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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Doctor:

JOSE MIGUEL DE LA CALLE RESTREPO
Superintendente de Industria y Comercio
Ministerio de Comercio, Industria y Turismo
Ciudad

Radicación No. 06 – 127373

**Patente: NUEVA COMPOSICION DE UN INHIBIDOR
DE LA CORRIENTE SINUSAL If Y DE UN INHIBIDOR
CALCICO Y LAS COMPOSICIONES FARMACEUTICAS
QUE LO CONTIENEN**

Recurso de Reposición

MARIA VICTORIA LIEBBE LOZANO, domiciliada en ésta ciudad, identificada con cédula de ciudadanía No. 51.819.220 de Bogotá portadora de la tarjeta profesional No. 54.845 del C.S. de la J., en mi calidad de apoderada de la sociedad **LES LABORATOIRES SERVIER**, por medio de la presente y estando dentro del término legal, me dirijo a Usted para presentar **RECURSO DE REPOSICION** contra la Resolución No. 72900 del 24 de diciembre de 2010, mediante el cual se negó el privilegio de la patente de invención de la referencia y en concordancia con ello solicito lo siguiente:

I. PETICIONES

Respetuosamente solicito que se revoque la Resolución 72900 del 24 de diciembre de 2010 y en consecuencia:

1. Solicito que se revoque el artículo primero de la resolución en mención, y
2. Solicito que sea concedido el privilegio de la patente de invención

Para que las anteriores solicitudes me sean satisfechas pido que se tengan en cuenta los siguientes fundamentos de hecho y de derecho.

II. HECHOS

PRIMERO: Mediante escrito radicado el 20 de diciembre de 2006 con el No. 06 – 127373, mi representada solicito la patente de invención denominada "NUEVA ASOCIACION DE UN INHIBIDOR DE LA CORRIENTE SINUSUAL I_f Y DE UN INHIBIDOR CÁLCICO Y LAS COMPOSICIONES FARMACEUTICAS QUE LA CONTIENEN, la cual posteriormente fue modificada para ser denominada: NUEVA COMPOSICION DE UN INHIBIDOR DE LA CORRIENTE SINUSAL I_f Y DE UN INHIBIDOR CALCICO Y LAS COMPOSICIONES FARMACEUTICAS QUE LO CONTIENEN.

SEGUNDO: Que una vez efectuado el examen de forma, la Superintendencia ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que una vez solicitado el examen de patentabilidad y luego de realizado el examen de fondo la Superintendencia efectuó requerimientos mediante oficios No. 5010 y 9810 notificados el 15 de abril y el 5 de agosto de 2010 respectivamente, debido a una supuesta falta de claridad de los capítulos descriptivo y reivindicatorio, y la carencia de novedad y nivel inventivo de la misma.

CUARTO: Que estando dentro del término legal se presentó respuesta a cada uno de los requerimientos efectuados por la Superintendencia, realizando las aclaraciones y modificaciones pertinentes de acuerdo a los requerimientos efectuados; entre estas, la modificación del capítulo reivindicatorio conforme al artículo 34 de la Decisión 486.

QUINTO: Que como complemento de los argumentos y aclaraciones presentadas en las respuestas a los requerimientos, se aportaron múltiples documentos científicos que soportaban los argumentos de mi mandante.

COLOMBIA
Jefe Crisóculo
ACULO DE BOGOTÁ

- TARDIF J-C: "Ivabradine in clinical practice: Benefits of I(f) inhibition." European Heart Journal Supplement, vol. 7, No. H. Pp H29-H32. Refs.: 26 ISSN: 1520-765X, Coden: EHJSFT, 2005.
- Lopez-BESCOS ET AL: "Long term safety and antianginal efficacy of the If current inhibitor ivabradine." Eur. Heart J. Vol. 25(Supl), 2004, p. 138.
- RUZYLLO ET AL: "Antianginal and antiischemic effects of the If current inhibitor ivabradine". Eur. Heart J. Vol. 25 (Supl), 2004, p. 138.

SEXTO: Mediante comunicación radicada el 21 de diciembre de 2010, presentamos copia oficial del Certificado de Concesión de la patente Europea No. 1800683 correspondiente a la patente NUEVA ASOCIACION DE UN INHIBIDOR DE LA CORRIENTE SINUSUAL If Y DE UN INHIBIDOR CÁLCICO Y LAS COMPOSICIONES FARMACEUTICAS QUE LA CONTIENEN, concedida por el INPI de Francia a favor de mi mandante, es decir, concediendo la patente que se niega dentro de este trámite.

SEPTIMO: Que el día 24 de diciembre de 2010, esta Entidad profirió Resolución No. 72900, negando la patente de invención solicitada.

III. FUNDAMENTOS

1. Sobre la claridad del capítulo reivindicatorio:

Manifiesta el examinador que "(...) el capítulo reivindicatorio no es conciso, por cuanto se refiere a las actividades de los fármacos que estarían en la composición farmacéutica"

Similar manifestación efectuó esta Entidad mediante requerimiento hecho por Oficio 005010, y en contestación a dicho requerimiento mi representada procedió a modificar las reivindicaciones número 1, 3, 4, 5, 6, 7, 8, 9, 10, 11 y a eliminar las reivindicaciones 2 y 12.

Valga aclarar también que las expresiones "un inhibidor selectivo y específico de la corriente sinusal If" y "un inhibidor de calcio" se encuentran claramente definidas

para cualquier hombre capacitado en la técnica, por lo cual no es cierto como lo menciona esta Entidad que las mismas no sean concisas y solamente mencionen actividades terapéuticas.

Incluso, es un hecho bien conocido que un *"inhibidor de calcio"* se relaciona con una clase de medicamentos de la dihidropiridina de bloqueadores de los canales de calcio y que bloquean la conducción de calcio de los canales de calcio, lo cual conlleva a la reducción de la contracción muscular.

Como prueba de lo anterior, mediante comunicación del 14 de julio de 2010 se adjuntó literatura general relacionada con los inhibidores de los canales de calcio, lo cual refuerza lo mencionado previamente.

Adicionalmente, la expresión *"un inhibidor selectivo y específico de la corriente sinusal I_f"* se refiere a un inhibidor de la corriente iónica del marcapasos cardíaco que está altamente expresada en un nódulo sinusal y en el nódulo atrioventricular. La ivabradina es un inhibidor de (la corriente) I_f mas selectivo y específico. Por lo tanto mi mandante reemplazó la expresión *"un inhibidor selectivo y específico de la corriente sinusal I_f"* por *"Ivabradina"* a fin de acceder al requerimiento previamente efectuados.

