All information, including demographic data, overall and personal health history, diabetes health status, current medications, smoking status and risk factors for complications, was obtained in a face to face interview at baseline and at 3, 6, 12, 18 and 24 months of follow-up. Similarly, all self-administered questionnaires (ADDQoL-19, BDI-II, DES-SF, DDS2, DIATEK, MEDAS, STAI-S, MGLS and MNSI) were distributed and collected at baseline, and at 12 and 24 months follow-up. ADDQol-19, MEDAS and MGLS were also applied at 6 and 18 months.

Two other questionnaires were included in the trial registry and the published protocol,[12] the *International Physical Activity Questionnaire* and a scale developed for this project to assess patients' attitudinal changes regarding lifestyles (INDICA-LSQ). However, the data quality checking identified many inconsistent or meaningless responses to these questionnaires, which indicates that patients did not correctly understand the instructions. Therefore, we decided to exclude them from the analyses.

Statistical analysis

Multilevel mixed models including the baseline value of dependent variables and time elapsed since diagnosis (in years) as covariates were implemented for all PROMs. First level variables are those corresponding to each measurement along follow-up (repeated time measurements). The second level includes patient variables (the baseline value of dependent variables and time elapsed since diagnosis) and third level variables correspond to PHCP in which patients are grouped (the variable arm to which PHCP was assigned is included in this level). The effect that identifies the intervention arm has been considered fixed for the different PHCP, while the intercept has been considered random. The model also included an interaction term between arm and month, which allows for differences in the intervention effect between follow-up assessments.[31] The intraclass correlation coefficient (ICC) was obtained for each model for the PHCP and by patient according to their PHCP. The adjusted estimated mean was calculated for each follow-up moment compared with baseline; and its statistical significance was calculated by means of the model already set out. The relative improvement for each follow-up was obtained as the ratio between the adjusted difference in mean between the intervention and control group and the mean of the control group.

A logistic regression model was implemented to compare the proportion of patients who quit smoking at each follow-up, by intervention arm. Only basal smokers were included in the analysis.

Analysis was performed on an intention-to-treat basis, that is, participants were analysed in the group to which they were randomised. Missing values were treated by means of multiple imputation procedures,[32] with results based on 100 imputed datasets (missing values from all follow-up visits were imputed). Analysis under multiple imputation is valid for randomly missing data.[33] We compared the results of imputed and non-imputed data. All the analyses were conducted using STATA V.15.0.[34] Differences were considered statistically significant if $p<0.05$.

RESULTS

Study participants

A total of 2334 patients and 211 healthcare professionals were included. Figure 1 shows the flowchart with cluster randomisation of patients for each intervention, attendance at educational/training sessions of patients and professionals and the number of PROMs questionnaires

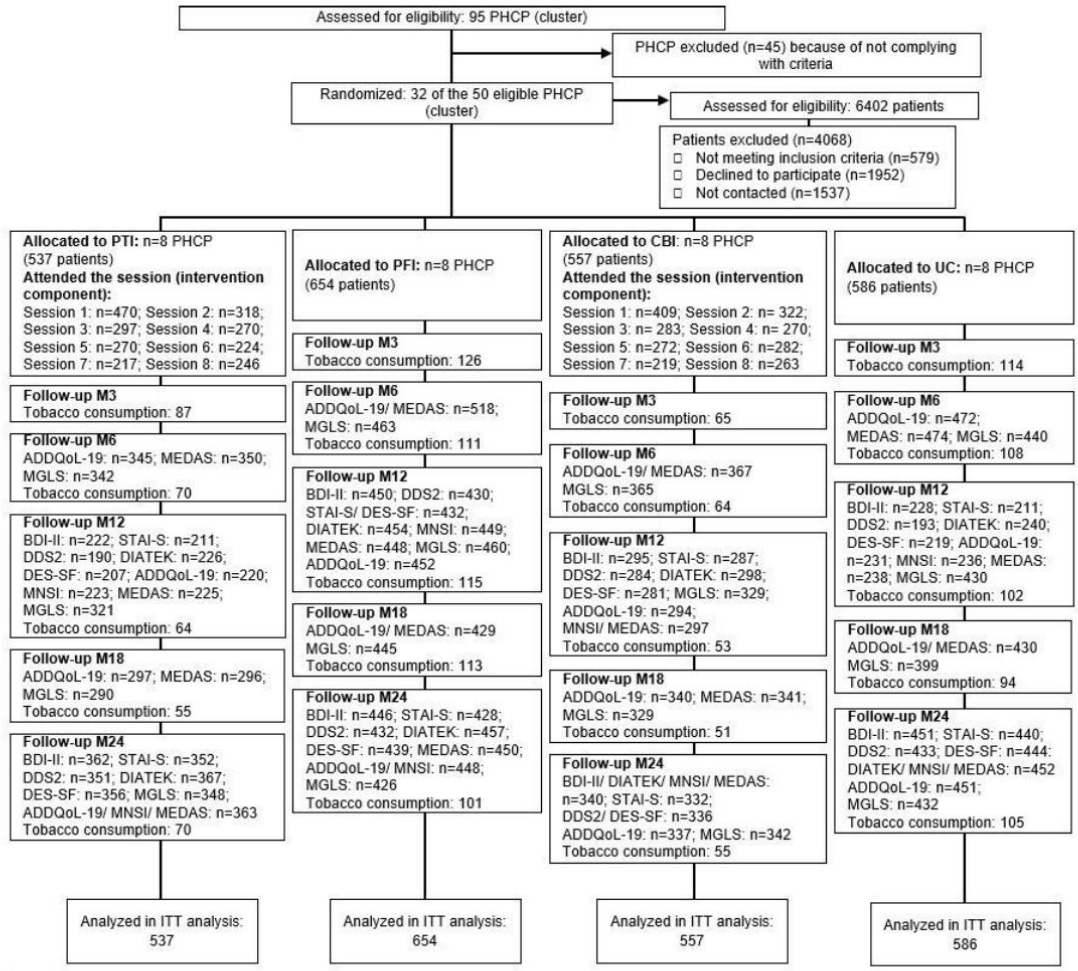

Figure 1 Consolidated Standards of Reporting Trials flow diagram. ADDQoL, Audit of Diabetes-Dependent Quality of life; BDI-II, Beck Depression Inventory II; CBI, combined intervention for patients and professionals; DDS2, Diabetes Distress Scale; DES-SF, Diabetes Empowerment Scale-Short Form; MEDAS, Mediterranean Diet Adherence Screener; MGLS, Morisky Medication Adherence Scale; MNSI, Michigan Neuropathy Screening Instrument; PFI, intervention for professionals; PHCP, Primary Care Health Practices; PTI, intervention for patients; STAI-S, State Trait Anxiety Inventory.

received for each follow-up assessment. The patients' baseline characteristic according to the intervention assignment can be seen in Ramallo-Fariña *et al*.[13] Mean age of the whole population was 55.7±7.1 years, with 51.9% women. Mean baseline HbA1c was 7.3%/56 mmol/mol. From baseline, 49.4% of patients started with HbA1c levels within the accepted therapeutic goal (≤7%/53 mmol/mol). There were no statistically significant differences among groups in terms of their baseline characteristics.

Intention-to-treat results (ITT), reported below, were very similar to those obtained with non-imputed data. Only three discrepancies were observed that will be discussed in the corresponding outcome section. Results at all time points are shown in table 1 (intergroup differences), tables 2 and 3 (intragroup changes).

Cognitive-attitudinal outcomes

Table 1 shows that the level of knowledge about diabetes is significantly higher for PTI (p=0.007) and CBI (p=0.008), compared with UC at 12 months; and for PTI (p=0.005) at 24 months.

Patient empowerment was significantly higher for PFI and CBI groups, compared with UC at 12 months (p<0.001 for both comparisons). Analysis of non-imputed data led to a p value of 0.05 for the difference between PTI and UC, favouring the former, at this time point. At

Table 1 Adjusted difference in the mean of each group compared with the control group

	6 Months	P value	12 Months	P value	18 Months	P value	24 Months	P value
Cognitive-attitudinal outcomes								
Knowledge (DIATEK): F=47.3 *P*<0.001; ICC PHCP=0.06; ICC subject|PHCP=0.35								
PTI	–	–	0.64 (0.17 to 1.11)	**0.007**	–	–	0.65 (0.2 to 1.11)	**0.005**
PFI	–	–	−0.38 (−0.85 to 0.09)	0.11	–	–	−0.6 (−1.06 to −0.14)	**0.01**
CBI	–	–	0.63 (0.16 to 1.11)	**0.008**	–	–	0.34 (−0.12 to 0.8)	0.15
Empowerment (DES-SF): F=17.3 *P*<0.001; ICC PHCP=0.08; ICC; subject|PHCP=0.08								
PTI	–	–	1.58 (−0.59 to 3.75)	0.15	–	–	3.04 (1.08 to 4.99)	**0.002**
PFI	–	–	3.95 (1.9 to 6)	**<0.001**	–	–	1.84 (−0.11 to 3.79)	0.07
CBI	–	–	3.97 (1.9 to 6.04)	**<0.001**	–	–	2.63 (0.68 to 4.58)	**0.008**
Behavioural outcomes								
Adherence dietary recommendations (MEDAS): F=25.0 *P*<0.001; ICC PHCP=0.03; ICC subject|PHCP=0.20								
PTI	0.22 (−0.25 to 0.69)	0.36	0.71 (0.17 to 1.24)	**0.01**	0.93 (0.46 to 1.41)	**<0.001**	0.87 (0.4 to 1.35)	**<0.001**
PFI	−0.58 (−1.04 to −0.11)	**0.01**	−0.96 (−1.46 to −0.47)	**<0.001**	0.17 (−0.31 to 0.64)	0.49	0.03 (−0.44 to 0.5)	0.90
CBI	0.44 (−0.03 to 0.91)	0.06	0.06 (−0.47 to 0.58)	0.83	0.88 (0.4 to 1.35)	**<0.001**	0.7 (0.22 to 1.17)	**0.004**
Medication adherence (MGLS): F=14.4 *P*<0.001; ICC PHCP=0.04; ICC subject|PHCP=0.20								
PTI	0.09 (−0.11 to 0.3)	0.37	0.09 (−0.12 to 0.3)	0.39	0.13 (−0.09 to 0.34)	0.24	0.16 (−0.04 to 0.36)	0.12
PFI	0.01 (−0.2 to 0.22)	0.90	−0.13 (−0.34 to 0.08)	0.24	−0.06 (−0.26 to 0.15)	0.58	0.09 (−0.11 to 0.3)	0.39
CBI	0.03 (−0.18 to 0.24)	0.77	−0.19 (−0.41 to 0.03)	0.08	0 (−0.21 to 0.21)	0.98	−0.1 (−0.31 to 0.11)	0.36
Affective outcomes								
Depression (BDI-II): F=53.6 *P*<0.001; ICC PHCP=0.05; ICC subject|PHCP=0.34								
PTI	–	–	−1.91 (−3.99 to 0.17)	0.07	–	–	−0.76 (−2.68 to 1.16)	0.44
PFI	–	–	−2.99 (−4.99 to −1)	**0.003**	–	–	0.37 (−1.56 to 2.3)	0.71
CBI	–	–	−3 (−5.13 to −0.87)	**0.006**	–	–	0.23 (−1.73 to 2.19)	0.82
Anxiety (STAI-S): F=36.0 *P*<0.001; ICC PHCP=0.07 ICC; subject|PHCP=0.32								
PTI	–	–	−2.25 (−5.75 to 1.25)	0.21	–	–	−2.18 (−5.54 to 1.18)	0.20
PFI	–	–	−3.47 (−6.95 to 0.02)	**0.05**	–	–	−0.39 (−3.78 to 2.99)	0.82
CBI	–	–	−5.4 (−8.99 to −1.81)	**0.003**	–	–	−0.50 (−3.9 to 2.9)	0.77
Distress (DDS2): F=14.9 *P*<0.001; ICC PHCP=0.05 ICC; subject|PHCP=0.25								
PTI	–	–	−0.23 (−0.53 to 0.07)	0.13	–	–	−0.34 (−0.62 to −0.07)	**0.01**
PFI	–	–	−0.24 (−0.53 to 0.05)	0.10	–	–	−0.31 (−0.58 to −0.04)	**0.03**
CBI	–	–	−0.36 (−0.65 to −0.07)	**0.01**	–	–	−0.24 (−0.51 to 0.03)	0.08
Health-related quality of life and symptoms								

Continued

Table 1 Continued

	6 Months	P value	12 Months	P value	18 Months	P value	24 Months	P value
Health-related quality of life (ADDQoL-19): F=25.3 *P*<0.001; ICC PHCP=0.04; ICC subject|PHCP=0.34								
PTI	0.09 (−0.24 to 0.42)	0.60	0.40 (0.04 to 0.76)	**0.03**	0.39 (0.05 to 0.72)	**0.02**	0.16 (−0.17 to 0.48)	0.34
PFI	−0.09 (−0.42 to 0.23)	0.56	0.51 (0.16 to 0.86)	**0.005**	−0.02 (−0.35 to 0.31)	0.89	−0.06 (−0.38 to 0.26)	0.71
CBI	0.03 (−0.3 to 0.35)	0.88	0.84 (0.49 to 1.18)	**<0.001**	0.21 (−0.13 to 0.54)	0.23	−0.05 (−0.38 to 0.28)	0.77
Neuropathic symptom (MNSI): F=59.8 *P*<0.001; ICC PHCP=0.02 ICC; subject|PHCP=0.32								
PTI	–	–	−0.35 (−0.8 to 0.09)	0.12	–	–	−0.08 (−0.49 to 0.33)	0.70
PFI	–	–	−0.42 (−0.87 to 0.03)	0.07	–	–	0.35 (−0.07 to 0.78)	0.11
CBI	–	–	−0.57 (−1.04 to −0.1)	**0.02**	–	–	0.31 (−0.12 to 0.74)	0.16

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.
ADDQoL, Audit of Diabetes-Dependent Quality of life; BDI-II, Beck Depression Inventory II; CBI, combined intervention for patients and professionals; DDS2, Diabetes Distress Scale; DES-SF, Diabetes Empowerment Scale-Short Form; ICC, intraclass correlation coefficient; MEDAS, Mediterranean Diet Adherence Screener; MGLS, Morisky Medication Adherence Scale; MNSI, Michigan Neuropathy Screening Instrument; PFI, intervention only for healthcare professionals at primary care; PHCP, Primary Care Health Practices; PTI, intervention only for patients and family members; STAI-S, State Trait Anxiety Inventory.

24 months, PTI and CBI also attained significantly higher scores than UC (p=0.002 and p=0.008, respectively); while differences with PFI are marginally significant.

Behavioral outcomes

Table 1 shows that the PTI group is significantly more adherent to the diet recommendations, compared with UC, after 12 months of follow-up. There is a difference of 0.87 (p<0.001) at 24 months. Adherence improves for CBI from 18 months, compared with UC, with differences of 0.7 (p=0.004) at 24 months. Adherence levels remain moderate for all patient groups throughout follow-up (see table 2).

No differences were found in medication adherence, compared with UC (table 1). However, average levels of medication adherence were significantly improved in all four groups, despite the high baseline levels (>3) (see table 2).

Table 3 shows the reduction in the proportion of smokers who quit smoking during follow-up in PTI (12 months), and CBI (18 months), compared with UC. With non-imputed data the reduction was statistically significant from month 6 for PTI (p=0.023) and month 12 for CBI (p=0.025). The percentage of patients who quit smoking at 24 months was 41.5% for PTI (p=0.012) and 42.3% (p=0.012) for CBI, versus 21.2% for UC group. There were no statistically significant differences between groups in the baseline percentage of smokers (p=0.99).

Affective outcomes

Compared with UC, both PFI and CBI show statistically significant differences at 12 months for depression (p=0.003 and p=0.006, respectively), and anxiety (p=0.05 and p=0.003, respectively) (table 1). These differences disappear at 24 months because all groups of patients improved (table 2).

The diabetes distress score improved significantly compared with the UC group for CBI at 12 months (p=0.01) and for PTI and PFI at 24 months (p=0.01 and p=0.03, respectively). The score remained marginally significant for CBI (table 1). At baseline, all patient groups showed moderate distress, which decreased to a low level from 12 months, except for the UC group, which did so at 24 months (table 2).

Health-related quality of life and symptoms

HRQoL significantly improved for all intervention groups, at 12 months, compared with UC; a difference only maintained for PTI at 18 months (p=0.02) (table 1).

