

CAVELIER

ABOGADOS

www.cavelier.com
cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 N° 73-25
BOGOTÁ 8,

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Teléfono: (57-1) 347 3611
Telefax: (57-1) 211 8650
0 4814
7743

Señor Director
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.



No. 05-074973- -00014-0000

Fecha: 2011-03-10 16:40:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 523 RESPUESTA Folios: 100

Trámite : 011
Evento : 379
Actuación : 444

Referencia : Expediente No. 05.074.973
Asunto : Solicitud de patente para **MEDICAMENTO PARA LA PROFILAXIS Y EL TRATAMIENTO DE ARTERIOSCLEROSIS E HIPERTENSION**
Solicitante : **DAIICHI SANKYO COMPANY, LIMITED**
Clase : A61K 045/006, A61P 009/000, A61P 009/010, A61P 009/012
Fecha de Solicitud : 29 de julio de 2005

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **14387** notificado por fijación en lista del 5 de noviembre de 2010.

2. Mediante memorial radicado el día 27 de enero de 2011 solicité plazo de treinta (30) días para atender el oficio No. **14387**.

3. Mediante oficio No. **14387** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio son las siguientes:

3.1 Reivindicaciones

El Examinador considera que "se caracteriza inapropiadamente una composición farmacéutica en las reivindicaciones 2-21 por ser usada para ciertas condiciones o enfermedades y en las 6 y 22 porque el compuesto A y el B se administran al mismo tiempo ó por separado a ciertos intervalos".

Adicionalmente, afirma que el término “además” de las reivindicaciones 23 a 26 es inapropiado debido a que los elementos de dichas reivindicaciones ya se encuentran definidos en la reivindicación 1.

Finalmente, considera que “no existe soporte para toda la materia reclamada, pues la descripción sólo presenta un ejemplo de una composición que contiene olmesartan medoxomil y azelnidipina”. Adicionalmente, considera que “el efecto técnico está basado en la combinación de estos activos mediante un método de tratamiento (al ser co-administrados cada uno en dosis mg/fg/día; folio 119-122, pág. 36-39) y no mediante una composición que los contenga como se reclama”.

3.2 Análisis de patentabilidad

3.2.1 Nivel Inventivo

Considera el Examinador que “la materia reclamada es obvia a las enseñanzas de D1 (composición de valsartán –un bifeniltetrazol antagonista de angiotensina II- y un bloqueo de canales de calcio derivado de dihidropiridinas –como amlodipino o amlodipino besilato, entre otros-) y las sugerencias de D2 (cambiar el derivado de bifeniltetrazol: valsartán por olmesartan medoxomil) para un experto en la materia, por lo que tal materia no tienen nivel inventivo”.

4. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea poner de presente las siguientes modificaciones, aclaraciones y argumentos:

4.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento

del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 5 reivindicaciones.

La reivindicación 1 ha sido modificada con el fin de revelar de manera completa las características esenciales de la formulación reclamada. Así, de acuerdo con dicha modificación, dicha reivindicación revela que la composición comprende tanto el receptor de angiotensina que corresponde al compuesto (5-metil-2-oxo-1,3-dioxolen-4-il)metilo -4-(1-hidroxi-1-metiletil)-2-propil-1-[[2'-(1H-tetrazol-5-il)bifenil-4-il]metil]imidazol-5-carboxilato o a una sal farmacológicamente aceptable del mismo, como el bloqueador de los canales de calcio que se selecciona de azelnidipina, amlodipina ó besilato de amlodipina.

De otro lado, las reivindicaciones 2 a 22 no han sido incluidas en el nuevo pliego reivindicatorio con el fin de evitar hacer referencia al uso de la composición reclamada. En consecuencia, las anteriores reivindicaciones 23 a 26 (ahora reivindicaciones 2 a 5) se han modificado con el fin de evitar hacer referencia al término “además”. Sin embargo, deseamos poner de presente que dichas nuevas reivindicaciones dependientes 2 a 5 delimitan la materia ya revelada en la nueva reivindicación independiente 1.

Solicitamos atentamente tener en cuenta este nuevo pliego reivindicatorio que consideramos, cumple con las disposiciones de la Decisión 486 y permite además, superar las objeciones formuladas por el Examinador.

4.2 Aclaraciones con respecto a la objeción por falta de sustento

El Examinador considera que “no existe soporte para toda la materia reclamada, pues la descripción sólo presenta un ejemplo de una composición que contiene olmesartan medoxomil y azelnidipina”. Adicionalmente, considera que “el efecto técnico está basado en la combinación de estos activos mediante un método de tratamiento (al ser co-administrados cada uno en dosis mg/fg/día; folio 119-122, pág. 36-39) y no mediante una composición que los contenga como se reclama”.

De lo anterior, deseamos aclarar que nos alejamos de la posición de Examinador debido a que la afirmación citada reconoce que la descripción de la presente solicitud revela un

Ejemplo de composición que contiene olmesartan medoxomil y azelnidipina, los cuales corresponden a los componentes revelados en la nueva reivindicación 3 (haciendo referencia al Ejemplo de preparación revelado en la página 40 de la descripción). Más ampliamente, con relación a los componentes A) y B) de la composición reclamada, cabe aclarar que dicha composición se encuentra revelada en la página 27 de la descripción. El componente B) se encuentra ejemplificado mediante la azelnidipina revelada en la página 23 de la descripción y mediante el besilato de amlodipina revelado en la página 26 de la descripción.

Adicionalmente, con respecto a la afirmación del Examinador en cuanto a que el efecto técnico mejorado revelado en la descripción, haciendo referencia a los ejemplos 1 a 3, fue establecido mediante un tratamiento en donde el componente A) (olmesartan medoxomil) y el bloqueador de los canales de calcio (el compuesto B) son administrados por separado, deseamos poner de presente que es usual que dos medicamentos se administren por separado debido a la practicidad que implica en la determinación del efecto de una composición que comprende dos componentes (medicamentos), la administración de dichos dos medicamentos por separado. Sin embargo, cabe aclarar que a pesar de que el hecho de administrar los dos medicamentos por separado resulte conveniente para probar la combinación inventiva de los mismos, dicho hecho no debe restarle valor a que a lo largo de la descripción se revela explícitamente que la presente invención corresponde a una composición que comprende dos medicamentos como ingredientes activos.

Adicionalmente, deseamos aclarar que las enseñanzas presentes en la especificación permiten a una persona versada en la materia reproducir la composición reclamada.

Así las cosas, solicitamos respetuosamente se de por superada la objeción relacionada con la falta de sustento en la descripción de la composición reclamada.

4.3 Argumentos a favor del nivel inventivo de la solicitud

En concordancia con el Artículo 18 de la Decisión 486, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia.

Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que le indiquen cómo llegar a la invención reivindicada.

