UNIVERSITAT AUTÒNOMA DE BARCELONA

Departamento de Cirugía

Facultad de Medicina

EVENTOS ISQUÉMICOS Y MANIFESTACIONES CLÍNICAS EN PACIENTES AFECTADOS DE ISQUEMIA CRÓNICA DE MIEMBROS INFERIORES. INFLUENCIA DEL HÁBITO TABÁQUICO.

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Tesis presentada por Lorenzo Ramón Álvarez Rodríguez

para acceder al grado de doctor en medicina y cirugía.

Dirigida por los doctores Manel Monreal i Bosch,

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Lorenzo Álvarez Rodríguez

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1-INTRODUCCIÓN:

1.1-CONCEPTO DE ATEROSCLEROSIS:

En la actualidad el conocimiento de la fisiopatología de la formación del ateroma es esencial para conducir una buena conducta preventiva o terapéutica ante la aparición de eventos isquémicos que pueden comprometer a diferentes territorios vasculares. Para entender este proceso hay que retroceder hasta el inicio de la aparición de la aterosclerosis e incidir en los factores que influyen en su desarrollo.
La aterosclerosis es un proceso caracterizado por la alteración patológica de la pared de las arterias que conlleva la pérdida de su elasticidad y a la formación de placas de ateroma, originando con ello una reducción progresiva de la luz del vaso en relación con el depósito de colesterol a nivel de la pared arterial (1).

1.2-DESCRIPCIÓN HISTOLÓGICA DE LA ATEROSCLEROSIS:

El primer escalón en el desarrollo de la aterosclerosis es la aparición de la estría grasa, que macroscópicamente se identifica como una mancha o raya amarilla en la íntima de las arterias y esta formadas por células espumosas, protruyendo en la luz del vaso. Estas se objetivan en la mayoría de las personas jóvenes de todos los grupos raciales y geográficos mayores de 3 años, siendo benignas y asintomáticas.
La estría grasa puede progresar al siguiente estadio denominado placa fibrosa que consiste en una elevación de la capa íntima que contiene un núcleo central amorfo y amarillento llamado ateroma. En la estría grasa los macrófagos son el principal constituyente, sin embargo las placas fibrosas están formadas fundamentalmente por células musculares lisas. Durante este proceso de aterogénesis los ésteres de colesterol que penetran en la pared arterial son fagocitados por macrófagos y se forman las llamadas células espumosas (2).
Bajo esta descripción global existe una gran heterogeneidad en las lesiones ateroscleróticas, variando tanto en su composición como en la consistencia. En base a

estas puede definirse un prototipo de lesión como "vulnerable" o de alto riesgo para presentar una complicación isquémica (3).

Este proceso sistémico presenta también características diferenciales según el territorio vascular afecto.

El territorio más estudiado ha sido el coronario, dónde se ha objetivado que las lesiones tienen un gran núcleo o core lipídico extracelular, una alta densidad de macrófagos saturados de lípidos y convertidos en células espumosas y un reducido número de células musculares lisas, todo ello recubierto por una fina capa fibrosa. El core es avascular, con muy pocas células, a diferencia de la gran población de macrófagos y células espumosas presentes en el margen. Existe gran cantidad de ésteres de colesterol y ausencia de un soporte de colágeno (2,4).

Las lesiones carotídeas "vulnerables" son más estenóticas que las lesiones coronarias, más heterogéneas, más fibróticas y presentan una acumulación lipídica bastante difusa (5).

En la aorta torácica estas placas consideradas de alto riesgo se caracterizan por un gran contenido de macrófagos en relación al número de células lisas que se encuentran en la región de la cápsula fibrosa.

En las extremidades inferiores las placas son muy estenóticas y fibróticas como a nivel carotídeo (7).

Esta diferente composición y la predilección por unos determinados territorios es la que origina una predisposición diferente hacia la complicación isquémica.

1.3-EVOLUCIÓN DE LA ATEROSCLEROSIS:

El desarrollo de la placa aterosclerótica suele ser lento, evolucionando normalmente a lo largo de los años, sin embargo no presenta una evolución lineal. El crecimiento y progresión de la placa dentro de la pared de los vasos no es uniforme ni difuso, sino excéntrico y focal. Inicialmente su afectación se limita a la capa íntima del vaso, apareciendo la estría grasa, posteriormente puede extenderse al resto de capas.

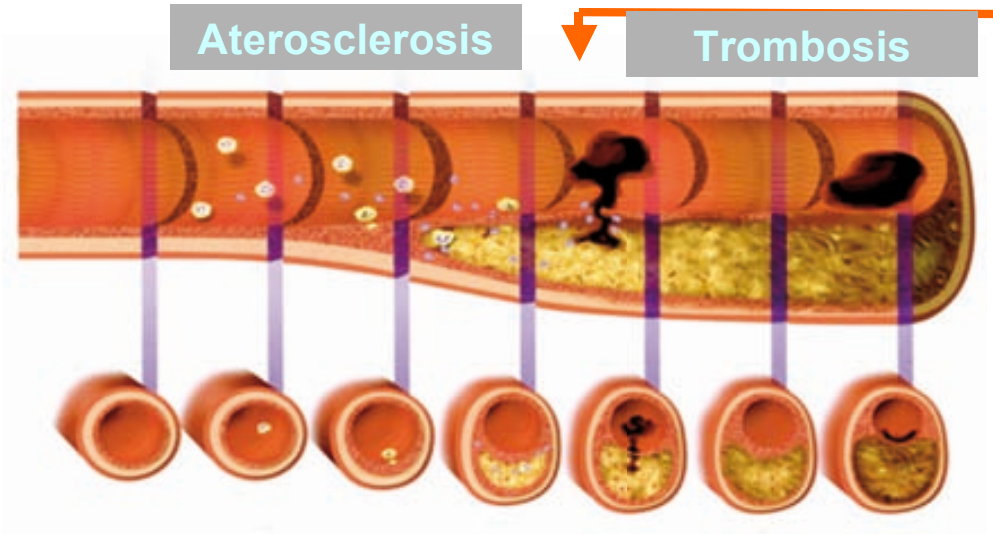
La migración de las células musculares lisas hacia el espacio subendotelial y su posterior división preceden a la síntesis de diversos productos de la matriz extacelular.

Aquí tienen un importante papel los macrófagos y con ellos aparece el concepto de la inflamación en la aterosclerosis. Esta progresión de la lesión origina la llamada placa fibroadiposa. El crecimiento progresivo de la placa tiene lugar en el interior de la pared arterial y se orienta hacia la zona adventicial, sin producir inicialmente compromiso de la luz del vaso, ayudado por un remodelado positivo de la pared vascular, que en los primeras etapas compensa con un agrandamiento progresivo del vaso mediante una atrofia de la capa media (8).

La evolución de estas lesiones con crecimiento progresivo de la placa puede ir originando una lenta obstrucción de la luz hasta llegar a un nivel crítico en el que la reducción del flujo sanguíneo tendría una repercusión clínica importante. Este sería un proceso lento y normalmente bien compensado, sin embargo y tomando como ejemplo la afectación coronaria, los síntomas clínicos de la aterosclerosis, sobre todo los relacionados con síndromes agudos, presentan una menor relación con el crecimiento progresivo de la placa que con su degeneración y rotura (9). Se consigue así una trombosis secundaria que originaría un episodio isquémico con una placa poco estenótica. Esto queda recogido en un metaanálisis en el que se ponía de manifiesto que en el 70% de los éxitus de causa coronaria las lesiones eran leves y estenosaban menos del 50% de la luz (3,8).

Mediante este proceso fisiopatológico se puede producir la obstrucción parcial o total de la luz del vaso y con ello presentar una manifestación aguda (como un infarto de miocardio) o pasar clínicamente desapercibida contribuyendo a la evolución de la enfermedad con un crecimiento progresivo de la placa (9). También hay que destacar que este proceso es diferente según el mecanismo de lesión, la trombosis que se origina por ruptura de placa se suele observar en las arterias que presentan bajo grado de obstrucción y las trombosis producidas por erosión endotelial en los sitios con estenosis de mayor grado (más común en hombres jóvenes con factores de riesgo y en mujeres) (2).

Con el estudio de este mecanismo de oclusión arterial y considerando a la trombosis como una complicación del ateroma surge el concepto de aterotrombosis y la terapéutica se dirige hacía el control de los mecanismo de coagulación extrínseco e intrinseco, así como a la inhibición de la activación plaquetaria (10).



AI
IM
SCA

Ictus isquémico/AIT

Isquemia crónica miembros inferiores

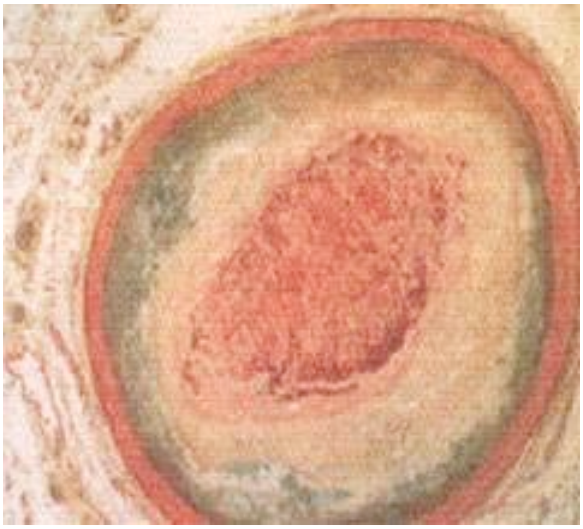
SCA: Sdr.Coronario agudo

AI: Angina inestable

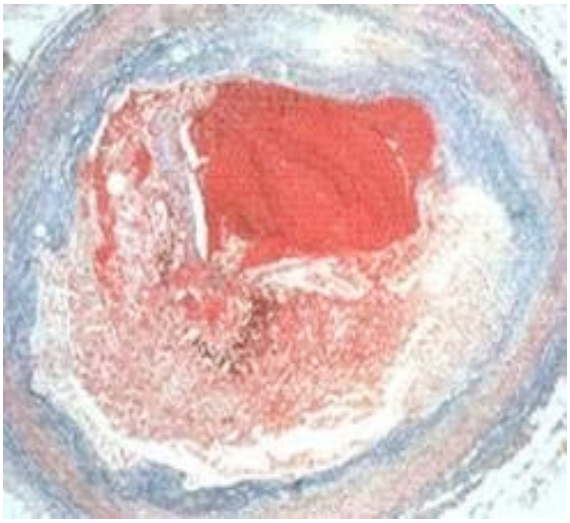
IM: Infarto miocardio

Adabtado de Libby P. Circulation 2001: 104:365-372

Drouet L.Cerebrovasc Dis 2002; 13 (Suple 1) 1-6



***Erosión de una placa**



 # Rotura de una placa

* Falk E et al. *Circulation* 1995; 92: 657–671.
# Arbustini E et al. *Heart* 1999; 82: 269–272.

1.4-ATEROTROMBOSIS:

El término aterotrombosis es un término que engloba la complejidad del proceso y describe la trombosis superpuesta a la lesión ateromatosa. Se caracteriza por la rotura súbita (impredecible) o por la erosión de una placa aterosclerótica que desencadena la activación plaquetaria y la formación de trombos (11).

El mecanismo de formación del trombo sobre una placa aterosclerótica es complejo y su base fisiopatológica puede estar relacionada con la rotura del ateroma, la erosión superficial de la íntima o con los diferentes fenómenos hemorreológicos que se producen distalmente al ateroma con relación a la corriente sanguínea.

El conocimiento de la fisiopatología, tanto de la formación del ateroma como de las causas de su inestabilidad y rotura que llevan a la trombosis, se ha ampliado y ha permitido el desarrollo de nuevas terapéuticas con el propósito de disminuir los acontecimientos trombóticos que siguen a un episodio isquémico (en concreto episodios coronarios que es en los que se han desarrollado los estudios) (1,12).

1.5-EL PAPEL DE LA INFLAMACIÓN EN LA ATEROTROMBOSIS:

El estudio de la aterotrombosis ha permitido objetivar procesos biológicos complejos, como la inflamación, la apoptosis o el papel del factor tisular, que contribuyen a determinar el inicio de los episodios isquémicos agudos.

El concepto de participación de la inflamación en los cuadros miocárdicos isquémicos agudos tiene más de 60 años (13).

El proceso inflamatorio juega un importante papel en la patogénesis de la aterosclerosis, dónde los diferentes mecanismos inmunes interaccionan con los diferentes factores de riesgo metabólicos para iniciar, propagar y activar las lesiones en el árbol arterial.

Actualmente se tiene una visión más global y compleja de la aterosclerosis considerándola algo más que un proceso de acumulación pasiva de lípidos en las paredes de los vasos y entendiendo que es un proceso activo en el que la inflamación juega un papel clave. La teoría de Ross considera a la aterosclerosis como una respuesta inflamatoria a una lesión del endotelio vascular (1).

El endotelio es un epitelio plano simple que recubre la superficie interna del árbol vascular y tiene entre otras funciones endocrinas, paracrinas y autocrinas. Modula la permeabilidad de las lipoproteínas plasmáticas, la adhesión leucocitaria, la liberación de diversos factores de crecimiento, protrombóticos, antitrombóticos y sustancias vasoactivas. El deterioro de sus funciones presenta un importante papel en el desarrollo de la aterosclerosis y puede considerarse como el precursor del proceso aterosclerótico **(14)**.

La disfunción endotelial consiste en la reducción de la biodisponibilidad de vasodilatadores como el óxido nítrico producido por la célula endotelial y en el aumento de los vasoconstrictores como la endotelina, también de origen endotelial. Los estímulos de diferente naturaleza como mecánicos, químicos, biológicos, tóxicos, immunológicos...originarían la lesión endotelial física o tan sólo funcional. Este suceso provocaría la activación de diversos mecanismos para compensar la agresión.

La disfunción endotelial permitiría el paso de monocitos, lípidos plasmáticos y proteinas dentro de la pared del vaso. El endotelio disfuncionante secretaría citoquinas y quimiocinas que potenciarían el proceso de inflamación, activaría las moléculas de adhesión (VCAM-1, ICAM-1...), y favorecería la migración e internalización de monocitos, así como la proliferación de las células de músculo liso. Todo este proceso añadido a la acumulación de lípidos y al incremento de la síntesis de tejido conectivo acabaría desencadenando la formación de la placa ateromatosa.

El mantenimiento de este proceso inflamatorio incrementaría más la migración de macrófagos y linfocitos al centro de la lesión. Su activación posterior implicaría la liberación de diversas encimas hidrolíticas, citocinas, quimocinas y factores de crecimiento que potenciarían el proceso inflamatorio y podrían debilitar la matriz extracelular y la capa fibrosa mediante fagocitosis directa o por la secreción de encimas proteolíticos como TNF-alfa, metaloproteinasas (colagenasas, gelatinasas...) y mediante la producción de radicales libres oxidantes y productos de la oxidación lipídica, colaborando en la inestabilidad de la placa.

Tras la ruptura de la placa aterosclerótica se exponen al torrente circulatorio los componentes del núcleo lipídico, siendo en su mayoría lípidos, microcalcificaciones y restos celulares, así como macrófagos activados y células musculares lisas. Estos son productos trombogénicos que junto con el factor tisular expuesto condicionan a nivel

local la formación de trombina, la activación plaquetar y finalmente la formación de fibrina.

El factor tisular es una glicoproteina transmembrana que juega un importante papel en la formación del trombo a través de la activación de la vía extrínseca de la coagulación. Se expresa de forma natural en la superficie de las células subendoteliales tras el estímulo de los macrófagos. En los pacientes que han presentado un síndrome coronario agudo se ha observado unos niveles más elevados del factor tisular. Este a nivel de la placa se encuentra en gran concentración en la región acelular , en el "hombro" de la placa y en el core lipídico.

La activación de la vía extrínseca lleva a la producción de trombina y con ella la activación plaquetar. La trombina además cataliza la polimerización de la fibrina, siendo esta última la que da consistencia al trombo plaquetario en el torrente sanguíneo y le confiere protección ante las sustancias fibrinolíticas **(14,15)**.

FACTORES QUE ORIGINAN DISFUNCIÓN ENDOTELIAL **(14,15)**

FACTORES AMBIENTALES: Hipoxia, Flujo turbulento	**FACTORES INFECCIOSOS:** Infección crónica por virus herpes simple, Citomegalovirus, virus respiratorio sincitial y Chlamydia pneumoniae
FACTORES DE RIESGO CARDIOVASCULAR: HTA, Tabaco, Hipercolesterolemia, DM, edad...	**FACTORES SEROLÓGICOS:** Hiperhomocisteinemia, elevación de lipoproteína a, Proteina C reactiva, triglicéridos y LDL-colesterol.

1.6-LA PLACA VULNERABLE:

El riesgo de ruptura de una placa depende básicamente de su composición y de los factores extrínsecos, que son representados básicamente por las fuerzas que interaccionan con la placa (flexión circunferencial, estrés compresivo, estrés hemodinámico...). La composición determina el riesgo intrínseco y se caracteriza básicamente por el tamaño y la consistencia del núcleo ateromatoso, a mayor núcleo mayor vulnerabilidad, por la estructura y firmeza de la capa fibrosa, menos resistencia a menor contenido de células musculares, menor contenido de colágeno y mayor presencia de lípido extracelular y finalmente el papel que juegan en la composición los monocitos y macrófagos activados **(3,15)**.

1.7-DISTRIBUCIÓN DE LA ATEROTROMBOSIS:

La progresión de las lesiones ateroscleróticas no ocurre por igual en todo el árbol vascular, existen determinados territorios por los que hay predilección, como por ejemplo en las bifurcaciones arteriales, probablemente por existir una cierta tensión hemodinámica. Existe correlación entre la disfunción endotelial y las áreas de baja presión de rozamiento y flujo oscilatorio con reversión del flujo, proceso más marcado en las bifurcaciones arteriales.

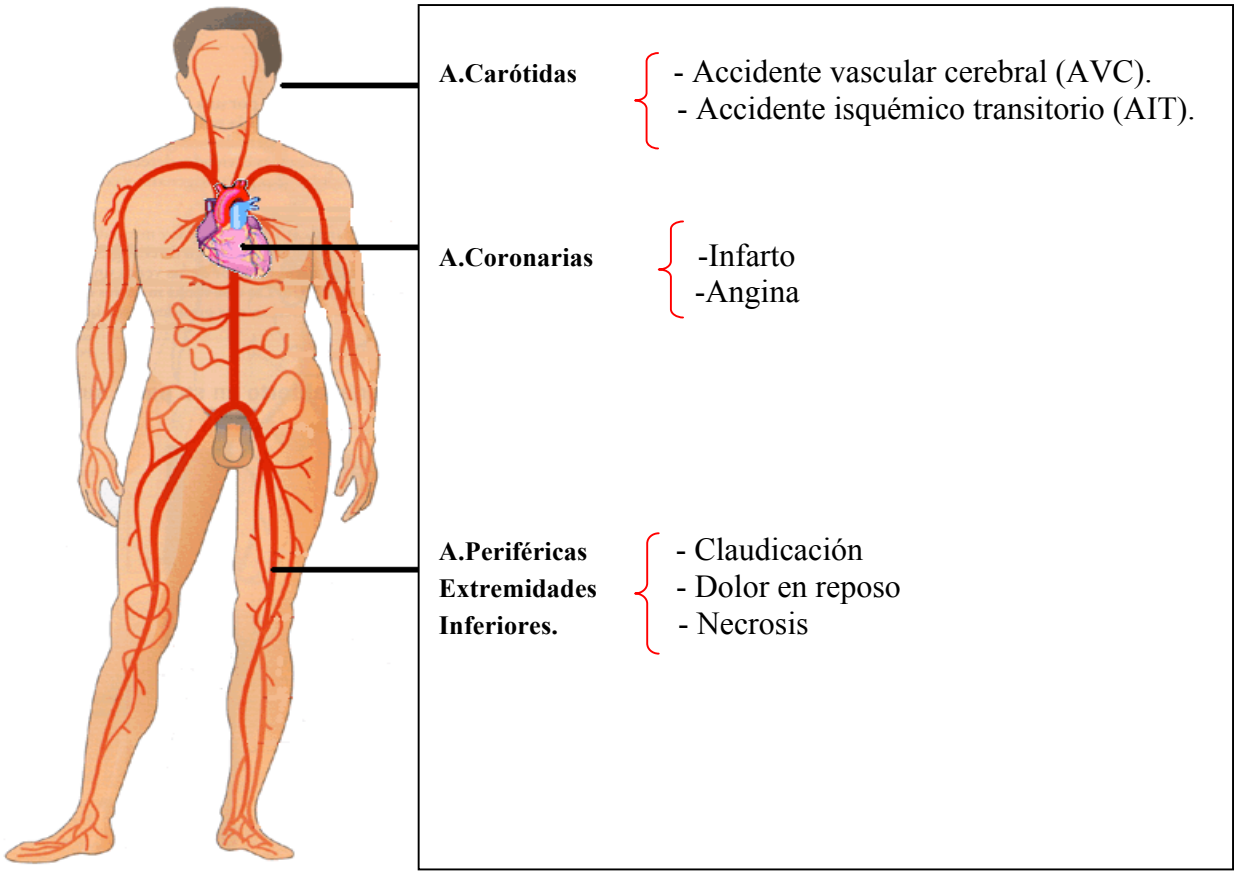
Esta tensión originaría una lesión intimal de tipo mecánico o disfuncional y en respuesta existiría una proliferación intimal, un incremento de la permeabilidad para el paso de lipoproteínas al subendotelio y en consecuencia el desarrollo de lesiones ateroscleróticas **(15)**.

Esta afectación preferencial tiene lugar en el territorio de las arterias coronarias, en el territorio aórtico infrarenal, en el territorio carotídeo y en el territorio que irriga las extremidades inferiores.