Neuropathic symptom scores were significantly lower for the CBI group at 12 months (p=0.02) compared with the UC group (the analysis of non-imputed data led to a non-significant result, p=0.12). This difference disappeared at 24 months (table 1). Mean baseline scores for all groups were under 4, considerably below the cut-off point of 7 for abnormal classification (table 4).

Table 2 Adjusted means for each group and intragroup differences compared with the baseline measurement (cognitive-attitudinal, behavioural and affective outcomes)

	Adjusted means in each group (95% CI)						Difference in intragroup of adjusted means compared with baseline (95% CI)					
	Baseline	6 Months	12 Months	18 Months	24 Months	B-6M	P value	B-12M	P value	B-18M	P value	B-24M	P value
Cognitive-attitudinal outcomes													
Knowledge (DIATEK)													
PTI	6.4 (6.3 to 6.5)	–	7.2 (6.9 to 7.5)	–	7.4 (7.1 to 7.7)	–	–	0.82 (0.48 to 1.2)	**<0.001**	–	–	1.03 (0.71 to 1.36)	**<0.001**
PFI	6.5 (6.3 to 6.7)	–	6.2 (5.8 to 6.5)	–	6.1 (5.8 to 6.5)	–	–	−0.31 (−0.63 to 0.02)	0.07	–	–	−0.32 (−0.64 to 0.01)	0.058
CBI	6.5 (6.4 to 6.6)	–	7.2 (6.8 to 7.5)	–	7.1 (6.8 to 7.4)	–	–	0.7 (0.36 to 1.03)	**<0.001**	–	–	0.6 (0.27 to 0.94)	**<0.001**
UC	6.2 (6.1 to 6.3)	–	6.5 (6.2 to 6.9)	–	6.7 (6.4 to 7.1)	–	–	0.3 (−0.04 to 0.63)	**0.08**	–	–	0.5 (0.18 to 0.82)	**0.002**
Empowerment (DES–SF)													
PTI	26.4 (25.8 to 27.0)	–	29.5 (27.9 to 31.0)	–	33.5 (32.1 to 34.9)	–	–	3.08 (1.6 to 4.6)	**<0.001**	–	–	7.1 (5.7 to 8.5)	**<0.001**
PFI	26.3 (25.2 to 27.4)	–	31.9 (30.5 to 33.2)	–	32.3 (30.9 to 33.7)	–	–	5.6 (4.2 to 6.9)	**<0.001**	–	–	6.02 (4.7 to 7.4)	**<0.001**
CBI	27.6 (27.0 to 28.3)	–	31.9 (30.4 to 33.3)	–	33.1 (31.7 to 34.5)	–	–	4.3 (2.8 to 5.7)	**<0.001**	–	–	5.7 (4.1 to 6.9)	**<0.001**
UC	26.1 (25.5 to 26.7)	–	27.9 (26.4 to 29.4)	–	30.5 (29.1 to 31.8)	–	–	1.8 (0.26 to 3.3)	**0.02**	–	–	4.3 (2.9 to 5.7)	**<0.001**
Behavioural outcomes													
Adherence dietary recommendations (MEDAS)													
PTI	8 (7.8 to 8.1)	7.6 (7.2 to 7.9)	9.1 (8.7 to 9.4)	8.3 (7.9 to 8.6)	8.7 (8.3 to 9)	−0.43 (−0.77 to −0.09)	**0.01**	1.1 (0.71 to 1.5)	**<0.001**	0.27 (−0.07 to 0.62)	0.12	0.68 (0.34 to 1.02)	**<0.001**
PFI	8.2 (7.9 to 8.5)	6.8 (6.4 to 7.1)	7.4 (7.1 to 7.7)	7.5 (7.1 to 7.8)	7.8 (7.5 to 8.2)	−1.5 (−1.8 to −1.1)	**<0.001**	−0.82 (−1.2 to −0.49)	**<0.001**	−0.82 (−1.2 to −0.49)	**<0.001**	−0.4 (−0.74 to −0.07)	**0.018**
CBI	8.3 (8.1 to 8.5)	7.8 (7.4 to 8.1)	8.4 (8.0 to 8.8)	8.2 (7.9 to 8.5)	8.5 (8.1 to 8.8)	−0.51 (−0.84 to −0.17)	**0.003**	0.13 (−0.24 to 0.51)	0.49	−0.08 (−0.43 to 0.26)	0.63	0.2 (−0.14 to 0.54)	0.26
UC	8.02 (7.9 to 8.2)	7.3 (7.0 to 7.7)	8.4 (8.0 to 8.7)	7.3 (7.0 to 7.7)	7.8 (7.5 to 8.1)	−0.69 (−1.0 to −0.36)	**<0.001**	0.34 (−0.02 to 0.7)	0.07	−0.7 (−1.0 to −0.37)	**<0.001**	−0.24 (−0.57 to 0.1)	0.16
Medication adherence (MGLS)													
PTI	3.1 (3.1 to 3.2)	3.5 (3.4 to 3.7)	3.6 (3.4 to 3.7)	3.6 (3.5 to 3.8)	3.6 (3.5 to 3.7)	0.41 (0.26 to 0.56)	**<0.001**	0.45 (0.29 to 0.6)	**<0.001**	0.5 (0.35 to 0.65)	**<0.001**	0.48 (0.33 to 0.62)	**<0.001**
PFI	3.3 (3.2 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	3.4 (3.3 to 3.6)	3.5 (3.4 to 3.7)	0.18 (0.03 to 0.33)	**0.02**	0.08 (−0.07 to 0.22)	0.32	0.16 (0.02 to 0.31)	**0.026**	0.25 (0.11 to 0.4)	**0.001**
CBI	3.3 (3.3 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.1 to 3.4)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	0.17 (0.02 to 0.32)	**0.02**	−0.01 (−0.18 to 0.15)	0.87	0.2 (0.05 to 0.35)	**0.01**	0.04 (−0.11 to 0.2)	0.60
UC	3.2 (3.1 to 3.3)	3.4 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.4 (3.3 to 3.6)	0.23 (0.08 to 0.38)	**0.002**	0.27 (0.12 to 0.42)	**<0.001**	0.29 (0.14 to 0.43)	**<0.001**	0.23 (0.08 to 0.37)	**0.002**
Affective outcomes													
Depression (BDI–II)													
PTI	10.9 (10.4 to 11.5)	–	8.5 (7.1 to 9.9)	–	6.1 (4.7 to 7.5)	–	–	−2.4 (−3.7 to −0.96)	**0.001**	–	–	−4.9 (−6.2 to −3.5)	**<0.001**
PFI	11.0 (9.9 to 12.1)	–	7.5 (6.1 to 8.8)	–	7.2 (5.8 to 8.6)	–	–	−3.6 (−4.9 to −2.2)	**<0.001**	–	–	−3.8 (−5.2 to −2.4)	**<0.001**
CBI	11.7 (10.9 to 12.4)	–	7.5 (5.9 to 8.9)	–	7.1 (5.7 to 8.5)	–	–	−4.2 (−5.7 to −2.7)	**<0.001**	–	–	−4.6 (−5.9 to −3.1)	**<0.001**
UC	11.4 (10.9 to 11.9)	–	10.5 (8.9 to 11.9)	–	6.7 (5.5 to 8.2)	–	–	−0.94 (−2.4 to 0.55)	0.22	–	–	−4.5 (−5.9 to −3.2)	**<0.001**
Anxiety (STAI–S)													
PTI	21.5 (20.7 to 22.2)	–	18.4 (15.9 to 20.9)	–	14.5 (12.0 to 16.9)	–	–	−3.0 (−5.5 to −0.55)	**0.017**	–	–	−7 (−9.4 to −4.6)	**<0.001**
PFI	20.6 (18.8 to 22.4)	–	17.2 (14.8 to 19.6)	–	16.2 (13.8 to 18.7)	–	–	−3.4 (−5.8 to −1)	**0.006**	–	–	−4.4 (−6.8 to −1.9)	**<0.001**
CBI	23.2 (22.0 to 24.3)	–	15.3 (12.8 to 17.8)	–	16.1 (13.7 to 18.6)	–	–	−7.9 (−10.4 to −5.4)	**<0.001**	–	–	−7.0 (−9.5 to −4.6)	**<0.001**
UC	21.9 (21.2 to 22.7)	–	20.7 (18.1 to 23.2)	–	16.6 (14.3 to 19.0)	–	–	−1.3 (−3.8 to 1.3)	0.32	–	–	−5.3 (−7.7 to −2.9)	**<0.001**
Distress (DDS2)													
PTI	2.8 (2.6 to 2.8)	–	1.9 (1.7 to 2.2)	–	1.6 (1.4 to 1.8)	–	–	−0.72 (−0.93 to −0.51)	**<0.001**	–	–	−1.1 (−1.2 to −0.86)	**<0.001**
PFI	2.5 (2.3 to 2.6)	–	1.9 (1.8 to 2.1)	–	1.7 (1.5 to 1.9)	–	–	−0.5 (−0.7 to −0.31)	**<0.001**	–	–	−0.79 (−0.98 to −0.6)	**<0.001**
CBI	2.7 (2.6 to 2.8)	–	1.8 (1.6 to 2.0)	–	1.7 (1.5 to 1.9)	–	–	−0.91 (−1.1 to −0.71)	**<0.001**	–	–	−1.01 (−1.2 to −0.82)	**<0.001**

Continued

Table 2 Continued

	Adjusted means in each group (95% CI)						Difference in intragroup of adjusted means compared with baseline (95% CI)					
	Baseline	6 Months	12 Months	18 Months	24 Months	B-6M	P value	B-12M	P value	B-18M	P value	B-24M	P value
UC	2.6 (2.5 to 2.6)	–	2.1 (1.9 to 2.4)	–	1.97 (1.8 to 2.2)	–	–	−0.36 (−0.58 to −0.15)	**0.001**	–	–	−0.58 (−0.77 to −0.39)	**<0.001**

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.
B, baseline; BDI-II, Beck Depression Inventory II; CBI, combined intervention for patients and professionals; DDS2, Diabetes Distress Scale; DES-SF, Diabetes Empowerment Scale-Short Form; M, month; MEDAS, Mediterranean Diet Adherence Screener; MGLS, Morisky Medication Adherence Scale; PFI, intervention only for healthcare professionals at primary care; PTI, intervention only for patients and family members; STAI-S, State Trait Anxiety Inventory; UC, usual care or control group.

Satisfaction

Table 5 shows the patients' satisfaction with the intervention received. While average scores were higher than 9/10, in all dimensions, for the group educational sessions, satisfaction with the web platform and SMS obtained scores above 8.

Table 6 shows a summary of the results at 12 and 24 months. For all PROMs, ICC values were close to zero at the PHCP levelthus reflected a very small effect associated with PHCP for interventions and control groups (similar results among PHCP in every arm). The ICC at the patient level was broad, accounting for considerable variations among individuals.

DISCUSSION

This article assesses the effect of interventions implemented by the INDICA study to improve T2DM outcomes on several health measures self-perceived by patients in the cognitive-attitudinal (knowledge, empowerment), behavioural (ie, adherence to the dietary recommendations, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. The INDICA study is a pragmatic cluster-randomised study with 2years follow-up that assesses the effectiveness of multicomponent interventions for knowledge transfer and behaviour modification of patients, families and healthcare professionals (physicians and nurses) at the primary care level.

At 1year follow-up, the combined intervention lead to obtaining significant results in all outcomes except diet and medication adherence. Relative improvements compared with UC ranged between 9.6% (knowledge) and 52.2% (HRQoL), with intermediate values for anxiety (26.1%) and depression (28.7%). Significant improvements in HRQoL were also obtained for the PTI and PFI groups, although of less intensity (24.8% and 31.7%, respectively). However, they showed different results in the remaining variables: the PTI group improved in terms of knowledge and behavioural outcomes (ie, diet and smoking), while the PFI improved in regard to empowerment and depression, but obtained a significantly worse result than the UC group for diet adherence.

After 2years of follow-up, there were no significant differences in HRQoL, anxiety or depression, mainly due to the improvement experienced by the UC group in these variables. The PTI group obtained the best overall results, with significant improvements in the cognitive (ie, knowledge, empowerment), affective (ie, diabetes distress) and behavioural (ie, diet and tobacco) variables. The same significant results were obtained for the combined intervention, except for knowledge and distress. Finally, the PFI group outperformed UC only for distress, and showed a significantly worse result in regard to knowledge. There were no statistically significant differences in medication adherence during all the follow-up, although a ceiling effect could have occurred, since all groups showed high scores at baseline.

Table 3 Proportion of patients who stop smoking at each follow-up compared with the control group

	PTI (n=114)	PFI (n=156)	CBI (n=109)	UC (n=145)	P value global	P value PTI versus UC	P value PFI versus UC	P value CBI versus UC
3 Months	12.8	8.7	15.4	10.4	0.54	0.99	0.99	0.99
6 Months	28.5	7.5	24.2	15.4	0.003	0.11	0.22	0.99
12 Months	33.1	17.4	28.4	14.3	0.014	0.018	0.99	0.11
18 Months	36.7	19.6	37.6	18.8	0.004	0.04	0.99	0.03
24 Months	41.5	23.4	42.3	21.2	0.002	0.012	0.99	0.012

Only basal smokers were included in the analysis.
CBI, combined intervention for patients and professionals; PFI, intervention only for healthcare professionals at primary care; PTI, intervention only for patients and family members; UC, usual care or control group.

Therefore, the best results were observed in both groups including patients (PTI and CBI), similar to the findings observed on clinical outcomes.[13] This is not surprising, given the straightforward and continuous application of these patient interventions, and the high reported satisfaction levels with all the intervention components (educational sessions, web resources and SMS). Previous studies that combined education and training with support phone calls, assessing interventions aimed at empowering diabetes patients to improve self-care and outcomes, showed inconsistent results between clinical variables and PROMs.[8 9] The use of one-way messages such as those used in INDICA appears to significantly and consistently improve HbA1c levels, although with a small-to-moderate effect-size (−0.38%, 95% CI −0.53 to −0.23).[10] In addition, continuous advances in smart mobile technology provide new possibilities for diabetes self-management, despite the fact that evidence on the effectiveness of these new functionalities remains scarce and uncertain.[11 35]

Reduction in the number of smokers in interventions applied directly to patients (PTI and CBI) in regard to UC that remain significant at 24 months with percentages of approximately 42% which is 2.5 times the result obtained by the most extended pharmacological intervention (replacement nicotine therapy). This is according to a meta-analysis published recently[36] which puts this reduction at 16.9% of the intervened group compared with 10.4% of the control group in studies with follow-up varying from 6 to 24 months.

The intervention effect on professionals raises questions. At 1 year of follow-up, the PFI and CBI groups obtained improvements in psychological variables not affected by the intervention targeted exclusively at patients (PTI) (ie, empowerment, anxiety, depression). These findings could be interpreted as the lasting result of better shared decision-making/patient-centred care by professionals trained in this care model. However, the PTI group was the only group to show significant improvements in behavioural variables (diet adherence and tobacco consumption); while PFI obtained significantly worse results for diet adherence from the sixth month, and CBI did not show significant benefits for these two outcomes until 18 months. These negative findings from groups containing professionals are repeated after 2 years in the case of knowledge, a variable in which the CBI group did not obtain significant differences. This interpretation should be considered cautiously given the analysis limitations, since the differences between intervention groups have not been statistically contrasted. As a recent Cochrane review[37] reported, current evidence on the effect of interventions to promote shared decision-making by healthcare professionals shows benefits when decision-making is assessed by external observers but not by patient's assessment; furthermore, no significant effects were observed in most patient-reported outcomes.[37] Given the paucity and limited quality of available studies, more focused research is needed to draw solid conclusions about the effect of interventions aimed at professionals, and the mechanisms by which these interventions translate into psychological, behavioural and health changes of patients.

The assessment of clinical outcome measures in the INDICA study[13] for the total sample recruited regardless of Hb1Ac levels (only 50.6% of all participants had baseline HbA1c concentrations>7%, with a mean of 7.3%), showed an early and significant but temporary reduction in HbA1c for the PTI group, compared with UC, from 3 to 6 months. Even so, more than 30% of the intervened patients (PTI and CBI) attained statistically and clinically relevant reductions in HbA1c (>0.4%); significantly higher than UC at 12 and 18 months.