- Inicialmente, deseamos poner de presente lo siguiente con respecto a las anterioridades citadas:

La anterioridad D1 (US2001049384) revela un método de tratamiento y una composición farmacéutica que comprende un antagonista de la angiotensina II, valsartan, en combinación con un bloqueador de los canales de calcio, el cual se encuentra ejemplificado mediante 18 compuestos, los cuales incluyen los tres bloqueadores de canales de calcio revelados en la nueva reivindicación 1 de la presente invención.

Así en el párrafo [0017] dicha anterioridad afirma que la combinación de valsartan y un bloqueador de los canales de calcio "...resulta no solo en un efecto sinérgico sino también

en...". Lo anterior es la única mención en D1 con respecto a un efecto sinérgico; sin embargo, D1 no incluye prueba alguna en donde se establezca la efectividad terapéutica de las composiciones allí reveladas, o en donde dicha efectividad corresponda a un efecto sinérgico.

Para el análisis de la anterioridad D2 (JP2002145770) deseamos poner de presente que se ha tomado su equivalente EP1314425A1. De esta manera, la anterioridad D2 revela en el resumen lo siguiente:

"La presente invención se relaciona con composiciones farmacéuticas, que contienen un inhibidor selectivo de la HMG-CoA reductasa seleccionado del grupo que consiste de pravastatina, simvastatina, lavastatina, pitavastatina y ZD-4522; y un antagonista del receptor de la angiotensina II y opcionalmente comprende adicionalmente un bloqueador de los canales de calcio".

Cabe aclarar que D2 no revela una composición que comprenda olmesartan o olmesartan medoxomil y un bloqueador de los canales de calcio.

Ahora bien, con respecto al análisis realizado por el Señor Examinador, deseamos poner de presente lo siguiente:

Inicialmente, es importante aclarar que es bien sabido que una persona versada en la materia como regla general no puede concluir a partir de una formulación para un ingrediente activo, las características que se requieren para una formulación con otro ingrediente activo. Lo anterior se debe básicamente a las diferentes propiedades químicas y biológicas de los dos ingredientes activos, entre otras cosas.

- De otro lado, deseamos se tengan en cuenta los siguientes datos comparativos:

El ejemplo de prueba 1 de la presente solicitud establece el efecto sinérgico de la combinación de olmesartan y azelnidipina para la inhibición de la proliferación de células musculares lisas vasculares. Los ejemplos de prueba 2 y 3 establecen el efecto sinérgico de la combinación de olmesartan medoxomil y azelnidipina en el tratamiento de la hipertensión.

Adicionalmente, deseamos hacer referencia a los resultados de ensayos comparativos, los cuales fueron allegados junto con el memorial (Anexo I del presente memorial) radicado el 8 de mayo de 2008, en respuesta al Oficio No. 14640 en donde se informaba la oposición presentada por la sociedad PROCAPS S.A.

Dichos resultados de ensayos comparativos (Adjuntos a su vez a este memorial) muestran el efecto sinérgico de la combinación de olmesartan medoxomil con besilato de amlodipina. Igualmente, demuestran los resultados inferiores obtenidos a partir de la combinación de besilato de amlodipina y el compuesto del estado del arte losartán potásico (el cual fue comercializado en Estados Unidos por Merck mediante el nombre de COZAAR).

Los datos comparativos, los cuales se mencionarán en detalle más adelante, los cuales están presentes en la publicación médica de C.V.S Ram (Anexo VIII) establecen que la combinación de olmesartan medoxomil y amlodipina proporciona beneficios inesperados en comparación con la combinación de valsartan y amlodipina.

- Teniendo en cuenta lo anterior, deseamos adicionalmente, presentar los siguientes argumentos a favor de la patentabilidad de la presente invención:

La objeción hecha por el Examinador consiste en que considera que la anterioridad D1 revela composiciones que contienen valsartan y bloqueadores de los canales de calcio, tal como amlodipina y besilato de amlodipina y teniendo en cuenta que D2 revela composiciones que contienen dos componentes (y opcionalmente un tercer componente) en donde uno de los componentes es un antagonista de la angiotensina II el cual se encuentra ejemplificado por seis compuestos que incluyen el valsartan, olmesartan

medoxomil, candesartan y losartan, y que por lo tanto el hecho de presentar una composición en donde el valsartan de las composiciones de D1 se reemplace con olmesartan medoxomil no representa altura inventiva.

Inicialmente, deseamos poner de presente que la anterior objeción se basa en que una persona versada en la materia consideraría a partir de las enseñanzas de D2 que los seis antagonistas de la angiotensina II pueden ser equivalentes en la combinación de dicha anterioridad con un inhibidor de la HMG-CoA reductasa; y que por lo tanto, dicha persona versada en la materia esperaría reemplazar el valsartan de la combinación de d1 con el olmesartan medoxomil, con el fin de obtener los resultados que se alcanzan mediante las composiciones de D1. De lo anterior, cabe aclarar que una persona versada en la materia sabría que existen características diferentes entre los diferentes antagonistas de la angiotensina II. Adicionalmente, aclaramos que una persona versada en la materia estaría consciente que dos medicamentos individuales operan por medio de mecanismos diferentes, y no es de esperarse que la combinación de dos medicamentos tenga necesariamente un efecto benéfico. De esta manera, la composición de la presente solicitud se diferencia además de la combinación de D1 en que dicha composición produce un efecto superior al que produce la combinación revelada en D1. Así, cada uno de estas afirmaciones se desarrolla a continuación.

Deseamos se tenga en cuenta el Anexo II (Publicación: Cevenka et al "Association of Candesartan vs Losartan With All-Cause Mortality in Patients With Heart Failure", JPM January 12, 2011, pages 175-182), en donde se establece que el antagonista de la angiotensina II candesartan y losartan tienen efectos diferentes en pruebas cara a cara de la mortalidad de pacientes con insuficiencia cardíaca.

En el campo farmacéutico es bien sabido que cuando se combinan dos o más medicamentos, no solo existe la posibilidad de que no se presente un efecto mejorado, sino que también existe la posibilidad de que exista una dificultad potencial debido a las interacciones entre los medicamentos. Por ejemplo, deseamos se tenga en cuenta el Anexo III (Yusuf et al, "Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular

Events", New England Journal of Medicine, vol. 358, no. 15. pp. 1547-1559, Abril 10, 2008).

En dicho Anexo III se describe un ensayo clínico del inhibidor ACE ramipril, el telmisartan ARB y la combinación de estos dos medicamentos en varios pacientes. La conclusión obtenida por los investigadores es que mientras el telmisartan "era equivalente al ramipril en pacientes con enfermedades vasculares o alto riesgo de diabetes y estaba asociado con menor angioedema" la combinación de los dos medicamentos "estaba asociada mayormente asociada con eventos adversos sin que hubiera un incremento en los beneficios" (Véase el Anexo III p.1547, último párrafo). Así, teniendo en cuenta los resultados del estudio realizado en el Anexo III, una persona de la Heart and Stroke Foundation de Canada afirmó que la "combinación de dichos dos medicamentos es una fuente de mayor stress en los riñones", y que los dos medicamentos "no ofrecen ningún beneficio adicional en combinación sino que cada uno se asocia con efectos secundarios, lo que hace que se dupliquen los efectos secundario" (Véase Anexo IV. Heart and Stroke Foundation of Canada Press Release quoting Dr Sheldon Tobe, Enero 16, 2009).