Ahora bien, dando alcance a nuestra contestación de requerimiento del 29 de octubre de 2010, por medio del cual aclaramos que la expresión *"inhibidor de ivabradina"* correspondía a un error de traducción en la modificación de las reivindicaciones, y de conformidad con lo expresado por esta Entidad en la Resolución recurrida, a continuación presentamos el estado final en que fueron presentadas las reivindicaciones, con la correcta traducción:

REIVINDICACIONES

- 1- Composición farmacéutica constituida por el inhibidor selectivo y específico del nodo de la corriente sinusal I_f, que es la ivabradina, o 3-{-[{(7S)-3,4-dimetoxibiciclo [4,2,0]octa-1,3,5-trien-7-yl]metil}(metil)amino]propil}-7,8-dimetoxi-1,3,4,5-tetrahidro-2h-3-benzazepina-ona, o uno de sus hidratos,

formas cristalinas o sales de adición con un ácido farmacéuticamente aceptable y un inhibidor de calcio.

2- Composición farmacéutica conforme a la reivindicación 1, en que el inhibidor selectivo y específico de la corriente I_f del nodo sinusal es ivabradina, o hidrocloreuro de 3-{-[{[(7S)-3,4-dimetoxibiciclo[4,2,0]octa-1,3,5-trien-7-yl]metil}(metil)amino]propil}-7,8-dimetoxi-1,3,4,5-tetrahidro-2h-3-benzazepina, o uno de sus hidratos o formas cristalinas.

3- Composición farmacéutica conforme a la reivindicación 1, en que el inhibidor de calcio pertenece al tipo de las dihidropiridinas.

4- Composición farmacéutica conforme a la reivindicación 1, en que el inhibidor de calcio es amlodipino, o uno de sus hidratos o sales de adición con un ácido farmacéuticamente aceptable.

5- Composición farmacéutica conforme a la reivindicación 1, en que el inhibidor de calcio es besilato de amlodipino o uno de sus hidratos o formas cristalinas.

6- Composición farmacéutica conforme a la reivindicación 1, que comprende ivabradina, o uno de sus hidratos, formas cristalinas o sales de adición con un ácido farmacéuticamente aceptable, y amlodipino, o uno de sus hidratos, formas cristalinas o sales de adición con un ácido farmacéuticamente aceptable.

7- Composición farmacéutica conforme a la reivindicación 1, que comprende hidrocloreuro de ivabradina, o uno de sus hidratos o formas cristalinas, y besilato de amlodipino, o uno de sus hidratos o formas cristalinas.

8- Composiciones farmacéuticas constituidas por un ingrediente activo, el inhibidor selectivo y específico de la corriente I_f del nodo sinusal, que es ivabradina, o 3-{-[{[(7S)-3,4-dimetoxibiciclo[4,2,0]octa-1,3,5-trien-7-yl]metil}(metil)amino]propil}-7,8-dimetoxi-1,3,4,5-tetrahidro-2h-3-benzazepina, o uno de sus hidratos, formas cristalinas o sales de adición con un ácido

farmacéuticamente aceptable y un inhibidor de calcio, conforme a una de las reivindicaciones 1 a 7, solos o en combinación con uno o más excipientes farmacéuticamente aceptables.

9- Composiciones farmacéuticas conformes a la reivindicación 8, que se componen del ingrediente activo hidrocloreto de ivabradina, o uno de sus hidratos o formas cristalinas, en asociación con besilato de amlodipino, o uno de sus hidratos o formas cristalinas, solos o en combinación con uno o más excipientes farmacéuticamente aceptables.

10- Composiciones farmacéuticas conformes con una de las reivindicaciones 1 a 9 para usarse en la fabricación de un medicamento para el tratamiento de la angina.

2. Novedad:

El examinador se pronuncia contra la novedad y la actividad inventiva de la composición de la presente invención a la luz de los siguientes documentos de la técnica anterior: Tardif = D1, López-Bescós et.al. = D2, EP1362590 = D3 y Yang et al. =D4.

D1 (Tardif) y D2 (López-Bescós et al.)

D1 revela la terapia combinada con ivabradina establecida en pacientes con angina estable que ya han sido tratados con nitratos o bloqueantes de los canales de calcio tipo dihidropiridinas: Dicho argumento de D1 se fundamentaría en una interpretación del estudio clínico de López Bescós et al. (=D2).

El estudio clínico de López-Bescós et al. Consiste de un medicamento concomitante que incluye medicamentos antianginosos AAS, agentes reductores de lípidos del suero, nitratos de acción prolongada, o bloqueantes de canales tipo dihidropiridinas) más ivabradina como inhibidor selectivo y específico de la corriente I_f del nodo sinusal. Por tanto, el medicamento concomitante según el estudio clínico de D2 consiste de la administración a los pacientes de dos tabletas constituidas cada una de un principio activo. Por el contrario, la presente invención

describe una composición farmacéutica, esto es, una tableta compuesta de ivabradina y un bloqueante de los canales de calcio.

Por consiguiente, la composición farmacéutica de la presente invención y el objeto de D1/D2 son distintos, pues resulta que el contenido de D1/D2 no prevé la presente invención.

En conclusión, habida cuenta de la técnica anterior, no puede deducirse que las reivindicaciones de la invención carezcan de novedad.

D1 (Tardif et al.) examina la práctica clínica de la ivabradina y los beneficios de la inhibición de (la corriente) If. El párrafo relacionado con la "Terapia antianginal combinada" de D1 sostiene que *"La eficacia y la seguridad de la terapia combinada con ivabradina se ha establecido durante un (1) año en 386 pacientes con angina estable que ya fue tratada con nitratos o bloqueantes tipo dihidropiridinas de los canales de calcio"*. Esa alegación de D1 es una interpretación incorrecta del estudio clínico de López-Bescós et al. (=D2).

El estudio clínico de López-Bescós et al. Es un estudio "complementario" que consiste de un medicamento concomitante que incluye AAS, agentes reductores de lípidos del suero, nitratos de acción prolongada o bloqueantes tipo dihidropiridinas de los canales de calcio, autorizados durante el estudio, más ivabradina como agente selectivo y específico de la corriente If del nodo sinusal.