In the group of patients with baseline HbA1c greater than 7% (uncontrolled patients), the magnitude of the intervention effect on clinical outcomes was greater, especially in the PTI group compared with the UC group, with significant differences up to 18 months, and a significant area under the curve at 24 months for PTI compared with UC.[13] These results are supported by other studies that report greater intervention effects in patients with higher HbA1c levels.[38 39] Longer term reductions in blood pressure were also found in the two groups in which professionals were intervened, with smaller effects in the remaining clinical measures (lipid profile, body mass index, serum creatinine and glomerular filtration

Table 4 Adjusted means for each group and intragroup differences compared with the baseline measurement (health-related quality of life and symptoms)

	Adjusted means in each group (95% CI)						Difference in intragroup of adjusted means compared with baseline (95% CI)					
	Baseline	6 Months	12 Months	18 Months	24 Months	B-6M	P value	B-12M	P value	B-18M	P value	B-24M	P value
Health-related quality of life and symptoms													
Health-related quality of life (ADDQoL-19)													
PTI	−1.7 (−1.8 to −1.6)	−1.0 (−1.3 to −0.8)	−1.2 (−1.5 to −0.97)	−0.85 (−1.1 to −0.61)	−0.76 (−0.99 to −0.53)	0.69 (0.46 to 0.93)	**<0.001**	0.52 (0.27 to 0.76)	**<0.001**	0.89 (0.65 to 1.1)	**<0.001**	0.97 (0.74 to 1.2)	**<0.001**
PFI	−1.7 (−1.8 to −1.5)	−1.2 (−1.5 to −1)	−1.1 (−1.3 to −0.88)	−1.3 (−1.5 to −1.0)	−0.98 (−1.2 to −0.75)	0.43 (0.21 to 0.66)	**<0.001**	0.55 (0.32 to 0.78)	**<0.001**	0.4 (0.17 to 0.63)	**0.001**	0.68 (0.45 to 0.9)	**<0.001**
CBI	−1.8 (−1.9 to −1.6)	−1.1 (−1.3 to −0.87)	−0.78 (−1.0 to −0.54)	−1.0 (−1.3 to −0.79)	−0.97 (−1.2 to −0.73)	0.65 (0.42 to 0.88)	**<0.001**	0.98 (0.74 to 1.2)	**<0.001**	0.73 (0.49 to 0.96)	**<0.001**	0.78 (0.54 to 1.0)	**<0.001**
UC	−2.1 (−2.2 to −1.9)	−1.1 (−1.4 to −0.9)	−1.6 (−1.9 to −1.4)	−1.2 (−1.5 to −1)	−0.92 (−1.2 to −0.69)	0.92 (0.7 to 1.2)	**<0.001**	0.44 (0.18 to 0.7)	**0.001**	0.82 (0.59 to 1.1)	**<0.001**	1.1 (0.9 to 1.4)	**<0.001**
Neuropathic symptom (MNSI)													
PTI	3.1 (3 to 3.2)	–	2.8 (2.5 to 3.1)	–	2.4 (2.1 to 2.7)	–	–	−0.29 (−0.61 to 0.02)	0.07	–	–	−0.69 (−0.99 to −0.4)	**<0.001**
PFI	3.3 (3.0 to 3.6)	–	2.8 (2.5 to 3.1)	–	2.9 (2.5 to 3.2)	–	–	−0.55 (−0.86 to −0.23)	**0.001**	–	–	−0.45 (−0.76 to −0.13)	**0.005**
CBI	3.3 (3.1 to 3.4)	–	2.6 (2.3 to 2.9)	–	2.8 (2.5 to 3.1)	–	–	−0.67 (−1.0 to −0.31)	**<0.001**	–	–	−0.46 (−0.78 to −0.13)	**0.006**
UC	3.3 (3.2 to 3.5)	–	3.1 (2.9 to 3.5)	–	2.5 (2.2 to 2.8)	–	–	−0.15 (−0.47 to 0.17)	0.36	–	–	−0.82 (−1.1 to −0.54)	**<0.001**

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.
ADDQoL-19, Audit of Diabetes-Dependent Quality of life; B, baseline; CBI, combined intervention for patients and professionals; M, month; MNSI, Michigan Neuropathy Screening Instrument; PFI, intervention only for healthcare professionals at primary care; PTI, intervention only for patients and family members; UC, usual care or control group.

Table 5 Patient satisfaction with the intervention received (only those who made use of each intervention component)

	n	Mean (95% CI)
Conventional group educational programme		
Usability		
Environment generated	592	9.53 (9.46 to 9.60)
Exchange of experiences with participants and educator	588	9.59 (9.53 to 9.66)
Educator's work	587	9.79 (9.74 to 9.83)
Quality of materials	587	9.56 (9.49 to 9.64)
Personal satisfaction		
The sessions helped me get to know my diabetes better	591	9.67 (9.61 to 9.73)
I found the sessions useful	593	9.60 (9.52 to 9.67)
The sessions motivated me to look after my health better	590	9.62 (9.55 to 9.69)
General		
General satisfaction	589	9.70 (9.65 to 9.76)
I would recommend the sessions	588	9.77 (9.72 to 9.82)
Website platform		
Usability		
Access to the content	253	8.30 (8.02 to 8.58)
Usability of the web	251	8.59 (8.33 to 8.85)
Patient outcomes follow-up charts	215	8.37 (8.03 to 8.72)
Quality of materials	229	8.81 (8.53 to 9.08)
Access to videos of the sessions	216	8.76 (8.47 to 9.05)
General		
General satisfaction	237	8.56 (8.30 to 8.82)
I would recommend using the website	239	8.81 (8.56 to 9.05)
Semi-automated mobile phone messages		
Usability		
Reading SMS	585	9.51 (9.41 to 9.61)
Usefulness of reminders	576	9.33 (9.22 to 9.45)
Personal satisfaction		
They adapt to my needs	579	9.04 (8.90 to 9.18)
They motivate me to look after myself	576	9.15 (9.02 to 9.28)
I would like to continue receiving them	552	8.80 (8.59 to 9.00)
General		
General satisfaction	572	9.23 (9.09 to 9.37)

rate). Some of these results are more related to changes in medication than lifestyles. From a cost-effectiveness perspective, small differences were observed between groups after 2 years follow-up. The PTI was more effective and less costly than CBI and PFI, in patients with HbA1c>7%.[14] This prompted the conclusion that interventions focused on patients with the highest needs would limit the impact on the healthcare sector budget.

This study has several limitations. The high number of instruments and measurement times increase the risk of type 1 error, which explains the decision not to compare intervention groups with each other. Moreover, the use

Table 6 Significant differences compared with usual care for the three intervention groups

	PTI		PFI		CBI	
	12 months	24 months	12 months	24 months	12 months	24 months
Cognitive/attitudinal						
Knowledge (DIATEK)	**	**		↓**	**	
Empowerment (DES-SF)		**	***		***	**
Behavioural						
Diet (MEDAS)	**	***	↓***			**
Adherence (MGLS)						
Smoking	*	*			*	*
Affective						
Depression (BDI-II)			**		**	
Anxiety (STAI-S)			*		**	
Diabetes Distress (DDS2)		**		*	**	
HRQOL						
HRQoL (ADDQoL-19)	*		**		***	
Neuropathy (MNSI)					*	

↓Represent worsening compare to usual care.
*$P \leq 0.05$. **$P \leq 0.01$. ***$P \leq 0.001$.
ADDQoL, Audit of Diabetes-Dependent Quality of life; BDI-II, Beck Depression Inventory II; CBI, combined intervention for patients and professionals; DDS2, Diabetes Distress Scale; DES-SF, Diabetes Empowerment Scale-Short Form; MEDAS, Mediterranean Diet Adherence Screener; MGLS, Morisky Medication Adherence Scale; MNSI, Michigan Neuropathy Screening Instrument; PFI, intervention only for healthcare professionals at primary care; PTI, intervention only for patients and family members; STAI-S, State Trait Anxiety Inventory.

of PROMs makes it necessary to know the minimum clinically significant differences of every instrument used. This difference, however, has not been investigated for most of them, and there is currently no consensus on the appropriate method (distribution or anchor-based) and/or statistics (eg, absolute vs relative reduction).[40] Furthermore, the use of PROMs implies by definition an unblind assessment of results, which is added to the impossibility of blinding the participants regarding the intervention. Finally, the INDICA study was not designed to test the efficacy of every single component of the interventions assessed (eg, text messages vs patient education vs web content). Despite these limitations, the INDICA study presents some distinctive characteristics from other published studies that assess the impact of interventions promoting empowerment, self-management and behaviour modification to patients and professionals: (1) a robust design (pragmatic cluster-randomised controlled trial with a factorial design for intervention arms) with a long follow-up (2 years); (2) incorporation of the different actors involved in disease management (patients and family caregivers and primary care professionals; (3) greater external validity by including patients regardless of their baseline HbA1c levels; (4) incorporation of ICT-based components to the intervention that favours applicability and access, in a cost-effective manner, to a growing number of patients; and (5) inclusion of a large sample size with 2334 patients and 211 healthcare professionals.

In conclusion, all the interventions assessed improved patients HRQoL at 1 year of follow-up, with differences according to the intervention in the remaining PROMs examined. The intervention targeted exclusively at patients (PTI) significantly improved knowledge, empowerment, distress, dietary recommendation adherence and tobacco cessation, up to 2 years of follow-up. Although the clinical relevance of these effects is uncertain, except in the case of smoking cessation, these results are promising since they reflect improvements in all personal domains assessed (cognitive, attitudinal, affective, behavioural), which highlight the importance of behavioural factors to attain good health outcomes. The intervention on professionals improved affective variables at 1 year of follow-up, but showed virtually no effects at 2 years together with a negative effect on diet adherence and no effect on tobacco consumption, which emphasises the need for more focused evaluative research on this type of intervention. For both target groups (patients and professionals), the use of ICT can be a major help to improve care access and continuity; as well as effectiveness and cost-effectiveness in T2DM self-management.

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Contributors YR-F is the guarantor. YR-F, LG-P, LR-R, AMW, MR-R and PGS-A contributed to the study design. SK-G, GM-M, CG-M, CD-A and MR-R developed the contents and gave the educational sessions to patients. Also, SK-G, GM-M, CG-M, CD-A and MR-R recruited participants and collected data. YR-F, MAG-B and HG-P contributed to the statistical analyses. YR-F, AR-S, LG-P, AMW and PGS-A were part of the writing committee of the manuscript. All authors reviewed, commented on, and approved the final manuscript.

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Publicación 4.

Open access Original research

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Cost-effectiveness of multicomponent interventions in type 2 diabetes mellitus in a cluster randomised controlled trial: the INDICA study

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ABSTRACT

Objective To analyse the cost-effectiveness of multicomponent interventions designed to improve outcomes in type 2 diabetes mellitus (T2DM) in primary care in the Canary Islands, Spain, within the INDICA randomised clinical trial, from the public health system perspective.

Design An economic evaluation was conducted for the within-trial period (2 years) comparing the four arms of the INDICA study.

Setting Primary care in the Canary Islands, Spain.

Participants 2334 patients with T2DM without complications were included.

Interventions Interventions for patients (PTI), for primary care professionals (PFI), for both (combined intervention arm for patients and professionals, CBI) and usual care (UC) as a control group.

Outcomes The main outcome was the incremental cost per quality-adjusted life-years (QALY). Only the intervention and the healthcare costs were included.

Analysis Multilevel models were used to estimate results, and to measure the size and significance of incremental changes. Missed values were treated by means of multiple imputations procedure.

Results There were no differences between arms in terms of costs (p=0.093), while some differences were observed in terms of QALYs after 2 years of follow-up (p=0.028). PFI and CBI arms were dominated by the other two arms, PTI and UC. The differences between the PTI and the UC arms were very small in terms of QALYs, but significant in terms of healthcare costs (p=0.045). The total cost of the PTI arm (€2571, 95% CI €2317 to €2826) was lower than the cost in the UC arm (€2750, 95% CI €2506 to €2995), but this difference did not reach statistical significance. Base case estimates of the incremental cost per QALY indicate that the PTI strategy was the cost-effective option.

Conclusions The INDICA intervention designed for patients with T2DM and families is likely to be cost-effective from the public healthcare perspective. A cost-effectiveness model should explore this in the long term.

Trial registration number NCT01657227.

Strengths and limitations of this study

- This paper presents an individual-based cost-effectiveness analysis of the INDICA study, a large randomised clinical trial.
- This paper analyses the cost-effectiveness of knowledge transfer and behaviour modification interventions from the public healthcare perspective in the Canary Islands, Spain.
- The outcome was quality-adjusted life-years, estimated using the EQ-5D-5L, and the costs were obtained from the local healthcare providers.
- We present the results of the whole sample, 2334 individuals, and the results of the subgroup of patients with glycated haemoglobin >7%.
- From the point of view of the economic evaluation, the main limitation is the relatively short duration of the trial, 2 years.

INTRODUCTION

Diabetes is a prevalent chronic disease with a major global impact. A worldwide prevalence of 8.5% in adults, 7.3% in Europe,[1] and a direct annual cost to the world higher than US$825 billion[2 3] has been estimated. The prevalence of type 2 diabetes mellitus (T2DM) in the population aged 15 and over in the Canary Islands is 7.74%,[4] which is slightly higher than the Spanish average (6.99%).[5] Moreover, the Canary Islands show a higher mortality and a higher incidence of complications than the rest of Spain.[6 7] This situation has prompted the implementation of secondary prevention strategies that, nevertheless, should be evaluated before and after their implementation.[8]

Given these circumstances, the INDICA study was designed with the aim of evaluating evidence-based interventions. Several reviews

were undertaken and various relevant systematic reviews and guidelines were identified.[9–11] Some trials, such those conducted by Trento *et al*[12] were inspirational. Despite the increasing healthcare expenditure[13] and availability of services[14] and guidelines,[15] the adherence to recommended actions of T2DM self-management and lifestyle changes is limited.[16] Furthermore, healthcare professionals and family members play an important role in supporting patients with T2DM. There is also evidence on the effectiveness of the information and communication technologies (ICT) to transfer the knowledge of diseases and support patients and professionals in their decisions.[10 17–20] Based on all this evidence, the INDICA interventions were designed, implemented and evaluated. As both effectiveness and cost-effectiveness are criteria for health technologies reimbursement in Spain,[21] and bearing in mind that the efficiency of complex interventions is not easily transferable,[22] an economic evaluation was conducted alongside a clinical trial.

The INDICA study is a randomised controlled trial (RCT) that evaluates the effectiveness and cost-effectiveness of three different ICT-based multicomponent interventions to support decision making in patients with T2DM and primary healthcare professionals in the Canary Islands.[23 24] Results on the effectiveness of the interventions are reported elsewhere.[25 26] In this paper, we present the cost-effectiveness analyses.

METHODS

Trial design

The INDICA study is an open, community-based, multicentre, controlled clinical trial with random cluster allocation to one of four arms, one of them a control group. We estimated the cost-effectiveness for the 'within-trial' period (2years) where incremental cost per quality-adjusted life-year (QALY) was the main outcome.[23 24]

Ethical approval and consent to participate

All participants provided written informed consent. The study fulfilled the regulatory requirements, Good Clinical Practice standards, Declaration of Helsinki, and received the approval of the Scientific and Ethics Committees of two hospitals (University Hospital of Canarias (ID: 2012_44) and University Hospital Nuestra SEñora de la Candelaria (ID: EPA-07/10)). General guidelines for economic evaluation and clinical trials were followed.[27–29] The methods were reported in the published protocol.[23]

Interventions

The intervention for patients and family members (PTI) included a diabetes-coaching programme using a combination of educational workshops with automated and personalised phone messages and a web-based platform. The intervention for primary care healthcare professionals (physicians and nurses) (PFI) included workshops to update clinical management, a decision support tool nested into the electronic clinical record system; and periodic feedback reports on patient outcomes. In the combined intervention arm for patients and professionals (CBI), both received the reported interventions. The control group received usual care (UC), that is, neither patients nor professionals received any educational intervention or supporting activities beyond the usual healthcare provided by Servicio Canario de la Salud (SCS), an organisation that is part of the National Health System and provides public healthcare in the Canary Islands (Spain).

Subjects

Patient inclusion criteria were T2DM diagnosed at least 1year prior to study enrolment, 18–65 years of age, formal consent to participate in the study, and regular use of a mobile phone. Patients with serious comorbidities, insufficient (Spanish) language skills, physical disability limiting participation in group education activities or concurrent participation in another clinical study were excluded.