Debido a lo anterior, cabe recalcar que es claro que se debe tener gran cuidado en el desarrollo de combinaciones de hipertensivos para alcanzar una eficiente disminución de la presión arterial mientras que se evita un nivel inaceptable de efectos secundarios. En el Anexo III se demuestra que el resultado de la combinación de diferentes tipos de antihipertensivos impredecible y continua fallando a pesar de conocimiento preexistente con respecto a los medicamentos antihipertensivos por separado. La literatura técnica en el campo de agentes antihipertensivos proporciona ejemplos de fallas en alcanzar combinaciones de agentes antihipertensivo; por lo tanto, no existe expectativa considerable de éxito para una persona versada en la materia para que alcance una combinación efectiva de agentes antihipertensivos simplemente mediante la combinación aleatoria de dos agentes antihipertensivos.

La composición farmacéutica de la presente invención, la cual comprende una combinación de olmesartan medoxomil y besilato de amlodipina, amlodipina o azelnidipina proporciona un beneficio inesperado en comparación con el estado el arte, ya que dicha

composición no solo proporciona mayores efectotes de disminución de la presión arterial en comparación con la monoterapia con cualquiera de los componentes, sino que también permite que una mayor cantidad de los pacientes tratados con dicha composición alcancen sus metas de presión arterial. Como evidencia de dicho resultado inesperado, deseamos hacer referencia al Anexo V (Chrysant, "Amlodipine/ARB Fized Dose Combination" Drugs Today, vol. 44, issue 6, pages 443-453, 2008) en donde se discuten datos que fueron inicialmente reportados como parte del estudio realizado en el Anexo VI (Chysant et al, Clinical Therapeutics, vol. 30, no 4, 2008).

En dicho Anexo V se presentan datos comparativos entre la combinación de olmesartan medoxomil y amlodipina contra cualquiera de los dos componentes tomados individualmente. (Véase Anexo V Tabla II). En dichos datos presentados en la tabla II del Anexo V se tiene lo siguiente:

Monotherapy						
Treatment	PL	AB	AB	OM	OM	OM
Dose (mg/day)	0	5	10	10	20	40
SDBP (mmHg)	-3.1	9.4	12.7	8.3	9.2	10.2
SSBP (mmHg)	-4.8	14.9	19.7	11.5	13.8	16.1
Combination Therapy						
Treatment	AB/OM	AB/OM	AB/OM	AB/OM	AB/OM	AB/OM
Dose (mg/day)	5/10	5/20	5/40	10/10	10/20	10/40
SDBP (mmHg)	-13.8	14.0	15.5	16.0	17.0	19.0
SSBP (mmHg)	-24.2	23.6	25.4	25.3	29.2	30.1

Así, en el Anexo V se afirma que "todos los grupos de tratamiento muestran una reducción mas grande en la presión arterial en comparación con el placebo ($P<0.001$) y los efectos de disminución en la presión arterial son mas grandes que los de las monoterapias ($P<0.001$)" (Véase Anexo V p. 446, columna izquierda, líneas 36 a 40). En otras palabras, a diferencia del Ejemplo del Anexo III, mencionado anteriormente, la combinación de olmesartan medoxomil y besilato de amlodipina proporciona un beneficio relacionado con la disminución en la presión arterial en comparación con la monoterapia de los componentes tomados individualmente. Adicionalmente, los datos proporcionado en la Figura 2 del Anexo V muestran que mayor numero de pacientes tratados con la

terapia de combinación alcanzaron las metas de presión arterial (<140/90 mmHg) que los que recibieron solo la monoterapia. Específicamente, los datos de dicha Figura 2 del Anexo V muestran que más del 50% de los pacientes que recibieron 5/40, 10/10, o 10/20 mg/día de amlodipina/olmesartan alcanzaron el control de la presión arterial (definido como <140/90 mmHg), mientras a un porcentaje mucho más bajo de pacientes suministrados con el máximo de la dosis de la monoterapia de amlodipina (10 mg/día, 36.1% de pacientes que alcanzaron el objetivo) o de olmesartan (40 mg/día, 38.5% de pacientes que alcanzaron el objetivo), alcanzó el control de presión arterial. Se encontraron diferencias aún más grandes cuando se comparan dosis de monoterapia menores a las máximas con las dosi de las terapias de combinación (véase Anexo V, página 449, Figura 2).

En consecuencia, el elevado número de pacientes que alcanzaron los controles de presión arterial corresponde a un resultado ventajoso y sorprendente. Por ejemplo, no existe evidencia alguna para predecir que en donde solo el 36% o el 38% de pacientes que recibían las dosis máximas de amlodipina (es decir 10mg/día) o de olmesartan (es decir 40mg/día), pudieran controlar su presión arterial de, un porcentaje mayor de pacientes (es decir el 46.6%) que recibían dosis más bajas de cada ingrediente en combinación (es decir 5mg/día de amlodipina y 20mg/día de olmesartan), pudieran controlar so presión arterial. Es así como dicho incremento en el porcentaje de pacientes que son capaces de controlar su presión arterial, no es predecible a partir de las enseñanzas del estado del arte (D1 o D2) y por lo tanto, corresponde a un resultado ventajoso.

Aún más, los datos mencionados anteriormente resuelven una necesidad largamente sentida, ya que la hipertensión sin control representa una necesidad largamente sentida y los datos mencionados anteriormente proporcionan evidencia de que la composición farmacéutica de la presente invención se comporta de manera defrente a las composiciones enseñanzas en el estado del arte. Específicamente, deseamos aclarar que la composición de la presente invención permite que un número mas elevado de pacientes alcancen el control de la presión arterial, que lo que alcanzarían con las dosis máximas de la monoterapia con amlodipina (es decir 10mg/día) o con olmesartan

(40mg/día), respectivamente, tal como se reporta en el Anexo V. Así, dicho incremento es altamente significativo ya que hace que ocurran disminuciones sustanciales en eventos cardiovasculares aún con pequeñas disminuciones en la presión arterial. Deseamos se tenga en cuenta el Anexo VII (Lewington, S., et al, "Age-specific relevant of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies", Lancet, col. 360, pp. 1903-1913, 2002), en donde se reporta un hallazgo en cuanto a que cada diferencia de 20mmHg en la presión arterial sistólica se encuentra asociado a mas del doble de la diferencia en la tasa de muerte re racionada con un derrame cerebral, una cardiopatía isquémica, u otras causas vasculares (Véase Anexo VII, página 1903).