El presente estudio clínico "complementario" únicamente puede evaluar la seguridad a largo plazo y la eficacia antianginal de dosis de ivabradina. Por tanto, la organización de dicho ensayo terapéutico no permite concluir sobre la seguridad y la eficacia antianginal de la asociación específica de ivabradina + amlodipino. Por consiguiente, esa interpretación de Tardif et al. Es una interpretación incorrecta del estudio de López-Bescós et al. (La seguridad a largo plazo y la eficacia antianginal del inhibidor de la corriente If, ivabradina, en pacientes con angina crónica estable, prueba aleatoria multicéntrica de doble ciego, Eur. Heart J., 2004, 25-876).

La organización de un estudio clínico "complementario" de D1 es distinta de la organización del estudio clínico "de asociación" de la presente solicitud de patente.

El estudio "de asociación" se lleva a cabo en pacientes que estaban siendo tratados con antagonistas de calcio de tipo dihidropiridinas y que seguían quejándose de dolorosos ataques de angina de pecho pese al antagonista de calcio. Además, el estudio "de asociación" consiste de la comparación de grupos paralelos: por una parte la referencia, esto es, la monoterapia con amlodipino y por la otra la asociación de ivabradina + amlodipino.

En consecuencia, el análisis estadístico y la interpretación de estudios "complementario" y "de asociación" no pueden ser equivalentes.

D3=EP1362590

WO 2004/011006 se relaciona con el uso de cilobradina para la preparación de una composición farmacéutica para el tratamiento o la prevención de la insuficiencia cardíaca y asimismo con el uso de cilobradina en combinación con otros agentes terapéuticos para el tratamiento o la prevención de la insuficiencia cardíaca. La Solicitante hace hincapié en que el inhibidor de calcio se utiliza para reducir la resistencia vascular sistémica y la presión arterial en individuos que sufren de hipertensión. Por tanto, no es posible encontrar en WO 2004/011006 enseñanza o información alguna que pudiese informar al individuo capacitado en la técnica que la combinación de ivabradina y un inhibidor de calcio producen un efecto sinérgico.

Por consiguiente, respetuosamente manifestamos que el asunto de la invención es novedoso e inventivo con respecto a la técnica anterior WO 2004/011006.

D4= Yang et al.

D4 revela características generales de medicamentos antiarrítmicos. D4 no describe una composición constituida por ivabradina y un inhibidor de calcio. Por tanto, la presente invención es novedosa a la luz de la técnica anterior D4.

3. Sobre el nivel inventivo:

La Superintendencia considera que la materia de las reivindicaciones carece de actividad inventiva a la luz de la técnica anterior D1-D5.

Manifiesta en la Resolución que *"El problema técnico planteado en la solicitud consiste en la necesidad de nuevos tratamientos que permitan beneficiarse de los efectos positivos de los inhibidores cálcicos, aumentando su margen de seguridad, específicamente cardiovascular"*.

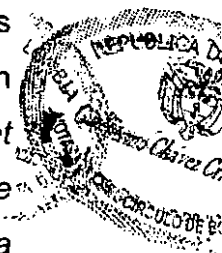
Consideramos al respecto que el Examinador ha introducido la solución en problema técnico y tiene un argumento *a posteriori*.

El problema técnico de la presente invención es la necesidad de una composición farmacéutica que mejore el tratamiento de la angina de pecho.

Respecto del pronunciamiento de la Superintendencia según el cual la presente invención es obvia para una persona versada en la materia a la luz de las enseñanzas de combinaciones de los documentos anteriores D1, D5 y D3 – D1, D5 y D4 – D2 y D3, reiteramos que en el campo de los medicamentos, teóricamente es de rutina para la persona versada en la materia usar una pluralidad de ingredientes activos juntos con diversos fines, como por ejemplo, el incremento del efecto médico y la disminución del efecto secundario. No obstante, el éxito de una asociación de ingredientes activos no puede predecirse.

En la medida en que la persona versada en la materia podría evaluar una multitud de combinaciones de ingredientes activos, resulta incorrecto considerar que sea obvio combinar específicamente ivabradina con amlodipino. De hecho, la persona versada en la materia combinaría cualesquiera familias de ingredientes activos con probabilidades de mejorar las condiciones de los pacientes con angina de pecho.

Incluso si la persona versada en la materia sabe que constituye un método racional tratar la angina de pecho con diversas clases de medicamentos antianginosos dotados de distintos mecanismos de acción, la persona versada en la materia sabe igualmente, gracias a literatura tal como el metaanálisis de Klein et al. (*La eficacia de la monoterapia en comparación con la combinación de medicamentos antianginosos en el tratamiento de angina de pecho crónica estable: un metaanálisis*, Klein et al., *La Enfermedad de las arterias coronarias*, 2002, 13:427-436), que esas combinaciones no son sistemáticamente "mejores" que las monoterapias. Efectivamente, según Klein et al., no se obtiene de las terapias combinadas mejora o seguridad que superen a las de las monoterapias. Por el contrario: la presente invención demuestra un incremento inesperado de la seguridad del uso de amlodipino combinado con ivabradina.



Además, la técnica anterior no proporciona orientación alguna que motive a la persona con conocimiento medio de la materia a realizar la combinación fija de los productos medicinales ivabradina + amlodipino. Ni D1, D5 y D3 – D1, D5 y D4, ni D2 y D3 incitan a formular una composición farmacéutica compuesta de ivabradina + un inhibidor de calcio.

Por último, la presente invención demuestra la sinergia entre ambos principios activos de la asociación ivabradina + amlodipino, puesto que se observa una reducción de 60% de los ataques de angina de pecho. La presente invención demuestra asimismo que la combinación de ivabradina con amlodipino incrementa la seguridad del uso de amlodipino, especialmente su seguridad cardiaca.

IV. ANEXOS

Para complementar toda la información obrante en el Expediente, anexamos el siguiente documento:

- Werner W. Klein, Graham Jackson and Luigi Tavazzi: "Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta analysis"

V. NOTIFICACIONES

Recibiré notificaciones en la secretaria de su Despacho y en la Carrera 11 No. 86 – 32 Oficina 101, de esta ciudad.

Atentamente,


MARIA VICTORIA LIEBBE LOZANO
C.C. No. 51.819.220 de Bogotá.
T.P.A. No. 54.845 del C.S de la J.

COLOMBIA
Despacho
101

PRESENTACION PERSONAL

El anterior escrito fue presentado ante el

NOTARIO CIVIL DEL CIRCULO DE BOGOTA D.C.

personalmente por

Blanca Victoria
Jesús Coronado

quien exhibió la c.c.

31819222 *Blanca*

y Tarjeta Profesional No.

34895 C.S.J.

26 ENE 2014

Fecha

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Guillermo Chávez Cristancho
[Signature]
Guillermo Chávez Cristancho
NOTARIO CIVIL DEL CIRCULO DE BOGOTA D.C.