Setting, recruitment and randomisation

The study was conducted in the primary care setting in the Canary Islands, Spain. In the more populated islands (Tenerife and Gran Canaria) three different strata were created according to the geographic areas. In the less populated islands (La Palma and Lanzarote) each island was divided into four zones. Randomisation was applied at different levels: Primary Care Health Practices (PHCP), Family Care Units (FCU) and patients. First, in each strata of Tenerife and Gran Canaria, four PHCP (clusters) were randomly recruited, providing 12 PHCP in total. The two other islands, La Palma and Lanzarote, provided four PHCP each (one in each area). Block permutation was used to assign PHCPs to study arms, with PHCP as the sampling unit. In every island and each strata, all arms were equally distributed. Second, six FCU, composed of a family physician and a nurse, were randomly selected from all those consenting to participate in each PHCP. And thirdly, the electronic clinical records (ECR) of patients at each participating FCU were screened and 15 patients were randomly selected from all patients fulfilling the inclusion criteria and consenting to participate. Cluster allocation avoids contamination bias among participants, also facilitating logistics in group interventions. PHCP (in Tenerife and Gran Canaria), FCU and patient randomisation were performed by simple generation from a list of random numbers. FCUs were blinded to the intervention assignment until the last patient was recruited.

Patient and public involvement

Patients were actively involved in design of the trial. Two associations of patients with T2DM in the Canary Islands were included from the beginning of the study as part of the research team, with an active participation in the design of the interventions and selection of the outcomes measured. In the same way, primary care professionals and clinical management staff participated in preparation

of the protocol. The patients and professionals included in the study could express their satisfaction with the interventions through a questionnaire, as well as through focus groups and in-depth interviews that will be the subject of another study. Finally, we established a commitment with patients and healthcare professionals to share the results with them in an easy-to-understand way.

Healthcare utilisation and costs

Direct costs were evaluated from the public healthcare service perspective (SCS). Hence the following resources and services were included: costs related to the development and implementation of each intervention (including materials and development of ICTs) and the use of healthcare in all arms (including UC arm), which included the costs of contacts with primary care services, hospital admissions, outpatient visits, emergency visits, tests and medications. Those resources not very commonly accessed (visits to neurologists, physiotherapy or Doppler echocardiography, eg) were excluded from the analysis. Resource use was collected from questionnaires completed by patients, ECR and administrative data. Unit costs were obtained from different sources, that is, public sources, administrative accounts and specific suppliers (see online supplemental appendix 1 tables A1 and A2 for further details). The costs of medicines were obtained from the database of dispensed medicines charged to the public healthcare sector and included: antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, calcium-channel blockers, diuretics and beta blockers), lipid-lowering agents, antithrombotic drugs, amitriptyline, duloxetine, pregabalin and tramadol. Unit costs were adjusted for inflation when needed. Costs are reported in Euros from 2017.

Quality-adjusted life years

Patients completed at baseline and every 6 months the EQ-5D-5L, a generic health-related quality of life questionnaire[30] that evaluates five domains: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each domain is scored at one of five levels, yielding a descriptive system that can be combined into a five-digit number that reports the patient's state of health. Each EQ-5D-5L health state can be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension. A number of formulae, or value sets are available for different countries, based on the valuation of EQ-5D health states from general population samples. In this study, the value set estimated for Spain by Ramos-Goñi *et al* was used.[31] After applying these weights, or utilities, an EQ-5D-5L index score of 1 represents full health, a score of 0 is equivalent to death and negative scores represent health states perceived as worse than death by population. Patient-specific utility profiles over the 2-year follow-up were estimated assuming a straight line relation between each patient score at each follow-up point. The QALYs from baseline to month 24 were calculated as the area under the curve.[28]

Sample size calculation

The sample size calculation was based on the primary endpoint of the effectiveness study, that is, the mean change in glycated haemoglobin (HbA1c) from baseline to month 24. A total of 2330 patients was estimated (482 patients per arm).

Statistical methods

QALYs and costs were estimated using multilevel models.[28] The first level included patients characteristics, and the second level variables correspond to PHCPs. QALYs were adjusted by time elapsed since diagnosis and baseline utility as covariates.[32] Costs were adjusted by age, sex and baseline utility. To estimate use of resources a negative-binomial regression model, adjusted by time since diagnosis and baseline resource use, was used. The final model for each dependent variable included the covariates that modified the treatment effect of the estimates by at least 10%. As suggested in the Consolidated Standards of Reporting Trials statement, decisions about covariates will not be based on the p value.[33 34]

Patient characteristics were compared at baseline with a χ^2 test for the variable sex and using a multilevel model for age, duration of diabetes, HbA1c and EQ-5D-5L Index. Only the arm was included as independent variable.

Intergroup differences were considered statistically significant if $p<0.05$. For multiple comparisons, the p value was adjusted with Bonferroni correction.

Missing values were treated by means of multiple imputation procedures,[35] with results based on 100 imputed datasets. The missing data patterns were published as Multimedia Appendix in Ramallo-Fariña *et al*.[26] The model of imputation used for variables involved in the cost-effectiveness evaluation can be found in online supplemental appendix 2. Analysis was performed on an intention-to-treat basis.

Incremental cost-effectiveness ratio (ICER), that is, the differences between costs divided by the differences in QALYs, was calculated when one alternative was more (less) effective and more (less) costly than another, once the dominated alternatives were excluded. The results were re-estimated using alternative values for some parameters (costs) in a deterministic one-way sensitivity analysis (±20% of unit costs). Finally, a post hoc subgroup analysis was conducted with only subjects with HbA1c above the treatment target, that is, baseline HbA1c >7%. For reference, €25 000 per QALY was considered the cost-effectiveness threshold as this is the latest value estimated following robust methods in Spain.[36] All analyses were conducted using STATA V.15.0 (StataCorp).

RESULTS

Between February 2013 and October 2016, 32 PHCP and 2334 patients (mean age: 55.7±SD: 7.1 years;

Table 1 Baseline characteristics of the participants in the study

	PTI arm (n=537)	PFI arm (n=654)	CBI arm (n=557)	UC arm (n=586)	P value
Age (years) (mean±SD)	55.9±7.0	56.2±7.0	55.5±7.1	55.2±7.3	0.216
Sex: male (%)	52.9*	44.0	47.4	48.8	0.024
Duration of diabetes (years) (mean±SD)	8.4±6.8	8.2±6.1	8.9±6.3	8.6±6.8	0.471
Glycated haemoglobin (%) (mean±SD)	7.3±1.5	7.2±1.4	7.4±1.5	7.3±1.5	0.224
<7%	48.0	53.7	43.3	51.9	
7%–8%	27.2	25.2	29.6	24.1	
8%–9%	12.3	11.5	14.7	11.4	
≥9%	12.5	9.6	12.4	12.6	
EQ-5D-5L Index (mean±SD)	0.86±0.19	0.88±0.16	0.86±0.19	0.85±0.20	0.796

Sex: $\chi 2$ test.
Age, duration of diabetes, glycated haemoglobin and EQ-5D-5L index: multilevel model with arm as independent variables, without adjusting by covariates.
*Statistically significant differences between arms PTI and PFI (p=0.002).
CBI, combined intervention for patients and professionals; PFI, intervention only for healthcare professionals at primary care; PTI, intervention only for patients and family members; UC, usual care (control group).

51.9% women) were recruited and included in the RCT. There were no statistically significant differences among the groups in terms of their baseline characteristics, except for sex between the PTI and PFI arm (p=0.002) (table 1). The flowchart of included patients by arm in each follow-up can be seen in Ramallo-Fariña *et al*.[26]

Quality-adjusted life-years

Statistically significant differences in QALYs were found at month 18 (p=0.030) and 24 (p=0.028). The differences are found between the CBI arm and the UC arm (1.24 vs 1.29 at 18 months; 1.63 vs 1.72 at 24 months), favouring the UC arm; and between the CBI arm and PTI arm (1.24 vs 1.29 at 18 months; 1.63 vs 1.71 at 24 months), with CBI showing the lowest values (table 2). Representations of the profile of utilities for patients in each arm for the 2 year period can be found in online supplemental appendix 1 figure A1.

Use of resources and healthcare costs

Statistically significant differences were found between arms for the following resources: hospital admissions (p=0.025), laboratory procedures (p<0.001), visits to primary care (doctors and nurses) (p<0.001) and non-hospital emergency room visits (p=0.002) (see online supplemental appendix 1 table A3). In regard to healthcare costs, we found differences between arms in hospital admissions (p=0.019), laboratory procedures (p=0.044), and visits to primary care (p=0.002), but no differences were found in the aggregated healthcare cost (excluding INDICA interventions costs). The highest mean healthcare cost was found in the UC arm (€2750, 95% CI €2506 to €2995), followed by the CBI arm (€2698, 95% CI €2449 to €2948), the PFI arm (€2664, 95% CI €2432 to €2896) and, lastly, the PTI arm (€2391, 95% CI €2137 to €2646) (table 2). The only significant difference was found in the healthcare cost between the PTI and the UC arms (p=0.045).

Cost of INDICA interventions and total costs

The costs of INDICA interventions over the 2 years of implementation are reported in online supplemental appendix 1 table A2. The mean intervention costs for patients was higher than the cost for professionals (€180 vs €130). The total cost, that is the result of adding the INDICA intervention costs and the healthcare costs, was found to be highest in the CBI arm (€3025, 95% CI €2776 to €3274), followed by the PFI arm (€2794, 95% CI €2562 to €3026), the UC arm (€2750, 95% CI €2506 to €2995), and, finally, the PTI arm (€2571, 95% CI €2317 to €2826) (table 2). Although no differences in total cost were identified among arms (p=0.093), statistically significant differences were found between two specific arms, the PTI arm and the CBI arm (p=0.013).

Cost-effectiveness analysis: base case

Table 3 shows the incremental cost, the incremental effect and the ICER. The PFI and the CBI arms were dominated by other alternatives, so they cannot be considered cost-effective. Between the other two arms, PTI and UC arms, the difference in effects and costs were found to be small and non-statistically significant (p=0.319). The ICER is estimated at €38 486 per QALY. This ratio should be interpreted with care since the intervention evaluated (PTI arm) is (slightly) less effective but also less expensive than the control (UC arm) and the differences in total costs and QALYs were not found to be statistically significant.

Cost-effectiveness analysis: sensitivity analysis

The results of the sensitivity analysis are very similar to the base case (see online supplemental appendix 1 table A4). The PFI and CBI arms are in all cases dominated by the other two arms, while the PTI arm is less expensive than the UC arm. There are only significant differences in costs between arms when a lower cost of hospital stay

Table 2 Adjusted means (95% CI) of QALYs and healthcare costs per arm (€), multilevel model

QALYs per period					
Period	**PTI arm**	**PFI arm**	**CBI arm**	**UC arm**	**P value**
0–6 months	0.43 (0.42 to 0.44)	0.43 (0.42 to 0.44)	0.42 (0.41 to 0.43)	0.43 (0.42 to 0.44)	0.352
0–12 months	0.86 (0.84 to 0.88)*	0.85 (0.84 to 0.87)	0.83 (0.81 to 0.85)†	0.86 (0.85 to 0.88)	0.087
0–18 months	1.29 (1.26 to 1.32)*	1.27 (1.25 to 1.3)	1.24 (1.21 to 1.27)†	1.29 (1.27 to 1.32)	0.030
0–24 months	1.71 (1.67 to 1.75)*	1.69 (1.65 to 1.73)	1.63 (1.59 to 1.68)†	1.72 (1.68 to 1.76)	0.028
Healthcare costs in 2years					
Resource	**PTI arm**	**PFI arm**	**CBI arm**	**UC arm**	**P value**
Hospital stays	462.06 (287.6 to 636.52)‡	554.31 (398.15 to 710.47)	400.58 (230.24 to 570.91)†	757.72 (590.70 to 924.74)	0.019
Laboratory tests	46.12 (40.68 to 51.56)*§	56.35 (51.36 to 61.34)	54.15 (48.62 to 59.69)	51.47 (46.33 to 56.61)	0.044
Retinography	117.78 (91.24 to 144.32)	127.57 (101.83 to 153.32)	117.18 (90.44 to 143.91)	115.69 (89.67 to 141.72)	0.920
Primary care visits	293.13 (205.04 to 381.21)*	293.13 (297.35 to 472.18)¶	481.99 (393.78 to 570.21)†	263.11 (175.4 to 350.92)	0.002
Specialist visits	37.49 (26.74 to 48.24)	46.94 (37.22 to 56.66)	43.88 (33.07 to 54.70)	44.38 (34.21 to 54.54)	0.634
Emergency room visits	275.89 (191.09 to 360.69)	264.88 (183.39 to 346.37)	337.16 (251.86 to 422.46)	251.90 (169.24 to 334.56)	0.505
Medication	1156.96 (1016.23 to 1297.7)	1222.31 (1090.12 to 1354.5)	1242.16 (1102.59 to 1381.72)	1269.47 (1132.53 to 1406.42)	0.715
Healthcare cost (without INDICA interventions related costs)	2391.22 (2136.87 to 2645.58)‡	2663.6 (2431.57 to 2895.63)	2698.25 (2448.72 to 2947.78)	2750.44 (2506.19 to 2994.69)	0.191
INDICA interventions related costs	180.26	130.28	326.76	0	–
Total cost	2571.53 (2317.17 to 2825.88)*	2793.91 (2561.86 to 3025.95)	3025.12 (2775.55 to 3274)	2750.44 (2506.18 to 2994.71)	0.093

Healthcare costs: multilevel model, adjusted by age, sex and baseline utility.
QALYs: multilevel model, adjusted by time elapsed since diagnosis and baseline utility.
*Statistically significant differences between PTI and CBI
†Statistically significant differences between CBI and UC
‡Statistically significant differences between PTI and UC
§Statistically significant differences between PTI and PFI
¶Statistically significant differences between PFI and UC
CBI, combined intervention for patients and professionals; CI, Confidence interval; PFI, intervention only for healthcare professionals in primary care; PTI, intervention only for patients and family members; QALY, quality-adjusted life-years; UC, usual care (control group).

(p=0.039) or a higher cost of the intervention on professionals (p=0.036) is assumed.

Analysis of subgroups: patients with baseline HbA1c >7%

The subgroup of patients with baseline HbA1c >7% revealed some benefits of interventions. The PTI arm had the highest effect in terms of QALYs and is dominant over all the other arms after the multilevel model adjustment (table 4). In terms of costs, statistically significant differences were observed only in visits to primary care professionals (p=0.003) (see online supplemental appendix 1 table A5). The highest average healthcare cost per patient, not including the cost of INDICA interventions,

Table 3 Cost, effectiveness and ICER

Arm	Mean total cost (€) (95% CI)	Mean QALYs (95% CI)	Incremental cost and incremental QALYs (95% CI)
CBI	3025.01 (2775.55 to 3274.69)	1.63 (1.59 to 1.68)	Dominated
PFI	2793.88 (2561.86 to 3025.95)	1.69 (1.65 to 1.73)	Dominated
PTI	2571.48 (2317.17 to 2825.88)	1.71 (1.67 to 1.75)	-178.95996 € (–499.61 to 141.69)
UC	2750.44 (2506.18 to 2994.71)	1.72 (1.68 to 1.76)	-0.00465 QALYs (–0.036 to 0.027)
ICER between PTI and UC			38486.0129 €/QALY

CBI, combined intervention for patients and professionals; CI, Confidence interval; ICER, incremental cost-effectiveness ratio; PFI, intervention only for healthcare professionals in primary care; PTI, Intervention only for patients and family members; QALY, quality-adjusted life-years; UC, usual care (control group).

Table 4 Cost and effectiveness in subgroup with baseline HbA1c >7%

Arm	Mean total cost (€) (95% CI)	Mean QALYs (95% CI)	Cost-effectiveness
CBI	3516.44 (3207.58 to 3825.31)	1.62 (1.59 to 1.67)	Dominated
UC	3492.08 (3092.06 to 3892.1)	1.70 (1.66 to 1.73)	Dominated
PFI	3310.96 (2981.6 to 3640.32)	1.71 (1.68 to 1.75)	Dominated
PTI	3117.46 (2763.4 to 3471.53)	1.72 (1.69 to 1.75)	Dominant

CBI, combined intervention for patients and professionals; CI, Confidence interval; HbA1c, glycated haemoglobin; PFI, intervention only for healthcare professionals in primary care; PTI, intervention only for patients and family members; QALY, quality-adjusted life-years; UC, usual care (control group).

was found in the UC arm (€3492, 95% CI €3092 to €3892), followed by the CBI arm (€3189, 95% CI €2881 to €3498), the PFI arm (€3181, 95% CI €2851 to €3510) and, lastly, the PTI arm (€2937, 95% CI €2583 to €3291). These costs were higher than those observed for the entire sample. The only statistically significant difference was found between the average cost of the PTI arm and the average cost of the UC arm, as was the case for the total sample. No differences between arms were found in total cost in patients with baseline HbA1c>7% (p=0.399). The highest total cost per patient was estimated for the CBI arm (€3516, 95% CI €3208 to €3825), followed by the UC arm (€3492, 95% CI €3092 to €3892), the PFI arm (€3311, 95% CI €2982 to €3640) and, lastly, the PTI arm (€3117, 95% CI €2763 to €3471) (see table 4).