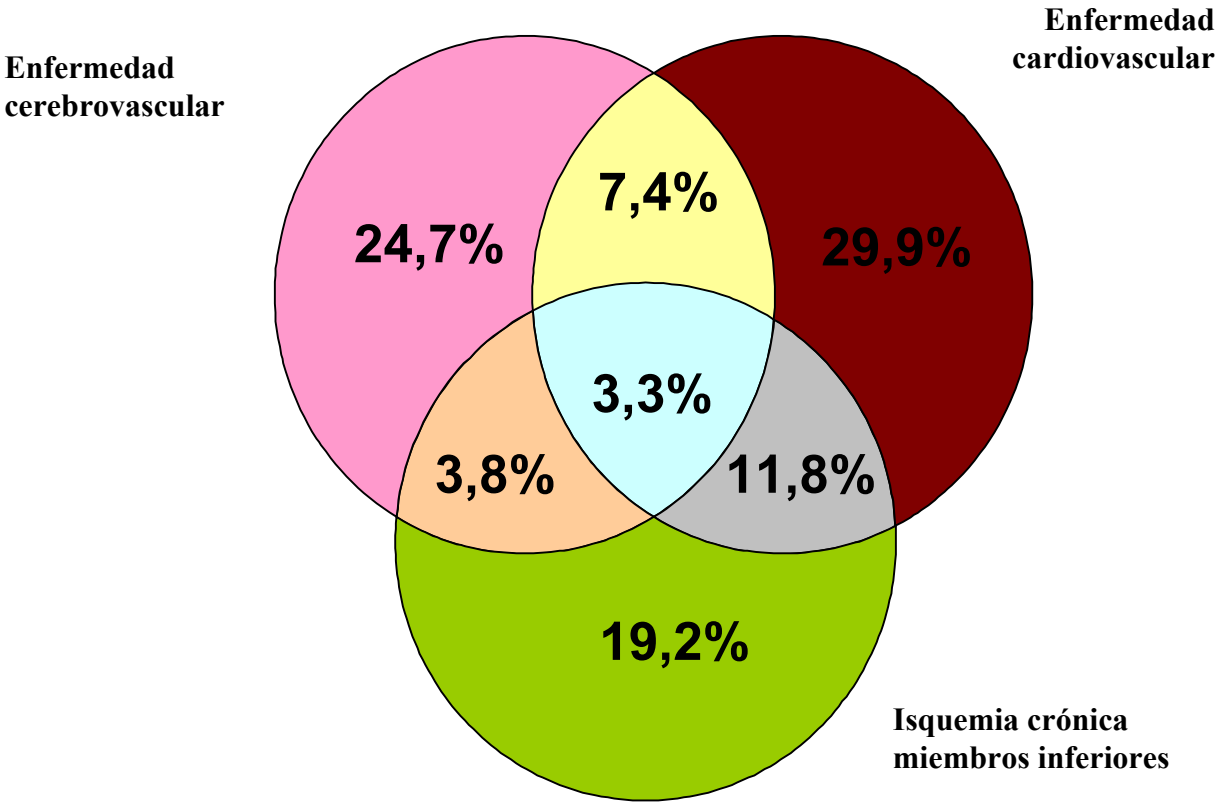
La aterotrombosis en las arterias coronarias puede originar síndromes coronarios agudos (angina inestable e infarto de miocardio con onda Q o sin onda Q), el no tratarla puede también ocasionar enfermedades de tipo crónico como la insuficiencia cardíaca congestiva.

La afectación aterotrombótica de las arterias carotídeas y cerebrales puede originar a su vez un ataque isquémico transitorio o un ictus isquémico, con déficit neurológico y deterioro cognitivo asociado.

La afectación de las arterias periféricas contribuye a la evolución de la enfermedad arterial periférica de las piernas con claudicación intermitente o isquemia crítica de los miembros según la gravedad (16).



Afectación concomitante de diversos territorios por aterotrombosis.



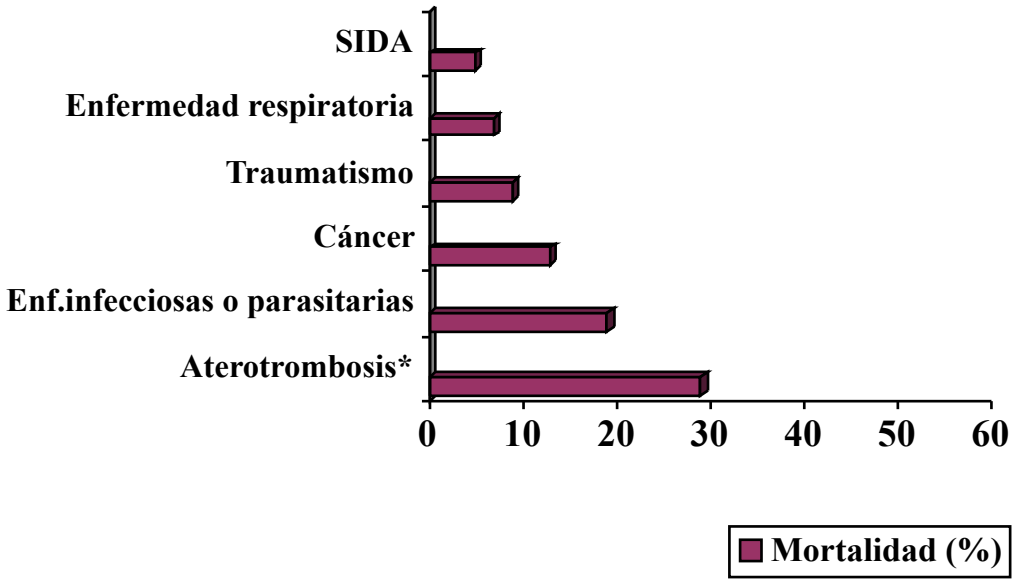
***Datos del estudio CAPRIE (*Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events,* Clopidrogrel frente a aspirina en pacientes con riesgo de padecer episodios isquémicos) (n=19 185 pacientes)**

Coccheri S. *Eur Heart J* 1998; 19(Suppl): 227.

1.8-IMPORTANCIA DE LA ATEROTROMBOSIS:

La aterotrombosis es la principal causa de muerte y discapacidad en los países desarrollados según los datos recogidos del proyecto The World Health Report 2001 y los resultados presentados por la OMS del Informe sobre la Salud en el Mundo 2004. En España según los datos del INE (Instituto Nacional de estadística) presentados durante el 2010 y correspondientes al año 2008 las enfermedades cardiovasculares representan la primera causa de muerte con un 31.8% de los fallecimientos, seguida por la enfermedad neoplásica con un 26.9% y las enfermedades del sistema respiratorio con un 11.4%. La previsión para el 2020 es la misma, a pesar de contar con avances médicos y quirúrgicos

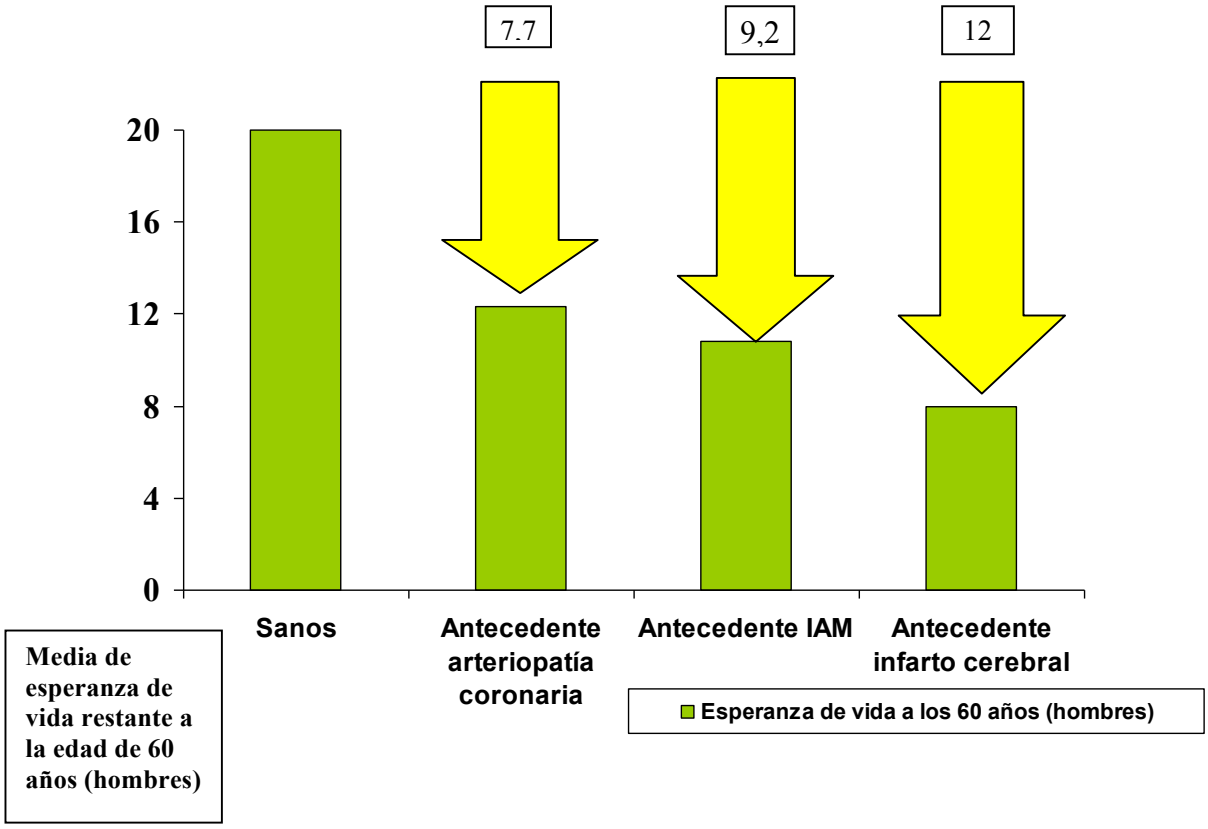
***Informe sobre la Salud en el Mundo 2004. OMS Ginebra, 2004.**



Porcentaje total defunciones en 2002

***Mortalidad por enfermedad isquémica coronaria, enfermedad cerebrovascular, cardiopatía hipertensiva, cardiopatía inflamatoria y cardiopatía reumática. (Estados miembros de la OMS-Africano, americano, mediterráneo oriental, europeo, sudeste asiático y pacífico oeste)**

La aterotrombosis genera además una reducción de la esperanza de vida como mostró el estudio Framingham Heart. En hombres con edad superior a 60 años y aterotrombosis llegaba a representar una reducción de 8-12 años **(18).**



***IAM= Infarto agudo de miocardio. Anàlisis de datos del Framinghan Heart Study.**

Otro elemento clave de las enfermedades cardiovasculares es que suponen una carga económica significativa. Se calcula que en 2005 el coste de las enfermedades cardiovasculares y el ictus en Estados Unidos rondó los 400.000 millones de dólares. Los costes representan los costes directos y los indirectos. En los directos se incluyen los costes de los médicos y demás personal sanitario, los servicios de asistencia sanitaria doméstica, medicamentos, otros cuidados domiciliarios y otros bienes de consumo médico. Los costes indirectos incluyen la pérdida de productividad provocada por la morbimortalidad. **(19).**

1.9-FACTORES DE RIESGO:

Desde una perspectiva epidemiológica un *factor de riesgo* es una condición o característica de un individuo o población que se asocia con un mayor riesgo de desarrollar una enfermedad en un futuro. Este puede ser un rasgo hereditario, una enfermedad subyacente (como la diabetes), una variable paraclínica (como el nivel sérico elevado de PCR) o un comportamiento o hábito. Para considerar causal al marcador, este debe preceder el comienzo de la enfermedad y tener plausibilidad biológica.

En la enfermedad aterotrombótica los factores de riesgo cardiovascular convencionales se pueden dividir de forma grosera en dos grupos: No modificables (edad, sexo y la historia familiar) y modificables (hipertensión (HTA), hipercolesterolemia, diabetes mellitus, hábito tabáquico) y obesidad. Estos son predictores de morbilidad y mortalidad de causa renal o cardiovascular y su control (si es modificable) origina una reducción de los eventos clínicos **(20, 21, 22,23).**

Recientemente han comenzado a considerarse nuevos factores de riesgo como la proteina C reactiva (PCR), microalbuminuria e insuficiencia renal (calculada mediante la estimación por fórmulas del filtrado glomerular). Estos dos últimos son marcadores de lesión de órganos diana y en los últimos años han llegado a considerarse factores de riesgo cardiovascular independientes **(24).**

La edad, el tabaquismo, la diabetes y la hipertensión fueron considerados como factores de riesgo en el desarrollo de claudicación intermitente en los estudios *Quebec Vascular Study y Framingham.* **(25,18).**

Este último mostró un incremento del riesgo de 2’5 a 4 veces en el desarrollo de arteriopatía periférica en hipertensos, fueran hombres o mujeres **(26)**.

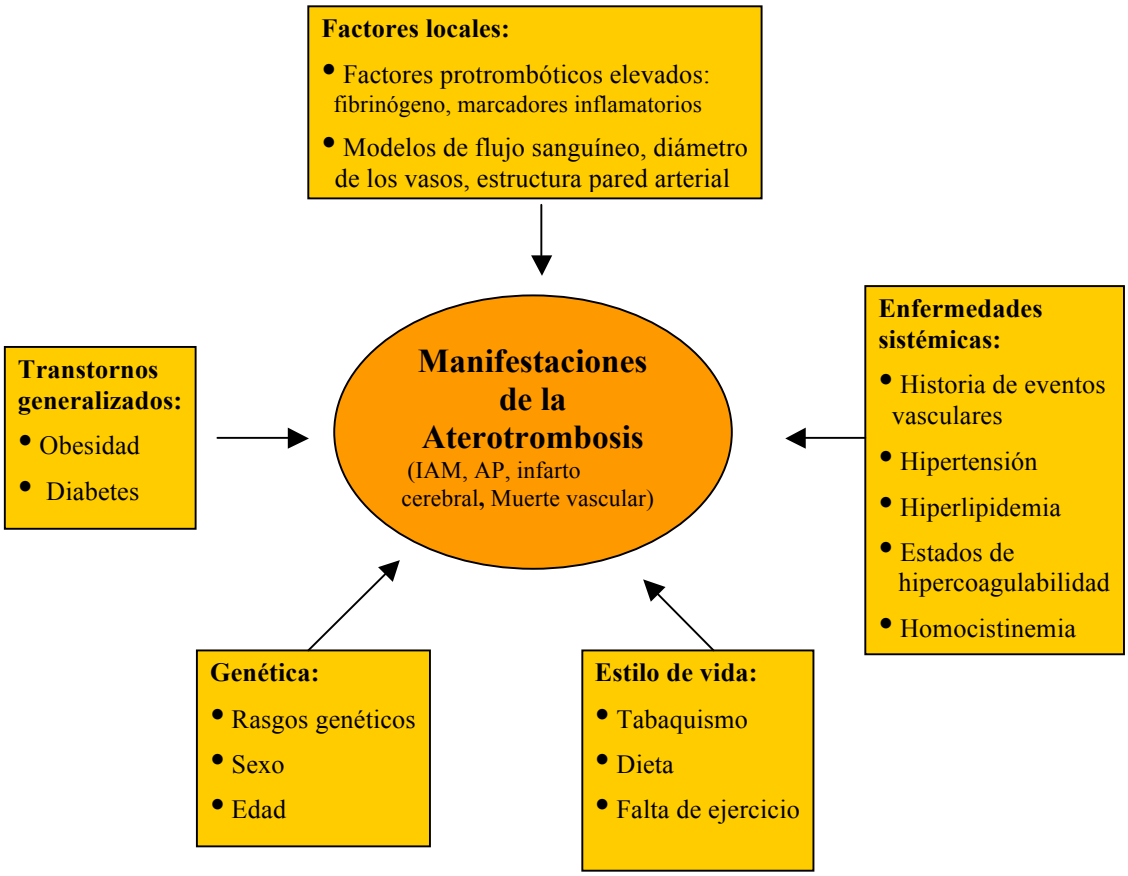
La hipertensión así como el resto de factores de riesgo cardiovascular clásicos como el tabaquismo, la diabetes o la hipercolesterolemia presentan una fuerte asociación con la arteriopatía periférica, presentando un 95% de las personas con arteriopatía por lo menos uno de estos factores de riesgo **(27)**, siendo la hipertensión una comorbilidad frecuentemente asociada **(28)**. Sin embargo en el estudio de Dormandy y Murray, que incluia pacientes con control terapéutico de la tensión, corrigiendo la presencia de

otros factores de riesgo mediante análisis multivariante, concluyó que la hipertensión no influía en la progresión local de la enfermedad arterial periférica **(29).**

Es por esto que se sabe que existe relación entre hipertensión y arteriopatía periférica, pero no se acaba de precisar de que tipo en los diferentes estudios de la literatura. Lo que si queda claro es que aunque todos los factores de riesgo favorecen el desarrollo de la enfermedad aterotrombótica, el valor predictivo de cada uno varía según el territorio vascular que se considera: el colesterol total tiene más valor predictivo para la enfermedad coronaria, la hipertensión arterial para el cerebro y el tabaco para la enfermedad vascular periférica.

Personas con riesgo de aterotrombosis

(Drouet L. Atherothrombosis as a systemic disease. Cerebrovasc Dis 2002;13 (Supl 1):1-6. Review)



IAM: Infarto agudo de miocardio
AP: Arteriopatía periférica
AVC: Accidente vascular cerebral.

1.10-ASPECTOS EPIDEMIOLÓGICOS DE LA ARTERIOPATÍA PERIFÉRICA:

La isquemia crónica de las extremidades inferiores es la manifestación del deterioro progresivo del flujo arterial del miembro, llegando no tan sólo a afectar a su función sinó también a su supervivencia. Representa un importante problema de salud pública, sin embargo la información epidemiológica sobre esta enfermedad es muy escasa y existen pocos datos publicados que sean concluyentes. El cálculo de su incidencia esta sujeto a contradicciones y existen diferencias según los diferentes estudios, probablemente por la metodología aplicada y por la dificultad que representa detectar a los diferentes pacientes, pues gran número no se queja de síntomas por presentar una actividad limitada o considerarlo un proceso normal del envejecimiento **(30).**

Se estima que afecta a 27 millones de personas entre Europa y Norte America **(31).** Se considera que 10'5 millones presentarían manifestaciones clínicas y 16'5 millones serían asintomáticos **(19).** La prevalencia aumenta con la edad y con la asociación de factores de riesgo como la diabetes o el tabaco **(32).**

La evolución natural de la isquemia crónica de los miembros inferiores ha sido objeto de estudio en varios ensayos, tanto en lo que concierne a la progresión de la enfermedad a nivel local como a la morbimortalidad a largo plazo derivada de una patología aterosclerótica generalizada y recurrente.

La causa de muerte entre los pacientes con isquemia crónica de los miembros inferiores raramente es el resultado directo de la propia afectación periférica; los síntomas de la claudicación son habitualmente benignos y el riesgo de la progresión y pérdida de la extremidad es superado por el riesgo de episodios a otros niveles como el cerebral o el coronario y la muerte asociada a estos.

En el estudio *Framingham* mostró que tras un seguimiento de 8'5 años de media, siete (4'3%) de los 162 claudicantes recogidos presentaron progresión de los síntomas hasta requerir una amputación. Por otro lado el *Edinburgh Artery study* tras cinco años de seguimiento, siete (9'6%) de los 73 claudicantes presentaron una evolución hasta isquemia crítica, requiriendo una intervención quirúrgica o incluso una amputación **(26,33).**

La mortalidad como hemos comentado va asociada a la afectación concomitante de otros territorios. Aproximadamente el 55% de los pacientes con afectación periférica fallecen por complicaciones coronarias, el 10% por complicaciones cerebrovasculares y el 25% por causas no vasculares. Menos del 10% mueren por otras causas de origen vascular, sobre todo por aneurismas aórticos fisurados **(7).**

Algunos pacientes sólo presentan clínica en un sólo territorio y permanecen asintomáticas en otros.

El presentar aterosclerosis en múltiples regiones vasculares se asocia con una peor evolución que los que tan sólo estan afectatados en un sólo territorio, viéndose que los pacientes con enfermedad coronaria y con afectación arterial periférica conjunta presentan peor pronóstico **(34, 35).**

Los pacientes con antecedentes de ictus isquémico presentan riesgo no sólo de un nuevo ictus, sino también de infarto de miocardio **(36).**

El presentar antecedentes isquémicos previos se relaciona a su vez con un elevado riesgo de recidiva en el mismo territorio **(37).**

Criqui et al. Llevaron a cabo un estudio para evaluar la mortalidad por cualquier enfermedad cardiovascular en pacientes afectos de arteripatía periférica de grandes vasos. En el cribado inicial de 565 pacientes, 67 (11'9%) fueron indentificados con ensayos incruentos (medición segmentaria de tensión arterial, uso de ecografía Doppler). Estos pacientes fueron seguidos prospectivamente 10 años. En los resultados se objetivó un aumento de 15 veces en la mortalidad por procesos cardiovasculares entre los pacientes con afectación periférica grave y sintomática. Las curvas de supervivencia de los pacientes mostravan un pronóstico desfavorable. Aunque parece existir una relación directa entre la gravedad y la reducción de la supevivencia, incluso los pacientes asintomáticos presentan una supervivencia inferior si son comparados con los sujetos sanos. Tras diez años, casi la mitad de los pacientes asintomáticos seguían vivos**. (38).**

El presentar isquemia crónica de miembros inferiores implica en estos pacientes que tengan el mismo riesgo de muerte de origen cardiovascular que los pacientes con enfermedad coronaria o cerebrovascular, así como cuatro veces más riesgo de morir en los siguientes 10 años que los pacientes que no la presentan **(39).**

Los pacientes con isquemia crónica de miembros inferiores, sin embargo, son pacientes infratratados y sin una percepción real de su riesgo, probablemente por una falta de información sobre su enfermedad **(40,41,42).**

1.11-CLASIFICACIÓN CLÍNICA DE LA ISQUEMIA CRÓNICA DE MIEMBROS INFERIORES:

Existe una clasificación sencilla para los pacientes con isquemia crónica de los miembros inferiores que fue presentada por R.Fontaine en 1954 y se aplica de forma general a la practica clínica **(43).**

CLASIFICACIÓN FUNCIONAL DE FONTAINE EN LA ISQUEMIA CRÓNICA MIEMBROS INFERIORES.

Pousti TJ, Wilson SE, Williams RA. Clinical examination of the vascular system. En: Veith FJ, Hobson Williams RA. Vascular surgery. Principles and practice. McGraw Hill. 1994:77.

GRADOS	CLÍNICA
Grado I	Lesiones asintomáticas
Grado II IIa IIb	Claudicación intermitente Tras 150 m de marcha en llano Tras menos de 150 m de marcha en llano
Grado III	Dolor en reposo
Grado IV	Lesiones de necrosis y gangrena

La mayoría de los casos son asintomáticos (Fontaine grado I) o presentan síntomas de claudicación intermitente (Fontaine grado II), el resto presentan síntomas de forma continua con dolor en reposo (Fontaine grado III) o lesiones de necrosis-gangrena (Fontaine grado IV), siendo estos dos últimos los considerados como estadio de isquemia crítica de la extremidad **(45).**

Existe otra clasificación, la de Rutherford, con categorías del 0 al 6, que permitiría una evolución más descriptiva y presentaría una correspondencia con la de Fontaine, sin embargo esta clasificación no es tan utilizada como la primera.