La combinación de olmesartan medoxomil y el bloqueador de los canales de calcio 1, 4 dihidropiridina, amlodipina, proporciona un resultado inesperado en comparación con la combinación de valsartan y amlodipina. Como evidencia de lo anterior, deseamos poner de presente el Anexo VIII (C.V.S. Ram, "Antihypertensive efficacy of olmesartan medoxomil or valsartan in combination with amlodipine: A review of factorial-design studies", Current Medical Research and Opinión, vol. 25, no. 1, p. 177-185, 2009), en donde se discuten datos que fueron originalmente reportados en el Anexo VII.

En dicho Anexo VIII se proporciona evidencia relacionada con el hecho de que la composición de la presente invención produce un efecto material más alto en comparación con la combinación de valsartan y amlodipina. Específicamente, de acuerdo con lo revelado en dicho Anexo VIII, la combinación "amlodipina 10mg/olmesartan medoxomil 40mg proporcionó las reducciones corregidas por placebo mas altas en tanto el promedio de mínimos cuadrados para presión arterial sistólica en posición sedente (SeSBP) como para la presión arterial diastólica en posición sedente (SeDBP) (15.9 y 25.7 mmHg, respectivamente, por el contrario de 9.8 y 15.5 mmHg, con dosis máximas de amlodipina (10mg) y de valsartan (320mg), respectivamente)" (Véase Anexo VIII, p. 184, columna izquierda, líneas 37 a 52). De esta manera en el Anexo VIII se proporciona una comparación gráfica de los resultados de cada comparación (Véase Anexo VIII p. 181). Con relación a la reducción de la presión arterial diastólica en posición sedente (SeDBP), los datos reportados por el Anexo VIII demuestran que el promedio de mínimos cuadrados

para la SEDBP para la reducción máxima corregida por placebo de amlodipina y olmesartan medoxomil, es de 6.1 mmHg o acerca de 62% (6.1mmHg / 9.8 mmmHg) más alta que la máxima reducción corregida por placebo de amlodipina y valsartan, tal como se reporta en el Anexo VIII. De igual manera, los datos revelados para el promedio de mínimos cuadrados de la SeSBP para la reducción más alta corregida por placebo para una combinación de amlodipina y olmesartan medoxomil es de 10.2mmHg o cerca del 66% (10.2mmHg/15.5mmHg) más alta que el la reducción máxima corregida por placebo de una combinación de amlodipina y valsartan, como se reporta en el Anexo VIII. Aún más, en dicho Anexo VIII se afirma que “se ha demostrado que la morbilidad por riesgo cardiovascular se duplica con cada incremento de 20/10 mmHg en la presión arterial arriba de 115/75 mmHg” (Véase Anexo VIII, columna derecha, página 177, líneas 2 a 5).

En consecuencia, teniendo en cuenta la información revelada en el Anexo VIII, una persona versada en la materia apreciaría que la magnitud de la mejora en la reducción del promedio de mínimos cuadrados tanto de la SeDBP como de la SeSBP mediante la composición de la presente invención en comparación con la combinación de amlodipina con valsartan, proporciona cerca del doble de la reducción en el riesgo de muerte cardiovascular, el cual es claramente un resultado inesperado y ventajoso. Por lo tanto, no puede ser afirmado que la composición de la presente invención podría ser derivada de manera obvia, ya que por medio de los resultados mencionados, específicamente en el Anexo VIII, se ha demostrado el efecto mayor al esperado alcanzado por la composición de la presente invención en comparación con el resultado obtenido en la anterioridad D1, lo que es demuestra a su vez que la presente invención no pudo haber sido derivada de manera obvia a partir de D1.

Adicionalmente, además de las reducciones más bajas en el presión arterial, en comparación con la composición de la presente invención, la combinación de amlodipina y valsartan tiene ciertas deficiencias, tal como se afirma en el Anexo VIII en donde se dice que “la terapia de combinación con valsartan 160mg con 10mg de amlodipina ha sido reportada como incapaz de atenuar la activación simpática inducida por la amlodipina” (Ver Anexo VIII, Pág. 184, columna derecha, líneas 1 a 4). En dicho Anexo VIII no se proporciona explicación para dicha diferencia entre la combinación de

amlodipina/valsartan en comparación con la combinación de amlodipina/olmesartan (Ver Anexo VIII, Pág. 184, columna derecha, líneas 5 a 10), lo que proporciona evidencia adicional acerca del resultado inesperado alcanzado por la composición de la presente solicitud, lo que a su vez documenta lo impredecible de combinar dos ingredientes activos.

Por lo tanto, el Anexo VIII proporciona evidencia significativa de los resultados inesperados y mejorados de la combinación de amlodipina y olmesartan medoxomil, en comparación con la combinación de amlodipina y valsartan; particularmente, en vista de la mayor reducción en la presión arterial obtenido por la combinación de la presente invención, así como el hecho de que para el autor de dicho Anexo VIII no es posible dar explicación porque la combinación de olmesartan con amlodipina no es capaz de atenuar la activación simpática inducida por la amlodipina, mientras que las combinaciones de valsartan con amlodipina son incapaces de proporcionar el mismo efecto.

La composición farmacéutica de la presente invención proporciona que un mayor número del porcentaje de pacientes alcancen el control de la presión arterial, en comparación con las dosis máximas de monoterapia con amlodipina (es decir, 10 mg/día) o de olmesartan (es decir, 40 mg/día), tal como se revela en el Anexo VI. Así, el porcentaje más alto de pacientes con control de la presión arterial es significativo debido a que la hipertensión corresponde al mayor factor de riesgo para infarto al miocardio, insuficiencia cardíaca congestiva, derrame cerebral y enfermedad terminal de riñón. Un meta-análisis de 61 casos, incluyendo cerca de un millón de adultos, reportó que la presión arterial se relacionaba con el riesgo de enfermedad cardíaca isquémica a lo largo del rango normal de la presión arterial normal (debajo de al menos 115/75 mmHg), tal como se reporta en el Anexo VII). Es así como el riesgo de dicho incremento 20 mmHg en la presión arterial sistólica (ó 10mmHg en la presión arterial diastólica) duplica el riesgo de un evento coronario fatal. La evidencia sugiere que la reducción de 5 a 6 mmHg de la presión arterial puede disminuir el riesgo de derrame cerebral en un 40%, de enfermedades cardíacas en un 15 a 20%, y reducir la probabilidad de demencia, falla cardíaca, y mortalidad por causa de enfermedades vasculares (Véase Anexo VIII, página 1903).

Como tal, el solicitante ha presentado pruebas de que el uso de la composición farmacéutica de la presente invención se comporta de manera diferente a los productos conocidos en el estado del arte (Véase Anexo V), y que la diferencia es significativa (Véase Anexo VII).