The estimate of costs and QALYs was similar for all imputed, non-imputed and completed data. The same arms stayed as dominant and the same conclusion with regard to ICER was upheld.

DISCUSSION

This paper presents the results of an economic evaluation conducted alongside a RCT, the INDICA Study (n=2334), in the Canary Islands, Spain, and from the healthcare perspective. The alternatives evaluated were ICT-based PTI and for professionals in primary care, developed to improve self-management and health outcomes in people with T2DM and prevent serious comorbidity or advanced complications of the disease.

The lowest mean cost was found in the PTI arm, that is, the group where patients received a diabetes-coaching programme combining group education workshops, personalised phone messages and a web-based platform. At the other end, as expected, the cost of the CBI arm, where both PTI and for professionals were included, was higher than in any other arm. The main costs driver was the healthcare costs, lower in the PTI arm than in any other arm and higher in the control group than in any intervention arm. To be precise, the differences between arms were partly explained due to differences in the use of resources and costs of visits to primary care, lab tests and hospital admissions. Regarding the effectiveness of the interventions, although the ICT-based interventions developed for the INDICA trial improved HbA1c and other clinical measures after 24 months of follow-up,[26] these results were not translated into large differences in terms of QALYs between arms. Taking into account costs and QALYs, the CBI and the PFI arms were dominated, that is, were less effective and more costly than other alternatives. Meanwhile, the PTI arm was found to be slightly less effective and less costly than the control group (non-significant differences). The sensitivity analysis confirmed this result. Furthermore, we estimated that the incremental cost per QALY of the UC strategy compared with the PTI arm was above the cost-effectiveness threshold in Spain (€25 000 per QALY),[36] indicating that the PTI intervention is likely to be a cost-effective option.[37] This ICER must be cautiously interpreted given that CIs for both costs and QALYs show uncertainty around the estimates. To complement the results, we conducted a subgroup analysis (not included in the trial protocol) that revealed that in the sample of patients with uncontrolled T2DM (baseline HbA1c >7%) the PTI arm was dominant over all the other arms. This suggests that the INDICA intervention designed for patients and their families is likely to be more cost-effective, especially in patients with poorly controlled blood glucose levels. Transferability to real clinical practice of cost-effective interventions could be even more efficient as their application can be extended to thousands of patients with T2DM, with minimal cost increases.

The INDICA study was designed to be ambitious, inspired by several systematic reviews.[9 10] More recent reviews confirmed the pertinence of studies as INDICA. Lian *et al* conducted a systematic review of cost-effectiveness studies on self-management education programmes for T2DM.[38] This review found two interesting results. First, the number of studies of sufficiently good quality was low, only five cost-effectiveness studies alongside clinical trials. The longest follow-up was 12 months and the largest sample size was 1570. Consequently, from the point of view of these two methodological characteristics, the INDICA study is superior. The second conclusion from Lian *et al* is that the cost of these interventions is not very high and likely to be cost-effective in the long-term. In fact, the only study they identified that found that the intervention was not cost-effective was conditioned by the short-term analysis and could benefit from a long term modelling analysis.[38 39] More recently, Siegel *et al* found strong evidence that multicomponent interventions (involving behaviour change and education and pharmacological therapy) compared with UC are cost-saving or cost-effective (range of the ICERs from cost-saving to US$58 587 per QALY; median: US$2315 per QALY, based on six studies).[40] Interestingly, they also found uncertain evidence about the cost-effectiveness of a computerised decision support system linked to ECR.

Finally, the generalisability of the INDICA findings and the transferability of its results to other settings are not straightforward. Interventions were designed and implemented considering the level of health and digital literacy of the population in the Canary Islands, that is quite similar to the average in Spain (and above the EU mean), and the organisation of the primary healthcare provision by the public system in the region.[41 42] Although not all regions in Spain offer the same support to patients with diabetes, primary healthcare is quite homogeneous throughout the country[43] so the interventions could be implemented with few modifications in regions other than the Canary Islands. Therefore, we could conclude that the intervention and the cost-effectiveness results could be transferable to other regions in Spain, but the transferability to other countries would need a thorough analysis of the care for T2DM in other foreign settings.

Strengths and limitations

The strengths of the INDICA Study as a trial include the pragmatic nature, its large sample size, the duration of follow-up when compared with other trials and, especially, the high rate of patient retention at the last control visit in month 24. There is prior evidence supporting the effectiveness of similar interventions in the reduction of HbA1c in the short term[18 44 45] but not in the long term.[46] The INDICA study revealed differences in clinical outcomes between the intervention arms and the control group that remained statistically and clinically significant at the end of 24 months despite the gradual reduction of effectiveness over time.[26] These findings highlight the importance of conducting trials with long follow-up and sufficient statistical power to evaluate interventions of limited effect sizes but of potential efficacy. In addition, this study applied careful randomisation methods and hierarchical modelling techniques to minimise potential bias due to sample selection or due to baseline differences across subjects. Further explanations can be found in the main article with the clinical results of the INDICA study.[26]

As an economic evaluation, the most important strength comes from the quality and quantity of data on resource use. Medication was collected from the information system for the electronic drugs prescriptions, a very reliable register that includes data on prescription and collection of drugs from community pharmacists. But most data were collected from the patients in common face-to-face meetings to avoid recall bias, and checked against the ECR for those considered critical as healthcare visits and hospital admissions. These meetings also facilitated the high rate of completed EQ-5D-5L questionnaires.

The main limitations of this study are as follows. First, there was some degree of missing data addressed by the robust imputation technique. Multiple Imputation methods were used instead of the technique specified in the protocol, since this is the best option for our missing data patterns.[47] Related to this limitation, due to the complexity of our models, which included multilevel analyses and imputed data, it was not possible to apply bootstrapping techniques that could effectively characterise the uncertainty around the ICER point estimates. This also prevented estimate of the cost-effectiveness acceptability curve. Instead, we presented the CIs for costs and QALYs separately and conducted comprehensive deterministic sensitivity analyses.

Second, we conducted the costs analysis in the framework of the clinical trial. Intervention costs might differ in real life as implementation all over the Canary Islands would require the escalation of resources in a fragmented territory as it is an archipelago if other criteria such as access equity have to be taken into consideration. Nonetheless, the sensitivity analysis applied to costs confirmed the main result as reported in this study.

Third, we found some unexpected results that were further explored. For instance, the small effect observed in the PFI and CBI arms in comparison to PTI was potentially explained by the high staff turnover noted among primary care professionals around the time the study was ongoing. Similarly, the unexpected results with regard to the outcomes measured in the UC arm might be accounted for by the intensive trial follow-up that all the arms experienced (ie, answering questions about diet, physical activity and self-care six times in 2years, plus blood tests and other examinations) that could be seen as a kind of intervention.[44 45 48 49] Therefore, the intensity of the follow-up in the study might have also impacted patient behaviour in the UC arm, to the point of reducing the differences in effects at the end of the 2-year period.

Finally, the lack of important differences in QALYs is potentially due to two main reasons. First, it is difficult to observe large changes when most patients included in the study were already well controlled at baseline (49.4% of the whole sample had an HbA1c <7%).[44] Second, the time horizon is too short to observe changes in diabetes-related complications that are the main cause of variations in quality of life.[50] We will aim to overcome these limitations by implementing the INDICA-DOS study, a follow-up of patients included in the INDICA study that aims to collect outcomes and healthcare costs in the longer term. This information will be useful to complement the within-trial economic evaluation presented in this paper with a lifetime Markov model.[23 24]

Conclusions

In summary, the multicomponent intervention designed by INDICA for patients with T2DM and their families is likely to be a cost-effective option, and particularly so in patients with not so well controlled TD2M (baseline HbA1c >7%). This kind of intervention is likely to be effective, cost-effective and, if focused on those with the highest needs, its impact on the public health budget would be limited.

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Contributors LGP, YRF, LVT, LRR, AMW and PGSA contributed to the study design. YRF, LVT, HGP, BSH and MAGB contributed to the statistical analyses. LGP, YRF, LVT, HGP, MC and PGSA were part of the manuscript's writing committee. All authors reviewed, commented and approved the final manuscript. LGP is the guarantor.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets generated and/or analysed during the current study, including deidentified participant data are available from the corresponding author on reasonable request in the next 10 years. The study protocol is available at https://implementationscience.biomedcentral.com/articles/10.1186/s13012-015-0233-1.

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Appendix 1. Supplementary data: Inputs and outputs

List of tables:

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Table A1. Health care resources included in the analysis and their unit costs

	Unit cost (€)	Source
Hospital stay (*)	5171.77	Assumption based on Crespo et al. 2013
Lab test by general practitioner	15	Assumption based on eSalud
Lab test by specialist	20	Assumption based on eSalud
Retinography	100	Assumption base on several sources
Visit to general practitioner	28.78	Public tariff, Servicio Canario de la Salud (2017)
Visit to nurse at primary care	26.62	Public tariff, Servicio Canario de la Salud (2017)
Visit to endocrinologist	110	Assumption based on public tariff, Servicio Canario de la Salud (2017)
Visit to accident & emergency	227.78	Public tariff, Servicio Canario de la Salud (2017)
Medication	Unit costs varied depending on the medication. The source was the database of dispensed medicines in community pharmacy offices.	

(*) As the mean stay of INDICA patients was 9 days, the unit cost reported by Crespo et al. (Av Diabetol. 2013) is considered adequate for the estimation of hospital stay costs.

Sources:

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Table A2. Cost of INDICA interventions (€)

Resource	Patients	Professionals	Both
Time dedicated to developing the materials used by the study nurses (educators)	20163	(-)	20163
Time spent by other professionals on reviewing the materials	1523	(-)	1523
Training in empowerment received by the nurses	229	(-)	229
Training in emotional management received by the nurses	414	(-)	414
Time for educational workshops to patients and their relatives by nurses	27824	(-)	27824
Laptops	3620	(-)	3620
Printed materials for group education	780	(-)	780
Transport by nurses to visit centres	5004	(-)	5004
Diaries for patients	7910	(-)	7910
Video recording of educational workshops given by nurses	1091	(-)	1091
Website with educational materials for the patients	12120	(-)	12120
SMSs sent to patients	16119	(-)	16119
Time dedicated to developing the materials: review of studies and design of INDICA guideline for GPs	(-)	44460	44460
Edition and printing of INDICA guideline	(-)	1292	1292
Development and maintenance of computerized decision support system	(-)	26477	26477
Development of feedback system	(-)	7284	7284
Folders for professionals in primary care	(-)	1452	1452
Catering for training workshops for professionals in primary care	(-)	1741	1741
Training workshops of professionals in primary care (introduction to INDICA guideline and shared decision making)	(-)	2500	2500
Total cost (€)	96798	85206	182004
Number of patients	537	654	557
Mean cost per patient (€)	180.26	130.28	326.76

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Figure A1. EQ-5D-5L Index profile per arm

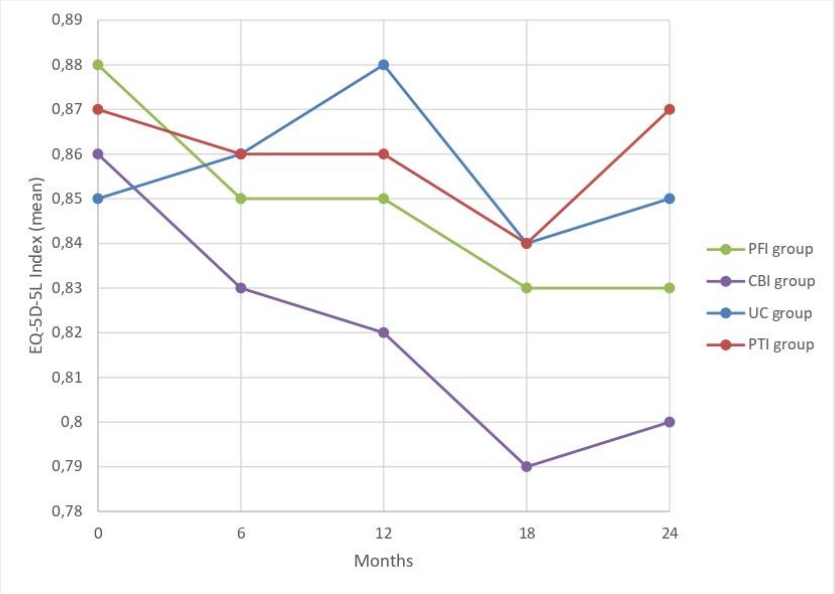

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Table A3. Adjusted mean (95%CI) of use of resources for all follow-up per arm. Negative-binomial regression model

Resource	PTI arm	PFI arm	CBI arm	UC arm	p-value
Hospital stays	0.09 (0.06 to 0.12)[a]	0.10 (0.07 to 0.13)	0.08 (0.04 to 0.11)[b]	0.15 (0.12 to 0.18)	**0.025**
Lab tests by general practitioner	2.04 (1.88 to 2.19)[d e]	2.60 (2.47 to 2.74)[c]	2.51 (2.34 to 2.68)[b]	2.12 (1.98 to 2.27)	**<0.001**
Lab tests by specialist	0.77 (0.62 to 0.92)	0.85 (0.71 to 0.98)	0.85 (0.70 to 1.0)	0.95 (0.91 to 1.09)	0.373
Retinography	1.20 (1.08 to 1.32)	1.29 (1.18 to 1.38)	1.18 (1.07 to 1.31)	1.15 (1.04 to 1.25)	0.323
Visits to general practitioner	5.96 (5.56 to 6.36)[a d e]	8.08 (7.53 to 8.59)[c f]	9.73 (9.3 to 10.67)[b]	5.35 (4.93 to 5.71)	**<0.001**
Visits to nurse at primary care	4.59 (4.07 to 5.11)[d e]	5.71 (5.24 to 6.17)[c f]	7.31 (6.78 to 7.86)[b]	4.66 (4.17 to 5.15)	**<0.001**
Visits to endocrinologist	0.39 (0.30 to 0.48)	0.46 (0.37 to 0.53)	0.45 (0.36 to 0.55)	0.43 (0.35 to 0.52)	0.693
Visit to accident & emergency (outpatient centre)	0.95 (0.77 to 1.13)[a]	0.86 (0.70 to 1.02)[e]	1.13 (0.94 to 1.31)[b]	0.78 (0.62 to 0.94)	**0.002**
Visit to accident & emergency (hospital)	0.33 (0.25 to 0.40)	0.29 (0.23 to 0.35)	0.36 (0.28 to 0.43)	0.33 (0.27 to 0.4)	0.577

Negative-binomial regression model, adjusted by time since diagnosis and baseline resource use.

Statistically significant differences between arms: a, UC and PTI; b, UC and CBI; c, UC and PFI; d, CBI and PTI; e, PFI and PTI; f, CBI and PFI.

CBI, Combined intervention for patients and professionals; PFI, Intervention only for health care professionals in primary care; PTI, Intervention only for patients and family members; UC, usual care (control group).