PU32099ENG0

THERAPY AND PREVENTION

Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis

Werner W. Klein^a, Graham Jackson^b and Luigi Tavazzi^c

Objective To determine the relative efficacy of antianginal drugs administered as monotherapy or in combination in patients with chronic stable angina.

Methods A meta-analysis was performed on randomized trials, published in English between 1980 and 1999, that directly compared combined treatment and monotherapy. Twenty-two articles were included, all on the comparison of β -blocker monotherapies to their combination with a calcium antagonist and 10 on the comparison of calcium antagonist monotherapies to their combination with a β -blocker.

Results Time to 1 mm ST-segment depression, total exercise duration and time to onset of anginal pain were significantly increased with the combined therapy compared to β -blocker alone (by 8, 5 and 12%, respectively). Only time to 1 mm ST-segment depression was significantly increased with the combined therapy compared to calcium antagonist alone (by 9%). For all these parameters, the adjusted differences were significant only within 6 h following drug intake and were not significant after 6 h. No analysis of safety data could be performed.

Conclusion As far as exercise testing is concerned, the combination of a calcium antagonist and a β -blocker is statistically more effective than either monotherapy. Further studies are needed to confirm the higher efficacy after the first 6 h following drug intake. *Coron Artery Dis* 13:427–436 © 2002 Lippincott Williams & Wilkins.

Coronary Artery Disease 2002, 13:427–436

Keywords: meta-analysis, chronic stable angina, β -blocker, calcium antagonist, monotherapy, combined antianginal drugs

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Conflict of interest: None.

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Introduction

The aim of the treatment of chronic stable angina pectoris is to improve the prognosis by preventing myocardial infarction and death, and to minimize or abolish symptoms [1,2]. It has been shown that more than 50% of treated patients report a poor or fair quality of life [3], thus emphasizing the need for careful monitoring of symptom evolution under treatment. Despite the increasing popularity of interventional procedures such as coronary artery bypass grafting and angioplasty, non-invasive treatment remains the mainstay of antianginal management [3,4]. Because long-term use of β -blockers has been shown to reduce mortality following myocardial infarction, recent guidelines on the treatment of stable angina recommend the use of β -blockers as first-line agents [1,2]. However, no single class of therapy has been proven to be prognostically superior in the treatment of chronic stable angina [5].

The use of combination therapy is often considered to be the most rational approach to the treatment of stable angina because of somewhat different mechanisms of action of the various classes of antianginal drugs [4]. However, not all of the published trials showed a greater efficacy of combined therapies over monotherapies and according to the Task Force of the European Society of Cardiology, when a single agent is ineffective, it is probably best to evaluate an alternative single drug before starting combination treatment [1]. Therefore, we performed a meta-analysis of randomized trials that directly compared combined treatment with monotherapy in order to determine the relative efficacy of combined treatment and monotherapy in patients with stable angina.

Methods

Data sources

Clinical studies published in English between 1980 and December 1999 were identified by a Medline search, references from review articles on the medical treatment of stable angina and the Cochrane library. Search criteria were (1) stable angina pectoris, (2) the publication type (randomized clinical trial or controlled clinical trial) and (3) human use. Finally, bibliographies of identified trials were reviewed to locate other relevant studies.

Study selection

Trials were included when the enrolled patients had a history of stable angina and a direct comparison between monotherapy and combined therapy was available. Studies with a duration of less than 1 week were excluded. Criteria for selection of treatment were double-blind randomized trials where patients were treated by a combination of two drugs of two different classes among β -blockers, calcium antagonists or long-acting nitrates in comparison with monotherapy with one of the above.

Outcome measures

Measures of antianginal efficacy were examined. Measures of antianginal efficacy were those evaluated on exercise testing performed on a treadmill or an upright bicycle. No data were available on clinical outcome such as death or myocardial infarction, except in one trial [6]. Clinical data in the articles were not always available and not consistently reported (heterogeneous reporting in the number of angina episodes or short-acting nitrate consumption). Therefore, it was decided to exclude clinical parameters from the meta-analysis. Thus, the meta-analysis was restricted to the exercise-test parameters: total duration of exercise, time to onset of pain and time to 1 mm ST-segment depression. Not enough data were available to allow an estimation of the difference in the rate-pressure product.

Tolerance data were secondary criteria for this analysis. However, not enough data were available in the selected articles to allow a comparison on safety data.

Data extraction

Full texts of all the retrieved publications were assessed by a cardiologist who extracted the data from each article. Then the selection of the articles was performed by the cardiologist and a clinical statistician. The exercise-test data entry was double-checked.

Statistical analysis

Only one trial comparing long-acting nitrates in monotherapy or in combination fulfilled the selection criteria [7]. Therefore, the meta-analysis could be conducted only on β -blockers and calcium antagonists. Two separate analyses were performed, one for the comparison of β -blocker monotherapies to their combination with a calcium antagonist (BB+CA) and one for the comparison of calcium antagonist monotherapies to their combination with a β -blocker (CA+BB). Trials that compared a β -blocker to a calcium antagonist and to their combination were included in both BB+CA and CA+BB.

Trials that compared several doses of a drug to a combination were included as many times as the number of tested doses.

SEMs were converted to SDs. The absolute difference and the percentage of the difference of combined therapy to monotherapy were estimated for each trial and for all the trials together.

The standardized mean differences were estimated following Hedges' method [8] that remains adapted for small sample sizes. Unbiased standardized mean differences and their 95% confidence intervals (CIs) were estimated for each trial and for all the studies together. A difference was considered statistically significant when the zero value was not included in the 95% CI. These results are displayed in Figures 1–3.

An overall heterogeneity test was performed for each exercise-test parameter [9].

In order to differentiate 'peak' and 'trough' effects, secondary analyses were performed independently on two subgroups identified according to the time of exercising: within or later than 6 h following drug intake.

Secondary analyses were also performed independently on cross-over and parallel trials and on short- and long-acting calcium antagonists.

The percentage of patients with no angina and the percentage of patients without 1 mm ST-segment depression at the end of the trial were compared using Mantel-Haenszel adjusted χ -square.

Results

Selected studies

A total of 83 articles were identified. Finally, 23 trials were selected; this selection is graphically represented in Figure 4, as recommended by the QUOROM consensus guidelines [10]. Only one trial comparing long-acting nitrates in monotherapy or in combination fulfilled our selection criteria [7]. The remaining 22 articles (26.5%), comparing the combination of a β -blocker with a calcium antagonist were abstracted and included in the analysis (Table 1).