En la práctica no existe previsibilidad con respecto a que si alguna combinación específica de medicamentos del estado del arte pueda o no proporcionar un tratamiento beneficioso para pacientes sin que se presenten efectos secundarios. Los documentos discutidos anteriormente establecen que dentro de los medicamentos revelados en el estado del arte útiles en el tratamiento de la hipertensión, no existe previsibilidad acerca de que una combinación específica pueda proporcionar un efecto beneficioso sin que se presenten efectos secundarios. Dichos documentos establecen también que la composición farmacéutica tiene un efecto inesperado y ventajoso cuando se usa para tratar la hipertensión, a saber, una disminución sustancial en la presión arterial lo que resulta en los beneficios discutidos anteriormente.

Deseamos aclarar que en la presente invención se han seleccionado dos monoterapias del voluminoso número de monoterapias del estado del arte para proporcionar la composición farmacéutica de la invención, la cual presenta un efecto inesperado y significativo en el tratamiento de pacientes, la cual no podría ser predicho de manera obvia por una persona versada en la materia.

De esta manera, respetuosamente solicitamos que en la medida en que las referencias citadas son pertinentes con respecto al nivel inventivo, se tenga por superada la objeción a este respecto ya que las mismas demuestran que las reivindicaciones de la presente invención se encuentran dirigidas a una invención que posee nivel inventivo.

Por consiguiente, teniendo en cuenta los argumentos presentados, se concluye que las enseñanzas de las anterioridades citadas por su Despacho no llevan a un técnico versado en la materia a obtener la presente invención ya que no revelan o enseñan las características técnicas esenciales relacionadas con la misma, tal como acá es reivindicada. Lo anterior si se tiene en cuenta que para el estudio de nivel inventivo el

Examinador no puede adoptar la posición de un inventor y que además no puede partir de la solución dada sino simplemente de lo que expresamente revelen el o los documentos más cercanos del estado del arte.

Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación. Sin embargo, en el evento que el Despacho considere que una modificación adicional es necesaria, respetuosamente le solicito hacer uso de la facultad que le otorga el artículo 45 inciso 2 de la Decisión 486 de la Comisión de la Comunidad Andina a efecto de requerir nuevamente de nuestra parte cualquier complementación o aclaración.

5. ANEXOS

- Nuevo pliego reivindicatorio conformado por 5 reivindicaciones
- Formulario de modificaciones.
- Anexo I
- Anexo II
- Anexo III
- Anexo IV
- Anexo V
- Anexo VI
- Anexo VII
- Anexo VIII

Señor Director,

Luiz Clemencia Sobrera
LUZ CLEMENCIA DE PÁEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555



Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1

SOLICITUD DE:
☐ Corrección de Error Material ☒ Modificación a una solicitud

2

SOLICITANTE

Nombre: DAICHI SANKYO COMPANY, LIMITED
Sociedad constituida y existente bajo las leyes de Japón.
Dirección: 3-5-1, Nihonbashi Honcho,
Chuo-ku,
Tokio 103-8426,
Japón
Domicilio: Tokio,
Japón
Teléfono: 546 09 70 **Fax:** 249 40 70
E-mail: clientes@cavelier.com

IDENTIFICACION

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Número: _____

3

REPRESENTANTE O APODERADO

Nombre: Luz Clemencia de PAEZ
Dirección: Carrera 4ª No. 72-35
Teléfono: 347 36 11 **Fax:** 217 92 11
E-mail: cavelier@cavelier.com

IDENTIFICACION

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Número: 35.456.344 TP 23.555

4

Número de expediente: 05.074.973

5

Descripción de la corrección o modificación solicitada:
Presento nuevo capítulo reivindicatorio compuesto por 5 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.

6

Comprobante de pago No. _____ **Fecha:** _____

7

Anexos

☐ Comprobante de pago de la tasa por \$118.000, por concepto de modificaciones.
☐ Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por.
☐ Poderes, si fuere el caso
☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

8

NOMBRE: LUZ CLEMENCIA DE PAEZ **FIRMA:** Luz Clemencia de Paez
C.C. 35.456.344 de Usaquén T.P.A. 23.555

REIVINDICACIONES

1. Una composición farmacéutica que comprende:

(A) un antagonista de los receptores de angiotensina II seleccionado de (i) (5-metil-2-oxo-1,3-dioxolen-4-il)metilo-4-(1-hidroxi-1-metiletil)-2-propil-1-[[2'-(1H-tetrazol-5-il)bifenil-4-il]metil]imidazol-5-carboxilato o (ii) una sal farmacológicamente aceptable del mismo; y

(B) un bloqueador de los canales de calcio seleccionado de (i) azelnidipina, (ii) amlodipina ó (iii) besilato de amlodipina.

2. Una composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque el antagonista de los receptores de angiotensina II es (5-metil-2-oxo-1,3-dioxolen-4-il)metilo-4-(1-hidroxi-1-metiletil)-2-propil-1-[[2'-(1H-tetrazol-5-il)bifenil-4-il]metil]imidazol-5-carboxilato.

3. Una composición farmacéutica de conformidad con las reivindicaciones 1 a 2, caracterizada porque el bloqueador de los canales de calcio es azelnidipina.

4. Una composición farmacéutica de conformidad con las reivindicaciones 1 a 2, caracterizada porque el bloqueador de los canales de calcio es besilato de amlodipina.

5. Una composición farmacéutica de conformidad con las reivindicaciones 1 a 2, caracterizada porque el bloqueador de los canales de calcio es amlodipina.

ANEXO I

Test Example: Antihypertensive activity

40, 49-week old male spontaneously hypertensive rats (SHR) were orally administered amlodipine besylate (2 mg/kg), olmesartan medoxomil (0.3 mg/kg) + amlodipine besylate (2 mg/kg), losartan potassium (0.3 mg/kg) + amlodipine besylate (2 mg/kg), or the vehicle (0.5 % carboxymethyl cellulose Na solution, 2 mL/kg) once a day, for 5 days, in groups of 6 animals. Mean blood pressure was measured by a telemetry method during the 3-day observation period and the 5-day treatment period. The 24-hour average value of mean blood pressure was calculated for analysis. Analysis of variance (ANOVA) for repeated measures with the baseline value as a covariate was applied to compare between antihypertensive effects of amlodipine besylate alone and combined with olmesartan medoxomil or losartan potassium. Changes in blood pressure are shown in Table 1. Excellent antihypertensive effects were observed in animals in the group co-administered olmesartan medoxomil + amlodipine besylate. ANOVA for repeated measures revealed that although treatment with losartan potassium did not potentiate the antihypertensive effect of amlodipine besylate ($P=0.2429$), treatment with olmesartan medoxomil potentiated the antihypertensive effect of amlodipine besylate ($P<0.0001$). It was also demonstrated that the antihypertensive effect of combined administration of amlodipine besylate and olmesartan medoxomil was greater than that of combined administration of amlodipine besylate and losartan potassium ($P=0.0004$).