Rutherford dividiría a los pacientes en grado 0 o asintomático, grados 1,2 y 3 para la claudicación (leve, moderada, severa), grado 4 para el dolor en reposo y finalmente los grados 5 y 6 dónde existiría afectación tisular, siendo en el grado 6 la mayor pérdida tisular, con extensión por encima del tobillo y con imposibilidad de recuperar el pie **(46) .**

1.12-EL REGISTRO INFORMATIZADO SOBRE FACTORES DE RIESGO Y ENFERMEDAD ARTERIOSCLERÓTICA (FRENA):

1.12.1- Introducción

Las modernas tecnologías han facilitado la creación de registros de pacientes, a partir de una base de datos consensuada y unificada, compartida por múltiples especialistas en una enfermedad, con el objetivo de recoger toda la información de utilidad sobre los pacientes, sin las limitaciones de los ensayos clínicos.
El registro FRENA nace en 2002, gracias a un grupo amplio de facultativos de toda la geografía nacional con el deseo de compartir la experiencia clínica de la enfermedad aterotrombótica en los diferentes territorios del árbol vascular y con la finalidad última de mejorar la calidad asistencial que se brinda al paciente. La intención es disponer de una base de datos en la que se reflejen las características individuales de un amplio número de pacientes con enfermedad arteriosclerótica sintomática, los tratamientos que reciben a lo largo del tiempo y la aparición tanto de nuevos eventos vasculares como la de posibles efectos adversos de la medicación.
Los registros reflejan los datos exactos de los pacientes del área geográfica donde se realizan, incluyen los tratamientos y las dosis que cada facultativo libremente considera más adecuados para cada paciente individual, y dan

testimonio de la evolución de todos y cada uno de los pacientes, tanto los que tienen múltiples enfermedades asociadas como los que no. El acceso en tiempo real (vía Internet) a la totalidad de los datos permite a todos los miembros de un registro poseer información sobre la totalidad de los pacientes, comparar actitudes terapéuticas, simular pronósticos, conocer mejor el efecto de un tratamiento, y, en definitiva, mejorar nuestra información.

1.12.2- Metodología de trabajo

Se incluye en el registro a todos los pacientes con un episodio reciente (3 meses máximo) de isquemia arterial (infarto de miocardio; angina estable o inestable; AVC isquémico o AIT; claudicación intermitente o dolor en reposo en las piernas). A partir de la primera visita ambulatoria se entran los datos del ingreso y los factores de riesgo en una base de datos unificada, así como los principales datos biológicos y el tratamiento administrado. Posteriormente se entra la información obtenida en visitas posteriores, hasta completar un período de seguimiento de entre uno y tres años. La periodicidad de las visitas son como mínimo cada 4-5 meses (un mínimo de 3 visitas al año, incluyendo la visita inicial). El tratamiento a administrar y la rigurosidad con que hay que controlar los factores de riesgo, son a criterio del facultativo.
Todos los pacientes proporcionan su consentimiento informado para participar en el estudio, de acuerdo a los requerimientos de los Comités Éticos de cada hospital.
El objetivo del estudio es precisamente mejorar la información de las variables que influyen sobre la evolución (en términos de supervivencia y recidiva de episodios isquémicos) de estos pacientes, a partir de datos generados por nuestros propios pacientes, con las pautas que habitualmente utilizamos. La información electrónica se procesa directamente mediante el software del programa, y se expone en Internet en forma de tablas que permiten evaluar en tiempo real la eficacia y la seguridad de las diversas actuaciones terapéuticas.

1.12.3.- Miembros y patrocinio del Registro

El registro nace dentro del grupo de trabajo de riesgo vascular de la Sociedad Española de Medicina Interna, pero tiene vocación multidisciplinar, y por tanto abierto a todos los facultativos interesados en participar. Tanto en la asistencia primaria como en los hospitales. El registro desea recabar además los auspicios de todas las sociedades científicas que puedan estar interesadas. Se trata de un proyecto independiente, aunque se pretende conseguir la esponsorización de la industria farmacéutica.

1.13-TEMÁTICA DE LA TESIS:

La aterotrombosis es la principal causa de muerte y discapacidad en los países desarrollados y se prevé que siga siéndolo en un futuro inmediato. Sin embargo tanto su evolución como su tratamiento siguen siendo muy desconocidos.

Consideramos la aterosclerosis como una enfermedad global que afecta a todo el árbol vascular, pero como hemos comentado presenta una variada heterogeneidad en las características de la diferentes lesiones, con una composición variable que la puede predisponer a un mayor riesgo de complicación. Su distribución presenta además diferencias según el territorio afectado y los diversos factores de riesgo tampoco actúan por igual en los diferentes lechos arteriales.

La mayoría de estudios se han realizado en pacientes con afectación aterosclerosa a nivel coronario, existiendo menos información de los pacientes con afectación a nivel cerebrovascular o periférico.

Los pacientes con enfermedad arterial periférica (EAP) presentan una manifestación aterosclerosa especialmente extensa, con afectación de otros territorios, en muchas ocasiones de forma crítica y asintomática. Esto les confiere un elevado riesgo de sufrir un evento cardiovascular, pero este riesgo es a menudo subestimado. La falta de percepción del riesgo probablemente justifique que sean el grupo afectado de enfermedad aterosclerosa con peor

control de los factores de riesgo, a diferencia de los pacientes con afectación cerebrovascular o coronaria.

La mayoría de ensayos clínicos no incluye la isquemia crítica dentro del grupo de eventos cardiovasculares mayores, probablemente por su baja incidencia en los pacientes con ateromatosis coronaria o cerebrovascular, però si representa una complicación común y grave en los pacientes EAP, existiendo poca información de los factores que pueden influir en su desarrollo.

El efecto del buen control de los diferentes factores de riesgo como el tabaquismo o la diabetes tampoco es del todo conocido. Existen numerosos estudios observacionales que sugieren que dejar de fumar podría reducir la mortalidad en pacientes con enfermedad coronaria, pero no tenemos tanta información de su efecto en pacientes con una manifestación isquémica en otros territorios, como a nivel cerebrovascular o periférico. Por este motivo las guías que disponemos se basan en el consenso de expertos más que en la evidencia clínica.

Algunos estudios han mostrado incluso una relación controvertida, entre los eventos cardiovasculares y el hábito tabáquico. El tabaquismo podría estar asociado con una mejor evolución en los pacientes con enfermedad coronaria aguda (smoker's paradox), sin embargo existe poca información al respecto y si este fenómeno se produce también en los pacientes con afectación de otros territorios, como a nivel cerebrovascular o periférico.

El buen control glicémico ha sido enfatizado también en las guías de manejo de la enfermedad coronaria y del ictus, pero no se ha comprobado un resultado beneficioso en su control estricto. No se ha objetivado una reducción en la aparición de nuevos eventos isquémicos ni una reducción de la mortalidad, por este motivo sólo se ha realizado una recomendación clase IIb y un nivel de evidencia A en el mantenimiento de los niveles de HbA1c por debajo de 7% (Ameriacan Heart Association and the American Diabetes Association). No tenemos información si es aplicable a nivel periférico y extrapolamos conclusiones.

El registro FRENA (Factores de Riesgo y Enfermedad Arterial), con la inclusión de más de 3500 pacientes, nos permite recoger la evolución de la enfermedad

arterial en diferentes territorios del árbol vascular, en un grupo de pacientes no seleccionados. Esto contrasta con las rigurosas condiciones de control que existen en los estudios clínicos randomizados y nos permite identificar los factores que intervienen en una mejor o peor evolución de los eventos isquémicos que presentan los pacientes incluidos en el registro. Obtenemos información de la situación clínica real en la que esta envuelta la patología aterotrombótica, a pesar de las limitaciones que este tipo de registro implica.

Los siguientes artículos publicados intentan dar respuesta a algunas de las dudas planteadas sobre la aterotrombosis y su evolución, sobretodo a nivel arterial periférico, y a la relación existente con sus factores de riesgo, en concreto con la diabetes mellitus y especialmente con el tabaquismo.

- Differences in cardiovascular mortality in smokers, past-smokers and non-smokers. Findings from the FRENA Registry. JM Suriñach; LR. Álvarez; R. Coll; JA. Carmona; C. Sanclemente; E. Aguilar; M. Monreal and the FRENA Investigators. Eur J Intern Med. 2009 Sep;20(5):522-6.

- Glucose control and outcome in patients with stable diabetes and previous coronary, cerebrovascular or peripheral artery disease. Findings from the FRENA Registry. M. Camafort; LR. Álvarez; JF. Sánchez Muñoz-Torrero; JC Sauquillo; L. López Jiménez; R.Coll; M. Monreal. Diabet Med. 2011 Jan;28(1):73-80.

- Smoking cessation and outcome in stable outpatients with coronary, cerebrovascular or peripheral artery disease. LR. Álvarez; JM. Balibrea; JM. Suriñach; R. Coll; MT. Pascual; J.Toril; L. López-Jiménez; M.Monreal. European Journal of Cardiovascular Prevention and Rehabilitation (Published online before print October 3, 2011, doi: 10.1177/1741826711426090).

Añadido en el Anexo:

- Clinical Outcome in Patients with Peripheral Artery Disease. Results from a Prospective Registry (FRENA). M. Monreal; LR. Álvarez; B. Vilaseca; R. Coll; C. Suárez; J. Toril; C. Sanclemente and the FRENA Investigators. Eur J Intern Med. 2008 May;19(3):192-7

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2-ARTÍCULOS

- Differences in cardiovascular mortality in smokers, past-smokers and non-smokers. Findings from the FRENA Registry. JM Suriñach; LR. Álvarez; R. Coll; JA. Carmona; C. Sanclemente; E. Aguilar; M. Monreal and the FRENA Investigators. Eur J Intern Med. 2009 Sep;20(5):522-6.

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Original article

Differences in cardiovascular mortality in smokers, past-smokers and non-smokers Findings from the FRENA registry

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ABSTRACT

Background: The influence of smoking on outcome in patients with coronary artery disease (CAD) is controversial. Even less is known about its influence in patients with cerebrovascular (CVD), or peripheral artery (PAD) disease.

Patients and methods: FRENA is an ongoing, observational registry of consecutive outpatients with symptomatic CAD, CVD, or PAD. We reviewed their cardiovascular mortality according to smoking status.

Results: As of May 2008, 2501 patients had been enrolled in FRENA. Of these, 439 (18%) were current smokers, 1086 (43%) past-smokers, 976 (39%) had never smoked. Current- and past-smokers were 10 years younger, more often males, and more likely to have chronic lung disease, but had diabetes, hypertension, heart failure, or renal insufficiency less often than non-smokers. Over a mean follow-up of 14 months, 123 patients died (cardiovascular death, 68). On univariate analysis, current smokers had a significantly lower rate of cardiovascular death: 1.1 (95% CI: 0.4–2.4) per 100 patient-years in current smokers; 1.9 (95% CI: 1.2–2.8) in past-smokers; 3.5 (95% CI: 2.5–4.7) in non-smokers, with no differences between patients with CAD, CVD or PAD. Mean age at cardiovascular death was 82 ± 6.4; 70 ± 9.9 and 67 ± 15 years, respectively. On multivariate analysis, smoking status was not independently associated with a lower risk for cardiovascular death.

Conclusions: Current and past-smokers with CAD, CVD or PAD had a less than half cardiovascular mortality than those who never smoked, but this may be explained by the confounding effect of additional variables. They died over 10 years younger than non-smokers.

1. Introduction

The relationship between smoking habit and outcome in patients with established arterial disease remains controversial. In the general population, smoking is usually associated with an increased risk of coronary (CAD), cerebrovascular (CVD) or peripheral artery disease (PAD) [1–7], and smoking cessation almost certainly has beneficial effects on subsequent mortality [8–12]. Hence, current guidelines for the secondary prevention of coronary artery disease from the American College of Cardiology/American Heart Association recommend smoking cessation for all patients [13]. However, some studies have found that smoking may be associated with a better outcome among patients with acute coronary disease (the so-called smoker's paradox) [14–21]. As for patients with CVD or PAD, there is little information on the influence of smoking on outcome.

The FRENA (*F*actores de *R*iesgo y *EN*fermedad *A*rterial or, in English: Risk Factors and Arterial Disease) Registry was initiated in March 2003 to prospectively record the current clinical management and outcome of patients with arterial disease in Spanish hospitals [22,23]. It is an ongoing, multicenter, observational registry of consecutive patients designed to gather and analyze data on treatment patterns and outcomes in patients with symptomatic ischemic disease of the heart, brain, and/or major peripheral arteries. Given the uncertain role of smoking habit in the clinical management of these patients, we compared the incidence of cardiovascular death during follow-up of all enrolled patients in the registry according to their smoking habit.

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[1] A full list of FRENA investigators is given in Appendix A.

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2. Patients and methods

2.1. Study design

The primary outcome was cardiovascular death. Secondary outcomes were the incidence of major cardiovascular events (myocardial infarction, ischemic stroke or critical limb ischemia) and overall mortality. Patients were categorized as non-smokers, past-smokers or current smokers. Smoking habits were recorded with regard to current and previous daily consumption, duration of smoking, and, for past-smokers, time since quitting smoking. Daily consumption of cigarettes and cigars was calculated by equating 1 cigarette to 1 g, and 1 cigar to 5 g of tobacco, as previously reported [25]. Advice on modification of cardiovascular risk factors (including quitting smoking) was part of the usual treatment.

2.2. Inclusion criteria

Participating hospitals in the FRENA registry prospectively enrolled consecutive outpatients with symptomatic artery disease with at least one recent (<3 months prior to enrollment) episode of CAD (manifesting as angina or acute coronary syndrome); CVD (manifesting as transient ischemic attack or ischemic stroke); or PAD (either intermittent claudication with an ankle-brachial index <0.9, or previous vascular intervention or limb amputation for PAD). The Fontaine classification was used for categorisation of PAD [24]. All patients provide oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

2.3. Data collection

The attending physicians ensure that eligible patients are consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Patient identities remain confidential because they are identified by a unique number assigned by the study coordinating center, which is responsible for all data management. Data quality is regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals, by contract research organizations, who compare the medical records with the data in the web. A full data audit is performed at periodic intervals.

2.4. Follow-up

A detailed history was performed on all patients at study entry (<3 months after an acute ischemic episode). Comorbid conditions were

Table 1
Clinical characteristics and therapeutic details of the patients.

	Never smoked	Past-smokers	Current smokers	OR (95% CI) and p value	OR (95% CI) and p value
	N (%)	N (%)	N (%)	Past- vs. non-smokers	Current- vs. non-smokers
Patients, N	976	1086	439		
Number of visits (mean ± SD)	4.1 ± 2.3	4.5 ± 2.4	4.4 ± 2.0	$p<0.001$	$p=$ NS
Clinical characteristics					
Mean age (years ± SD)	72 ± 11	64 ± 12	62 ± 11	$p<0.001$	$p<0.001$
Gender (males)	379 (39%)	1038 (96%)	403 (92%)	34 (25–47)‡	18 (12–25)‡
BMI (mean ± SD)	29 ± 4.9	28 ± 4.0	27 ± 4.2	$p<0.001$	$p<0.001$
Underlying diseases					
Cancer	37 (3.8%)	88 (8.1%)	17 (3.9%)	2.2 (1.5–3.3)‡	1.0 (0.6–1.8)
Chronic lung disease	64 (6.6%)	201 (19%)	97 (22%)	3.2 (2.4–4.4)‡	4.0 (2.9–5.7)‡
Chronic heart failure	117 (12%)	86 (7.9%)	19 (4.3%)	0.6 (0.5–0.8)†	0.3 (0.2–0.5)‡
Hypertension	756 (78%)	676 (62%)	260 (59%)	0.5 (0.4–0.6)‡	0.4 (0.3–0.5)‡
Diabetes mellitus	424 (44%)	412 (38%)	145 (33%)	0.8 (0.7–0.9)*	0.6 (0.5–0.8)‡
Clinical presentation					
Angina	162 (17%)	114 (11%)	36 (8.2%)	0.6 (0.5–0.8)‡	0.4 (0.3–0.7)‡
Myocardial infarction	221 (23%)	360 (33%)	76 (17%)	1.7 (1.4–2.1)‡	0.7 (0.5–0.96)*
Acute ischemic stroke	346 (36%)	156 (14%)	104 (24%)	0.3 (0.2–0.4)‡	0.6 (0.4–0.7)‡
Transient ischemic attack	123 (13%)	47 (4.3%)	27 (6.2%)	0.3 (0.2–0.4)‡	0.5 (0.3–0.7)‡
PAD Fontaine stage II	88 (9.0%)	311 (29%)	168 (38%)	4.0 (3.1–5.2)‡	6.2 (4.7–8.4)‡
PAD Fontaine stage III	17 (1.7%)	53 (4.9%)	14 (3.2%)	2.9 (1.7–5.0)‡	1.9 (0.9–3.8)
PAD Fontaine stage IV	37 (3.8%)	44 (4.1%)	15 (3.4%)	1.1 (0.7–1.7)	0.9 (0.5–1.7)
Physical examination					
Arrhythmia	177 (16%)	113 (10%)	31 (7.1%)	0.5 (0.4–0.6)‡	0.2 (0.1–0.4)‡
Mean SBP levels (mm Hg)	139 ± 17	134 ± 18	138 ± 17	$p<0.001$	$p=$ NS
Mean DBP levels (mm Hg)	76 ± 9.4	74 ± 9.4	76 ± 9.6	$p<0.001$	$p=$ NS
Mean laboratory levels					
CrCl (mL/min)	64 ± 25	77 ± 30	79 ± 28	$p<0.001$	$p<0.001$
Total cholesterol (mg/dL)	184 ± 37	177 ± 35	188 ± 38	$p<0.001$	$p=$ NS
HDL-cholesterol (mg/dL)	50 ± 15	44 ± 12	46 ± 12	$p<0.001$	$p<0.001$
LDL-cholesterol (mg/dL)	110 ± 30	106 ± 29	115 ± 32	$p=0.020$	$p=0.002$
Glucose (mg/dL)	121 ± 42	119 ± 37	116 ± 40	$p=$ NS	$p=0.038$
Drugs					
Diuretics	470 (48%)	388 (36%)	140 (32%)	0.6 (0.5–0.7)‡	0.5 (0.4–0.6)‡
Beta-blockers	363 (37%)	487 (45%)	130 (30%)	1.4 (1.1–1.6)†	0.7 (0.6–0.9)†
ACE-inhibitors	437 (45%)	528 (49%)	181 (41%)	1.2 (0.98–1.4)	0.9 (0.7–1.1)
Angiotensin-II antagonists	374 (38%)	275 (25%)	124 (28%)	0.5 (0.4–0.7)‡	0.6 (0.5–0.8)‡
Calcium antagonists	284 (29%)	281 (26%)	87 (20%)	0.8 (0.7–1.0)	0.6 (0.5–0.8)‡
Antiplatelets	835 (86%)	992 (91%)	417 (95%)	1.7 (1.3–2.3)‡	3.1 (2.0–5.0)‡
Anticoagulants	208 (21%)	160 (15%)	33 (7.5%)	0.6 (0.5–0.8)‡	0.3 (0.2–0.4)‡
Statins	708 (73%)	839 (77%)	337 (77%)	1.3 (1.0–1.6)*	1.2 (0.95–1.6)
Insulin	170 (18%)	148 (14%)	51 (12%)	0.7 (0.6–0.9)*	0.6 (0.4–0.9)†
Oral antidiabetics	276 (28%)	278 (26%)	114 (26%)	0.9 (0.7–1.1)	0.9 (0.7–1.1)

Comparisons between groups: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.
Abbreviations: SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; CrCl, creatinine clearance; ACE, angiotensin-conversive enzyme; NS, non significant; OR, odds ratio; CI, confidence intervals.

characterized, including a history of CAD, CVD or PAD, diabetes mellitus, hypertension, hyperlipidemia, chronic lung disease, chronic heart failure, cancer, and smoking status. Then, physical examination was performed comprising weight, height, heart rate and blood pressure on standard conditions, after 5 min of rest. An electrocardiogram was also recorded. After the initial visit, patients were followed-up at 3-month intervals for at least 12 months. At these visits, medical history and data from physical examination were recorded, with special attention to risk factors; laboratory tests; lifestyle habits; the type, dose, and duration of treatment received, and clinical outcome. Physicians were allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns.

2.5. Definitions

Patients were considered to be past-smokers when having permanently discontinued to smoke at least one month before inclusion in the study. A patient was classified as having diabetes when there was a clinical history of diabetes or when they were taking insulin or oral antidiabetic agents. Patients were classified as having hypertension when there was a clinical history of hypertension or when they were taking antihypertensive medications. Creatinine clearance levels were measured according to the Cockcroft and Gault formula [26]. Death was classified as cardiovascular when appearing within 15 days after the onset of signs or symptoms of a major cardiovascular event, or due to progressive heart failure, fatal arrhythmias, ruptured aneurysm, pulmonary embolism or sudden death. Major cardiovascular events were defined as the composite outcome of myocardial infarction, ischemic stroke, critical limb ischemia, or cardiovascular death. Angina was defined as the presence of ischemic symptoms with or without typical electrocardiogram signs. Myocardial infarction was defined as a transient increase of CK-MB or troponin in combination with ischemic symptoms and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 h, and had a brain CT or MRI that showed a compatible low-density lesion or was normal, or had findings compatible with hemorrhagic conversion of a cerebral infarct. Transient ischemic attack was considered for those patients with clinical events that resolved completely within 24 h. Critical limb ischemia was considered in patients with intermittent claudication when presenting symptoms at rest (Fontaine stages III or IV). In PAD patients with stage III or IV, critical limb ischemia was considered when needing amputation.

2.6. Statistical analysis

Incidence rates were calculated as both cumulative incidence and as incidence density (events/100 patient-years). Categorical variables were compared using the chi-square test. Odds ratios and corresponding 95% confidence intervals were calculated. Associations between smoking habit and cardiovascular mortality were assessed using Poisson regression model, in which age, heart failure, diabetes, smoking habit, prior artery disease, heart rhythm, creatinine clearance levels, cancer and drug therapy were adjusted as confounding factors. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

3. Results

As of May 2008, a total of 2501 patients have been enrolled in FRENA in 24 participating Spanish hospital centers, of whom 439 (18%) were current smokers, 1086 (43%) past-smokers, and 976 (39%) never smoked.