Eleven trials compared a β -blocker monotherapy to a combination of this β -blocker and a calcium antagonist [11–21]; three parallel-design and eight cross-over trials. One cross-over trial compared atenolol to its combination with either nisoldipine or nifedipine [22]. This trial was the only one with a comparison 2 h and 12 h after drug intake. Ten trials [23–32] compared a β -blocker, a calcium antagonist and their combination (four parallel-design and six cross-over trials). One out of these 10 trials tested two different doses of diltiazem [26].

Fig. 1

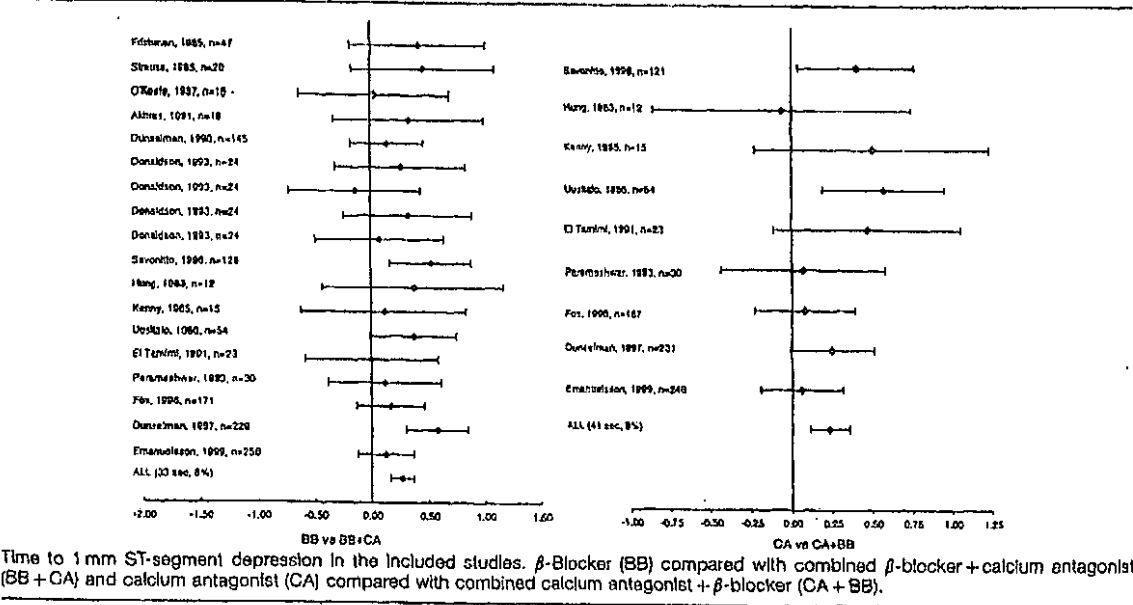
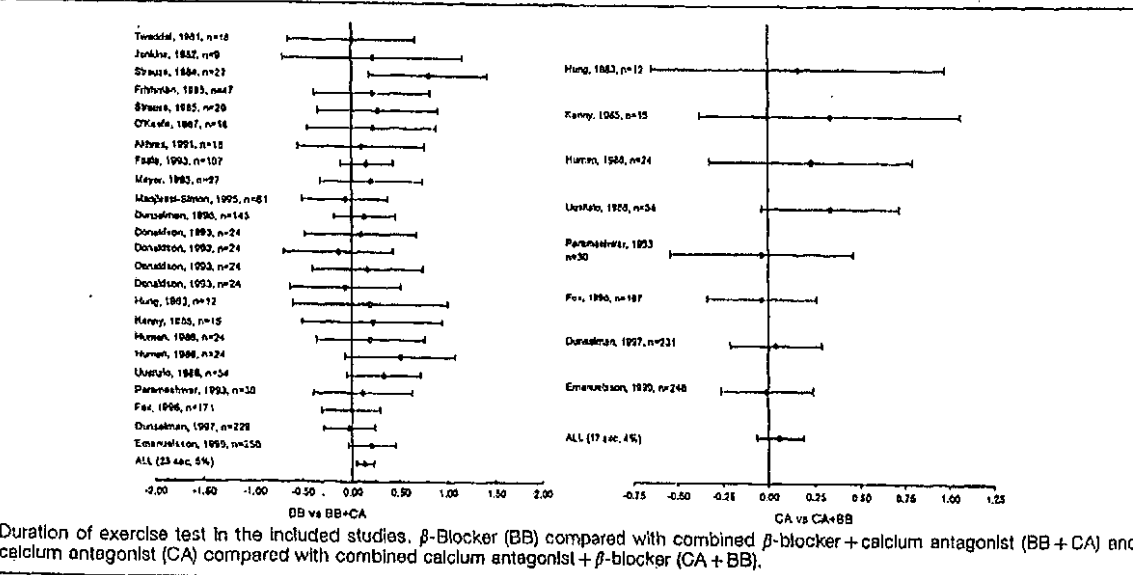


Fig. 2



Ten trials [11–16,21,22,31,32] specified that two exercise tests (ETTs) at least have to be performed before randomization. However, the reproducibility required was

detailed in only four articles: total exercise duration of two different ETTs differing by 2 min or less [15], 15% or less [31,32] and 20% or less [21].