Table 1

Test Substance	n	24-hour average of mean blood pressure (mmHg)				
		1 st Day	2 nd Day	3 rd Day	4 th Day	5 th Day
Vehicle	6	184±2	186±4	181±3	182±3	180±3
Amlodipine besylate	6	163±3	164±3	164±3	166±3	166±3
Amlodipine besylate + olmesartan medoxomil	6	149±2	147±1	149±1	151±1	152±2
Amlodipine besylate + losartan potassium	6	165±3	158±2	159±2	160±2	160±1

Values represent mean ± S.E.M.

ANEXO II

Association of Candesartan vs Losartan With All-Cause Mortality in Patients With Heart Failure

Maria Eklind-Cervenka, MD

Lina Benson, MSc

Ulf Dahlström, MD, PhD

Magnus Edner, MD, PhD

Mårten Rosenqvist, MD, PhD

Lars H. Lund, MD, PhD

ANGIOTENSIN II RECEPTOR blockers (ARBs) reduce cardiovascular mortality and heart failure (HF) hospitalization in patients with HF with reduced left ventricular ejection fraction (LVEF).¹ In patients not taking an angiotensin-converting enzyme (ACE) inhibitor and when added to an ACE inhibitor, candesartan and valsartan reduced the combined end point mortality and HF hospitalizations and morbidity.²⁻⁴ When compared with captopril, losartan was neutral with regard to all-cause mortality and HF hospitalization.³ A losartan dose of 150 mg/d compared with a dose of 50 mg/d reduced combined cardiovascular mortality and HF hospitalization.⁶ In contrast, ARBs do not appear to be effective in HF with preserved LVEF,⁷ although candesartan reduced HF hospitalization.⁸

Despite these variable effects, different ARBs have not been tested head to head. Major cardiology societies recommend ARBs for the treatment of HF with reduced LVEF but do not specify agents.^{9,10} However, there are reasons to believe different agents may have different efficacy. Candesartan com-

Context Angiotensin II receptor blockers (ARBs) reduce combined mortality and hospitalization in patients with heart failure (HF) with reduced left ventricular ejection fraction. Different agents have different affinity for the AT₁ receptor and may have different clinical effects, but have not been tested against each other in HF.

Objective To assess the association of candesartan vs losartan with all-cause mortality in patients with HF.

Design, Setting, and Patients An HF registry (the Swedish Heart Failure Registry) of 30 254 unique patients registered from 62 hospitals and 60 outpatient clinics between 2000 and 2009. A total of 5139 patients (mean [SD] age, 74 [11] years; 39% women) were treated with candesartan (n=2639) or losartan (n=2500). Survival as of December 14, 2009, by ARB agent was analyzed by Kaplan-Meier method and predictors of survival determined by univariate and multivariate proportional hazard regression models, with and without adjustment for propensity scores and interactions. Stratified analyses and quantification of residual confounding were also performed.

Main Outcome Measures All-cause mortality at 1 and 5 years.

Results One-year survival was 90% (95% confidence interval [CI], 89%-91%) for patients receiving candesartan and 83% (95% CI, 81%-84%) for patients receiving losartan, and 5-year survival was 61% (95% CI, 54%-68%) and 44% (95% CI, 41%-48%), respectively (log-rank $P < .001$). In multivariate analysis with adjustment for propensity scores, the hazard ratio for mortality for losartan compared with candesartan was 1.43 (95% CI, 1.23-1.65; $P < .001$). The results persisted in stratified analyses.

Conclusion In this registry of patients with HF, the use of candesartan compared with losartan was associated with a lower mortality risk.

JAMA. 2011;305(2):175-182

www.jama.com

pared with losartan has higher binding affinity for the AT₁ receptor,^{11,12} is more effective at lowering blood pressure,¹³ and is associated with less de novo HF when used in hypertension.¹⁴ In elderly patients with HF, losartan was associated with higher mortality than other ARBs.¹⁵

Randomized controlled trials (RCTs) minimize bias and confounding but have not been performed to address this issue. Therefore, our goal was to determine whether candesartan is asso-

Author Affiliations: Department of Cardiology, South Hospital, Stockholm (Drs Eklind-Cervenka and Rosenqvist); Karolinska Institutet, Department of Clinical Science and Education, SöS, Stockholm (Drs Eklind-Cervenka and Rosenqvist and Ms Benson); Department of Cardiology, Linköping University Hospital, and Department of Medical and Health Sciences, Linköping University, Linköping (Dr Dahlström); Division of Cardiovascular Medicine, Danderyd Hospital, and Karolinska Institutet, Department of Clinical Sciences, Danderyd, Stockholm (Dr Edner); and Department of Cardiology, Karolinska University Hospital, and Karolinska Institutet, Department of Medicine, Stockholm (Dr Lund), Sweden.

Corresponding Author: Lars H. Lund, MD, PhD, Department of Cardiology, Karolinska University Hospital, N305, 171 76 Stockholm, Sweden (lars.lund@alumni.duke.edu).

ciated with less all-cause mortality than losartan in a large cohort of unselected patients with HF.

METHODS

Study Protocol

The Swedish Heart Failure Registry (Rikssvikt) has been previously described.¹⁶ It was created as a pilot in 2000 and introduced throughout Sweden in 2003. Inclusion criteria are clinician-judged HF. Approximately 70 variables are recorded at discharge from hospital or after clinic visit on a case report form and entered into a database managed by the Uppsala Clinical Research Center, Uppsala, Sweden. The database is run against the Swedish death registry monthly. The protocol, registration form, and annual report are available at <http://www.ucr.uu.se/rikssvikt>. Establishment of the registry and registration and analysis of the data was approved by a multisite ethics committee. Individual patient consent was not required or obtained.

As of December 14, 2009, there were 44 548 registrations from 30 254 unique patients from 62 hospitals and 60 outpatient clinics. Of 30 254 unique patients, 5823 received an ARB (2639 received candesartan, 2500 received losartan, 357 received valsartan, and 327 received other ARBs) at the time of the first registration. Valsartan and other ARBs were excluded due to small numbers, resulting in 5139 individuals receiving candesartan (n=2639) or losartan (n=2500) for this study.

Statistical Analysis

To avoid bias due to missing baseline characteristics, multiple imputation (n=10) was performed for variables with missing data using predictive mean matching. All subsequent analyses, except for descriptive statistics, were performed on the imputed data. To adjust for selection bias, propensity scores for each patient were estimated with logistic regression. Quintiles of the estimated propensity scores were used to divide the patients into 5 strata.¹⁷ All patient and medical history and treatment variables (excluding outcome

variables and target dose ARB with losartan dose set at 150 mg/d) were used when creating the multiple imputation data sets as well as in the estimation of the propensity scores. To evaluate the propensity scores, logistic regressions with ARB agent as outcome were performed for each of the variables with and without adjustment for propensity score strata.