3.1. Clinical characteristics

During follow-up, 298 of the 439 patients (68%) who persisted to smoke had reduced their tobacco consumption: mean consumption during follow-up was 14 g/day, and the median reduction was 12 g/day. Current smokers were younger, more often males, weighed less, and had chronic lung disease more frequently, but heart failure, diabetes or hypertension less often than non-smokers (Table 1). They presented more often with intermittent claudication, but less often with CVD. Their serum levels of creatinine clearance or LDL-cholesterol at baseline were higher, but their levels of HDL-cholesterol were lower. They received antiplatelet therapy more often, but diuretics, beta-blockers, ARA-II antagonists, insulin and anticoagulants less often.

Mean consumption in past-smokers had been 28 g/day. Past-smokers also were younger, more often males, weighed less, and had more frequently chronic lung disease or cancer, but less often diabetes, hypertension or heart failure than non-smokers. They presented more often with myocardial infarction or intermittent claudication, but less often with angina or CVD. Their serum levels of creatinine clearance or LDL-cholesterol at baseline were higher, but their levels of HDL-cholesterol were lower. They received more often beta-blockers, antiplatelet therapy or statins, but less often diuretics, ARA-II antagonists, anticoagulants or insulin.

3.2. Follow-up

Over a mean follow-up of 14 months, there were 250 major cardiovascular events in 239 patients (9.6%): 69 (2.8%) had an acute myocardial infarction; 75 (3.0%) ischemic stroke; 106 (4.2%) acute limb ischemia (41 underwent limb amputation). Current smokers and past-smokers had an increased incidence of critical limb ischemia compared with non-smokers, but their incidence of myocardial infarction was similar (Table 2).

Overall, 123 (4.9%) patients died (cardiovascular death, 68) during follow-up. Current smokers and past-smokers had a significantly lower cardiovascular mortality than non-smokers. These findings were also seen when separately considering patients with CAD, CVD or PAD (Table 2). Most of the reported causes of death were less common in

Table 2
Clinical outcomes according to smoking habit.

	Never smoked	Past-smokers	Current smokers
All patients, *N*	976	1086	439
Follow-up (person-years)	1119	1274	469
Myocardial infarction	2.5 (1.7–3.6)	2.3 (1.6–3.3)	2.6 (1.4–4.4)
Acute ischemic stroke	4.1 (3.0–5.4)	1.4 (0.9–2.2)	2.6 (1.4–4.5)
Critical limb ischemia	2.4 (1.6–3.4)	4.3 (3.3–5.6)	5.7 (3.8–8.3)
Cardiovascular death	3.5 (2.5–4.7)	1.9 (1.2–2.8)	1.1 (0.4–2.4)
Overall death	5.5 (4.2–7.0)	4.2 (3.1–5.4)	1.9 (0.9–3.5)
CAD patients, *N*	378	472	111
Follow-up (person-years)	444	588	113
Myocardial infarction	5.1 (3.3–7.6)	2.6 (1.5–4.2)	5.4 (2.2–11)
Acute ischemic stroke	1.4 (0.6–2.8)	0.7 (0.2–1.6)	–
Critical limb ischemia	0.01 (0.2–1.1)	1.0 (0.4–2.1)	0.9 (0.04–4.4)
Cardiovascular death	4.3 (2.7–6.3)	1.0 (0.4–2.1)	2.7 (0.7–7.2)
Overall death	5.4 (3.5–7.9)	2.2 (1.2–3.7)	3.5 (1.1–8.5)
CVD patients, *N*	452	201	128
Follow-up (person-years)	528	263	146
Myocardial infarction	0.4 (0.06–1.3)	0.4 (0.02–1.9)	2.1 (0.5–5.8)
Acute ischemic stroke	5.6 (3.8–8.0)	3.1 (1.4–5.8)	4.3 (1.7–8.9
Critical limb ischemia	0.6 (0.1–1.6)	0.8 (0.1–2.5)	1.4 (0.2–4.6)
Cardiovascular death	2.7 (1.5–4.3)	1.1 (0.3–3.1)	0.7 (0.03–3.4)
Overall death	4.7 (3.1–6.9)	3.4 (1.7–6.3)	0.7 (0.03–3.4)
PAD patients, *N*	150	413	200
Follow-up (person-years)	149	429	209
Myocardial infarction	2.7 (0.9–6.5)	2.9 (1.5–4.9)	1.4 (0.4–3.9)
Acute ischemic stroke	6.2 (3.0–11)	1.4 (0.6–2.9)	2.9 (1.2–6.1)
Critical limb ischemia	16 (11–24)	11 (7.8–14)	12 (7.5–17)
Cardiovascular death	4.7 (2.1–9.3)	3.5 (2.0–5.6)	0.5 (0.02–2.3)
Overall death	8.7 (4.8–15)	7.2 (5.0–10)	1.9 (0.6–4.6)

Results expressed as incidence of events per 100 patient-years, and 95% confidence intervals (in brackets).
Abbreviations: CAD, coronary artery disease; CVD, cerebrovascular; PAD, peripheral artery disease.

current smokers (Table 3). However, mean age for cardiovascular death was 82 ± 6.4; 70 ± 9.9 and 67 ± 15 years, respectively. Mean age for non-cardiovascular death was 79 ± 13; 74 ± 8.6 and 69 ± 4.5 years, respectively (Table 3).

On univariate analysis, age > 70 years, BMI > 28, chronic lung disease, heart failure, diabetes, prior history of artery disease, non-smoking status, atrial fibrillation, renal insufficiency, and the use of some drugs were significantly associated with an increased cardiovascular mortality (Table 4). However, on multivariate analysis, none of these variables were independently associated with an increased risk for cardiovascular death. The adjusted relative risk for past-smokers was 0.6 (95% CI: 0.2–2.1), for current smokers 0.3 (95% CI: 0.02–4.6).

4. Discussion

Our data, obtained from a prospective series of consecutive outpatients with CAD, CVD or PAD in the FRENA registry, confirm that current smokers and past-smokers have a less than half cardiovascular mortality compared with those who never smoked. This reduction in cardiovascular death was consistently found in patients with CAD, CVD or PAD, but disappeared after multivariate adjustment. A number of cohort studies have reported that smokers who have an acute myocardial infarction have a better outcome than non-smokers [14–21]. These apparently contradictory findings have been coined as the "smoker's paradox". Up to now the smoker's paradox has been reported only in patients with CAD. Our findings confirm its existence also in patients with CVD or PAD. Most importantly, our data may serve to help explain this apparent paradox: current smokers died less often (either due to cardiovascular or non-cardiovascular reasons) because they were over 10 years younger than non-smokers, thus emphasizing the adverse influence of smoking on survival.

The underlying pathophysiology of the smoking's paradox is not well known. We found current smokers to be not only 10 years younger than non-smokers, but also to have hypertension, diabetes or heart failure less often. Thus, their better outcome might be explained by their younger age and a more favorable risk profile. Furthermore, two in every three current smokers in our series reduced smoking substantially. It is conceivable that severely disabled patients were more motivated to quit smoking, and thus may have been sicker than those who continued to smoke. These patients would presumably have recurrent events sooner rather than later after cessation. Finally, angiographic studies have demonstrated that coronary artery occlusion in smokers is predominantly caused by thrombosis and thus may have a better response to spontaneous or therapeutic thrombolysis [17,27].

Our findings might unintentionally lead to misunderstanding among the public. From the clinical standpoint the main question is not whether current smokers have a better outcome than those who quit smoking (or those who never smoked), but whether smoking habit is associated with the development of cardiovascular death at earlier stages. In our series, established vascular disease became symptomatic 10 years earlier and death appeared 13 years earlier in current smokers than in non-smokers. Thus, without any doubt, the best way for limiting the risk for smoking-related atherosclerosis is to stop smoking in the first place [28]. Current guidelines for the management of CAD, CVD or PAD recommend smoking cessation for all patients who smoke [13,29–31], and our findings go along with this recommendation.

The FRENA registry provides insights into the natural history of artery disease with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse patient outcomes, and provide feedback from real-world clinical situations which may be valuable when designing new randomized clinical studies. Despite our efforts to control any bias from underlying diseases, it is likely that we were unable to eliminate such bias completely. Thus, the increased mortality found in non-smokers in this study may reflect pre-existing, unrecognized, disease processes, even after making careful exclusions. Another limitation of this study lies on the likely underestimated incidence of cardiovascular death in some patients. Certainly, the death at home of some patients reported

Table 3
Causes of death according to smoking habit.

	Never smoked	Past-smokers	Current smokers
	N (%)	*N* (%)	*N* (%)
All patients, *N*	976	1086	439
Cardiovascular death,	39 (4.0%)	24 (2.2%)	5 (1.1%)
Fatal myocardial infarction	9 (0.9%)	4 (0.4%)	1 (0.2%)
Fatal ischemic stroke	10 (1.0%)	2 (0.2%)	1 (0.2%)
Fatal critical limb ischemia	0	7 (0.6%)	1 (0.2%)
Heart failure	12 (1.2%)	4 (0.4%)	0
Sudden death	4 (0.4%)	3 (0.3%)	2 (0.5%)
Ruptured aneurysm	0	3 (0.3%)	0
Arrhythmia	2 (0.2%)	1 (0.1%)	0
Pulmonary embolism	2 (0.2%)	0	0
Mean age (years ± SD) at death	82 ± 6.4	70 ± 9.9	67 ± 15
Non-cardiovascular death,	22 (2.3%)	29 (2.7%)	4 (0.9%)
Mean age (years ± SD) at death	79 ± 13	74 ± 8.6	69 ± 4.5
Overall death	61 (6.3%)	53 (4.9%)	9 (2.1%)
Mean age (years ± SD) at death	81 ± 9.1	72 ± 9.4	68 ± 11

Abbreviations: SD, standard deviation.

Table 4
Risk factors for cardiovascular mortality.

	CV death	No CV death	Relative Risk	*p* value
	N (%)	*N* (%)	(95% CI)	
Patients, *N*	68	2433		
Clinical characteristics				
Age > 70 years	50 (73%)	982 (40%)	4.4 (1.1–18)	0.038
Gender (males)	42 (62%)	1778 (73%)	0.6 (0.2–1.8)	0.344
BMI > 28	19 (32%)	1097 (47%)	0.5 (0.1–1.6)	0.209
Underlying diseases				
Cancer	5 (7.4%)	137 (5.6%)	1.6 (0.2–14)	0.690
Chronic lung disease	16 (24%)	346 (14%)	2.1 (0.5–7.8)	0.291
Chronic heart failure	18 (27%)	204 (8.4%)	4.5 (1.3–16)	0.019
Hypertension	50 (74%)	1647 (68%)	1.4 (0.4–4.9)	0.626
Diabetes	36 (53%)	945 (39%)	1.8 (0.6–5.6)	0.310
Smoking habit				
Never smoked (ref)	39 (57%)	937 (39%)	–	–
Past-smokers	24 (35%)	1062 (44%)	0.5 (0.2–1.8)	0.297
Current smokers	5 (7.4%)	434 (18%)	0.3 (0.03–2.9)	0.299
Initial clinical presentation				
Coronary artery disease	28 (41%)	933 (38%)	0.8 (0.2–3.1)	0.753
Cerebrovascular disease	18 (27%)	763 (31%)	0.6 (0.1–2.8)	0.543
Peripheral artery disease (ref)	23 (34%)	740 (30%)	–	
Physical examination				
Arrhythmia	17 (33%)	304 (12%)	2.5 (0.7–9.4)	0.145
Mean SBP levels > 140 mm Hg	22 (32%)	951 (39%)	0.9 (0.3–3.1)	0.873
Mean DBP levels > 90 mm Hg	4 (5.9%)	133 (5.5%)	1.3 (0.1–14)	0.834
Mean laboratory levels				
Creatinine clearance < 60 mL/min	48 (76%)	817 (35%)	6.1 (1.6–23)	0.008
Total cholesterol > 190 mg/dL	23 (37%)	924 (40%)	1.0 (0.3–3.5)	0.992
LDL-cholesterol > 100 mg/dL	31 (59%)	1316(%)	1.1 (0.3–3.9)	0.892
Glucose > 100 mg/dL	47 (75%)	1437 (63%)	1.7 (0.4–6.3)	0.464
Drugs				
Diuretics	42 (62%)	956 (39%)	2.5 (0.8–7.8)	0.125
Beta-blockers	17 (25%)	936 (40%)	0.4 (0.1–1.9)	0.279
ACE-inhibitors	26 (38%)	1120 (46%)	0.6 (0.2–2.0)	0.362
Angiotensin-II antagonists	22 (32%)	751 (31%)	1.0 (0.3–3.3)	0.937
Calcium antagonists	22 (32%)	630 (26%)	1.2 (0.3–4.1)	0.776
Antiplatelets	56 (82%)	2188 (90%)	0.5 (0.1–2.4)	0.392
Anticoagulants	21 (31%)	380 (16%)	2.4 (0.6–8.8)	0.192
Statins	44 (65%)	1840 (76%)	0.5 (0.1–1.7)	0.249
Insulin	15 (22%)	354 (15%)	1.7 (0.4–7.0)	0.454
Oral antidiabetics	18 (27%)	650 (27%)	1.0 (0.3–3.6)	0.985

Univariate analysis.
Abbreviations: CV, cardiovascular; BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; CVD, cerebrovascular; PAD, peripheral artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-conversive enzyme; CI, confidence intervals; NS, not significant.

to die of "unknown cause" may have been due to unrecognised cardiovascular death. However, since the incidence of most causes of death decreased in current smokers, it is unlikely that this could have influenced our conclusions. Finally, information on current smoking was self-reported and not validated by any biochemical marker. Self-reported smoking habits, however, have been found to be accurate in studies of different populations [32,33].

This study also has several strengths. To the best of our knowledge, this is the first time the prognostic importance of smoking has been assessed in a large study of patients with CAD, CVD or PAD. The information on smoking habit at regular intervals during follow-up may have better reflected changes after a cardiovascular event. Moreover, we did not exclude patients with underlying diseases, recent weight loss or cancer.

In summary, our data confirm that current smokers with arterial disease have less than half the mortality due to cardiovascular reasons when compared with patients who never smoked. However, they died one decade earlier. This reduction was found in patients with CAD, CVD or PAD, and disappeared after multivariate adjustment. The findings in this study complement our knowledge regarding the impact of smoking on outcome in patients with arterial disease, since any differences between current smokers and non-smokers, which might have prognostic implications, are of interest.

5. Learning points

- Current and past-smokers with coronary artery disease, cerebrovascular disease or peripheral artery disease had a less than half cardiovascular mortality than those who never smoked, but this may be explained by the confounding effect of additional variables.
- Non-smokers with arterial disease died over 10 years younger than current smokers.

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Appendix A. Members of the FRENA Group

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Article: Complications

Glucose control and outcome in patients with stable diabetes and previous coronary, cerebrovascular or peripheral artery disease. Findings from the FRENA Registry

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Abstract

Aim The aim of this study was to address the controversy over the influence of intensive glucose control on the risk for cardiovascular events in patients with Type 2 diabetes.

Methods FRENA is an ongoing registry of stable outpatients with symptomatic coronary artery disease, cerebrovascular disease or peripheral artery disease. We compared the incidence of subsequent ischaemic events (myocardial infarction, stroke or critical limb ischaemia) in patients with Type 2 diabetes and mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) vs. those with HbA_{1c} levels > 7.0% (> 53 mmol/mol).

Results Of 974 patients with Type 2 diabetes, 480 (49%) had mean HbA_{1c} levels < 7% (< 53 mmol/mol). Over a mean follow-up of 14 months, 126 patients (13%) had subsequent ischaemic events: myocardial infarction (43), stroke (29) and critical limb ischaemia (64). The incidence of subsequent ischaemic events was significantly lower in patients with mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) than in those with HbA_{1c} levels > 7.0% (> 53 mmol/mol) (8.6 vs. 14 per 100 patient-years; rate ratio 0.6; 95% CI 0.4–0.9). These differences persisted after adjusting for potential confounders. However, this better outcome was only found in patients presenting with coronary artery disease (rate ratio 0.4; 95% CI 0.2–0.8), not in those with cerebrovascular disease (rate ratio 0.9; 95% CI 0.4–2.0) or peripheral artery disease (rate ratio 0.8; 95% CI 0.5–1.3). Patients with mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) also had a lower mortality (rate ratio 0.6; 95% CI 0.3–0.99).

Conclusions In secondary prevention, patients with diabetes and HbA_{1c} levels < 7.0% (< 53 mmol/mol) had a lower incidence of subsequent ischaemic events and a lower mortality than those with HbA_{1c} levels > 7.0% (> 53 mmol/mol). These differences appeared only in patients with coronary artery disease.

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Keywords arterial disease, diabetes, glucose control, ischaemic events, secondary prevention

Introduction

Diabetes mellitus is a well-established risk factor for arterial disease and several observational studies have shown a positive correlation between blood glucose or HbA_{1c} levels and the incidence of major vascular events [1–3]. Hence, current guidelines for the management of ischaemic heart disease and stroke emphasize the importance of optimal glucose control in patients with Type 2 diabetes and recommend maintaining HbA_{1c} levels < 7.0% (< 53 mmol/mol) [4–9]. However, several recent trials that aimed to assess whether intensive glucose control improves outcome failed to show beneficial effects on the incidence of macrovascular events [10–13].

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[1]*A full list of FRENA investigators is given in the Appendix.*

The FRENA (Factores de Riesgo y ENfermedad Arterial) Registry is an ongoing, multi-centre, observational registry designed to gather and analyse data on treatment patterns and outcomes in stable outpatients with symptomatic coronary artery disease, cerebrovascular disease or peripheral artery disease in Spanish hospitals [14–16]. The aim of this study was to compare the incidence of subsequent ischaemic events (myocardial infarction, ischaemic stroke or critical limb ischaemia) in patients with Type 2 diabetes and mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) vs. those with mean HbA_{1c} levels > 7.0% (> 53 mmol/mol).

Patients and methods

Inclusion criteria

Participating hospitals in the FRENA registry prospectively enroll consecutive outpatients with symptomatic artery disease with at least one recent (< 3 months prior to enrollment) episode of coronary artery disease (manifesting as angina or acute coronary syndrome), cerebrovascular disease (manifesting as transient ischaemic attack or ischaemic stroke) or peripheral artery disease (either intermittent claudication with an ankle–brachial index < 0.9 or previous vascular intervention or limb amputation for peripheral artery disease). The Fontaine classification was used for categorization of peripheral artery disease [17]. All patients provided oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Study design

Patients with Type 2 diabetes were classified as having mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) or HbA_{1c} levels > 7.0% (> 53 mmol/mol). Mean values of HbA_{1c} levels during follow-up were assessed. Patients with missing data regarding HbA_{1c} levels were not considered for the study. The primary outcome was the incidence of subsequent ischaemic events (myocardial infarction, ischaemic stroke or critical limb ischaemia).

Definitions

Myocardial infarction was defined as a transient increase of creatine kinase MB (CK-MB) or troponin, in combination with ischaemic symptoms and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischaemic stroke was diagnosed if the patient had an appropriate clinical event, and had a brain computerized tomography (CT) or magnetic resonance imaging (MRI) scan that showed a compatible low-density lesion. Critical limb ischaemia was considered in patients with intermittent claudication when presenting symptoms at rest (Fontaine stages III or IV). In patients with peripheral artery disease, stage III or IV, critical limb ischaemia was considered when needing amputation. Creatinine clearance levels were measured according to the Cockcroft and Gault formula [18]. Angina was defined as the presence of ischaemic symptoms with or without typical electrocardiogram signs.

Follow-up

A clinical history was performed on all patients at study entry (< 3 months after an acute ischaemic episode). Co-morbid conditions were characterized, including a history of coronary artery disease, cerebrovascular disease or peripheral artery disease, hypertension, hyperlipidaemia, chronic lung disease, chronic heart failure, cancer and smoking status. Then, physical examination was performed comprising weight, height, heart rate and blood pressure under standard conditions, after 5 min of rest. An electrocardiogram was also recorded. After the initial visit, patients were followed up at 4-month intervals. At these visits, medical history and data from physical examination were recorded, with special attention to risk factors, laboratory tests, lifestyle habits, the type, dose and duration of treatment received and clinical outcome. Physicians were allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns.

Data collection

The attending physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. Patient identities remained confidential because they were identified by a unique number assigned by the study coordinating centre, which was responsible for all data management. Data quality was regularly monitored and documented electronically to detect inconsistencies or errors, which were resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals, by contract research organizations, who compared the medical records with the data on the Web. A full data audit was performed at periodic intervals.

Statistical analysis

Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the rate ratio [19]. Categorical variables were compared using the χ^2-test (two-sided). Odds ratios and corresponding 95% confidence intervals were calculated and a P-value < 0.05 was considered to be statistically significant. Associations between the two subgroups of patients and subsequent ischaemic events were assessed using the Cox regression model, in which age, gender, clinical presentation, systolic blood pressure levels, creatinine clearance levels and use of drugs were adjusted as confounding factors. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS Inc., Chicago, IL, USA).

Results

As of July 2009, 2794 patients had been enrolled in FRENA in 24 participating Spanish centres. Of these patients, 974 (35%) had Type 2 diabetes. In all, 320 patients presented with coronary artery disease (myocardial infarction 194, angina 126), 281 with cerebrovascular disease (ischaemic stroke 231, transient ischaemic attack 50), 373 had peripheral artery disease (intermittent claudication 254, pain at rest 47, skin ulcers 72). Of the 974 patients, 480 (49%) had mean HbA_{1c} levels < 7% (< 53 mmol/mol) during follow-up (mean blood measurements 2.7 ± 2.0 per patient). Patients with missing HbA_{1c} measurements were not considered for the study.

There were some differences between patients according to their initial presentation: those presenting with peripheral artery disease were more likely to be male and current smokers; those with cerebrovascular disease had higher blood pressure levels during follow-up; and those with coronary artery disease more often used β-blockers and statins (Table 1). Moreover, a small proportion of patients in each subgroup had two (or three) underlying cardiovascular diseases simultaneously. Patients with mean HbA_{1c} levels < 7% (< 53 mmol/mol) were 2 years older and were more likely to have hypertension than those with mean HbA_{1c} levels > 7% (> 53 mmol/mol) (Table 2). They presented more frequently with cerebrovascular disease, their mean serum levels of cholesterol, triglycerides and glucose were lower and they received insulin or β-blockers less often.