Fig. 3

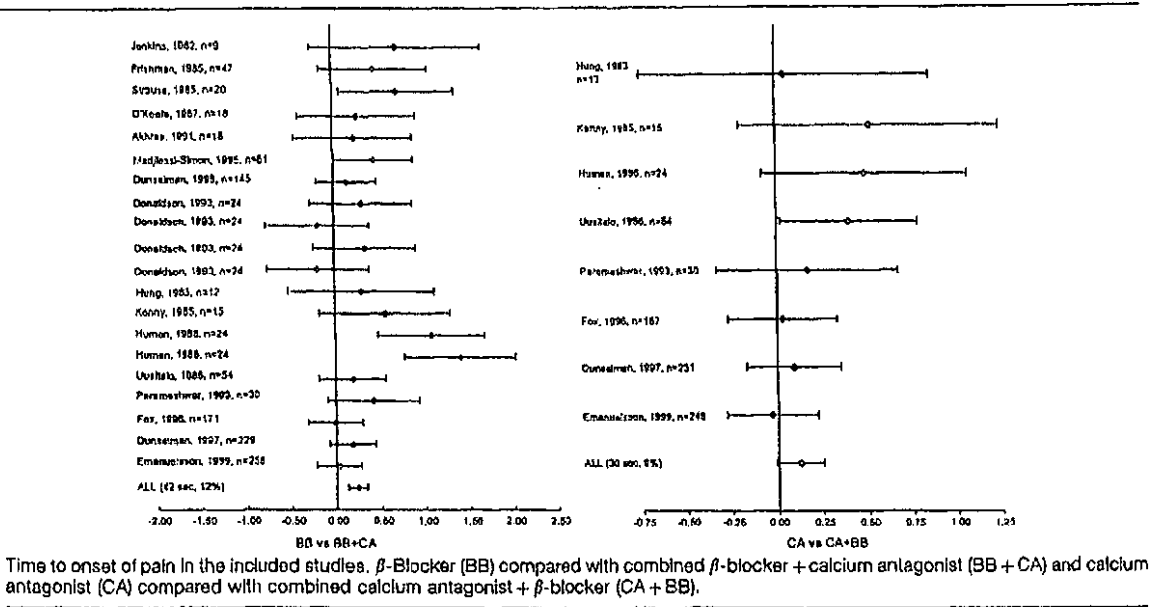
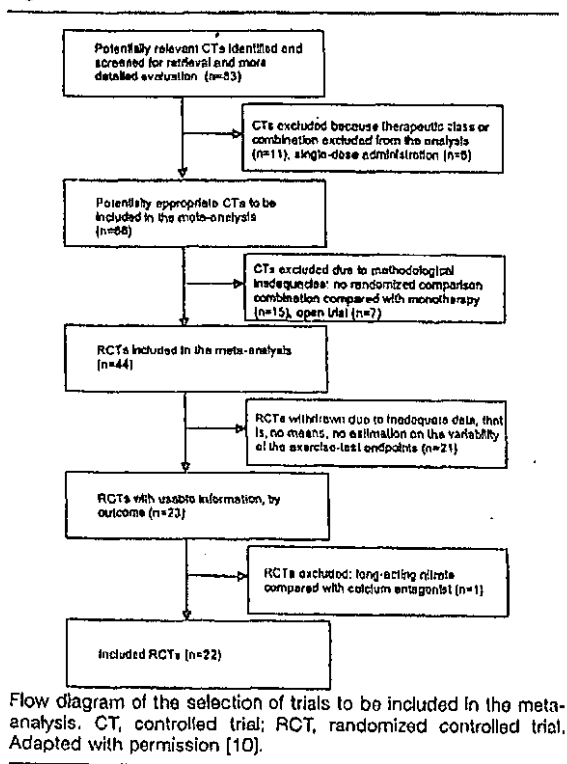


Fig. 4



Five trials [13,14,23,27,31] included no mention about documented coronary angiography or documented history of myocardial infarction while in five trials [16,17,20,22,28] documented coronary angiography or documented history of myocardial infarction were criteria of inclusion. In one trial [25] coronary angiography was performed in only one patient.

All the selected trials [11–32] were included in BB + CA and 10 trials [23–32] in CA + BB (Table 2). Two trials compared several doses of a drug to a combination and were included as many times as the number of tested doses [22,26]. The mean duration of the trials was less than 1 month (Table 3).

No overall heterogeneity test was statistically significant.

Comparison of a β -blocker to its combination with a calcium antagonist (BB + CA)

Time to 1 mm ST-segment depression

The time to 1 mm ST-segment depression was available in 630 patients treated by a monotherapy and 615 patients receiving combined treatment. The time to 1 mm ST-segment depression was 8% (33 s, $P < 0.001$) higher with the combined therapy. A graphical display is shown in Figure 1. There was a statistically significant difference of 9% (43 s, $P < 0.001$) at peak while the difference of 3% (10 s, $P = 0.21$) at trough was not statistically significant.

Total exercise duration

An estimation of total exercise duration was available for 818 patients receiving monotherapy and 796 patients receiving combined therapy. The adjusted difference in total exercise duration was 5% (23 s, $P = 0.002$), between the two groups, in favour of the combined therapy. A graphical display of the mean differences estimated according to Hedges' method with the corresponding 95% CI is shown in Figure 2. There was a insignificant difference at peak (5%, 29 s, $P = 0.21$) and no difference at trough (1%, 4 s, $P = 0.14$).

Time to onset of pain

A significant increase in the time to onset of pain was shown with the combined therapy compared to a β -blocker alone (Fig. 3). The difference in time to onset of pain was 12% (42 s, $P < 0.001$). The difference was significant in the analysis of the seven comparisons with an exercise test performed within 6 h following drug intake (+8%, +38 s, $P = 0.039$). No statistical difference was shown after 6 h (0%, -4 s, $P = 0.65$).

Similar results were noted when short- and long-acting preparations of calcium antagonists were evaluated separately, except for 1 mm ST-segment depression where the difference was not statistically significant in the two trials with the combination of short-acting calcium antagonists (+9%, 45 s, $P = 0.085$) [27,29].

Similar results were noted for the secondary analysis performed independently on cross-over and parallel trials, except for total duration of exercise test where the difference was not statistically significant in the parallel trials (+2%, 11 s, $P = 0.24$).

Comparison of a calcium antagonist to its combination with a β -blocker (CA + BB)**Time to 1 mm ST-segment depression**

Time to 1 mm ST-segment depression was available in 399 patients treated by monotherapy and 388 patients receiving combined treatment. Time to 1 mm ST-segment depression was 9% (41 s, $P < 0.001$) higher with the combined therapy. A graphical display with 95% CIs is shown in Figure 1. In the six trials with an exercise test performed within the 6 h following drug intake there was a statistically significant difference of 10% (46 s, $P < 0.001$), while there was no statistical difference (2%, 10 s, $P = 0.66$) in the only trial where the exercise test was performed after 6 h [31].

Total exercise duration

An estimation of the exercise duration was available for 338 patients treated by monotherapy and 330 patients treated by combined therapy. The total duration of exercise was 4% (17 s) higher with the combined therapy. However this

difference was not statistically significant ($P = 0.35$). A graphical display with 95% CIs is shown in Figure 2.

Time to onset of pain

As far as patients remaining with angina during exercise testing are concerned, the difference in time to onset of pain was of borderline significance (Fig. 3) favouring the combination. The unadjusted mean difference was 9% (30 s, $P = 0.067$).

Due to the small number of trials, short- and long-acting calcium antagonists could not be analysed separately.

The results of the secondary analysis performed independently on cross-over and parallel trials are not presented due to the small numbers of patients and of trials.