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Table A4. Results of the one-way sensitivity analysis

		Costs (€) Mean (95%CI)					PTI *vs* UC		
Resource	Unit cost (€)	PFI arm*	CBI arm*	PTI arm	UC arm	p-value	Incremental cost	Incremental QALYs	ICER (€/QALY)
Hospital stay	4137.42	2683 (2467.21 to 2898.79)	2942.75 (2711.91 to 3173.59)[b]	2479.59 (2244.96 to 2714.21)[a]	2598.18 (2372.31 to 2824.04)	**0.039**	-118.591	-0.00465	25503.44
	6206.12	2904.48 (2653.62 to 3155.33)	3107.11 (2836.14 to 3378.07)	2663.45 (2386.66 to 2940.24)	2903.04 (2637.74 to 3168.34)	0.164	-239.585	-0.00465	51523.66
Lab test by general practitioner	12	2786.09 (2553.97 to 3018.2)	3017.6 (2767.97 to 3267.22)	2565.41 (2311.0 to 2819.81)	2744.06 (2499.73 to 2988.39)	0.095	-178.652	-0.00465	38419.78
	18	2801.73 (2569.75 to 3033.71)	3032.65 (2783.13 to 3282.16)	2577.65 (2323.34 to 2831.96)	2756.83 (2512.63 to 3001.02)	0.091	-179.18	-0.00465	38533.33
Lab test by specialist	16	2790.46 (2558.83 to 3022.09)	3021.86 (2772.71 to 3271.02)	2568.42 (2314.48 to 2822.35)	2746.59 (2502.74 to 2990.44)	0.092	-178.177	-0.00465	38317.63
	24	2797.35 (2564.89 to 3029.82)	3028.38 (2778.4 to 3278.37)	2574.64 (2319.86 to 2829.41)	2754.29 (2509.61 to 2998.97)	0.094	-179.655	-0.00465	38635.48
Retinography	80	2768.43 (2535.88 to 3000.98)	3001.36 (2751.29 to 3251.42)	2547.57 (2292.82 to 2802.32)	2727.31 (2482.53 to 2972.09)	0.094	-179.739	-0.00465	38653.55
	120	2819.39 (2587.74 to 3051.05)	3048.87 (2799.68 to 3298.06)	2595.49 (2341.42 to 2849.56)	2773.56 (2529.7 to 3017.42)	0.092	-178.065	-0.00465	38293.55

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Visit to general practitioner	23.02	2746.8 (2521.19 to 2972.4)	2969.39 (2726.11 to 3212.67)	2536.77 (2288.5 to 2785.04)	2721.83 (2483.8 to 2959.85)	0.108	-185.058	-0.00465	39797.42
	34.54	2841.06 (2602.23 to 3079.88)	3080.72 (2824.54 to 3336.91)	2606.31 (2345.54 to 2867.07)	2779.03 (2528.20 to 3029.86)	0.080	-172.724	-0.00465	37144.95
Visit to nurse at primary care	21.30	2763.69 (2536.76 to 2990.61)	2984.26 (2739.65 to 3228.88)	2547.69 (2298.15 to 2797.22)	2727.94 (2488.62 to 2967.25)	0.104	-180.25	-0.00465	38763.44
	31.94	2824.11 (2586.79 to 3061.42)	3065.95 (2811.27 to 3320.62)	2595.39 (2336.06 to 2854.72)	2772.96 (2523.6 to 3022.33)	0.083	-177.572	-0.00465	38187.53
Visit to endocrinologist	88	2788.28 (2556.42 to 3020.13)	3019.83 (2770.46 to 3269.21)	2567.04 (2312.93 to 2821.15)	2745.12 (2501.06 to 2989.17)	0.093	-178.079	-0.00465	38296.56
	132	2808.92 (2576.33 to 3041.52)	3039.22 (2789.11 to 3289.34)	2583.5 (2328.46 to 2838.54)	2764.64 (2519.79 to 3009.5)	0.092	-181.146	-0.00465	38956.13
Visit to accident & emergency	182.22	2580 (2338.76 to 2821.25)	2743.24 (2486.37 to 3000.11)	2351.87 (2090.91 to 2612.83)	2561.98 (2309.3 to 2814.65)	0.216	-210.105	-0.00465	45183.87
	273.34	2607.18 (2363.74 to 2850.61)	2775.65 (2516.38 to 3034.93)	2381.07 (2117.76 to 2644.38)	2592.02 (2337.16 to 2846.89)	0.218	-210.951	-0.00465	45365.81
Cost of INDICA interventions (PTI and CBI	144.21-261.41	2793.91 (2561.86 to 3025.95)	2959.77 (2710.20 to 3209.34)	2535.48 (2281.12 to 2789.83)	2750.44 (2506.18 to 2994.71)	0.132	-214.966	-0.00465	46229.25

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arm)	216.31-392.11	2793.91 (2561.86 to 3025.95)	3090.47 (2840.9 to 3340.04)	2607.58 (2353.22 to 2861.93)	2750.44 (2506.18 to 2994.71)	0.055	-142.866	-0.00465	30723.87
Cost of INDICA interventions (PFI and CBI arm)	104.22-261.41	2767.85 (2535.8 to 2999.89)	2959.77 (2710.2 to 3209.34)	2571.53 (2317.17 to 2825.88)	2750.44 (2506.18 to 2994.71)	0.201	-178.917	-0.00465	38476.77
	156.34-392.11	2819.97 (2587.92 3052.01)	3090.47 (2840.9 to 3340.04)[b]	2571.53 (2317.17 to 2825.88)[a]	2750.44 (2506.18 to 2994.71)	**0.036**	-248.442	-0.00465	53428.39

*Arm dominated
Statistically significant differences between arms: [a] PTI and CBI; [b], CBI and UC.

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Table A5. Adjusted mean (95%CI) of healthcare costs per arm (€) in the subgroup with baseline HbA1c >7%. Multilevel model

Resource	PTI arm	PFI arm	CBI arm	UC arm	p-value
Hospital stays	586.27 (332.43 to 840.11)	619.88 (376.98 to 862.78)	465.11 (256.62 to 673.61)[b]	911.46 (604.52 to 1218.40)	0.104
Laboratory tests	46.64 (40.21 to 53.08)[e]	58.26 (52.78 to 63.75)	53.95 (49.02 to 58.89)	54.29 (48.33 to 60.25)	0.142
Retinography	124.54 (107.46 to 141.62)	128.22 (113.34 to 143.09)	125.20 (109.30 to 141.09)	118.99 (103.39 to 134.59)	0.987
Primary care visits	297.26 (269.30 to 325.22)[d]	385.42 (350.11 to 420.73)	506.72 (456.81 to 556.63)[b]	287.97 (256.28 to 319.66)	**0.003**
Specialist visits	40.90 (30.32 to 51.48)	57.91 (43.27 to 72.54)	54.19 (40.99 to 67.39)	58.58 (44.71 to 72.46)	0.371
Accident & emergency visits	269.82 (191.10 to 348.53)	275.62 (203.01 to 348.24)	348.99 (283.14 to 414.84)	278.52 (209.94 to 347.10)	0.738
Medication	1571.772 (1400.85 to 1742.69)	1655.37 (1457.79 to 1852.94)	1635.11 (1469.55 to 1800.67)	1770.71 (1591.67 to 1948.75)	0.811
Healthcare cost (without INDICA interventions related costs)	2937.20 (2583.14 to 3291.27)[a]	3180.68 (2851.32 to 3510.04)	3189.32 (2880.50 to 3498.13)	3492.08 (3092.06 to 3892.10)	0.264
INDICA interventions related costs	180.26	130.28	326.76	0	
Total cost	3117.46 (2763.40 to 3471.53)	3310.96 (2981.6 to 3640.32)	3516.44 (3207.58 to 3825)	3492.08 (3092.06 to 3892.1)	0.399

Multilevel model, adjusted by age, sex and baseline utility.

Statistically significant differences between arms: a, UC and PTI; b, UC and CBI; d, CBI and PTI; e, PFI and PTI.

CBI, Combined intervention for patients and professionals; PFI, Intervention only for health care professionals at primary care; PTI, Intervention only for patients and family members; UC, usual care (control group).

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Appendix 2. Description of mechanism for imputation of missed data.

Multiple imputation was performed by means of *mi impute chained* using the software Stata 15.0. Imputations were performed in a differentiated way for each of the four treatment groups. The following variables were considered regular and used as predictors to perform imputations: age of onset of the study, sex, baseline smoker status and baseline diabetes treatment. A total of 79 variables were imputed. Each variable was imputed in chronological order: baseline first and afterwards 3, 6, 12, 18 and 24 months. As a general rule, the latest available information of the variable to impute was used. When information from other variables was used the information from the same time moment was used. The imputation was not performed using secondary variables as random effects without fixed effects being used. A total of 90 imputations was performed for every missed data. For some imputations, predictor variables were omitted due to convergence problems.

The following table shows the order of imputation of the variables, the variables used in the imputation, the prediction model and the number of lost data for this variable.

	Imputed variable	**Variables used in the imputation**	**Imputation Model**	**N missed**
1	Mobility EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Duration of Diabetes	mlogit	21
2	Mobility EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L baseline	mlogit	573
3	Mobility EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 6 months	mlogit	670
4	Mobility EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 12 months	mlogit	745
5	Mobility EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 18 months	mlogit	671
6	Self-care EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L baseline	mlogit	27
7	Self-care EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 6 months	mlogit	577
8	Self-care EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 18 months	mlogit	743
9	Usual activities EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L baseline	mlogit	25
10	Usual activities EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months	mlogit	578
11	Usual activities EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 12 months	mlogit	671
12	Usual activities EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 18 months	mlogit	750
13	Usual activities EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline	mlogit	677
14	Pain/Discomfort EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L baseline	mlogit	22
15	Pain/Discomfort EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L baseline	mlogit	575

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
16	Pain/Discomfort EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 6 months	mlogit	670
17	Pain/Discomfort EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 12 months	mlogit	743
18	Pain/Discomfort EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 18 months	mlogit	672
19	Anxiety/Depression EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L Baseline, Usual activities EQ-5D-5L Baseline, Pain/Discomfort EQ-5D-5L baseline	mlogit	32
20	Anxiety/Depression EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L baseline	mlogit	575
21	Anxiety/Depression EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 6 months	mlogit	670
22	Anxiety/Depression EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 18 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 12 months	mlogit	745
23	Anxiety/Depression EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 18 months	mlogit	671
24	VAS EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	47
25	VAS EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months, Self-care EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, VAS EQ-5D-5L baseline	poisson	584
26	VAS EQ-5D-5L, 12 months	Age, Smoking status baseline, Mobility EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 6 months	poisson	686
27	VAS EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Mobility EQ-5D-5L 18 months, Self-care EQ-5D-5L 18 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 18 months, VAS EQ-5D-5L 12 months	poisson	746
28	VAS EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Mobility EQ-5D-5L 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 18 months	poisson	679
29	Lab tests by general practitioner, baseline	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L baseline, VAS EQ-5D-5L baseline	poisson	70
30	Lab tests by general practitioner, 3 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L 6 months, VAS		490

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
		EQ-5D-5L 6 months, Lab tests by general practitioner baseline		
31	Lab tests by general practitioner, 6 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Lab tests by general practitioner 3 months	poisson	593
32	Lab tests by general practitioner, 12 months	Age, Comorbidity 12 months, Pain/Discomfort EQ-5D-5L 12 months, Lab tests by general practitioner 6 months	poisson	670
33	Lab tests by general practitioner, 18 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Pain/Discomfort EQ-5D-5L 18 months, VAS EQ-5D-5L 18 months, Lab tests by general practitioner 12 months	poisson	746
34	Lab tests by general practitioner, 24 months	Age, Sex, Comorbidity 24 months, Lab tests by general practitioner 18 months	poisson	676
35	Lab tests by specialist, baseline	Age, Diabetes treatment baseline, Comorbidity baseline	poisson	83
36	Lab tests by specialist, 3 months	Age, Sex, Comorbidity baseline, Lab tests by specialist baseline		539
37	Lab tests by specialist, 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Lab tests by specialist 3 months	poisson	597
38	Lab tests by specialist, 12 months	Sex, Smoking status baseline, Comorbidity 12 months, Lab tests by specialist 6 months	poisson	676
39	Lab tests by specialist, 18 months	Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Lab tests by specialist 12 months	poisson	748
40	Lab tests by specialist, 24 months	Age, Sex, Diabetes treatment baseline, Comorbidity 24 months, Lab tests by specialist 18 months	poisson	677
41	Retinography, baseline	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline	poisson	78
42	Retinography, 3 months	Sex, Smoking status baseline, Comorbidity baseline, Retinography baseline	poisson	497
43	Retinography, 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Retinography 3 months	poisson	593
44	Retinography, 12 months	Age, Smoking status baseline, Comorbidity 12 months	poisson	669
45	Retinography, 18 months	Age, Smoking status baseline, Comorbidity 12 months	poisson	745
46	Retinography, 24 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 24 months, Retinography 18 months	poisson	676
47	Visits to general practitioner, baseline	Age, Sex, Diabetes treatment baseline, Comorbidity baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	147

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
48	Visits to general practitioner, 3 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L Baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, Visits to general practitioner baseline	poisson	505
49	Visits to general practitioner, 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Visits to general practitioner 3 months	poisson	615
50	Visits to general practitioner, 12 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, Visits to general practitioner 6 months	poisson	667
51	Visits to general practitioner, 18 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, Visits to general practitioner 12 months	poisson	746
52	Visits to general practitioner, 24 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 24 months, Mobility EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visits to general practitioner 18 months	poisson	672
53	Visits to nurse at primary care, baseline	Age, Sex, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	202
54	Visits to nurse at primary care, 3 months	Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, VAS EQ-5D-5L baseline, Visits to nurse at primary care baseline	poisson	511
55	Visits to nurse at primary care, 6 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Visits to nurse at primary care 3 months	poisson	626
56	Visits to nurse at primary care, 12 months	Age, Sex, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visits to nurse at primary care 6 months	poisson	668
57	Visits to nurse at primary care, 18 months	Sex, Comorbidity 12 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 18 months, Visits to nurse at primary care 12 months	poisson	747
58	Visits to nurse at primary care, 24 months	Age, Sex, Comorbidity 24 months, Mobility EQ-5D-5L 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visits to nurse at primary care 18 months	poisson	670

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
59	Visits to endocrinologist, baseline	Age, Sex, Smoking status baseline, Comorbidity baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, VAS EQ-5D-5L 12 months	poisson	227
60	Visits to endocrinologist, 3 months	Age, Sex, Comorbidity baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, Visits to endocrinologist baseline	poisson	524
61	Visits to endocrinologist, 6 months	Age, Sex, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Visits to endocrinologist 3 months	poisson	630
62	Visits to endocrinologist, 12 months	Age, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Visits to endocrinologist 6 months	poisson	668
63	Visits to endocrinologist, 18 months	Sex, Comorbidity 12 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, VAS EQ-5D-5L 18 months, Visits to endocrinologist 12 months	poisson	744
64	Visits to endocrinologist, 24 months	Age, Sex, Smoking status baseline, Comorbidity 12 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visits to endocrinologist 18 months	poisson	671
65	Visit to accident & emergency (outpatient centre), baseline	Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, VAS EQ-5D-5L baseline	poisson	229
66	Visit to accident & emergency (outpatient centre), 3 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, Visit to accident & emergency (outpatient centre) baseline	poisson	535
67	Visit to accident & emergency (outpatient centre), 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, Visit to accident & emergency (outpatient centre) 3 months	poisson	632
68	Visit to accident & emergency (outpatient centre), 12 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visit to accident & emergency (outpatient centre) 6 months	poisson	671
69	Visit to accident & emergency (outpatient centre), 18 months	Sex, Comorbidity 12 months, Mobility EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 18 months, Visit to accident & emergency (outpatient centre) 12 months	poisson	748
70	Visit to accident & emergency (outpatient centre), 24 months	Age, Sex, Diabetes treatment baseline, Comorbidity 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visit to accident & emergency (outpatient centre) 18 months	poisson	672

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
71	Visit to accident & emergency (hospital), baseline	Comorbidity baseline, Mobility EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	243
72	Visit to accident & emergency (hospital), 3 months	Comorbidity baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, VAS EQ-5D-5L baseline	poisson	532
73	Visit to accident & emergency (hospital), 6 months	Age, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months	poisson	630
74	Visit to accident & emergency (hospital), 12 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visit to accident & emergency (hospital) 6 months	poisson	670
75	Visit to accident & emergency (hospital), 18 months	Age, Sex, Comorbidity 12 months, Mobility EQ-5D-5L 18 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, VAS EQ-5D-5L 18 months	poisson	748
76	Visit to accident & emergency (hospital), 24 months	Sex, Diabetes treatment baseline, Comorbidity 24 months, Mobility EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Visit to accident & emergency (hospital) 18 months	poisson	672
77	Hospital stays, Baseline	Age, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L baseline, VAS EQ-5D-5L baseline, Visit to accident & emergency (hospital) baseline	poisson	11
78	Hospital stays, 12 months	Age, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visit to accident & emergency (hospital) 12 months	poisson	664
79	Hospital stays, 24 months	Age, Mobility EQ-5D-5L 24 months	poisson	670
VAS, Visual Analogue Scale.				