Over a mean follow-up of 14 months (range 1–78 months), 126 patients (13%) had subsequent ischaemic events: myocardial infarction 43; ischaemic stroke 29; critical limb ischaemia 64 (29 patients underwent limb amputation). Of these, 19 patients (15%) died within 15 days of the subsequent event

Table 1 Clinical characteristics of the patients, according to their initial presentation

	CAD	CVD	PAD	*P*-value
Patients, *n*	320	281	373	
Clinical characteristics,				
Mean age (years ± SD)	68 ± 10	69 ± 9	68 ± 10	0.069
Gender (males)	202 (63%)	165 (59%)	287 (77%)	< 0.001
Body mass index (± SD)	29 ± 5	29 ± 4	29 ± 13	0.906
Underlying conditions				
Cancer	17 (5.3%)	11 (3.9%)	28 (7.5%)	0.136
Hypertension	245 (77%)	236 (84%)	285 (76%)	0.035
Current smokers	33 (10%)	41 (15%)	83 (22%)	< 0.001
Simultaneous artery disease				
Coronary artery disease	—	40 (14%)	101 (27%)	< 0.001
Cerebrovascular disease	23 (7.2%)	—	55 (15%)	0.016
Peripheral artery disease	46 (14%)	30 (11%)	—	0.176
Physical examination				
Sinus rhythm	281 (90%)	244 (89%)	310 (87%)	0.403
Mean SBP levels (mmHg)	134 ± 16	141 ± 16	142 ± 16	< 0.001
Mean DBP levels (mmHg)	74 ± 9	77 ± 9	73 ± 9	< 0.001
Mean laboratory levels,				
Creatinine clearance (ml/min)	70 ± 30	70 ± 28	73 ± 28	0.985
Total cholesterol (mmol/l)	4.5 ± 1.0	4.5 ± 1.0	4.6 ± 1.0	0.682
LDL cholesterol (mmol/l)	2.6 ± 0.7	2.6 ± 0.8	2.7 ± 0.8	0.901
Triglycerides (mmol/l)	1.7 ± 1.0	1.5 ± 0.7	1.9 ± 1.6	0.030
Glucose (mmol/l)	7.9 ± 2.0	7.8 ± 2.1	8.4 ± 2.5	0.489
HbA_{1c} (%)	7.2 ± 1.2	7.0 ± 1.3	7.3 ± 1.3	0.017
Drugs				
Diuretics	142 (44%)	148 (53%)	198 (53%)	0.044
Beta-blockers	239 (75%)	45 (16%)	89 (24%)	< 0.001
ACE inhibitors	174 (54%)	137 (49%)	164 (44%)	0.024
Angiotensin II antagonists	118 (37%)	137 (49%)	165 (44%)	0.012
Calcium antagonists	113 (35%)	104 (37%)	121 (32%)	0.459
Anti-platelets	298 (93%)	256 (91%)	322 (86%)	0.009
Anticoagulants	54 (17%)	33 (12%)	57 (15%)	0.197
Statins	278 (87%)	213 (76%)	293 (79%)	0.001
Insulin	119 (37%)	96 (34%)	168 (45%)	0.012
Oral anti-diabetic medication	202 (63%)	205 (73%)	258 (69%)	0.032

ACE, angiotensin-converting enzyme. CAD, coronary artery disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; PAD, peripheral artery disease; SBP, systolic blood pressure.

Table 2 Clinical characteristics of the patients according to mean HbA_{1c} levels during follow-up

	HbA_{1c} levels < 7% (< 53 mmol/mol)	HbA_{1c} levels > 7% (> 53 mmol/mol)	*P*-value
Patients, *n*	480	494	
Clinical characteristics,			
Mean age (years ± SD)	69 ± 9.5	67 ± 9.5	0.016
Gender (males)	330 (69%)	324 (66%)	0.293
Body mass index (± SD)	29 ± 4.6	29 ± 12	0.416
Underlying conditions			
Cancer	29 (6.0%)	27 (5.5%)	0.699
Hypertension	392 (82%)	374 (76%)	0.023
Current smokers	73 (15%)	84 (17%)	0.446
Clinical presentation			
Coronary artery disease	152 (32%)	168 (34%)	0.437
Cerebrovascular disease	159 (33%)	122 (25%)	0.004
Peripheral artery disease	169 (35%)	204 (41%)	0.051
Physical examination			
Sinus rhythm	414 (89%)	421 (89%)	0.935
Mean SBP levels (mmHg)	138 ± 16	137 ± 21	0.008
Mean DBP levels (mmHg)	74 ± 8.7	74 ± 9.4	0.735
Mean laboratory levels,			
Creatinine clearance (ml/min)	68 ± 26	70 ± 30	0.241
Total cholesterol (mmol/l)	4.4 ± 0.9	4.7 ± 1.0	< 0.001
LDL cholesterol (mmol/l)	2.6 ± 0.7	2.7 ± 0.8	0.016
Triglycerides (mmol/l)	1.5 ± 0.9	1.8 ± 1.4	< 0.001
Glucose (mmol/l)	6.9 ± 1.4	9.1 ± 2.4	< 0.001
HbA_{1c} (%)	6.2 ± 0.6	8.1 ± 1.0	< 0.001
Drugs			
Diuretics	234 (49%)	254 (51%)	0.405
Beta-blockers	167 (35%)	206 (42%)	0.027
ACE inhibitors	243 (51%)	232 (47%)	0.253
Angiotensin II antagonists	203 (42%)	217 (44%)	0.606
Calcium antagonists	172 (36%)	166 (34%)	0.465
Anti-platelets	434 (90%)	442 (89%)	0.625
Anticoagulants	71 (15%)	73 (15%)	0.995
Statins	381 (79%)	403 (82%)	0.385
Insulin	111 (23%)	272 (55%)	< 0.001
Oral anti-diabetic medication	375 (78%)	334 (68%)	< 0.001

Comparisons between patients: **P* < 0.05; †*P* < 0.01; ‡*P* < 0.001.
ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; SBP, systolic blood pressure.

(myocardial infarction 10, stroke 3, critical limb ischaemia 6). In addition, 35 patients (3.6%) were lost to follow-up. The incidence of subsequent ischaemic events was lower in patients with mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) than in those with HbA_{1c} levels > 7.0% (> 53 mmol/mol) (8.6 vs. 14 events per 100 patient-years; rate ratio 0.6; 95% CI 0.4–0.9), as shown in Table 3. They also had a lower mortality rate (3.1 vs. 5.4 deaths per 100 patient-years; rate ratio 0.6; 95% CI 0.3–0.99). However, only patients presenting with coronary artery disease had a lower incidence of subsequent events (5.3 vs. 13 per 100 patient-years; rate ratio 0.4; 95% CI 0.2–0.8). There were no differences in those with cerebrovascular disease (6.8 vs. 7.9; rate ratio 0.9; 95% CI 0.4–2.0) or peripheral artery disease (14 vs. 18; rate ratio 0.8; 95% CI 0.3–1.8).

On univariate analysis, a number of variables were associated with an increased incidence of subsequent events (Table 4). On multivariate analysis (including the patient's age, hypertension, clinical presentation as coronary artery disease, cerebrovascular disease or peripheral artery disease, mean systolic blood pressure levels, serum cholesterol, LDL cholesterol, triglycerides, glucose and HbA_{1c} levels, and the use of β-blockers, insulin and oral anti-diabetic medication) only age < 70 years, mean HbA_{1c} levels < 7% (< 53 mmol/mol), creatinine clearance levels > 60 ml/min and the use of statins were independently associated with a significantly lower risk for subsequent events (Table 5). On a multivariate analysis performed separately for each subgroup of patients (according to initial presentation), the relative risk for subsequent events was 0.5 (95% CI 0.3–1.0) in those presenting with coronary artery disease, 0.9 (95% CI 0.4–1.9) in those with cerebrovascular disease and 0.8 (95% CI 0.5–1.3) in patients with peripheral artery disease (Table 5).

Table 3 Incidence (per 100 patient-years) of subsequent ischaemic events, according to different vascular territories

	HbA_{1c} levels < 7% (< 53 mmol/mol)	HbA_{1c} levels > 7% (> 53 mmol/mol)	Rate ratio (95% CI)	*P*-value
All patients, *n*	480	494		
Follow-up (years)	650	589		
Myocardial infarction	2.8 (1.7–4.4)	4.4 (2.9–6.4)	0.6 (0.3–1.2)	0.147
Acute ischaemic stroke	2.2 (1.3–3.6)	2.6 (1.5–4.2)	0.9 (0.4–1.8)	0.672
Critical limb ischaemia	4.1 (2.7–5.9)	6.7 (4.8–9.1)	0.6 (0.4–1.01)	0.055
Subsequent ischaemic events	8.6 (6.5–11)	14 (11–17)	0.6 (0.4–0.9)	0.012
Overall death	3.1 (1.9–4.7)	5.4 (3.8–7.6)	0.6 (0.3–0.99)	0.045
CAD patients, *n*	152	168		
Follow-up (years)	235	205		
Myocardial infarction	4.3 (2.2–7.8)	8.9 (5.3–14)	0.5 (0.2–1.1)	0.074
Acute ischaemic stroke	0.4 (0.02–2.1)	2.5 (0.9–5.5)	0.2 (0.01–1.2)	0.086
Critical limb ischaemia	0.4 (0.02–2.1)	2.5 (0.9–5.4)	0.2 (0.01–1.3)	0.090
Subsequent ischaemic events	5.3 (2.9–8.9)	13 (8.9–19)	0.4 (0.2–0.8)	0.007
Overall death	2.1 (0.8–4.7)	4.9 (2.5–8.7)	0.4 (0.1–1.3)	0.131
CVD patients, *n*	159	122		
Follow-up (years)	203	149		
Myocardial infarction	1.0 (0.2–3.3)	2.1 (0.5–5.7)	0.5 (0.1–3.2)	0.445
Acute ischaemic stroke	4.1 (1.9–7.8)	4.1 (1.7–8.5)	1.0 (0.3–2.1)	0.995
Critical limb ischaemia	2.5 (0.9–5.6)	1.3 (0.2–4.4)	1.9 (0.4–14)	0.477
Subsequent ischaemic events	6.8 (3.8–11)	7.9 (4.1–14)	0.9 (0.4–2.0)	0.725
Overall death	2.5 (0.9–5.5)	5.4 (2.5–10)	0.5 (0.1–1.4)	0.178
PAD patients, *n*	169	204		
Follow-up (years)	212	235		
Myocardial infarction	2.9 (1.2–6.0)	2.2 (0.8–4.8)	1.3 (0.4–4.7)	0.648
Acute ischaemic stroke	2.4 (0.9–5.4)	1.7 (0.5–4.1)	1.5 (0.4–5.9)	0.627
Critical limb ischaemia	10 (6.3–15)	14 (9.9–20)	0.7 (0.4–1.2)	0.209
Subsequent ischaemic events	14 (10–21)	18 (13–24)	0.8 (0.5–1.3)	0.440
Overall death	4.7 (2.4–8.4)	6.0 (3.4–9.8)	0.8 (0.3–1.8)	0.582

CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.

Discussion

Diabetes mellitus is a well-established risk factor for arterial disease and several observational studies have shown a positive correlation between measures of glucose control and both subsequent ischaemic events and microvascular disease [1–3]. Consequently, some randomized controlled trials have aimed to assess whether more intensive control of glucose reduces long-term ischaemic events compared with less intensive control [10–13]. Unexpectedly, these trials failed to show consistent beneficial effects on subsequent ischaemic events or mortality. Such inconsistency has resulted in the American Heart Association and the American Diabetes Association providing a conservative class IIb recommendation, with level of evidence 'A' for the benefit of glucose control on cardiovascular disease[20]. Our data, obtained from a prospective series of consecutive stable outpatients with Type 2 diabetes and coronary artery disease, cerebrovascular disease or peripheral artery disease, confirm that those who had mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) had a lower incidence of subsequent ischaemic events than those with mean HbA_{1c} levels > 7.0% (> 53 mmol/mol). This lower incidence persisted after multivariate adjustment, but was only found in patients presenting with coronary artery disease, not in those with cerebrovascular disease or peripheral artery disease.

Our data are consistent with those in two recent meta-analyses, in which intensive glucose control resulted in a 15% reduction in events of coronary heart disease, but had no significant effect on events of stroke or all-cause mortality [21, 22]. Another meta-analysis found that only patients with no history of macrovascular disease achieved benefit from intensive glucose control, whereas those with prior vascular disease did not [23]. Our findings confirm and extend these observations, suggesting that the potential benefit of glucose control in patients with Type 2 diabetes may vary for different patient subgroups and that glucose-lowering regimens should be tailored to the individual patient.

The FRENA registry provides insights into the natural history of artery disease with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse patient outcomes and provide feedback from real-world clinical situations. However, our study also has potential limitations that should be addressed. First, the

Table 4 Risk factors for subsequent ischaemic events*

	New events *n* (%)	No events *n* (%)	Relative risk (95% CI)	*P*-value
Patients, *n*	126	848		
Clinical characteristics				
Age < 70 years	54 (43%)	514 (61%)	0.5 (0.3–0.7)	< 0.001
Gender (males)	80 (64%)	574 (68%)	0.8 (0.6–1.2)	0.349
Body mass index > 25 kg/m^2	95 (81%)	675 (83%)	0.7 (0.5–1.4)	0.574
Underlying conditions				
Cancer	11 (8.7%)	45 (5.3%)	1.7 (0.9–3.4)	0.123
Hypertension	34 (27%)	174 (21%)	1.4 (0.9–2.2)	0.098
Current smoking	21 (17%)	136 (16%)	1.0 (0.9–1.7)	0.858
Diabetes control				
Mean HbA_{1c} levels < 7% (< 53 mmol/mol)	53 (42%)	427 (50%)	0.7 (0.5–1.04)	0.082
Initial clinical presentation				
Coronary artery disease	37 (29%)	283 (33%)	0.8 (0.6–1.3)	0.371
Cerebrovascular disease	24 (19%)	257 (30%)	0.5 (0.3–0.9)	0.009
Peripheral artery disease	65 (52%)	308 (36%)	1.9 (1.3–2.7)	0.001
Physical examination				
Sinus rhythm	103 (82%)	732 (90%)	0.5 (0.3–0.9)	0.016
Mean SBP levels > 140 mmHg	52 (41%)	385 (46%)	0.8 (0.6–1.2)	0.372
Mean DBP levels > 90 mmHg	5 (4.0%)	41 (4.8%)	0.8 (0.3–2.1)	0.665
Mean laboratory levels				
Creatinine clearance > 60 ml/min	53 (42%)	525 (62%)	0.5 (0.3–0.7)	< 0.001
Total cholesterol > 4.9 mmol/l	48 (38%)	293 (35%)	1.2 (0.8–1.7)	0.447
LDL cholesterol > 2.6 mmol/l	70 (58%)	413 (50%)	1.4 (0.9–2.0)	0.100
Triglycerides > 2.2 mmol/l	23 (18%)	162 (19%)	1.0 (0.6–1.7)	0.900
Drugs				
Diuretics	74 (59%)	414 (49%)	1.5 (1.0–2.2)	0.038
Beta-blockers	41 (33%)	332 (39%)	0.8 (0.5–1.1)	0.154
ACE inhibitors	71 (56%)	404 (48%)	1.4 (0.97–2.1)	0.068
Angiotensin II antagonists	52 (41%)	368 (43%)	0.9 (0.6–1.3)	0.653
Calcium antagonists	41 (33%)	297 (35%)	0.9 (0.6–1.3)	0.585
Anti-platelets	106 (84%)	770 (91%)	0.5 (0.3–0.9)	0.020
Anticoagulants	34 (27%)	110 (13%)	2.5 (1.6–3.9)	< 0.001
Statins	92 (73%)	692 (82%)	0.6 (0.4–0.9)	0.023
Insulin	74 (59%)	309 (36%)	2.5 (1.7–3.6)	< 0.001
Oral anti-diabetic medication	87 (69%)	622 (73%)	0.8 (0.5–1.2)	0.314

*Univariate analysis.
ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; SBP, systolic blood pressure.

study is relatively small in size (974 patients) and, during a mean follow-up of 14 months, only 126 patients had subsequent ischaemic events (myocardial infarction 43, stroke 29, critical limb ischaemia 64). Second, despite our efforts to control any bias from underlying diseases, it is likely that we were unable to eliminate such bias completely. Thus, the better outcome associated with intensive glucose control in this study may reflect pre-existing, unrecognized, disease processes, even after making careful exclusions. Third, patients were not treated with a standardized regimen: treatment varied with local practice and is likely to have been influenced by a physician's assessment of a patient's risk of hypoglycaemia. Fourth, as all our patients had symptomatic artery disease, we do not know whether our conclusions may apply to other subgroups of patients with diabetes. Finally, we have no data about the duration of diabetes, but all patients had symptomatic artery disease and 39% were on insulin therapy, thus suggesting that most of them had a long duration.

This study also has several strengths. To the best of our knowledge, this is the first time the prognostic importance of intensive glucose control has been assessed in a study of stable outpatients with symptomatic, established arterial disease. Several measurements of serum HbA_{1c} levels during follow-up may have better reflected changes in glucose control after a cardiovascular event. Moreover, we did not exclude patients with underlying diseases or smoking history.

In summary, our findings reveal that stable outpatients with Type 2 diabetes and mean HbA_{1c} levels < 7.0% (< 53 mmol/mol) have a lower incidence of subsequent ischaemic events than those with HbA_{1c} levels > 7.0% (> 53 mmol/mol). These differences persisted after adjusting for potential confounders and were apparent only in patients with coronary artery disease.

Table 5 Risk factors for subsequent ischaemic events*

	Relative risk (95% CI)	*P*-value
All patients (*n* = 974),		
Age < 70 years	0.6 (0.4–0.9)	0.012
Mean HbA_{1c} levels > 7% (> 53 mmol/mol)	1.0 (reference)	—
Mean HbA_{1c} levels < 7% (< 53 mmol/mol)	0.6 (0.4–0.9)	0.013
Creatinine clearance levels > 60 ml/min	0.7 (0.4–1.0)	0.040
Statin therapy	0.6 (0.4–0.9)	0.011
Only patients with CAD (*n* = 320)		
Mean HbA_{1c} levels > 7% (> 53 mmol/mol)	1.0 (reference)	—
Mean HbA_{1c} levels < 7% (< 53 mmol/mol)	0.5 (0.3–1.0)	0.052
Creatinine clearance levels > 60 ml/min	0.2 (0.1–0.5)	0.001
Statin therapy	0.3 (0.2–0.7)	0.004
Only patients with CVD (*n* = 281)		
Mean HbA_{1c} levels > 7% (> 53 mmol/mol)	1.0 (reference)	—
Mean HbA_{1c} levels < 7% (< 53 mmol/mol)	0.9 (0.4–1.9)	0.732
Only patients with PAD (*n* = 373)		
Age < 70 years	0.6 (0.3–1.0)	0.083
Mean HbA_{1c} levels > 7% (> 53 mmol/mol)	1.0 (reference)	—
Mean HbA_{1c} levels < 7% (< 53 mmol/mol)	0.8 (0.5–1.3)	0.352

*Multivariate analysis.
CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral artery disease.

Competing interests

Nothing to declare.

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Appendix

Members of the FRENA Registry

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Smoking cessation and outcome in stable outpatients with coronary, cerebrovascular, or peripheral artery disease

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Abstract

Background: The influence of smoking cessation on outcome in patients with peripheral arterial disease (PAD) has not been thoroughly studied.

Methods: FRENA is an ongoing registry of stable outpatients with symptomatic coronary artery disease (CAD), cerebrovascular disease (CVD), or PAD. We compared the mortality rate of those who quit vs. those who continued smoking.

Results: As of December 2010, 3523 patients were recruited, of whom 1182 (34%) were current smokers. Of these, 475 patients (40%) had CAD, 240 (20%) had CVD, and 467 (40%) had PAD. In all, 512 patients (43%) quit smoking. Over a mean follow-up of 14 months, 32 patients (2.7%) died and 95 (8.0%) had subsequent ischaemic events (myocardial infarction 32, ischaemic stroke 20, critical limb ischaemia/disabling claudication 53). In patients with CAD, the mortality rate was significantly lower in recent quitters (0.77 vs. 3.73 deaths per 100 patient-years; $p = 0.013$) than in persistent smokers. No quitter with CVD died (0.0 vs. 2.18 deaths; $p = 0.092$); but in patients with PAD there was a trend towards a higher mortality in quitters than in those who continued smoking (4.29 vs. 2.27 deaths; $p = 0.357$). On multivariate analysis, the relative risk for death in quitters was 0.20 (95% CI 0.05–0.75) in patients with CAD, 0.0 in those with CVD, and 1.83 (95% CI 0.65–5.15) in those with PAD.

Conclusions: Smoking cessation was associated with a significant decrease in mortality in patients with CAD, a non-significant decrease in those with CVD, and a non-significant increase in those with PAD.

Keywords

Arterial disease, mortality, secondary prevention, smoking

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Introduction

Smoking cessation by apparently healthy people is associated with lower cardiovascular morbidity and mortality than in those who continue smoking.[1–7] A number of observational studies in patients with either coronary artery disease (CAD)[8–14] or cerebrovascular artery disease (CVD)[15,16] suggest that smoking cessation may also be associated with a lower mortality rate, but there is few available information on its influence on outcome in patients with peripheral artery disease (PAD). Consequently, guidelines in this area are

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based on experts' consensus rather than on clinical evidence.[17–20]

The FRENA (Factores de Riesgo y ENfermedad Arterial) Registry was initiated in March 2003 to prospectively record the current clinical management and outcome of stable outpatients with arterial disease in Spanish hospitals.[21,22] It is an ongoing, multicentre, observational registry of consecutive patients designed to gather and analyse data on treatment patterns and outcomes in patients with symptomatic ischaemic disease of the heart, brain, and/or major peripheral arteries. Data from this registry have been used to study the influence of body weight, glucose control, alcohol consumption, or concomitant use of proton-pump inhibitors and clopidogrel on outcome.[21–25] The aim of the current study was to compare the mortality rate and the incidence of subsequent ischaemic events in quitters vs. persistent smokers.