Discussion

This quantitative overview shows that, as far as exercise testing is concerned, the combination of a calcium antagonist and a β -blocker is more effective than a monotherapy by either drug alone. However, the difference in efficacy is rather small and might be limited to the 6 h following drug intake. The limited data on combination with nitrates did not allow a meta-analysis.

Combination therapy was significantly superior to monotherapy by a calcium antagonist only for time to 1 mm ST-segment depression measured at peak. However, the number of studies was limited and there was a favourable trend in the three tested parameters.

Combined treatment was significantly superior to a β -blocker alone, but this difference was only statistically significant when the exercise test was performed less than 6 h after drug administration. Although mean heart rate was not available after treatment in most of the trials, it appears unlikely that the transient benefit is due to suboptimal blockade since the prescribed doses were in general those recommended for angina pectoris.

Limitations of the study

The included trials did not allow the estimation of differences in rate-pressure product. However, regarding the relatively small magnitude of the effect on the three analysed exercise-test parameters it appears unlikely that a major effect on the rate-pressure product might be observed.

No direct comparison of BB+CA and CA+BB was performed. Nevertheless, the difference between combination therapy and monotherapy was similar, independent of whether the initial monotherapy was a calcium

Table 1 Treatments, doses and exercise-testing methods used in the included trials

Reference	First author	Year of publication	β -Blocker monotherapy	C-antagonist monotherapy	Combined treatment	Duration of active treatment	Exercise test	Time of exercise after drug intake	Design	Number of randomized patients
11	Twaddell A	1981	Propranolol, increased weekly doses up to optimal β -blockade		+ Nifedipine 10 mg, 3 times daily	3-week periods	Ergometer bicycle	Not communicated	Cross-over	25
12	Jenkins R	1982	Metoprolol, 100–400 mg/day or oxprenolol, 240–320 mg/day		+ Nifedipine, 10 mg, 3 times daily	2-week periods	Ergometer bicycle	Not communicated	Cross-over (compared with placebo)	9
13	Strauss W	1984	Propranolol, 40, 60 or 80 mg, 4 times daily according to optimal β -blockade		+ Lidoflazine, 120 mg, once daily, for 1 week then 120 mg, twice daily, for 1 week then 120 mg, 3 times daily	16-week periods	Treadmill (modified Bruce protocol)	Not communicated	Cross-over (carry-over effect)	22
14	Frishman WH	1985	Usual dosages of propranolol, 20–240 mg (mean 131 mg/day)		+ Bepridil, 200 mg/day with 100 mg increments up or down every 2 weeks (mean dosage at week 6, 273 mg)	8 weeks	Treadmill (modified Bruce protocol)	24 h	Parallel	56
15	Strauss W	1985	Propranolol, 20 mg, once daily, with doses increased to 40, 60 and 80 mg, once daily at weekly intervals		+ Maximum tolerated dose of diltiazem, 360 mg/day	2-week periods (after titration)	Treadmill (modified Bruce protocol)	Not communicated	Cross-over	24
16	O'Keefe J	1987	β -blockers		+ Nisoldipine, 2 mg/day or nisoldipine, 10 mg/day (randomization)	2-week periods	Treadmill (Bruce protocol)	2 h	Cross-over	18
17	Akhras F	1991	Atenolol, 50 mg, twice daily		+ Slow-release nifedipine, 40 mg, twice daily	4-week periods	Treadmill (Bruce protocol)	Not communicated	Cross-over	22
18	Foale R	1993	Atenolol, 50 mg, twice daily		+ Slow-release nifedipine, 20 mg, twice daily	4-week periods	Treadmill (Bruce protocol)	2–5 h	Cross-over	114
19	Meyer T	1993	Atenolol, 50 mg, twice daily		+ Slow-release nifedipine, 20 mg, twice daily	4-week periods	Treadmill (Naughton protocol)	2–3 h	Cross-over	27
20	Madjlessi-Simon T	1995	Pre-treatment with a β -blocker for at least 2 weeks		+ Amlodipine, 10 mg, once daily	16 days	Treadmill or ergometer bicycle	Not communicated	Parallel	81
21	Dunselman P	1998	Atenolol, 50 or 100 mg, once daily		Atenolol, 50 or 100 mg, once daily + amlodipine, 5 or 10 mg, once daily	8 weeks	Ergometer bicycle	22–24 h	Parallel	147
22	Donaldson K	1993		Nifedipine, 20 mg, twice daily or nifedipine, 10 mg, twice daily (randomization)	+ Atenolol, 100 mg, once daily	3-week periods	Treadmill (modified Bruce protocol)	12 h and 2 h	Cross-over	25

23	Savonitto S	1996	Controlled-release metoprolol, 200 mg, once daily	Retard nifedipine, 20 mg, twice daily	Both	4 weeks	Ergometer bicycle	1-4 h	Parallel	249
24	Hung J	1983	Propranolol, 20 mg, 4 times a day, then the dose was doubled after 24 h and tripled after another 24 h to 60 mg, 4 times a day, if tolerated	Diltiazem, 30 mg, 4 times a day, then the dose was doubled after 24 h and tripled after another 24 h to 90 mg, 4 times a day, if tolerated	Both with the same schema of titration	2-week periods	Ergometer bicycle	2.5-3.5 h	Cross-over	12
25	Kenny J	1985	Propranolol, 80 mg, 3 times daily	Diltiazem, 60 mg, 3 times daily	Both	4-week periods separated by 1 week	Treadmill (Bruce protocol)	Not communicated	Cross-over	15
26	Humen D	1986	Propranolol to provide full β -blockade	Diltiazem, 240 mg/day, in divided doses	Propranolol to provide full β -blockade + diltiazem, 240 mg/day in divided doses or propranolol to provide full β -blockade + diltiazem, 360 mg/day in divided doses (randomization)	2 weeks for each of the 4 treatment periods	Treadmill (Bruce protocol)	Not communicated	Cross-over	24
27	Uusitalo A	1988	Metoprolol, 100 mg, twice daily	Nitidipine, 10 mg, 3 times daily	Both	3 weeks	Ergometer bicycle	1 h	Cross-over	62
28	El-Tamimi H	1992	Atenolol, 50 mg, twice daily	Slow-release nifedipine, 20 mg, twice daily	Both	3-week periods	Treadmill (modified Bruce protocol)	4-6 h	Cross-over	23
29	Paramashwar J	1993	Atenolol, 50 mg, once daily, for 3 weeks, increased to 100 mg, once daily, depending on efficacy and tolerance	Nicardipine, 20 mg, 3 times daily, for 3 weeks, increased to 30 mg, 3 times daily depending on efficacy and tolerance	Atenolol, 50 mg, once daily + nicardipine, 20 mg, 3 times daily for 3 weeks, increased to 100 mg, once daily and 30 mg, 3 times daily depending on efficacy and tolerance	5-week periods separated by a 1-week down-titration period	Treadmill (modified Bruce protocol)	Not communicated	Cross-over	30
30	Fox K	1996	Atenolol, 50 mg, twice daily	Slow-release nifedipine, 20 mg, twice daily	Both	6 weeks	Treadmill (Bruce protocol)	2-6 h	Parallel	608
31	Dunselman P	1997	Controlled-release metoprolol, 100 mg or 200 mg, once daily	Extended-release felodipine, 10 mg, once daily	Controlled-release metoprolol, 100 mg or 200 mg, once daily + extended-release felodipine, 5 mg, once daily, for 2 weeks then 10 mg, once daily	5 weeks	Ergometer bicycle	2-6 h	Parallel	353
32	Emanuelsson H	1999	Controlled-release metoprolol, 100 mg, once daily	Extended-release felodipine, 10 mg, once daily	Both	4 weeks	Ergometer bicycle	20-25 h	Parallel	397