Survival was charted by Kaplan-Meier method and compared with the log-rank test for all patients and separately for an LVEF of less than 40% and 40% or more. Several univariate and multivariate proportional hazard regression models with and without adjustment for interactions and propensity scores, as a covariate and strata variable, were performed, with ARB agent adjusted for single or combinations of clinically relevant variables.

Interactions between ARB agent and clinically relevant variables were estimated by a Cox proportional hazards regression model and are shown in a Forest plot. Interactions with ARB were tested for all variables in the model. The scaled Schoenfeld residuals from the proportional hazards regression model were investigated to assess the proportional hazards assumption, whereas the Martingale residuals were visually inspected to detect possible nonlinearity for the continuous variables.

Stratifications were performed by 5 clinically important variables that may affect choice of agent, prognosis, or both (year of inclusion [2001-2005 vs 2006-2009], duration of HF [<6 vs ≥6 months], age [≤70 vs >70 years], New York Heart Association [classes I-II {mild} vs III-IV {moderate to severe}], and LVEF [<40% vs ≥40%]). Losartan was available before candesartan and the cutoff at 2005-2006 was chosen because the European and US guidelines reflecting the CHARM studies^{3,38,18} were published in 2005.^{19,20}

A sensitivity analysis was performed to evaluate the effect of a possible unknown or unmeasured confounder.²¹ Hazard ratios (HRs) for

losartan vs candesartan adjusted for an unknown binary or continuous (normally distributed) confounder was derived assuming different hazards and distributions of the unmeasured confounder in the 2 treatments.

One clinically relevant and prespecified subgroup analysis was performed by LVEF, divided by less than 40% (n=2608) and 40% or more (n=1884) (647 patients had missing LVEF data). We also performed a prespecified analysis with target dose of 150 mg/d rather than 50 mg/d for losartan, in accordance with the HEAAL study.⁶

To test the null hypothesis that there is no difference in survival between candesartan and losartan at 1 year, 2270 patients would be needed (1135 in each group). This assumed an annual mortality rate of 8.1% (candesartan group in the CHARM-Overall trial¹⁸) and 11.7% (losartan group in the ELITE II trial³), respectively; a power of 80%; and that the 2-sided level of significance was set at .05. Statistics were performed in R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics and P values of patients and medical history and treatment for imputed data showing differences before and after adjustment for propensity scores strata are shown in TABLE 1 and TABLE 2. A total of 5139 patients were included (mean [SD] age, 74 [11] years; 39% women) in the analyses. Patients receiving candesartan were overall healthier but had lower LVEF and were less likely to reach target doses (defined as 32 mg/d and 50 mg/d for candesartan and losartan, respectively). If the target dose was set at 150 mg/d for losartan,⁶ there were still more patients in the candesartan group receiving 25% or less of the target dose. The unadjusted logistic regressions revealed a number of differences in baseline characteristics between patients receiving losartan and candesartan, but after adjustment for propensity scores, there were no longer any statistically significant differences, except for dose

of ARB, with target dose set at 150 mg/d. This target dose was analyzed as a pre-specified sensitivity analysis but a target dose of 50 mg/d was chosen for inclusion in multiple imputation and derivation of propensity scores. One variable, ACE inhibitor, had a P value of less than .10 ($P = .07$).

FIGURE 1 shows the overall survival between the 2 groups. One-year survival was 90% (95% confidence interval [CI], 89%-91%) for patients receiving candesartan and 83% (95% CI, 81%-84%) for patients receiving losartan, and 5-year survival was 61% (95% CI, 54%-68%) for patients receiving candesartan and 44% (95% CI, 41%-48%) for patients receiving losartan (log-rank $P < .001$). TABLE 3 shows HRs for all-cause mortality in patients receiving losartan vs candesartan. The univariate HR was 1.77 (95% CI, 1.58-1.99; $P < .001$) and the multivariate HR including stratification for propensity scores was 1.43 (95% CI, 1.23-1.65; $P < .001$) (HR=0.70 for candesartan vs losartan). Only β -blockers interacted with an ARB agent ($P = .04$). TABLE 4 shows HRs for all-cause mortality for patients receiving losartan vs candesartan after adjustment for this interaction, together with interactions with 4 variables with $P < .10$ (cardiac resynchronization therapy, duration of HF, creatinine, and lung disease). Losartan remained associated with increased mortality compared with candesartan for all categories except cardiac resynchronization therapy and lung disease.

Violations to the proportional hazards assumption were detected for location and this variable was therefore included as a strata variable in all proportional hazards regression models. Stratification did not change the results. Multivariate HRs with propensity score strata were 1.41 (95% CI, 1.22-1.64; $P < .001$) for year of inclusion; 1.43 (95% CI, 1.23-1.67; $P < .001$) for HF duration; 1.48 (95% CI, 1.28-1.72; $P < .001$) for age; 1.43 (95% CI, 1.24-1.67; $P < .001$) for NYHA class; and 1.44 (95% CI, 1.24-1.67; $P < .001$) for LVEF.

Quantification of the effects of a hypothetical confounder were calculated (eTable, available at <http://www.jama.com>). Given an HR of 2 for all-cause mortality for the binary confounder and an approximate differ-

Table 1. Baseline Patient Characteristics and P Values for Imputed Data Before and After Adjustment for Propensity Scores Strata^a

Characteristics	Candesartan (n = 2639)	Losartan (n = 2500)	P Value	
			Imputed	Imputed Stratified for Propensity Score
Follow-up time, median (range), d	563.0 (0-2565)	640.5 (0-2916)		
No. of dead	441	888		
Included in the Swedish Heart Failure Registry				
2001-2005	214 (8.1)	701 (28.0)	<.001	.13
2006-2009	2425 (91.9)	1799 (72.0)		
Age, mean (SD), y	72.0 (11.5)	75.3 (10.2)	<.001	.54
Sex				
Male	1633 (61.9)	1483 (59.3)	.06	.86
Female	1006 (38.1)	1017 (40.7)		
Civil status				
Married	1621 (64.6)	1378 (60.1)	<.001	.92
Single	890 (35.4)	916 (39.9)		
Clinic				
Medicine	1116 (44.6)	1123 (47.7)	.001	.91
Cardiology	1371 (54.8)	1198 (50.9)		
Geriatric	14 (0.6)	32 (1.4)		
Location				
Inpatient	1202 (45.5)	1519 (61.8)	<.001	.67
Outpatient	1437 (54.5)	981 (39.2)		
Duration of heart failure, mo				
<6	1061 (40.2)	736 (29.4)	<.001	.57
≥6	1578 (59.8)	1764 (70.6)		
NYHA class ^b				
I	234 (11.0)	164 (9.0)	<.001	.98
II	1068 (50.0)	734 (40.3)		
III	770 (36.0)	840 (46.2)		
IV	65 (3.0)	82 (4.5)		
LVEF, %				
<30	692 (29.0)	628 (29.8)	.02	>.99
30-39	701 (29.4)	587 (27.9)		
40-49	511 (21.4)	404 (19.2)		
≥50	481 (20.2)	488 (23.2)		
QRS duration, mean (SD), ms	111.9 (28.9)	114.0 (28.2)	<.001	.93
Potassium, mean (SD), mEq/L	4.5 (1.2)	4.4 (1.1)	<.001	.76
Heart rate, mean (SD), beats/min	71.9 (14.8)	72.7 (14.7)	.09	>.99
Creatinine, mean (SD), mg/dL	1.25 (0.64)	1.37 (0.70)	<.001	.61
MAP, mean (SD), mm Hg	92.6 (13.9)	91.5 (13.4)	.003	.79
Hemoglobin, mean (SD), g/dL	13.3 (1.7)	13.1 (1.7)	<.001	.84
Smokers				
Current	207 (10.0)	172 (9.4)	.41	>.99
Former	934 (45.0)	868 (47.4)		
Never	935 (45.0)	791 (43.2)		