Patients and methods

Inclusion criteria

Participating hospitals in the FRENA registry prospectively enrolled consecutive outpatients with symptomatic artery disease with at least one recent (<3 months prior to enrolment) episode of CAD (manifesting as acute coronary syndrome), CVD (manifesting as ischaemic stroke), or PAD (either intermittent claudication with an ankle-brachial index <0.9 or previous vascular intervention or limb amputation for PAD). The Fontaine classification was used for categorization of PAD.[26] All patients provided oral consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Study design

At baseline, data on demographics, risk factors, comorbidities, and drug therapy were collected. At follow-up visits every 4 months, smoking was assessed with the question, 'Is the patient currently smoking?' Answer options were 'yes' and 'no'. Currently smoking was defined as smoking at least one cigarette (or cigar or pipe) per day within the last month. Patients were categorized as never smokers, former smokers (ex-smokers who quit before entry in the FRENA Registry), recent quitters (those that reported not smoking at the first visit but who were current smokers at study entry), or persistent smokers (those who were smokers at study entry and reported smoking at any visit during follow-up). For the current study, only recent quitters and persistent smokers were considered. The primary outcome was all-cause mortality during follow-up. Secondary outcome was the incidence of subsequent ischaemic events (i.e. myocardial infarction, ischaemic stroke, or disabling claudication/ critical limb ischaemia).

Definitions

Myocardial infarction was defined as a transient increase of creatine-kinase-MB or troponin in patients with ischaemic symptoms and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischaemic stroke was diagnosed if the patient had an appropriate clinical event not resolving completely within 24 hours, and had a brain computed tomography or magnetic resonance imaging scan that showed a compatible low-density lesion. Disabling claudication/critical limb ischaemia was considered in patients with intermittent claudication when needing angioplasty, stenting, or surgery. In patients with Fontaine stages III or IV, critical limb ischaemia was considered when needing amputation. A patient was classified as having diabetes when there was a clinical history of diabetes or when they were taking insulin or oral antidiabetic agents. Patients were classified as having hypertension when there was a clinical history of hypertension or when they were taking antihypertensive medications. Creatinine clearance was calculated according to the Cockcroft and Gault formula.[27]

Follow-up

A detailed history was performed on all patients at study entry (<3 months after an acute ischaemic episode). Comorbid conditions were characterized, including a history of CAD, CVD, or PAD, diabetes mellitus, hypertension, hyperlipidaemia, chronic lung disease, chronic heart failure, cancer, smoking status, and alcohol consumption. Then, physical examination was performed comprising weight, height, heart rate, and blood pressure on standard conditions, after 5 min of rest. An electrocardiogram was also recorded. After the initial visit, patients were followed up at 4-month intervals for at least 12 months. At these visits, any change in medical history and data from physical examination were recorded, with special attention to risk factors, laboratory tests, lifestyle habits, the type, dose, and duration of treatment received, and clinical outcome. Physicians were allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns. They also provided to their patients a list of smoking cessation programmes and resources in their community and encouraged them to use stop medication aids.

Data collection

The attending physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. Patient identities remain confidential because they were identified by a unique number assigned by the study coordinating centre, which was responsible for all data management. Data quality was regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals, by contract research organizations, who compared the medical records with the data in the web. A data audit was performed at periodic intervals.

Statistical analysis

Categorical variables were compared using the chi-squared test (two-sided). Odds ratios and corresponding 95% confidence intervals were calculated, and a p-value <0.05 was considered to be statistically significant. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the rate ratio.[28] The association between smoking status and mortality was assessed using a forward stepwise logistic regression analysis. Significance level of $p < 0.10$ was considered to include variables and $p > 0.15$ to exclude variables in the final multivariate model. We used Kaplan–Meier plots to estimate the association of smoking status with the risk to die. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS).

Results

As of December 2010, 3523 patients were recruited in the FRENA registry, of whom 1182 (34%) were current smokers. Of these, 475 patients (40%) had CAD, 240 (20%) had CVD, and 467 (40%) had PAD. In all, 512 patients (43%) quit smoking and 670 continued smoking: 556 (83%) smoked cigarettes (10 ± 6.9 cigarettes/day), 43 (6.4%) smoked cigars (3.6 ± 4.5 cigars/day), and 57 all kinds of tobacco. Patients presenting with myocardial infarction more likely quit (60%), while those with intermittent claudication more likely continued smoking (75%), as shown in Table 1. When overall considered, recent quitters were 2 years younger and less likely had chronic lung disease than persistent smokers. During follow-up, quitters had lower mean levels of systolic blood pressure and total cholesterol or high-density lipoprotein cholesterol, but had higher creatinine clearance levels than persistent smokers. In addition, quitters more likely received beta-blockers or angiotensin-converting enzyme inhibitors.

Over a mean follow-up of 14 months (range 2–56 months), 32 patients (2.7%) died and 95 (8.0%) had subsequent ischaemic events (myocardial infarction 32, stroke 20, critical limb ischaemia/disabling claudication 53). In patients with CAD, the mortality rate was significantly lower in quitters (0.77 vs. 3.73 deaths per 100 patient-years; rate ratio: 0.21, 95% CI 0.05–0.73) than in persistent smokers (Table 2). No quitter with CVD died, but in patients with PAD there was a trend towards more deaths among quitters (4.29 vs. 2.27 deaths; $p = 0.357$). In patients with CAD, the improved survival started beyond the sixth month (Figure 1). In those with PAD, there were no differences at all (Figure 2). Most deaths in patients with CAD (75%), but only 44% of deaths in those with PAD were due to cardiovascular reasons (Table 3). As for the incidence of subsequent ischaemic events (myocardial infarction, ischaemic stroke, or critical limb ischaemia/disabling claudication), there were no differences between quitters and persistent smokers in any subgroup (Table 2).

Patients who died were significantly older, more likely had chronic lung disease, diabetes, atrial fibrillation, or renal insufficiency, and more frequently received anticoagulants or insulin, but less likely received statins than those who survived (Table 4). Among patients who continued smoking, there were no differences in the daily number of cigarettes between those who died and those who did not (7.1 ± 7.2 vs. 10 ± 6.9, respectively; $p = 0.301$). Multivariate analysis confirmed that quitters with CAD had a significantly lower mortality than persistent smokers (relative risk 0.20, 95% CI 0.05–0.75) and there was a trend towards a lower mortality in quitters with CVD (Table 5). However, quitters with PAD had a trend towards a higher mortality. The relative risk was 1.70 (95% CI 0.51–5.68) in patients with Fontaine stage II, 1.47 (95% CI 0.49–4.35) in those with Fontaine stage III, and 2.31 (95% CI 0.21–25.6) in those with Fontaine stage IV.

Discussion

A number of observational studies consistently found that smoking cessation rapidly decreases the incidence of subsequent myocardial infarction and stroke and the mortality rate in patients with CAD or CVD.[8–16] However, few studies have examined the effects of smoking cessation on outcome in patients with PAD,[29–33] and most of them had a small sample size and were conducted at a time when medical therapy was not as effective as it is today. Theoretically, similar benefits could be expected in patients presenting with

Table 1. Clinical characteristics and therapeutic details of the 1182 patients, according to their current smoking habit

	Quitters ($n = 512$)	Persistent smokers ($n = 670$)	p-value
Clinical characteristics			
Age (years)	59 ± 11	61 ± 11	0.004
Gender (males)	467 (91)	614 (92)	NS
Body mass index (kg/m^2)	28 ± 5	27 ± 4	NS
Underlying diseases			
Cancer	23 (4.5)	29 (4.3)	NS
Chronic lung disease	70 (14)	137 (21)	0.002
Chronic heart failure	12 (2.3)	14 (2.1)	NS
Hypertension	290 (57)	387 (58)	NS
Diabetes	363 (71)	439 (66)	0.069
Clinical presentation			
Angina	34 (6.6)	40 (6.0)	NS
Myocardial infarction	241 (47)	160 (24)	<0.001
Ischaemic stroke	87 (17)	106 (16)	NS
Transient ischaemic attack	18 (3.5)	29 (4.3)	NS
Intermittent claudication	95 (19)	287 (43)	<0.001
Ischaemic pain at rest	24 (4.7)	27 (4.0)	NS
Ischaemic skin lesions	13 (2.5)	21 (3.1)	NS
Physical examination			
Atrial fibrillation	11 (2.1)	12 (1.8)	NS
SBP (mmHg)	130 ± 17	136 ± 17	<0.001
DBP (mmHg)	75 ± 9	75 ± 10	NS
Laboratory levels			
CrCl (ml/min)	87 ± 29	83 ± 31	0.017
Total cholesterol (mg/dl)	179 ± 37	184 ± 38	0.025
HDL cholesterol (mg/dl)	59 ± 23	65 ± 27	<0.001
LDL cholesterol (mg/dl)	108 ± 31	111 ± 35	NS
Glucose (mg/dl)	117 ± 34	117 ± 39	NS
Drugs			
Diuretics	128 (25)	180 (27)	NS
Beta-blockers	271 (53)	213 (32)	<0.001
ACE inhibitors	253 (50)	293 (44)	0.057
Angiotensin-II antagonists	111 (22)	174 (26)	0.083
Calcium antagonists	95 (19)	130 (20)	NS
Antiplatelets	485 (95)	641 (96)	NS
Anticoagulants	54 (11)	40 (6.0)	0.004
Statins	430 (84)	541 (81)	NS
Insulin	45 (8.8)	76 (11)	NS
Oral antidiabetics	125 (25)	180 (27)	NS

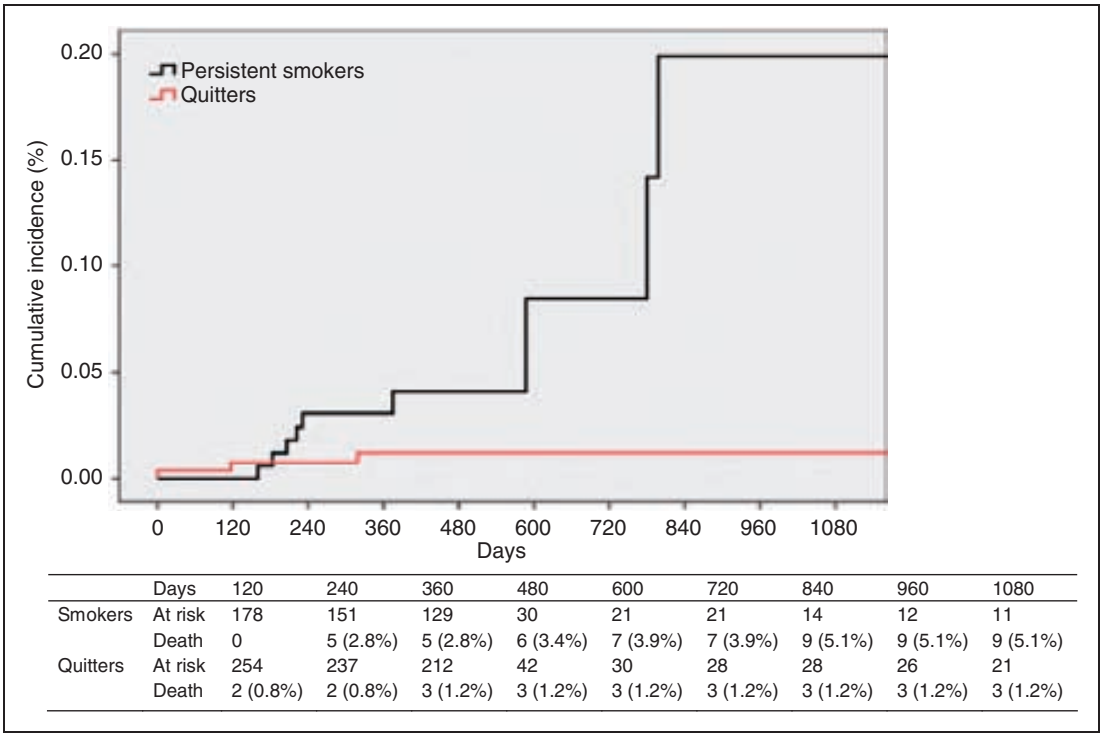
Values are mean±standard deviation or n (%). ACE, angiotensin-converting enzyme; CrCl, creatinine clearance; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, non-significant; SBP, systolic blood pressure.

CAD, CVD, or PAD, but our data do not support this hypothesis. Our data confirm that smoking cessation was associated with a substantially lower mortality rate in patients with recent myocardial infarction and a marginally lower mortality rate in patients with CVD, but quitters with PAD had a slightly (non-significantly) higher mortality than persistent smokers. This worse outcome was consistently found in patients presenting at different stages of the disease (Fontaine stages II, III, or IV) and persisted after multivariate adjustment.

Table 2 . Clinical outcomes according to type of disease and smoking habit

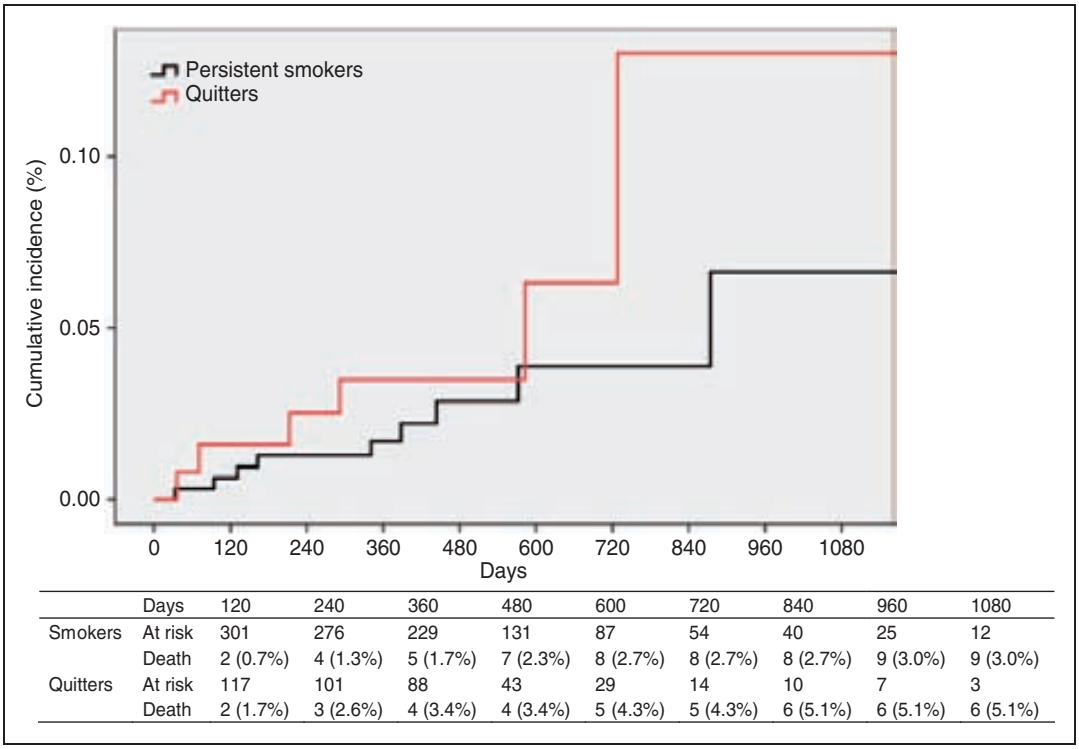
	Quitters	Persistent smokers	Rate ratio (95% CI)	*p*-value
CAD patients (*n*)	275	200		
Follow-up (years)	389	241		
Myocardial infarction	2.32 (1.13–4.25)	3.32 (1.54–6.30)	0.70 (0.26–1.88)	NS
Acute ischaemic stroke	0.26 (0.13–1.27)	0	–	NS
Disabling claudication/CLI	0.26 (0.13–1.27)	0.41 (0.02–2.05)	0.62 (0.02–24.2)	NS
Any of the above	2.32 (1.13–4.25)	3.32 (1.54–6.30)	0.70 (0.26–1.88)	NS
Overall death	0.77 (0.20–2.10)	3.73 (1.82–6.85)	0.21 (0.05–0.73)	0.013
CVD patients (*n*)	105	135		
Follow-up (years)	149	183		
Myocardial infarction	1.34 (0.22–4.43)	1.09 (0.18–3.60)	1.23 (0.13–11.8)	NS
Acute ischaemic stroke	4.02 (1.63–8.37)	1.64 (0.42–4.45)	2.46 (0.61–12.0)	NS
Disabling claudication/CLI	0.67 (0.34–3.31)	1.10 (0.18–3.60)	0.61 (0.02–8.08)	NS
Any of the above	4.69 (2.05–9.28)	2.73 (1.00–6.04)	1.72 (0.53–5.93)	NS
Overall death	0	2.18 (0.69–5.26)	0.0 (0.0–1.37)	0.092
PAD patients (*n*)	132	335		
Follow-up (years)	140	438		
Myocardial infarction	2.86 (0.91–6.89)	1.60 (0.70–3.16)	1.79 (0.46–6.17)	NS
Acute ischaemic stroke	1.43 (0.24–4.72)	1.82 (0.84–3.45)	0.78 (0.11–3.38)	NS
Disabling claudication/CLI	9.29 (5.16–15.5)	7.95 (5.62–10.9)	1.16 (0.59–2.16)	NS
Any of the above	11.4 (6.76–18.2)	11.4 (8.52–14.8)	1.00 (0.55–1.73)	NS
Overall death	4.29 (1.74–8.91)	2.27 (1.15–4.05)	1.88 (0.63–5.18)	NS

Values are incidence per 100 patient-years (95% confidence interval). CAD, coronary artery disease; CLI, critical limb ischaemia; CVD, cerebrovascular disease; NS, non-significant; PAD, peripheral artery disease.



	Days	120	240	360	480	600	720	840	960	1080
Smokers	At risk	178	151	129	30	21	21	14	12	11
	Death	0	5 (2.8%)	5 (2.8%)	6 (3.4%)	7 (3.9%)	7 (3.9%)	9 (5.1%)	9 (5.1%)	9 (5.1%)
Quitters	At risk	254	237	212	42	30	28	28	26	21
	Death	2 (0.8%)	2 (0.8%)	3 (1.2%)	3 (1.2%)	3 (1.2%)	3 (1.2%)	3 (1.2%)	3 (1.2%)	3 (1.2%)

Figure 1. Cumulative mortality during the first 3 years of follow-up for patients with coronary artery disease.



	Days	120	240	360	480	600	720	840	960	1080
Smokers	At risk	301	276	229	131	87	54	40	25	12
	Death	2 (0.7%)	4 (1.3%)	5 (1.7%)	7 (2.3%)	8 (2.7%)	8 (2.7%)	8 (2.7%)	9 (3.0%)	9 (3.0%)
Quitters	At risk	117	101	88	43	29	14	10	7	3
	Death	2 (1.7%)	3 (2.6%)	4 (3.4%)	4 (3.4%)	5 (4.3%)	5 (4.3%)	6 (5.1%)	6 (5.1%)	6 (5.1%)

Figure 2. Cumulative mortality during the first 3 years of follow-up for patients with peripheral artery disease.

Table 3 . Causes of death according to disease and smoking habit

	Coronary artery disease		Cerebrovascular disease		Peripheral artery disease	
	Quitters ($n=275$)	Smokers ($n=200$)	Quitters ($n=105$)	Smokers ($n=135$)	Quitters ($n=132$)	Smokers ($n=336$)
Sudden death	1 (0.4)	4 (2.0)	0	0	1 (0.8)	1 (0.3)
Fatal critical limb ischaemia	0	0	0	0	2 (1.5)	2 (0.6)
Heart insufficiency	1 (0.4)	1 (0.5)	0	1 (0.7)	0	0
Fatal myocardial infarction	0	1 (0.5)	0	0	1 (0.8)	0
Fatal ischaemic stroke	0	1 (0.5)	0	1 (0.7)	0	0
Bleeding	0	0	0	0	1 (0.8)	2 (0.6)
Infection	0	0	0	1 (0.7)	0	2 (0.6)
Disseminated cancer	1 (0.4)	0	0	0	1 (0.8)	0
Chronic lung disease	0	1 (1.5)	0	1 (0.7)	0	0
Liver cirrhosis	0	0	0	0	0	1 (0.3)
Unknown	0	1 (1.5)	0	0	0	2 (0.6)

Values are *n* (%).

Thus, our data suggest that the benefit of smoking cessation on survival may be lower in patients with PAD than in those with CAD. Alternatively, we hypothesize that any possible benefit in patients with PAD would need a longer follow-up to be found.

There is increasing evidence suggesting that different arterial risk factors may have a more intense effect on specific arterial beds. It is conceivable that PAD patients represent the end stage of the disease spectrum of atherosclerosis and that interventions that are beneficial at early stages of the disease process may not be beneficial when the disease process reaches the end stage. In autopsy studies, coronary arteries have a high prevalence of plaques, with lipid core plaques

Table 4 . Risk factors for mortality: univariate analysis

	Death ($n = 32$)	No death ($n = 1150$)	p-value
Clinical characteristics			
Age >60 years	25 (78)	569 (50)	0.002
Gender (males)	30 (94)	1051 (91)	NS
Body mass index >27 kg/m^2	12 (41)	580 (52)	NS
Underlying diseases			
Cancer	5 (16)	47 (4.1)	0.011
Chronic lung disease	13 (41)	194 (17)	<0.001
Chronic heart failure	1 (3.1)	25 (2.2)	NS
Hypertension	22 (69)	655 (57)	NS
Diabetes	16 (50)	360 (31)	0.018
Smoking habit			
Quitters	9 (28)	499 (44)	0.090
Initial clinical presentation			
Coronary artery disease	12 (38)	458 (40)	NS
Cerebrovascular disease	4 (13)	238 (21)	NS
Peripheral artery disease	16 (50)	451 (39)	NS
Physical examination			
Atrial fibrillation	3 (9.4)	20 (1.7)	0.002
Mean SBP >140 mmHg	13 (41)	395 (34)	NS
Mean DBP >90 mmHg	2 (6.3)	70 (6.1)	NS
Mean laboratory levels			
Creatinine clearance <60 ml/min	18 (60)	208 (19)	<0.001
Total cholesterol >190 mg/dl	8 (28)	433 (39)	NS
LDL cholesterol >100 mg/dl	14 (58)	644 (60)	NS
Glucose >100 mg/dl	23 (79)	687 (61)	0.080
Drugs			
Diuretics	13 (41)	295 (26)	NS
Beta-blockers	12 (38)	472 (41)	NS
ACE inhibitors	14 (44)	532 (46)	NS
Angiotensin-II antagonists	7 (22)	278 (24)	NS
Calcium antagonists	7 (22)	218 (19)	NS
Antiplatelets	29 (91)	1097 (96)	NS
Anticoagulants	9 (28)	85 (7.4)	0.001
Statins	19 (59)	952 (83)	<0.001
Insulin	7 (22)	114 (9.9)	0.015
Oral antidiabetics	6 (19)	299 (26)	NS

Values are *n* (%). ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; LDL, low-density lipoprotein; SBP, systolic blood pressure.

being more frequent than fibrous plaques, carotid arteries have more foam cell lesions, and femoral arteries are rich in fibrous plaques, while foam cell lesions are rare.[34–36] Since cigarette smoking impairs flow-mediated, endothelium-dependent arterial vasodilatation,[37] these anatomic differences might partly explain why the effects of smoking cessation on outcome may differ among patients presenting with CAD, CVD, or PAD.