Table 2 Study characteristics of the included trials

		Monotherapy	Combination
β -Blocker compared with combination (n = 22)	Age (years)	58.0 ^a	58.1
		(52-62) ^b	(52-63)
		n = 21	n = 21
	Sex (% men)	89%	89%
		n = 16	n = 16
Calcium antagonist compared with combination (n = 10)	History of myocardial infarction	35%	36%
		n = 15	n = 15
	Age (years)	60.0	59.7
		(56-64)	(56-63)
		n = 9	n = 9
	Sex (% men)	86%	87%
		n = 8	n = 8
	History of myocardial infarction	23%	23%
		n = 9	n = 9

n, number of studies. ^aMean of means. ^bMinimum-maximum of mean.

Table 3 Number of trials by outcome and study duration

	β -Blocker compared with combination (n = 22)	Calcium antagonist compared with combination (n = 10)
Study duration (weeks)	3.7 (2-8)	3.9 (2-8)
Total duration of exercise	20	8
Time to pain onset	16	8
Time to 1 mm ST-segment depression	15	9

antagonist or a β -blocker except for total exercise duration where the difference was greater in the BB + CA comparison. This minimal increase in total exercise duration might be explained by the reduced effort tolerance under treatment with β -blockers alone [33-35] being offset by the vasodilator action of calcium antagonists.

Besides, this meta-analysis did not allow the comparison of the efficacy of the association of a rate-slowing CA with BB and of the association of a dihydropyridine with BB.

Publication bias cannot be ruled out in the present report because only published data were selected [10]. However, because it is unlikely that trials with strong differences between treatments were not published, a publication bias underestimating treatment effects does not appear likely and if anything it rather might exist in the opposite direction (accordingly, the differences between treatments reported here are probably not underestimated). Furthermore, the present study was limited to the articles published before 2000. However, two recent publications seem to confirm the conclusion of this meta-analysis [36,37].

In only six trials were more than 100 patients randomized. Small trials with nominally significant *P*-values tend to overestimate the size of treatment effect, because the treatment effect must be large if statistical significance is to be reached with a small sample size [38]. Therefore, a meta-analysis that includes only small trials is more likely to overestimate treatment effects, leading to an overly favourable view of an agent's efficacy [39]. However, few of the included studies did demonstrate significant differences between monotherapy and combined therapy, suggesting that any such bias may be small. In addition, only English language articles were retrieved. Reports of randomized clinical trials with statistically positive results are more likely to be published in English than those with negative results [40]. Nevertheless, it has been established that language-restricted meta-analyses overestimate the treatment effect by only 2% compared with language-inclusive meta-analyses [10].

Exercise testing is less sensitive and less specific in women than in men [4]. The included trials do not allow for comparison of the differences between combination therapy and monotherapy with respect to sex. However, since higher percentages of men were included in the selected trials, sex is an unlikely explanation for the relatively small differences observed between combination therapy and monotherapy.

To our surprise, it was not always specified whether two or more reproducible exercise tests were required before randomization, which may have led to higher variability. The impact of such an effect will be more likely on the SD than on the estimated mean. We were also unable to compare efficacy according to the severity of the disease or to total ischaemic burden because few data on ambulatory monitoring were available.

Besides, the diagnosis of chronic stable angina was not confirmed by coronary angiography or documented myocardial infarction in all trials and some patients with other pathology than chronic stable angina might have been included in some trials [1,2]. This might have led to an underestimation of the treatment effect and a decrease in power.

Despite the fact that in addressing chronic stable angina the focus should be on the prevention and improvement of symptoms, the selected trials did not allow for performing a meta-analysis either on clinical data, on quality of life or on clinical events. Only one trial [6] reported data on the outcome in 682 patients followed up for 2 years and it showed an insignificant trend to a lower rate of hard endpoints in the group receiving combined therapy.

In the same way, no meta-analysis on safety data could be performed on the included trials when authors who had

reservations on the usefulness of combined therapy underlined the risk of side-effects with combination therapy [41–44].

When searching the literature for the present meta-analysis we were surprised by the lack of published data on combination therapy with long-acting nitrates, particularly in view of their frequency of use. In a recent meta-analysis comparing different monotherapies in the treatment of chronic stable angina, only 12 trials comparing long-acting nitrates to calcium antagonists, six trials comparing long-acting nitrates to β -blockers and one combination study were retrieved [5].

Interpretation

It could be argued that comparison of combined therapy and monotherapy is of limited importance because many patients undergo interventional procedures. However, this is often not the case due to large differences in availability of such procedures between countries, but also in particular patient groups, for example, in the elderly (systematically excluded from these comparative studies) in whom multicoronary, calcified stenoses are present and the risks of surgical procedures are substantial. Moreover, many patients after interventions still remain on anti-anginal therapy. Whether or not these patients should be treated with monotherapy or polytherapy is still left to the non-evidence-based decision of the individual physician.

The absolute differences observed in this meta-analysis seem only slightly smaller than the usually published difference between β -blockers and placebo or calcium antagonists and placebo [45,46]. However, because of the great heterogeneity in exercise-test protocols and in sample sizes only percentages and standardized mean differences are the parameters of choice. The observed difference in exercise performance between combined therapy and monotherapy is 4–12%.

Conclusion

In summary, this quantitative overview shows that, as far as exercise capacity is concerned, the combination of a calcium antagonist and a β -blocker is statistically more effective than a monotherapy. However, the difference seems restricted to the first 6 h following drug intake.

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