6. Conclusiones

A continuación, se encuentran las conclusiones del estudio INDICA relacionadas con cada uno de los objetivos señalados:

1) *En relación a la medida de resultado principal*. Solo en los grupos en los que se intervienen pacientes (PTI y CBI), independientemente de su nivel de control metabólico basal, se consigue una reducción estadísticamente significativa de la HbA1c comparada con el grupo de control hasta los 6 meses, diluyéndose el efecto a partir de ese momento. En estos mismos grupos, el porcentaje de pacientes que consigue una reducción clínicamente relevante de la HbA1c (>0,4%), es significativamente mayor a la del grupo de control, manteniéndose esta diferencia hasta los 12 meses en el grupo que se interviene solo a pacientes (PTI) y a los 18 meses en la intervención combinada (CBI).
2) *En relación al resto de medidas de resultado clínicas*. Los grupos en los que los profesionales son intervenidos directamente (PFI y CBI), muestran diferencias estadísticamente significativas en la presión arterial de los pacientes, con reducciones hasta los 24 meses, respecto al grupo de control. Y además, se observan pequeños cambios estadísticamente significativos, en el IMC para PTI hasta los 6 meses y para CBI a los 18 meses. Para el resto de medidas antropométricas o de laboratorio no se encontraron diferencias relevantes. La combinación de estos efectos, unido al de mejor control metabólico podrían contribuir a disminuir el riesgo cardiovascular que podría tener efecto en un seguimiento más a largo plazo de las complicaciones micro y macro vasculares y la mortalidad.
3) *En relación a las medidas de resultado autopercibidas por los pacientes*. Durante el seguimiento se observaron cambios estadísticamente significativos en los tres grupos intervenidos, respecto al grupo de control, y en todas las dimensiones examinadas: todos los pacientes intervenidos mejoraron su nivel de empoderamiento, sus niveles de angustia respecto a la enfermedad y su calidad de vida relacionada con la salud. Los grupos en los que se intervino directamente a los pacientes (PTI y CBI) mejoraron su grado de conocimiento respecto a la enfermedad y su nivel de adherencia respecto a las recomendaciones sobre dieta mediterránea. Los grupos de pacientes en los que se intervino directamente a sus profesionales (PFI y CBI) disminuyeron su nivel de depresión y ansiedad. Y solo los pacientes del grupo CBI mejoraron sus síntomas neuropáticos.

   En relación al hábito tabáquico, este se redujo considerablemente tanto para PTI como para CBI. Por tanto, se produjeron mejoras significativas en un amplio número de dimensiones, que salvo para el abandono del hábito tabáquico tienen una relevancia clínica incierta, aunque son mejorías prometedoras ya que se reflejan en todos los dominios evaluados.
4) *En relación al grado de control de la HbA1c basal*. En los pacientes no controlados basalmente en su nivel de HbA1c, se produce una reducción más intensa y más prolongada que para el total

de la muestra, diluyéndose a partir de los 18 meses. El efecto es mayor en los grupos en los que se interviene directamente a los pacientes (PTI y CBI).

5) En relación a la evaluación de coste-efectividad, solo se encontraron pequeñas diferencias en términos de años de vida ajustados por calidad (AVAC) entre las intervenciones comparadas, tras dos años de seguimiento. En pacientes no controlados en su nivel de HbA1c basal, la intervención solo a pacientes (PTI) fue más efectiva y menos costosa que la intervención a profesionales (PFI) y la combinación de ambas intervenciones (CBI). Esto nos hace concluir que las intervenciones centradas en pacientes con peor control metabólico limitarían el impacto presupuestario de su aplicación, y que su aplicación podría extenderse, en un segundo nivel de prioridad, a miles de pacientes con DM2, con un aumento mínimo de los costes.

Las intervenciones diseñadas en el estudio INDICA muestran efectos clínicos, que aunque pequeños, alcanzan la significación estadística y son clínicamente relevantes, y un impacto considerable en todas las dimensiones de las PROM incluidas. La suma de estos efectos, considerando sus costes de extensión al conjunto de pacientes con DM2 a los profesionales que los cuidan, podría tener una alta eficiencia potencial. Las intervenciones mediadas por las TICs permiten el uso generalizado y simultáneo de miles de personas y ayudan a complementar la actividad asistencial habitual. La aplicación a un mayor contingente de personas afectadas y profesionales, permitiría una mejor ratio coste- efectividad.

Los hallazgos obtenidos reflejan la necesidad de realizar ECA con periodos de seguimiento más largos, que permitan establecer la duración apropiada de la aplicación de las intervenciones y la necesidad de establecer mecanismos de refuerzo de las mismas en el tiempo para evitar que su efecto se diluya.

7. Anexo

7.1 Publicaciones adicionales a las incluidas en la tesis, publicadas durante el periodo de doctorado

2016

1. Ramos-Goñi JM, **Ramallo Fariña Y**. eq5dds: A command to analyze the descriptive system of EQ-5D quality-of-life instrument. Stata J. 2016;16(3):691-701. doi: 10.1177/1536867X1601600309
   Factor de impacto: 1,29; Cuartil: Q2

2017

2. Rivero-Santana A, Del Pino-Sedeño T, **Ramallo-Fariña Y**, Vergara I, Serrano-Aguilar P. (2017). Usefulness of scoring risk for adverse outcomes in older patients with the Identification of Seniors at Risk scale and the Triage Risk Screening Tool: a meta-analysis. Emergencias. 2017;29(1):49-60.
   Factor de impacto: 2,917; Cuartil: Q1
3. Suárez-Llanos, JP, Benítez-Brito N, Vallejo-Torres L, Delgado-Brito I, Rosat-Rodrigo A, Hernández-Carballo C, **Ramallo-Fariña Y**, Pereyra-García-Castro F, Carlos-Romero J, Felipe-Pérez N, García-Niebla J, Calderón-Ledezma EM, González-Melián TJ, Llorente-Gómez de Segura I, Barrera-Gómez MA. Clinical and cost-effectiveness analysis of early detection of patients at nutrition risk during their hospital stay through the new screening method CIPA: a study protocol. BMC Health Serv Res. 2017;17(1):292. doi: 10.1186/s12913-017-2218-z
   Factor de impacto: 1,827; Cuartil: Q3

2018

4. Ramos-Goñi JM, Craig BM, Oppe M, **Ramallo-Fariña Y**, Pinto-Prades JL, Luo N, Rivero-Arias O. Handling Data Quality Issues to Estimate the Spanish EQ-5D-5L Value Set Using a Hybrid Interval Regression Approach. Value Health. 2018;21(5):596-604. doi: 10.1016/j.jval.2017.10.023
   Factor de impacto: 4,23; Cuartil: Q1
5. Hernandez G, Garin O, Pardo Y, Vilagut G, Pont À, Suárez M, Neira M, Rajmil L, Gorostiza I, **Ramallo-Fariña Y**, Cabases J, Alonso J, Ferrer M. Validity of the EQ-5D-5L and reference norms for the Spanish population. Qual Life Res. 2018;27(9):2337-48. doi: 10.1007/s11136-018-1877-5
   Factor de impacto: 1,392; Cuartil: Q2
6. Salinero-Fort MA, Gómez-Campelo P, San Andrés-Rebollo FJ, Cárdenas-Valladolid J, Abánades-Herranz JC, Carrillo de Santa Pau E, Chico-Moraleja RM, Beamud-Victoria D,

de Miguel-Yanes JM, Jimenez-Garcia R, López-de-Andres A, **Ramallo-Fariña Y**, De Burgos-Lunar C, MADIABETES Research Group. Prevalence of depression in patients with type 2 diabetes mellitus in Spain (the DIADEMA Study): results from the MADIABETES cohort. BMJ Open. 2018;8(9):e020768. doi: 10.1136/bmjopen-2017-020768

Factor de impacto: 2,41; Cuartil: Q2

2019

7. León Salas B, Trujillo-Martín MM, García García J, **Ramallo Fariña Y**, García Quintana A, Quirós López R, Serrano-Aguilar P. Subcutaneous implantable cardioverter-defibrillator in primary and secondary prevention of sudden cardiac death: A meta-analysis. Pacing Clin Electrophysiol. 2019;42(9):1253-68. doi: 10.1111/pace.13774

   Factor de impacto: 1,34; Cuartil: Q2

8. Trujillo-Martín MM, **Ramallo-Fariña Y**, Del Pino-Sedeño T, Rúa-Figueroa Í, Trujillo-Martín E, Vallejo-Torres L, Imaz-Iglesia I, Sánchez-de-Madariaga R, de Pascual-Medina AM, Serrano-Aguilar P, SLE-CPG-Implementation Group. Effectiveness and cost-effectiveness of a multicomponent intervention to implement a clinical practice guideline for systemic lupus erythematosus: protocol for a cluster-randomized controlled trial. BMC Health Serv Res. 2019;19(1):783. doi: 10.1186/s12913-019-4589-9

   Factor de impacto: 1,932; Cuartil: Q3

2020

9. Suárez-Llanos JP, Vallejo-Torres L, García-Bello MA, Hernández-Carballo C, Calderón-Ledezma EM, Rosat-Rodrigo A, Delgado-Brito I, Pereyra-García-Castro F, Benitez-Brito N, Felipe-Pérez N, **Ramallo-Fariña Y**, Romero-Pérez JC. Cost-effectiveness of the hospital nutrition screening tool CIPA. Arch Med Sci. 2019;16(2):273-281. doi: 10.5114/aoms.2018.81128

   Factor de impacto: 2,34; Cuartil: Q1

10. Acosta FJ, **Ramallo-Fariña Y**, Ruiz L, Gómez S, Hernández A, Quesada I, Lastra C, Calviño MJ. Prospective study of variables associated with nonadherence to psychotherapy. J Ment Health. 2020;29(5):581-89. doi: 10.1080/09638237.2019.1581346

    Factor de impacto: 1,807; Cuartil: Q3

11. Acosta FJ, Rodríguez CJ, Cejas MR, **Ramallo-Fariña Y**, Fernández- Garcimartin H. Suicide Coverage in the Digital Press Media: Adherence to World Health Organization Guidelines and Effectiveness of Different Interventions Aimed at Media Professionals. Health Commun. 2020;35(13):1623-32. doi: 10.1080/10410236.2019.1654176

    Factor de impacto: 1,846; Cuartil: Q2

12. Acosta FJ, Navarro S, Cabrera B, **Ramallo-Fariña Y**, Martínez N. Painful insight vs. usable insight in schizophrenia. Do they have different influences on suicidal behavior?. Schizophr Res. 2020;220:147-54. doi: 10.1016/j.schres.2020.03.042
    Factor de impacto: 3,76; Cuartil: Q2
13. Del Pino-Sedeño T, González de León B, Pérez Martín EF, Martín Gandolfo AM, Estupián Ramírez E, Redondo M, **Ramallo-Fariña Y**, Trujillo Martín MM. Relationship between glycemic control and chronic obstructive pulmonary disease in patients with type 2 diabetes: A nested case-control study. Prim Care Diabetes. 2020;14(6):729-35. doi:10.1016/j.pcd.2020.05.007
    Factor de impacto: 4,96; Cuartil: Q1
14. Alvarado-Martel D, Boronat M, Alberiche-Ruano MP, Algara-González MA, **Ramallo-Fariña Y**, Wägner AM. Motivational Interviewing and Self-Care in Type 1 Diabetes: A Randomized Controlled Clinical Trial Study Protocol. Front Endocrinol (Lausanne). 2020;11:574312. doi: 10.3389/fendo.2020.574312
    Factor de impacto: 3,64; Cuartil: Q2
15. Figueira Gonçalves JM, Hernández Pérez JM, Acosta Sorensen M, Wangüemert Pérez AL, Martín Ruiz de la Rosa E, Trujillo Castilla JL, Díaz Pérez D, **Ramallo-Fariña Y**. Biomarkers of acute respiratory distress syndrome in adults hospitalised for severe SARS-CoV-2 infection in Tenerife Island, Spain. BMC Res Notes. 2020;13(1):555. doi: 10.1186/s13104-020-05402-w
    Sin factor de impacto

2021

16. Serrano Aguilar P, Gutiérrez-Ibarluzea I, Díaz P, Imaz-Iglesia I, González-Enríquez J, Castro JL, Espallargues M, García-Armesto S, Arriola-Bolado P, Rivero-Santana A, Perestelo-Pérez L, González-Pacheco H, Álvarez-Pérez Y, Faraldo-Vallés MJ, Puñal-Riobóo J, **Ramallo-Fariña Y**, Sánchez-Gómez LM, Asua-Batarrita J, Reviriego-Rodrigo E, Moreno-Rodríguez A, Juárez-Rojo C, Vicente-Saiz M. Postlaunch evidence-generation studies for medical devices in Spain: the RedETS approach to integrate real-world evidence into decision making.
    Int J Technol Assess Health Care. 2021;37(1):e63. doi: 10.1017/S0266462321000295
    Factor de impacto: 1,494; Cuartil: Q3
17. Figueira Gonçalves JM, Golpe R, **Ramallo Y**, García Talavera I, Dacal D. Should Pulse Oximeter Saturations Be Included in the Risk Stratification for Chronic Obstructive Pulmonary Disease Proposed by GesEPOC? Arch Bronconeumol. 2021;57(12):774-6. doi: 10.1016/j.arbr.2021.10.004
    Factor de impacto: 4,96; Cuartil: Q1

18. Hernández Pérez JM, Figueira Gonçálves JM, **Ramallo Fariña Y**. Alpha-1 antitrypsin as a risk marker in SARS-CoV-2 infection. Arch Med Sci. 2021;17(4):1134-36. doi: 10.5114/aoms/136562
    Factor de impacto: 1,494; Cuartil: Q3
19. Clavo B, Robaina F, Urrutia G, Bisshopp S, **Ramallo Y**, Szolna A, Caramés MA, Fiuza MD, Linertová R. Ozone therapy versus surgery for lumbar disc herniation: A randomized double-blind controlled trial. Complement Ther Med. 2021;59:102724. doi: 10.1016/j.ctim.2021.102724
    Factor de impacto: 2,063; Cuartil: Q2
20. Ayala A, Forjaz MJ, **Ramallo-Fariña Y**, Martín-Fernández J, García-Pérez L, Bilbao A. Response Mapping Methods to Estimate the EQ-5D-5L from the Western Ontario McMaster Universities Osteoarthritis in Patients With Hip or Knee Osteoarthritis. Value Health. 2021;24(6):874-883. doi: 10.1016/j.jval.2021.01.003
    Factor de impacto: 4,748; Cuartil: Q1
21. Rodríguez Rodríguez-Caro CJ, Acosta Artiles FJ, Cejas Méndez MR, **Ramallo-Fariña Y**, Fernández Garcimartin H. Diferencias en la adecuación de las noticias sobre suicidio en España frente a Victoria (Australia): ¿resultan efectivas las intervenciones sobre los medios de comunicación?. Rev Esp Salud Publica. 2021;95:e202106083
    Factor de impacto: 0,746; Cuartil: Q4
22. Wangüemert Pérez AL, Figueira Gonçalves JM, Hernández Pérez JM, **Ramallo Fariña Y**, Del Castillo Rodriguez JC. Prognostic value of lung ultrasound and its link with inflammatory biomarkers in patients with SARS-CoV-2 infection. Respir Med Res. 2021;79:100809. doi: 10.1016/j.resmer.2020.100809
    Factor de impacto: 0,16; Cuartil: Q4

2022

23. Gurbani N, Acosta-Sorensen M, Díaz-Pérez D, Figueira-Goncalves JM, **Ramallo-Fariña Y**, Trujillo-Castilla JL. Clinical outcomes and lung ultrasound findings in COVID-19 follow up: Calm comes after the storm? Respir Med Res. 2022;82:100907. doi: 10.1016/j.resmer.2022.100907
    Factor de impacto: 3,15; Cuartil: Q3
24. Clavo B, Rodríguez-Abreu D, Galván S, Federico M, Martínez-Sánchez G, **Ramallo-Fariña Y**, Antonelli C, Benítez G, Rey-Baltar D, Jorge IJ, Rodríguez-Esparragón F, Serrano-Aguilar P. Long-term improvement by ozone treatment in chronic pain secondary to chemotherapy-induced peripheral neuropathy: A preliminary report. Front Physiol. 2022;13:935269. doi: 10.3389/fphys.2022.935269
    Factor de impacto: 7,75; Cuartil: Q1