The classic arterial risk factors have different impact in different arterial territories. Cholesterol is particularly important in CAD, hypertension in CVD, and smoking and diabetes in PAD. There is considerable evidence showing that smoking is a potent risk factor for symptomatic PAD, with a consistent dose–response relationship. However, only few studies have examined the effects of smoking cessation on survival in patients with PAD, and most of them had a small sample size,

Table 5 . Risk factors for mortality: multivariate analysis

	All patients	Coronary artery disease	Cerebrovascular disease	Peripheral artery disease
Underlying diseases				
Cancer	3.59 (1.34–9.64)	4.98 (0.62–40.3)	–	2.59 (0.75–8.91)
Diabetes	5.42 (2.33–12.6)	–	–	3.24 (1.12–9.37)
Smoking habit				
Quitters	0.51 (0.22–1.15)	0.20 (0.05–0.75)	0	1.83 (0.65–5.15)
Physical examination				
Atrial fibrillation	6.78 (1.89–24.3)	10.0 (1.19–84.6)	–	22.2 (4.27–116)
Mean serum levels				
CrCl <60 ml/min	4.43 (2.09–9.40)	–	–	13.8 (3.74–51.2)
Drugs,				
Anticoagulants	–	–	16.6 (1.71–161)	–
Insulin	–	2.77 (0.58–13.1)	–	–

Values are relative risk (95% confidence interval). CrCl, creatinine clearance.

and limited information on confounding factors.[37–42] They suggest a potential benefit, but since it is conceivable that successful smoking cessation is associated with the control of additional risk factors and preventive medications, the favourable results could result from these confounding factors.

The FRENA registry provides insights into the natural history of artery disease with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse patient outcomes and provide feedback from real-world clinical situations which may be valuable when designing new randomized clinical studies. Despite our efforts to control any bias from underlying diseases, it is likely that we were unable to eliminate such bias completely. Finally, information on current smoking was self-reported and not validated by any biochemical marker. Self-reported smoking habits, however, have been found to be accurate in studies of different populations.[43,44]

Some limitations of our research merit emphasis. First, in our study, quitters were 2 years younger, had fewer comorbidities, and more likely received beta-blockers or angiotensin-converting enzyme inhibitors than persistent smokers. Thus, the different outcome in this study may reflect pre-existing, unrecognized diseases, even after making careful exclusions. Hence, despite our efforts to control any bias from underlying diseases, it is likely that we were unable to eliminate such bias completely. Second, people who quit smoking may have a different lifestyle from people who do quit, and the apparent healthy effects associated with smoking cessation may be mostly due to favourable risk profiles in quitters. Third, the definitions of quitting and persistent smoking relied on self-report, with no biological validation of smoking status. Thus, overreporting of smoking cessation seems possible and the effects of smoking cessation on outcome might have been underestimated. Fourth, patients were recruited from medical centres that provide specialty care for patients with arterial disease. It is possible that this patient population is not representative of all patients with CAD, CVD, or PAD, such as those primarily managed in primary care. Finally, since the events rate for mortality in our series was low (2.7%), the direct comparison between the two groups could be misleading. Unfortunately, randomized controlled trials to assess the influence of smoking cessation in patients with arterial disease are not feasible for several reasons, including ethical considerations, so we have to rely on data from observational studies.

The strengths of the study include its prospective design and the homogeneous study sample, which may have reduced confounding. The study had detailed records of the blood pressure levels, laboratory tests, and use of preventive medications at follow-up visits, enabling us to assess the effects of these important potential confounders. The information on smoking habit at regular intervals during follow-up may have better reflected changes after a cardiovascular event. Moreover, we did not exclude patients with underlying diseases, recent weight loss, or cancer.

In summary, our data confirm that after an arterial event, smoking cessation was associated with a significant decrease in mortality in patients with CAD, a non-significant decrease in those with CVD, and a non-significant increase in those with PAD. The findings in this study complement our knowledge regarding the impact of smoking cessation on outcome in patients with arterial disease, since any differences between current smokers and quitters are of interest.

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3-RESULTADOS Y DISCUSIÓN

3-RESULTADOS Y DISCUSIÓN:

Los resultados y las conclusiones obtenidas del registro son un proceso evolutivo iniciado en 2002.

En septiembre del 2007 fue publicado ***Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA)*** **en el** *European Journal of Internal Medicine.* Este artículo a pesar de no formar parte fundamental de la tesis fue el primero de un grupo de artículos que seguían una misma temática y mostraban resultados en su mayoría, de un mismo grupo de pacientes seguidos en el tiempo. He considerado oportuno añadirlo en el apartado Anexos para acabar de obtener una visión más completa del efecto de la aterotrombosis en nuestro grupo de pacientes.

En septiembre del 2009 con la publicación de ***Differences in cardiovascular mortality in smokers, past-smokers and non-smokers. Findings from the FRENA Registry*** en el *European Journal of Internal Medicine,* se presentaron los resultados obtenidos de 2501 pacientes, intentando dar respuesta a la controversia existente en la influencia del hábito tabáquico en la aparición de eventos isquémicos en pacientes con enfermedad coronaria y obtener más información de su efecto en los pacientes con EAP (Enfermedad arterial perifèrica) y ECV (Enfermedad cerebrovascular).
De los pacientes incluidos el 18% (439) eran fumadores, el 43% (1086) ex fumadores y el 39% (976) nunca había fumado. Tras un seguimiento de 14 meses murieron 123 pacientes (pero sólo 68 de muerte cardiovascular). En el análisis multivariante, los fumadores presentaron de forma significativa una menor mortalidad cardiovascular: 1.1 (95% CI: 0.4-2.4) por 100 pacientes-año, 1.9 (95% CI: 1.2-2.8) los exfumadores; y 3.5 (95% CI: 2.5-4.7) los no fumadores, sin encontrarse diferencias entre los pacientes con EAP, ECV o EC (Enfermedad coronaria).

La media de edad de la mortalidad cardiovascular fue de 82 +/-6.4, 70 +/-9.9 y 67 +/-15 años respectivamente.

Esta reducción en la muerte cardiovascular fue encontrada de forma consistente en los pacientes con EC, ECV y EAP, pero desapareció después del ajuste multivariante. Diversos estudios de cohortes han mostrado que los pacientes fumadores que presentaban un infarto de miocardio tenían una mejor evolución que los no fumadores, estos hallazgos aparentemente contradictorios son conocidos como "smoker's paradox". En este artículo encontramos también esta paradoja en el grupo de pacientes con EAP y ECV. La explicación que encontramos fue que la baja mortalidad del grupo de pacientes fumadores estaba justificada por la diferencia de edad, eran 10 años más jóvenes que los no fumadores, además presentaban con menos frecuencia otros factores de complicación como hipertensión, diabetes o insuficiencia cardiaca.

En el análisis multivariante el hábito tabáquico no se asoció de forma independiente con un menor riesgo de muerte cardiovascular.

Dejar de fumar supone la mejor medida para reducir la progresión de la aterosclerosis en este grupo de pacientes.

En enero del 2011 se publicó en el *Diabetic Medicine* el artículo ***Glucose control and outcome in patients with stable diabetes and previous coronary, cerebrovascular or peripheral artery diseasee. Findings from the FRENA Registry*** con la intención de resolver la controversia sobre si el control estricto de la glicemia en los pacientes diabéticos tipo 2 reducía el riesgo de nuevos eventos cardiovasculares.

La diabetes mellitus es un claro factor de riesgo cardiovascular y por este motivo algunos ensayos controlados y randomizados han intentado evaluar si un control estricto de las glicemias se asociaba a una reducción de los eventos isquémicos a largo plazo. Sin embargo estos estudios no han mostrado efectos beneficiosos de forma consistente en la aparición de eventos isquémicos, ni en la reducción de la mortalidad.

En nuestro artículo el seguimiento se realizó a un total de 974 pacientes diabéticos tipo 2, de los cuales el 49% (480) presentaban un nivel de HbA1c

<7%. Tras un seguimiento de 14 meses, el 13% (126) presentaron un evento isquémico. En forma de infarto de miocardio (43), como acidente vascular cerebral (29) o como isquemia crítica (64).
La incidencia de estos eventos fue significativamente baja entre los pacientes con una HbA1c baja, comparada con la de los pacientes con una HbA1c >7% (8.6 vs 14 por 100 pacientes-año; RR 0.6; 95% CI 0.4-0.9).
Las diferencias persistieron tras el ajuste de los factores de confusión. Sin embargo esta mejor evolución sólo se presentó en los pacientes con enfermedad coronaria (RR 0.4; 95% CI 0.2-0.8), no en aquellos con enfermedad cerebrovascular (RR 0.9; 95% CI 0.4-2.0) o enfermedad arterial periférica (RR 0.8; 95% CI 0.5-1.3).
Si se objetivó una menor mortalidad (RR 0.6; 95% CI 0.3-0.99) en los pacientes con unos niveles de HbA1c <7%.
Posiblemente el potencial beneficio del control glicémico en los pacientes diabéticos tipo 2 pueda variar entre diferentes subgrupos, por este motivo el control debería ser individualizado a cada paciente.

Finalmente se publicó en Octubre del 2011 en *European Journal of Cardiovascular Prevention and Rehabilitation* el artículo ***Smoking cessation and outcome in stable outpatients with coronary, cerebrovascular or peripheral artery disease*** con un total de 3523 pacientes en el registro. La intención del artículo fue conocer si existía un beneficio en la reducción de eventos cardiovasculares y en la muerte de origen cardiovascular entre los paciente con enfermedad arterial sintomática que habían dejado de fumar.
Del total de pacientes el 34% (1182) eran fumadores activos. De ellos el 40% (475) presentaban enfermedad coronaria, el 20% (240) presentaban enfermedad cerebrovascular y el 40% (467) enfermedad arterial periférica. De todos ellos el 43% dejó de fumar (512).
Durante el seguimiento, que fue de 14 meses, murieron 32 pacientes (2.7%) y 95 (8%) presentaron eventos isquémicos (infarto de miocardio 32, accidente vascular cerebral 20 y complicación isquémica periférica 53). Entre los pacientes con enfermedad coronaria la mortalidad fue significativamente menor

entre los reciente ex fumadores (0.77 vs 3.73 muertes por 100 pacientes-año; p=0.013) que entre los que habían seguido fumando. No hubo muertes entre los pacientes con ECV (0.0 vs. 2.18 muertes; p=0.092), pero si existió una tendencia hacía una mayor mortalidad entre los ex fumadores del grupo de pacientes con EAP (4.29 vs.2.27 muertes; p=0.357). Tras el análisis multivariante, el riesgo relativo de muerte entre los fumadores fue de 0.20 (95% CI: 005-0.75) en los pacientes con EC, 0 (95% CI: 0.0-@) en aquellos con ECV y 1.83 (95% CI: 0.65-5.15) entre los pacientes con EAP.

La mayoría de estudios que muestran un beneficio al dejar de fumar en pacientes con enfermedad arterial establecida son de pacientes que presentan enfermedad coronaria. Existe poca información sobre el hipotético beneficio que se presentaría en los pacientes con enfermedad en otros territorios.

En nuestro estudio, con 14 meses de seguimiento, se confirma el beneficio de dejar de fumar, reduciéndose la mortalidad, pero sólo en el grupo de pacientes con enfermedad coronaria, no en los pacientes con enfermedad cerebrovascular ni en los pacientes con enfermedad arterial periférica.

La aterosclerosis presenta diferentes características según el territorio afectado y las características de las placas de ateroma pueden presentar una diferente composición que la predisponga a una futura complicación. Las arterias coronarias como hemos comentado, presentan placas con un gran núcleo lipídico extracelular, con una gran densidad de macrófagos saturados de lípidos y convertidos en células espumosas. A nivel periférico, en las extremidades inferiores, las placas son más estenosantes y fibróticas, con una composición diferente. Estas características diferenciales podrían justificar una diferente respuesta al efecto de dejar de fumar. Además, el mecanismo más importante en la aparición de eventos cardiovasculares agudos es el estado de hipercoagulabilidad que acaba originando la trombosis aguda. El tabaco actúa a diferentes niveles, pero principalmente aumenta los niveles de fibrinógeno, promoviendo la aterogénesis e incrementa la viscosidad sanguínea mediante la poliglobulia producida por el CO, la activación y agregación plaquetaria y la estimulación protrombótica de los factores de coagulación. Este beneficio de dejar de fumar a corto plazo puede ser más acusado en los pacientes con enfermedad coronaria, ya que como hemos comentado los síntomas relacionados

con los síndromes agudos presentan una menor relación con el crecimiento progresivo de la placa, y más con su degeneración y rotura, provocando una trombosis secundaria sobre una placa poco estenosante.

4-CONCLUSIONES FINALES

4-CONCLUSIONES FINALES:

La aterotrombosis es un proceso progresivo, generalizado y difuso que se puede manifestar en varios lechos vasculares y representa la principal causa de muerte y discapacidad en nuestra sociedad .

La complicación trombótica de una placa aterosclerótica inestable conlleva graves consecuencias clínicas, como el ictus isquémico, el infarto de miocardio y la enfermedad arterial periférica. A pesar de ser manifestaciones de una misma enfermedad, el comportamiento de la placa aterosclerótica es diferente según el territorio afectado y los factores de riesgo, como el tabaco y la diabetes, pueden actuar también de diversa manera en su desarrollo.

Esta variabilidad existente puede contribuir a un diferente enfoque en el tratamiento de estos pacientes, requiriendo un control más o menos estricto de sus factores de riesgo con la intención de mejorar el pronóstico de su enfermedad.

La enfermedad arterial periférica es en muchos casos la gran olvidada y la afectación aterosclerosa de otros territorios como el coronario o el cerebrovascular eclipsan su importancia. La EAP supone un gran impacto sociosanitario y es el reflejo de una grave afectación aterosclerosa que puede comprometer a la vez otros territorios aparentemente asintomáticos.

El registro FRENA nos ha permitido comprobar que los pacientes con EAP presentan un mayor riesgo cardiovascular, presentando un mayor número de eventos isquémicos que los pacientes con EC o ECV. Este riesgo además se incrementa con la gravedad con la que se manifiesta la enfermedad a nivel periférico. Siguiendo la clasificación de Fontaine, los pacientes que presentan una mayor gravedad clínica de la enfermedad (G-III y G-IV) son los que presentan un mayor riesgo cardiovascular. Los pacientes con EAP no sólo presentan la misma incidencia de infarto de miocardio o de accidente vascular cerebral que los pacientes con EC o ECV, sino que su riesgo de isquemia crítica de las extremidades es mayor.

Los pacientes con EAP presentan también una mayor mortalidad no asociada a causas cardiovasculares y presentan un peor control de enfermedades y factores de riesgo concomitantes, como diabetes, hipertensión o dislipemia. Es posible que la falta de percepción de gravedad por parte de los pacientes se asocie a la falta de percepción de gravedad de los médicos que los controlan, al pensar sólo en la manifestación periférica y no en el riesgo global de la enfermedad aterotrombótica.

El hábito tabáquico favorece la progresión aterosclerosa y su complicación trombótica, por lo que las guías que aplicamos en el control de los pacientes con EAP, EC o ECV recomiendan dejar de fumar a todos los pacientes.

A pesar de existir esta clara relación, el fenómeno conocido como "smoker's paradox" suponía una contradicción, ya que los pacientes con enfermedad coronaria presentaban una menor mortalidad de origen cardiovascular que los que nunca habían fumado. Esta asociación hemos visto que también esta presente en los pacientes EAP y ECV. La justificación es debida a variables adicionales que actúan como factores de confusión. Los fumadores presentan una menor mortalidad (de causa cardiovascular o no) porque son 10 años más jóvenes que los no fumadores. Además presentan un perfil más favorable, presentan diabetes, hipertensión o insuficiencia cardiaca con menor frecuencia.

El grupo de pacientes del registro esta compuesto por pacientes que han presentado un evento isquémico previamente, es posible también que los pacientes más graves estén más motivados en dejar de fumar y acaben presentando un evento letal más probablemente que aquellos que siguen fumando.

Las características trombogénicas del tabaco también pueden justificar esta mejor evolución, ya que la complicación trombótica sobre una placa coronaria es más fácilmente solventable que la oclusión por evolución aterosclerosa sin trombosis sobreañadida.

Las características de la placa aterosclerosa a nivel de las extremidades inferiores es diferente a la de otros territorios como por ejemplo el coronario. Como hemos comentado es más fibrótica y con menos propensión a la trombosis

sobreañadida, es por este motivo que tal vez sólo encontramos que dejar de fumar se asocia con una menor mortalidad en el grupo de pacientes con EC. Estas diferencias también están presentes en otro factor de riesgo cardiovascular como la diabetes, su efecto en los diferentes territorios vasculares puede ser diferente. Un control estricto de la glicemia sólo se asoció con un menor número de eventos isquémicos y una menor mortalidad en el grupo de pacientes con enfermedad coronaria. Estos resultados no quieren decir que no deba realizarse un buen control glicémico, sino que tal vez este control deba ser más personalizado al tipo de manifestación aterotrombótica.

Finalmente podemos concluir:

-La aterotrombosis puede presentar una evolución diferente según el territorio vascular afectado por la diferente composición de las placas ateroscleróticas, las diferentes características hemodinámicas y el diferente efecto de los factores de riesgo.

-Debe realizarse un control estricto de los factores de riesgo, pero de forma más personalizada según la forma de presentación de la enfermedad aterotrombótica.

-En prevención secundaria, un peor control glicémico en pacientes DM 2, valorado con una HbA1c mayor del 7% implica un mayor riesgo cardiovascular. Estas diferencias aparecen sólo en pacientes con enfermedad coronaria.

-la “smoker’s paradox” esta presente no sólo en los pacientes con EC, sinó también en los pacientes con EAP y ECV. Esta aparente mejor evolución entre los pacientes fumadores que han presentado un evento isquémico se asocia con una aparición precoz de las complicaciones aterotrombóticas asociadas al hábito tabáquico.

-Tras un evento isquémico, dejar de fumar se asocia de forma precoz con una menor mortalidad entre los pacientes con EC, pero no entre los pacientes con EAP o ECV. Los beneficios cardiovasculares a largo plazo han sido claramente demostrados en estudios previos.

-Dejar de fumar es un requisito indispensable en el control de la aterosclerosis y en la reducción de la mortalidad de causa cardiovascular.

5-ANEXOS

En septiembre del 2007 fue **publicado *Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA)* en el *European Journal of Internal Medicine***. Este artículo a pesar de no formar parte fundamental de la tesis fue el primero de un grupo de artículos que seguían una misma temática y mostraban resultados en su mayoría, de un mismo grupo de pacientes seguidos en el tiempo. He considerado oportuno añadirlo en el apartado Anexos para acabar de obtenir una visión más completa del efecto de la aterotrombosis en nuestro grupo de pacientes.

Los resultados fueron obtenidos tras el seguimiento durante un año de 1265 pacientes, hasta Diciembre del 2006.

El 33% de los pacientes (417) presentaban enfermedad arterial periférica (EAP), el 37% (474) enfermedad coronaria y el 30% (374) enfermedad cerebrovascular. El seguimiento mostró que los pacientes con EAP presentaban una mayor incidencia de eventos cardiovasculares mayores por 100 pacientes-año: 17 (95% CI: 13-22) que aquellos con enfermedad coronaria (EC): 7.9 (5.5-11) o enfermedad cerebrovascular (ECV): 8.9 (6.1-13). La incidencia de ictus o infarto de miocardio era similar entre los tres grupos, pero en el grupo de pacientes con EAP existía una mayor incidencia de isquemia crítica, un mayor número de amputaciones y una mortalidad mayor. Esta incidencia se incrementaba con la severidad de los síntomas: 8.7 (95% CI: 5.3-13) en los pacientes Fontaine IIa; 25 (95% CI: 16-38) en los pacientes Fontaine IIb; 26 (95% CI: 13-47) en los pacientes Fontaine III y 42 (95% CI: 24-67) en los pacientes Fontaine IV.

Estos resultados confirmaron que el grupo de pacientes con isquemia crónica de miembros inferiores presentaba un mayor riesgo cardiovascular durante el seguimiento.

La clasificación de Fontaine nos muestra una escala de gravedad clínica en función de la manifestación a nivel periférico y una probable manifestación más severa de la aterosclerosis en los últimos niveles, es decir los grados III y IV.
En los pacientes Fontaine IIa el riesgo de presentar una complicación en forma de isquemia crítica, es decir, pasar a presentar un G-III o un G-IV, es menor que el riesgo de presentar un infarto de miocardio o un ictus. En cambio los pacientes con Fontaine G-III y G-IV presentan el doble de riesgo de desarrollar una complicación isquémica de la extremidad o una amputación, que de presentar un infarto de miocardio o un ictus.
Los resultados muestran como los pacientes con EAP, en muchos casos con un riesgo subestimado, requieren un control más estricto, independientemente de la resolución de su clínica de claudicación o la realización de una revascularización quirúrgica.

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Original article

Clinical outcome in patients with peripheral artery disease. Results from a prospective registry (FRENA)

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Abstract

Background: The risk of future cardiovascular events in patients with peripheral artery disease (PAD) is often underestimated.
Patients and methods: FRENA is an ongoing, observational registry of consecutive outpatients with symptomatic PAD, coronary artery disease (CAD) or cerebrovascular disease (CVD). We compared the incidence of major cardiovascular events (i.e., myocardial infarction, ischemic stroke, critical limb ischemia, or cardiovascular death) during a 12-month follow-up period in a series of consecutive outpatients with PAD, CAD or CVD.
Results: As of December 2006, 1265 patients had been enrolled in FRENA who completed the 12-month follow-up. Of these, 417 patients (33%) had PAD, 474 (37%) had CAD, 374 (30%) had CVD. Patients with PAD had an increased incidence of major cardiovascular events per 100 patient-years: 17 (95% CI: 13–22) vs. 7.9 (5.5–11) in those with CAD, or 8.9 (6.1–13) in those with CVD. Compared to patients with CAD or CVD those with PAD had a similar incidence of myocardial infarction or stroke, but a higher incidence of critical limb ischemia, limb amputation and death. This incidence increased with the severity of the symptoms: 8.7 (95% CI: 5.3–13) in patients in Fontaine stage IIa; 25 (95% CI: 16–38) in stage IIb; 26 (95% CI: 13–47) in stage III; 42 (95% CI: 24–67) in stage IV.
Conclusions: Our data confirm a higher incidence of major cardiovascular events for patients with PAD, as well as a correlation of these events with the severity of PAD.