25. Méndez Ojeda MM, Herrera Pérez M, Núñez JH, Aldea Perona AM, **Ramallo Fariña Y**, País Brito JL. Evolution of the indication of arthroscopic treatment for femoroacetabular impingement and of the indication of total hip arthroplasty in patients under 60 years of age. Rev Esp Artrosc Cir Articul En. 2022;29(3):174-8. doi: 10.24129/j.reacae.29377.fs2106020
Factor de impacto: 0,746; Cuartil: Q4
26. Valcárcel-Nazco C, **Ramallo-Fariña Y**, Linertová R, Ramos-Goñi JM, García-Pérez L, Serrano-Aguilar P. Health-Related Quality of Life and Perceived Burden of Informal Caregivers of Patients with Rare Diseases in Selected European Countries. Int J Environ Res Public Health. 2022;19(13):8208. doi: 10.3390/ijerph19138208
Factor de impacto: 4,61; Cuartil: Q1
27. Duarte-Díaz A, González-Pacheco H, Rivero-Santana A, **Ramallo-Fariña Y**, Perestelo-Pérez L, Álvarez-Pérez Y, Peñate W, Carrion C, Serrano-Aguilar P, On Behalf Of The Indica Team. Increased Patient Empowerment Is Associated with Improvement in Anxiety and Depression Symptoms in Type 2 Diabetes Mellitus: Findings from the INDICA Study. Int J Environ Res Public Health. 2022;19(8):4818. doi: 10.3390/ijerph19084818
Factor de impacto: 3,39; Cuartil: Q2
28. Duarte-Díaz A, González-Pacheco H, Rivero-Santana A, **Ramallo-Fariña Y**, Perestelo-Pérez L, Peñate W, Carrion C, Serrano-Aguilar P; INDICA Team. Factors associated with patient empowerment in Spanish adults with type 2 diabetes: A cross-sectional analysis. Health Expect. 2022;25(6):2762-74. doi: 10.1111/hex.13501
Factor de impacto: 3,38; Cuartil: Q2
29. Figueira-Gonçalves JM, Hernández-Pérez JM, Cabrera-López C, Wangüemert-Pérez AL, García-Talavera I, **Ramallo-Fariña Y**, Ramos-Izquierdo C, González-García LM, Guanche-Dorta S. Characteristics of patients referred to Canary Island pneumology outpatient services for chronic obstructive pulmonary disease: the EPOCan study. BMC Res Notes. 2022;15(1):36. doi: 10.1186/s13104-022-05930-7
Factor de impacto: 1,34; Cuartil: Q2
30. Méndez Ojeda MM, Herrera Pérez M, Núñez JH, Aldea Perona AM, **Ramallo Fariña Y**, País Brito JL. Evolution of the indication of arthroscopic treatment for femoroacetabular impingement and of the indication of total hip arthroplasty in patients under 60 years of age. Rev Esp Artrosc Cir Articul En. 2022;29(3):174-8. doi: 10.24129/j.reacae.29377.fs2106020
31. Clavo B, Rodríguez-Abreu D, Galván S, Federico M, Martínez-Sánchez G, **Ramallo-Fariña Y**, Antonelli C, Benítez G, Rey-Baltar D, Jorge IJ, Rodríguez-Esparragón F, Serrano-Aguilar P. Long-term improvement by ozone treatment in chronic pain secondary to chemotherapy-induced peripheral neuropathy: A preliminary report. Front Physiol. 2022; 13:935269. doi: 10.3389/fphys.2022.935269
Factor de impacto: 4.76; Cuartil: Q1

32. Gurbani N, Acosta-Sorensen M, Díaz-Pérez D, Figueira-Goncalves JM, Ramallo-Fariña Y, Trujillo-Castilla JL. Clinical outcomes and lung ultrasound findings in COVID-19 follow up: Calm comes after the storm? Respir Med Res. 2022; 82:100907. doi: 10.1016/j.resmer.2022.100907
Factor de impacto: 3,15; Cuartil: Q3
33. Harmand MGC, Concepción AT, Fuentes CD and Ramallo-Fariña Y. Relationship between Benzodiazepines and Other Sedatives and Sarcopenia in Patients with Hip Fracture. Gerontol Geriatr Res. 2022; 8(3): 1080

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34. Clavo B, Cánovas-Molina A, Ramallo-Fariña Y, Federico M, Rodríguez-Abreu D, Galván S, Ribeiro I, Marques da Silva SC, Navarro M, González-Beltrán D, Díaz-Garrido JA, Cazorla-Rivero S, Rodríguez-Esparragón F, Serrano-Aguilar P. Effects of Ozone Treatment on Health-Related Quality of Life and Toxicity Induced by Radiotherapy and Chemotherapy in Symptomatic Cancer Survivors. International Journal of Environmental Research and Public Health. 2023; 20(2):1479. doi: 10.3390/ijerph20021479
Factor de impacto: 4,61; Cuartil: Q2
35. Figueira-Gonçalves JM, Hernández-Pérez JM, Cabrera-Lopez C, Wangüemert-Pérez AL, García-Talavera I, Ramallo-Fariña Y, Golpe R, González-García LM. Relationship Between the Summation of GesEPOC High-Risk Factors and the Presence of Cardiovascular Disease. Arch Bronconeumol. 2023; 19;S0300-2896(23)00010-8. doi: 10.1016/j.arbres.2023.01.005
Factor de impacto: 6,33; Cuartil: Q1
36. Ayala A, Ramallo-Fariña Y, Bilbao-Gonzalez A, Forjaz MJ. Mapping the EQ-5D-5L from the Spanish national health survey functional disability scale through Bayesian networks. Qual Life Res. 2023; 32(6):1785-1794. doi: 10.1007/s11136-023-03351-y
Factor de impacto: 3,44; Cuartil: Q2
37. Wangüemert-Pérez AL, Figueira-Gonçalves JM, Ramallo-Fariña Y, Guanche-Dorta S, Golpe R. Valoración ecográfica de la dinámica diafragmática en pacientes con enfermedad pulmonar obstructiva crónica tras tratamiento con indacaterol/glicopirronio. Revista Clínica Española. 2023; 223(4):216-222. doi: 10.1016/j.rce.2023.01.008
Factor de impacto: 3,1; Cuartil: Q2

38. Trujillo-Martín MM, De Armas-Castellano A, González-Hernández Y, González-Pacheco H, Infante-Ventura D, Del Pino-Sedeño T, Ramallo-Fariña Y, Abt-Sack A, Rueda Domínguez A, Serrano-Aguilar P. Enfriamiento del cuero cabelludo para la prevención de la alopecia secundaria a quimioterapia: revisión sistemática y metanálisis. Rev Esp Salud Pública. 2023; 97: e202303024. PMID: 36999663

    Factor de impacto: 1,33; Cuartil: Q1

39. Duarte-Díaz A, Perestelo-Pérez L, Rivero-Santana A, Peñate W, Álvarez-Pérez Y, Ramos-García V, González-Pacheco H, Goya-Arteaga L, de Bonis-Braun M, González-Martín S, Ramallo-Fariña Y, Carrion C and Serrano-Aguilar P. The relationship between patient empowerment and related constructs, affective symptoms and quality of life in patients with type 2 diabetes: a systematic review and meta-analysis. Front Public Health. 2023; 11:1118324. 10.3389/fpubh.2023.1118324

    Factor de impacto: 6,46; Cuartil: Q1

40. Benítez-Brito N, González-Pacheco H, Pinto-Robayna B, Moreno-Redondo F, Díaz-Romero C, Ramallo-Fariña Y. Preliminary assessment of the degree of food addiction through the Spanish Yale Food Addiction Scale for Children (S-YFAS-C) in a pilot pediatric population. J Eat Disord.2023; 11:72. 10.1186/s40337-023-00798-9

    Factor de impacto: 6,46; Cuartil: Q1

Capítulos de libro

1. Libro: Notas metodológicas para la investigación en Servicios de Salud en Enfermedades Crónicas. Editores: Antonio Sarría Santamera, María Joao Forjaz y María José de Tena Ávila. Financiado por el Instituto de Salud Carlos III y cofinanciado por la Unión Europea (FEDER/FSE) ISBN: 978-84-09-20854-8
    - Capítulo 7. Metodología de la investigación en Servicios de Salud. Tipos de estudio. Itziar Vergara, Yolanda Ramallo y Amado Rivero.
    - Capítulo 8. Bioestadística. Yolanda Ramallo, Ane Antón, Amaia Bilbao y Urko Aguirre
    - Capítulo 9. Investigación y evaluación de Servicios Sanitarios. José María Quintana, Susana García, Lilisbeth Perestelo Yolanda Ramallo

7.2 Proyectos financiados en convocatorias competitivas

A. Como investigadora principal

1. **PIFUN32/17**. Evaluación del impacto de una aplicación móvil de salud para mejorar el autocontrol y los resultados de salud de los pacientes con diabetes mellitus tipo 2: estudio piloto "Novame".

Convocatoria de Financiación de Proyectos de investigación de la Fundación Canaria de Investigación y Salud (FUNCANIS).

Investigadores: Yolanda Ramallo Fariña (Investigadora principal); Pedro Serrano Aguilar, Iván Castilla Rodríguez, Sybille Kaiser Giraldot, Lidia García Pérez, Ignacio Llorente Gómez Segura, Dácil Alvarado Martel, Milagros Rico

Inicio: 01/01/2018 y Fin: 01/07/2020

Financiación: 16.909,88 €

2. **PI21/01273**. Atención centrada en la persona con enfermedad crónica en atención primaria: relación con conductas de salud, calidad de vida y uso de recursos.

   Convocatoria de Financiación: Proyectos de investigación en salud (FIS), Instituto de Salud Carlos III

   Investigadores: Yolanda Ramallo Fariña y Amado Rivero Santana (Co-Investigadores principales), Ana Toledo Chávarri, Yolanda Álvarez Pérez, Himar González Pacheco, Pilar Hilarión Madariaga, Jose Ramón Vásquez Díaz

   Inicio: 01/01/2022 y Fin: 31/12/2024

   Financiación n: 70.180 €

3. **PIFIISC21/06.** Eficacia y eficiencia de una intervención escolar para la prevención primaria de los trastornos alimentarios (PRETA).

   Convocatoria de Financiación: Proyectos de investigación de la Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC)

   Investigadores**:** Yolanda Ramallo Fariña (Investigadora principal), Candelaria Desireé Díaz Melián, María Paz López, Himar Gonzalez Pacheco, Laura Vallejo Torres, Josune Martín Corral, Carina González González, Tasmania del Pino Sedeño, Alezandra Torres Castaño, Néstor Benítez Brito, Alicia Hernández Rodríguez

   Inicio: 01/01/2021 y Fin: 31/12/2023

   Financiación: 26.586 €

B. Como investigador colaborador

4. **PIFUN12/18.** Coste-efectividad de la angioplastia carotídea y colocación de stents en la estenosis carotídea en Canarias: Una experiencia con Real-World Data (RWD)

   Investigadores: Cristina Valcarcel Nazco (IP), Manuel Maynar Moliner, Lidia García Pérez, Javier Mar Medina, Yolanda Ramallo Fariña, Enrique Bernal Delgado, Francisco Estupiñán Romero, Heliodoro Valles González, Tobias Zander, Yesid Giovanni García Vanegas.

   Convocatoria de Financiación: Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

   Inicio: 01/01/2019 y Fin: 31/12/2020

Financiación n: 13.584,42 €

5. **PIFUN23/18.** Modelado de la analgesia intraoperatoria para el diseño de estrategias de infusión automática de fármacos.

   Investigadores**:** José Antonio Reboso (IP), Ana María León Fragoso, María del Carmen Martín Lorenzo, Juan Albino Méndez Pérez, Yolanda Ramallo Fariña, Iván Castilla Rodríguez, José Francisco Gómez González, José Luis Calvo Rollé, Esteban Jove Pérez.

   Convocatoria de Financiación: Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

   Inicio: 01/01/2019 y Fin: 31/12/2020

   Financiación: 19.297,60 €

6. **PI16/00769.** Efectividad y coste-efectividad de intervenciones complejas de transferencia de conocimiento basadas en TICs a 5 años, para mejorar la salud en pacientes con DM2 (INDICA-DOS).

   Investigadores: Pedro Serrano Aguilar (IP), Yolanda Ramallo Fariña, Lidia García Pérez, Montserrat Carmona Rodríguez, Armando Carrillo Domínguez, Marcos Estupiñán Ramírez, Ana Toledo Chávarri, Esperanza Escortell Mayor.

   Convocatoria de Financiación: Proyectos de investigación en salud (FIS), Instituto de Salud Carlos III

   Inicio: 01/01/2017 y Fin: 31/06/2021

   Financiación: 50.215 €

7. **PI15/01377.** Efectividad y coste-efectividad de una estrategia multicomponente para implementar una guía de práctica clínica y mejorar los resultados de salud en personas con lupus

   Investigadores: María del Mar Trujillo Martín (IP), Iñaki Imaz Iglesia, Iñigo Rua-Figueroa Fernández de Larrinoa, Pedro Serrano Aguilar, Yolanda Ramallo Fariña, María Pilar García Sagredo, Roberto Luis Martín Fernández, Laura Vallejo Torres, Ana Mª de Pascual Medina.

   Convocatoria de Financiación: Proyectos de investigación en salud (FIS), Instituto de Salud Carlos III

   Inicio: 01/01/2016 y Fin: 31/12/2020

   Financiación: 45.980 €

8. **PIFIISC20/34.** Prevalencia de Trastornos de Alimentación en población escolar infantil y preadolescente de las Islas Canarias (estudio PRETA).

   Convocatoria de investigación de la Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

   Investigadores: Nestor Benítez Brito (IP), Yolanda Ramallo Fariña, Beatriz León Salas, Tasmania del Pino Sedeño, Mercedes Murray Hurtado, Candelaria Desirée Díaz Melián, María Paz López, Pedro Díaz Fernández, Pamela Álvarez Trenco, María José García

Mérida, Mónica Ruiz Pons, Eva María Herrera Rodríguez, Pedro Guillermo Serrano Aguilar, Carlos Díaz Romero, Lluis Serra Majem

Convocatoria de Financiación: Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

Inicio: 01/01/2021 y Fin: 31/12/2022

Financiación: 20.160 €

9. **PIFIISC20/05.** Utilización de datos sanitarios de vida real para el análisis de la adherencia a la terapia farmacológica de pacientes con trastorno depresivo

   Investigadores: Tasmania del Pino Sedeño (IP), Cristina Valcárcel Nazco, Isabel Hurtado Navarro, Francisco Ramón Estupiñán Romero, Gabino Suárez Rodríguez, Beatriz González de León, Lidia García Pérez, Yolanda Ramallo Fariña, Leticia Rodríguez-Rodríguez

   Convocatoria de Financiación: Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

   Inicio: 01/01/2021 y Fin: 31/12/2022

   Financiación: 20.160 €

10. **PMP21/00069.** ImpactT2D: una estrategia genómica para implementar medicina de precisión en la diabetes tipo 2

    Investigadores: Anna Wägner (IP), Nicolás Martel Suarez, Begoña Vega Guedes, Lidia García Pérez, Yolanda Ramallo Fariña, Cristina Valcarcel Nazco, Yeray Brito Casillas, Verónica Davila Batista, Ana María González Lleo, María del Carmen Valverde Tercedor, Alejandro Déniz Garíca, Dulce Hernández Correa

    Convocatoria de Financiación: Proyectos de investigación en Medicina Personalizada, Instituto de Salud Carlos III

    Inicio: 01/01/2022 y Fin: 31/12/2024

    Financiación: 140.855 €

11. **ST22/04.** Impacto de la pandemia por Covid-19 sobre la gestión clínica y los resultados de salud de las personas con DM2 en la AP de Canarias. Proyecto GesPeDia-INDICA. Financiado por la FIISC

    Investigadores: Himar González Pacheco (IP), Ángela Gutiérrez Pérez (Co- Investigador principal), Yolanda Ramallo Fariña, Pedro Serrano Aguilar, Sybille Kaiser Girardot, Ana María Wägner, Miguel García Hernández, Yadira González Hernández, Juan Antonio López Rodríguez

    Convocatoria de Financiación: Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

    Inicio: 01/01/2023 y Fin: 31/12/2024

    Financiación: 11.792 €

12. **PIFIISC22/25.** Evaluación del impacto clínico y económico del programa SPICA, un programa de integración y coordinación asistencial para garantizar la continuidad de cuidados tras el alta en pacientes hospitalizados complejos

    Investigadores: Cristina Valcárcel Nazco (IP), Tasmania del Pino Sedeño, Beatriz González de León, Ana Toledo Chávarri, Aránzazu Hernández Yumar, Elio Ramos Medina, Hermes Chevez Alarcón, José Ramón Vázquez Díaz, Juan Antonio López Rodríguez, Leticia Rodríguez Rodríguez, Miguel García Hernández, Pili Secada Gorrín, Vanesa Martínez Hernández, Yadira González Hernández (YGH), Yeiza Reyes Melián y Yolanda Ramallo Fariña

    Convocatoria de Financiación: Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC).

    Inicio: 01/01/2023 y Fin: 31/12/2025

    Financiación: 18.026,08 €

7.3 Redes de investigación a las que pertenece

1) Red Española de Agencias de Evaluación de Tecnología Sanitarias (RedETS) del Ministerio de Sanidad

2) Red de enfermedades crónicas, REDISSEC- ISCIII. Instituto de Salud Carlos III

3) Red de Investigación en Cronicidad, Atención Primaria y Promoción de la Salud (RICAPPS). Instituto de Salud Carlos III

4) Centro de Investigaciones Biomédicas de Canarias (CIBICAN), La Laguna, Tenerife, España