Keywords: Outcome; Peripheral arterial disease; Secondary prevention

1. Introduction

Even in the absence of a history of coronary artery disease (CAD), patients with peripheral artery disease (PAD) have a similar risk to die from a cardiovascular cause as patients with previous CAD.[1–3] Indeed, these patients are usually considered for secondary prevention strategies comparable to those for patients with CAD or cerebrovascular disease

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(CVD).[4,5] However, despite its frequency and severity, data on cardiovascular morbidity and mortality of patients with symptomatic PAD are scarce.[6–11]

The FRENA (Factores de Riesgo y ENfermedad Arterial) Registry is an ongoing, multicentre, observational registry of consecutive patients with symptomatic ischemic disease in the heart, brain, and/or major peripheral arteries. The aim of this study was to compare the incidence of major cardiovascular events during a 12-month follow-up period in patients with PAD, CAD or CVD.

2. Patients and methods

2.1. Inclusion criteria

Participating hospitals in the FRENA registry prospectively enroll consecutive outpatients with cardiovascular disease meeting at least one recent (<3 months prior to enrollment) episode of CAD (manifesting as angina or acute coronary syndrome); CVD (manifesting as transient ischemic attack or ischemic stroke); or PAD (either intermittent claudication with an ankle–brachial index <0.9, or previous vascular intervention or limb amputation for PAD). The Fontaine classification was used for categorisation of PAD.[5] Patients are not included if they are not available for the 12-month follow-up.

2.2. Study end points and definitions

The major outcome for this analysis was the composite outcome of myocardial infarction, ischemic stroke, critical limb ischemia, or cardiovascular death. Myocardial infarction was defined as a transient increase of CK-MB or troponin in combination with ischemic symptoms and/or typical electrocardiogram signs (development of pathologic Q-waves or ST-segment elevation or depression). Ischemic stroke was diagnosed if the patient had an appropriate clinical event not completely resolved within 24 h, and had a brain CT that showed a compatible low-density lesion, or had findings compatible with hemorrhagic conversion of a cerebral infarct. Transient ischemic attack was diagnosed if the patient had an appropriate clinical event with symptoms disappearing within 24 h, and had a brain CT that showed a compatible low-density lesion or was normal. Critical limb ischemia was considered in patients with intermittent claudication when presenting symptoms at rest (Fontaine stages III or IV). In PAD patients with stage III or IV, critical limb ischemia was considered when needing amputation. Death was classified as cardiovascular when appearing within 15 days after the onset of signs or symptoms of the acute outcome event (myocardial infarction, ischemic stroke or critical limb ischemia), or due to progressive heart failure, fatal arrhythmias, ruptured aneurysm, or sudden death.

2.3. Study variables

The following parameters were recorded: patient's baseline characteristics; clinical status including any coexisting or underlying conditions such as chronic heart or lung disease; risk factors for atherothrombosis; blood pressure levels and cardiac rhythm; the type of treatment received; and the 12-month outcome.

2.4. Follow-up

A detailed history was performed at study entry (<3 months after an acute ischemic episode). Comorbid conditions were characterized, including a history of advanced CAD; symptomatic CVD; diabetes mellitus; hypertension; hyperlipidemia; prior lower extremity artery reconstruction; chronic lung disease; chronic heart failure; cancer; and smoking status. Then, physical examination was performed comprising weight, height, and heart rate. Electrocardiogram was recorded and blood pressure was measured in the arm by auscultation after 5 min of rest. After the initial visit, all patients were followed-up for at least 12 months. At these visits, medical history and data from physical examination were recorded, with special attention to risk factors; laboratory tests; lifestyle habits; type, dose, and duration of treatment received, and clinical outcome. Physicians are allowed to use any and all appropriate medications, as dictated by their usual clinical practice patterns.

2.5. Data collection

All patients provide oral informed consent to participate in the registry, according to the requirements of the ethics committee in each hospital. Data are recorded on a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. Study end points are adjudicated by the attending physicians. At regular intervals, data quality is monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals.

2.6. Statistical analysis

Odds ratios and corresponding 95% confidence intervals were calculated using Confidence Interval Analysis software (version 2.0.0), and a p value<.05 was considered to be statistically significant. Incidence rates were calculated as the observed number of major cardiovascular events divided by the sum of individual patient-time by the entire patient series. The significance of a number of clinical variables on the risk of developing the composite event was evaluated by logistic regression. Candidate variables were based on published literature and on expert opinion. Those variables identified by the univariate analysis as potential risk factors and achieving a significance level of <.05 were considered for inclusion in a multivariate logistic regression analysis to determine the independent nature of the risk factors, while adjusting for other characteristics. Multivariate analysis was performed

Table 1
Clinical characteristics of the 1265 patients

	PAD	CAD	CVD	OR (95% CI) PAD vs. CAD	OR (95% CI) PAD vs. CVD
Patients	**417**	**474**	**374**		
No. of visits at follow-up	4.8±1.4	4.9±2.3	4.6±2.3	$p=0.157$	$p=0.170$
Clinical characteristics					
Gender (males)	345 (83%)	364 (77%)	222 (59%)	1.4 (1.0–2.0)*	3.3 (2.4–4.6)‡
Age (years)	67±10	64±12	70±10	$p<0.001$	$p<0.001$
Body weight (kg)	72±13	77±13	74±13	$p<0.001$	$p=0.023$
Risk factors					
Current smokers	100 (24%)	46 (9.7%)	66 (18%)	2.9 (2.0–4.3)‡	1.5 (1.0–2.1)*
Diabetes mellitus	180 (43%)	156 (33%)	135 (36%)	1.6 (1.2–2.0)†	1.3 (1.0–1.8)*
Underlying diseases					
Cancer	56 (13%)	16 (3.4%)	9 (2.4%)	4.4 (2.5–7.9)‡	6.3 (3.1–13)‡
Chronic heart failure	36 (8.6%)	36 (7.6%)	17 (4.6%)	1.2 (0.7–1.9)	2.0 (1.1–3.6)*
Chronic lung disease	97 (23%)	58 (12%)	42 (11%)	2.2 (1.5–3.1)‡	2.4 (1.6–3.5)‡
Arterial disease					
Prior CAD	111 (27%)	128 (27%)	44 (12%)	1.0 (0.7–1.3)	2.7 (1.9–4.0)‡
Prior CVD	56 (13%)	23 (4.9%)	70 (19%)	3.0 (1.8–5.0)‡	0.7 (0.5–0.99)*
Prior PAD	334 (80%)	57 (12%)	30 (8.0%)	29 (20–42)‡	46 (30–72)‡
Physical examination					
Mean SBP levels (mm Hg)	141±19	129±17	140±24	$p<0.001$	$p=0.627$
Mean DBP levels (mm Hg)	73±9.7	73±10	78±8.1	$p=0.442$	$p<0.001$
Sinus rhythm	363 (91%)	444 (94%)	307 (84%)	0.6 (0.3–0.97)*	1.8 (1.2–2.8)†
Mean serum levels					
Total cholesterol (mg/dL)	189±37	181±35	189±37	$p=0.001$	$p=0.178$
LDL-cholesterol (mg/dL)	118±30	110±29	112±28	$p<0.001$	$p=0.002$
Glucose (mg/dL)	126±46	114±35	116±33	$p<0.001$	$p<0.001$
Drugs					
Antiplatelets	359 (86%)	436 (92%)	306 (82%)	0.5 (0.4–0.8)†	1.4 (0.9–2.0)
Anticoagulants	62 (15%)	65 (14%)	74 (20%)	1.1 (0.8–1.6)	0.7 (0.5–1.0)
Beta-blockers	64 (15%)	353 (75%)	46 (12%)	0.06 (0.04–0.1)‡	1.3 (0.9–1.9)
Calcium antagonists	111 (27%)	119 (25%)	100 (27%)	1.1 (0.8–1.5)	1.0 (0.7–1.4)
Angiotensin II antagonists	111 (27%)	84 (18%)	114 (31%)	1.7 (1.2–2.3)†	0.8 (0.6–1.1)
ACE inhibitors	159 (38%)	255 (54%)	171 (46%)	0.5 (0.4–0.7)‡	0.7 (0.6–0.97)*
Diuretics	177 (42%)	128 (27%)	157 (42%)	2.0 (1.5–2.6)‡	1.0 (0.8–1.4)
Statins	258 (62%)	361 (76%)	254 (68%)	0.5 (0.4–0.7)‡	0.8 (0.6–1.0)
Insulin	85 (20%)	45 (9.5%)	33 (8.8%)	2.4 (1.7–3.6)‡	2.6 (1.7–4.1)‡
Oral antidiabetic agents	106 (25%)	100 (21%)	94 (25%)	1.3 (0.9–1.7)	1.0 (0.7–1.4)
Nitrates	66 (16%)	223 (47%)	27 (7.2%)	0.2 (0.1–0.3)‡	2.4 (1.5–3.9)‡

Comparisons between patients: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.
Abbreviations: PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin converting enzyme; OR, odds ratio; CI, confidence intervals.

using the Statistical Package for Social Sciences (SPSS) program (version 11.5; SPSS Inc., Chicago, IL, USA).

3. Results

As of September 2005, a total of 1350 outpatients with symptomatic atherothrombotic disease had been enrolled in FRENA in 20 participating Spanish centers. One year later, 1265 (94%) had finished their 12-month follow-up. Of those who withdrew, 66 patients did so because of missed site visits and 19 because their enrolling physicians had withdrawn from the registry. Of the 1265 patients who finished, 417 (33%) had PAD (intermittent claudication 327, ischemia at rest 90); 474 (37%) had CAD (myocardial infarction 342, angina 132); 374 (30%) had CVD (ischemic stroke 290, transient ischemic attack 84).

3.1. Clinical characteristics

Patients with PAD were more commonly males, current smokers, had more often diabetes, cancer or chronic lung disease, and their mean values of serum LDL-cholesterol or glucose were significantly higher than those in patients with CAD or CVD (Table 1). Moreover, patients with PAD were

Table 2
Clinical outcome in 417 patients with PAD, according to the severity of the symptoms

	Fontaine Stage IIa	Fontaine Stage IIb	Fontaine Stage III	Fontaine Stage IV
Patients, N	**234**	**93**	**43**	**47**
12-month outcome [a]				
Myocardial infarction	9 (3.8%)	2 (2.2%)	0 (0%)	2 (4.3%)
Ischemic stroke	3 (1.3%)	1 (1.1%)	2 (4.7%)	5 (11%)
Critical limb ischemia [b]	5 (2.1%)	13 (14%)	5 (12%)	9 (19%)
Amputation	0 (0%)	5 (5.4%)	5 (12%)	9 (19%)
By-pass	5 (2.1%)	6 (6.5%)	4 (9.3%)	5 (11%)
Other surgery	9 (3.8%)	5 (5.4%)	1 (2.3%)	1 (2.1%)
Cardiovascular death	2 (0.9%)	4 (4.3%)	4 (9.3%)	4 (8.5%)
Overall death	10 (4.3%)	7 (7.5%)	5 (12%)	9 (19%)
Major vascular events, *N*	17 (7.3%)	19 (20%)	9 (21%)	15 (32%)
Incidence rate [c]	8.7 (5.3–13)	25 (16–38)	26 (13–47)	42 (24–67)

[a] Some patients developed >1 new cardiovascular events.
[b] Some patients underwent >1 surgical procedures.
[c] Incidence of major cardiovascular events per 100 patient-years.

older, more often had a prior history of CVD, and had higher mean levels of systolic blood pressure than those with CAD. However, they were younger, had more often sinus rhythm and had lower levels of diastolic blood pressure than those with CVD. In addition, there were significant differences among groups in the prescribed therapies (Table 1).

3.2. 12-month outcome

Sixty-one patients with PAD (15%) developed major cardiovascular events during the 12-month follow-up period: myocardial infarction 13 (3.1%); ischemic stroke 11 (2.6%); critical limb ischemia 42 (10%); cardiovascular death 14 (3.4%). Six of these patients died within 15 days after an ischemic event (myocardial infarction 1, critical limb ischemia 5). The incidence of myocardial infarction, stroke, or critical limb ischemia increased according to the severity of the symptoms (Table 2). Nineteen of the 32 patients (59%) who developed critical limb ischemia needed amputation (major amputation in 14).

Their incidence rate of 17 events per 100 patient-years (95% CI: 13–22) increased with the severity of the symptoms (Table 2) and was significantly higher than the 7.9 (95% CI: 5.5–11) found in patients with CAD, or the 8.9 (95% CI: 6.1–13) in those with CVD, as shown in Table 3. There were no differences in the incidence of myocardial infarction or stroke among the 3 groups (5.7%, 5.3% or 5.3%, respectively), but patients with PAD had an increased incidence of critical limb ischemia and overall mortality compared to those with CAD or CVD (Table 3).

3.3. PAD patients at increased risk of major cardiovascular events

Those who developed the composite event were more frequently females, older, and had more often diabetes or chronic heart failure (Table 4). Their mean levels of diastolic blood pressure were significantly lower, their serum levels of glucose were higher and they had more often atrial fibrillation. Finally, patients taking anticoagulants or insulin had an increased incidence of major cardiovascular events, while those on antiplatelet therapy had a lower incidence.

Multivariate analysis confirmed that only the patient's gender, age, past history of CVD, the presence of PAD symptoms at rest, and serum glucose levels were independently associated with an increased risk of major cardiovascular events. On the contrary, patients taking antiplatelets had a lower risk (Table 5).

4. Discussion

The data in this analysis, obtained from a prospective series of consecutive patients in the FRENA registry, confirm that patients with PAD are at increased risk for major cardiovascular events during follow-up, independently of the presence of other covariates, such as patient's age, gender or underlying diseases. Furthermore, we found that this incidence increased with the severity of the symptoms, ranging from 8.7 events per 100 patient-years in patients in Fontaine stage IIa (intermittent claudication >150 m) to 42 events in those in Fontaine stage IV (ulceration or gangrene).

Compared to patients with CAD or CVD those with PAD had a similar incidence of myocardial infarction or stroke, but a higher incidence of critical limb ischemia. Critical limb

Table 3
Clinical outcome at 12 months in the overall series

	PAD	CAD	CVD	Odds ratio (95% CI) PAD vs. CAD	Odds ratio (95% CI) PAD vs. CVD
Total patients, N	**425**	**508**	**417**		
Lost for follow-up	8 (1.9%)	34 (6.9%)	43 (10%)	0.3 (0.1–0.6)‡	0.2 (0.1–0.4)‡
Evaluable patients	417	474	374		
12-month outcome					
Myocardial infarction	13 (3.1%)	19 (4.0%)	2 (0.5%)	0.8 (0.4–1.6)	6.0 (1.3–27)†
Ischemic stroke	11 (2.6%)	6 (1.3%)	18 (4.8%)	2.1 (0.8–5.8)	0.5 (0.3–1.2)
Critical limb ischemia	42 (10%)	3 (0.6%)	5 (1.3%)	18 (5.4–57)‡	8.3 (3.2–21)‡
Cardiovascular death	14 (3.4%)	8 (1.9%)	12 (3.2%)	1.8 (0.8–4.2)	1.0 (0.5–2.3)
Overall death	31 (7.4%)	1 (3.2%)	14 (3.7%)	2.5 (1.3–4.6)†	2.1 (1.1–3.9)*
Major vascular events	61 (15%)	32 (6.8%)	30 (8.0%)	2.4 (1.5–3.7)‡	2.0 (1.2–3.1)†
Incidence rate	17 (13–22)	7.9 (5.5–11)	8.9 (6.1–13)		

Comparisons between patients: *$p<0.05$; †$p<0.01$; ‡$p<0.001$.
Abbreviations: PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; C.I., confidence intervals.

Table 4
Univariate analysis of the risk to develop major cardiovascular events during follow-up, for the 417 patients with peripheral artery disease

	Major cardiovascular events	No major cardiovascular events	Odds ratio (95% CI)	*p* value
Patients, N	**61**	**356**		
Clinical characteristics				
Gender (males)	41 (67%)	304 (85%)	0.4 (0.2–0.6)	0.001
Age	71±9.7	66±10.1	–	0.001
Body weight (kg)	70±13	72±13	–	0.188
Risk factors				
Current smokers	11 (18%)	89 (25%)	0.7 (0.3–1.3)	0.239
Diabetes mellitus	35 (57%)	145 (41%)	2.0 (1.1–3.4)	0.016
Underlying diseases				
Cancer	8 (13%)	48 (14%)	1.0 (0.4–2.2)	0.938
Chronic heart failure	13 (21%)	23 (6.5%)	3.9 (1.9–8.3)	<0.001
Chronic lung disease	14 (23%)	83 (23%)	1.0 (0.5–1.9)	0.950
Arterial disease				
Prior CAD	13 (21%)	98 (28%)	0.7 (0.4–1.4)	0.310
Prior CVD	16 (26%)	40 (11%)	2.8 (1.4–5.4)	0.002
PAD, Fontaine stages III–IV	24 (42%)	64 (20%)	2.9 (1.6–5.2)	<0.001
Physical examination				
Mean SBP levels (mm Hg)	138±21	142±18	–	0.232
Mean DBP levels (mm Hg)	70±9.7	73±9.7	–	0.054
Sinus rhythm	48 (79%)	315 (93%)	0.3 (0.1–0.6)	0.001
Mean serum levels				
Total cholesterol (mg/dL)	192±46	189±34	–	0.559
LDL-cholesterol (mg/dL)	120±31	118±30	–	0.712
Glucose (mg/dL)	141±63	124±42	–	0.040
Drugs				
Antiplatelets	44 (72%)	315 (89%)	0.3 (0.2–0.6)	0.001
Anticoagulants	18 (30%)	44 (12%)	3.0 (1.6–5.6)	0.001
Beta-blockers	9 (15%)	55 (15%)	0.9 (0.4–2.0)	0.889
Calcium antagonists	14 (23%)	97 (27%)	0.8 (0.4–1.5)	0.483
Angiotensin II antagonists	11 (18%)	100 (28%)	0.6 (0.3–1.1)	0.101
ACE inhibitors	26 (43%)	133 (37%)	1.3 (0.7–2.2)	0.434
Diuretics	30 (49%)	147 (41%)	1.4 (0.8–2.4)	0.249
Statins	32 (53%)	226 (64%)	0.6 (0.4–1.1)	0.101
Insulin	19 (31%)	66 (19%)	2.0 (1.1–3.6)	0.024
Oral antidiabetic agents	18 (30%)	88 (25%)	1.3 (0.7–2.3)	0.427
Nitrates	11 (18%)	55 (15%)	1.2 (0.6–2.5)	0.610

Abbreviations: PAD, peripheral artery disease; CAD, coronary artery disease; CVD, cerebrovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin converting enzyme; C.I., confidence intervals.

ischemia has not been considered a major outcome in most clinical trials of secondary prevention of atherothrombosis, probably because of its low incidence in patients with CAD or CVD. However, it is a common and severe complication in patients with PAD and, up-to-date, there is scarce information on the factors that might influence its development.

In clinical practice physicians' attention is often focused on the resolution of claudication symptoms through increasingly aggressive revascularization procedures. Our findings reveal that the threat of critical limb ischemia in PAD patients in Fontaine stage IIa is lower than their risk for myocardial infarction or ischemic stroke. Thus, our findings confirm that a more accurate risk-assessment would imply the heart and not the leg in these patients. On the other hand, PAD patients with symptoms at rest (Fontaine stages III or IV) had an over 2-fold risk of critical limb ischemia than of myocardial infarction or stroke.

Moreover, patients with PAD in our series also had an increased mortality due to non-cardiovascular reasons. This may be partly due to the more frequent occurrence of coexisting underlying conditions such as cancer, diabetes or chronic lung disease. However, it could also be attributed to their worse controlled hypertension, serum cholesterol or glucose levels. This observation, which is consistent with observations from other series,[12–16] attests to a critical need for the development and implementation of treatment guidelines for patients with PAD, and particularly those with the most advanced clinical stage of the disease. Thus, a worse control of the risk factors, combined with a less favorable prognosis due to concomitant diseases, could contribute to the higher mortality seen in patients with PAD.

4.1. Limitations

As an observational study, the FRENA registry is not designed to answer questions regarding the relative efficacy and safety of different modalities of therapy. Enrolled patients were treated according to standard practice, and prospective follow-up was completed for most of them. The main limitation lies in the likely underestimated incidence rate of events in patients lost for follow-up. Follow-up rates were

Table 5
Multivariate analysis

	Odds ratio (95% CI)	*p* value
Clinical characteristics		
Gender (males)	0.468 (0.227–0.967)	0.040
Age	1.037(1.001–1.075)	0.046
Arterial disease		
Prior CVD	3.245 (1.543–6.821)	0.002
PAD, Fontaine stages III–IV	1.994 (1.013–3.926)	0.046
Mean serum levels		
Glucose (mg/dL)	1.007 (1.001–1.014)	0.031
Drugs		
Antiplatelets	0.414 (0.196–0.875)	0.021

Abbreviations: CVD, cerebrovascular disease; PAD, peripheral artery disease; C.I., confidence intervals.

high, but 6.3% of the patients missed visits and, thus, we cannot actually exclude a small margin of error in the estimates of event rates. However, the clinical characteristics of patients with and without follow-up appear quite similar and suggest no systematic bias. Another limitation consists of the lack of information about how many patients were initially considered for inclusion but were actually excluded. Despite these limitations, our data may serve as an important reminder to physicians that patients with PAD face inordinately high risks of cardiovascular events, and thus should be strongly considered whenever possible for intensive risk reducing therapy. Adequate clinical trials are needed to ascertain the most effective and safe therapy for these patients.

5. Learning points

Patients with PAD had an increased incidence of major cardiovascular events. Compared to patients with CAD or CVD they had a similar incidence of myocardial infarction or stroke, but a higher incidence of critical limb ischemia, limb amputation and death. This incidence increased with the severity of the symptoms of PAD.

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