Abbreviations: LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NYHA, New York Heart Association. SI conversions: To convert creatinine to $\mu\text{mol/L}$, multiply by 88.4; hemoglobin to g/L, multiply by 10.0. ^aData are presented as No. (%) unless otherwise specified. Percentages may not total 100 due to rounding. ^bNYHA class I indicates no symptoms; NYHA class II, symptoms with moderate exertion; NYHA class III, symptoms with mild exertion; and NYHA class IV, symptoms at rest.

ence of 30% between the 2 ARBs in the probability of having the confounder, the HR for losartan vs candesartan would no longer be statistically significant. Alternatively, the corresponding numbers would have to be an HR of 3 and a difference in probability of 20% (eTable). For a normally distributed continuous confounder, if the difference in mean units between the 2 ARBs were at least 0.3 and the HR for the confounder were larger than 1.005 per unit,

the HR for losartan vs candesartan would no longer be statistically significant (eTable).

In prespecified subgroup analysis according to LVEF, patients with an LVEF of 40% or more were older, more commonly women, and had more atrial fibrillation, but were otherwise healthier than patients with an LVEF of less than 40%. For patients with an LVEF of less than 40%, 1-year survival for candesartan and losartan was 91% (95% CI, 89%-92%) and 82% (95% CI, 80%-85%), respectively; and 5-year survival was 68% (95% CI, 60%-76%) and 44% (95% CI, 40%-49%), respectively ($P < .001$). For patients with an LVEF of 40% or more, the corresponding data for candesartan and losartan were 91% (95% CI, 89%-93%) and 86% (95% CI, 83%-88%) for 1-year survival and 54% (95% CI, 40%-72%) and 50% (95% CI, 44%-56%) for 5-year survival, respectively ($P < .001$).

The HRs for losartan vs candesartan were similar for an LVEF of less than 40% and an LVEF of 40% or more, and similar to the whole population (all were statistically significant in favor of candesartan). For an LVEF of less than 40%, the univariate HR was 2.08 (95% CI, 1.76-2.46; $P < .001$) and the multivariate HR including propensity score strata was 1.41 (95% CI, 1.14-1.76; $P = .002$). For an LVEF of 40% or more, the univariate HR was 1.42 (95% CI, 1.17-1.73; $P < .001$) and the multivariate HR including propensity score strata was 1.37 (95% CI, 1.06-1.79; $P = .02$). When the target dose of losartan was set at 150 mg/d, the HR adjusted only for dose was 1.91 ($P < .001$) and the HR from the multivariate model stratified for propensity score strata was 1.36 ($P = .02$). The propensity scores and the multiple imputations used in the LVEF subgroup and losartan dose of 150 mg/d analyses were the same as those derived for the full population and target dose of losartan of 50 mg/d.

No additional subgroup analyses were performed. However, interactions between ARB agent and clinical parameters were estimated and are shown in Figure 2.

Table 2. Baseline Characteristics of Medical History and Treatment and P Values for Imputed Data Before and After Adjustment for Propensity Scores Strata

Characteristics	No. (%) of Patients		P Value	
	Candesartan (n = 2639)	Losartan (n = 2500)	Imputed	Imputed Stratified for Propensity Score
Medical History				
Hypertension	1411 (55.0)	1296 (53.7)	.40	.88
Ischemic heart disease	1286 (50.7)	1461 (60.6)	<.001	.70
Dilated cardiomyopathy	366 (14.4)	297 (12.5)	.06	.93
Hypertrophic cardiomyopathy	49 (1.9)	63 (2.7)	.09	.88
Valve disease	468 (18.4)	501 (21.4)	.01	.78
Atrial fibrillation	1149 (43.8)	1222 (49.4)	<.001	.91
Diabetes mellitus	764 (29.2)	844 (34.0)	<.001	.94
Lung disease	413 (16.2)	515 (21.3)	<.001	.87
History of PCI and/or CABG surgery	773 (29.7)	803 (33.0)	.02	.93
Pacemaker	298 (11.4)	382 (15.5)	<.001	>.99
Cardiac resynchronization therapy	78 (3.0)	105 (4.3)	.01	.95
Implantable cardioverter defibrillator	87 (3.3)	96 (3.9)	.24	.97
Heart transplantation	7 (0.3)	12 (0.5)	.22	.97
Medical Treatment				
ACE inhibitor	420 (16.0)	76 (3.1)	<.001	.07
β -Blocker	2295 (87.1)	2049 (82.3)	<.001	.73
Aldosterone antagonist	802 (30.6)	904 (36.4)	<.001	.84
Diuretic	2065 (78.4)	2190 (87.8)	<.001	.74
Digoxin	440 (16.8)	500 (20.1)	.002	.88
Insulin	416 (15.9)	484 (19.5)	<.001	.93
Oral antidiabetic	362 (13.8)	380 (15.3)	.11	>.99
Aspirin	1281 (48.7)	1260 (50.5)	.19	.81
Oral anticoagulants	1056 (40.2)	997 (40.1)	.93	.89
Statin	1335 (50.8)	1245 (50.0)	.56	.95
Nitrates	459 (17.5)	632 (25.4)	<.001	.61
Amiodarone	81 (3.3)	84 (3.6)	.61	.87
Sotalol	14 (0.5)	29 (1.2)	.02	.87
Inotropic agent	35 (1.4)	44 (1.9)	.21	.92
Target dose of ARB				
Losartan, 50 mg/d				
≤25%	970 (36.8)	204 (8.2)	<.001	.24
26%-50%	714 (27.1)	330 (13.2)		
51%-75%	77 (2.9)	15 (0.6)		
≥76%	878 (33.3)	1951 (78.0)		
Losartan, 150 mg/d				
≤25%	970 (36.7)	549 (22.0)	<.001	<.001
26%-50%	714 (27.1)	1501 (60.0)		
51%-75%	77 (2.9)	445 (17.8)		
≥76%	878 (33.3)	5 (0.2)		

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

COMMENT

Our findings show that in an unselected HF population, candesartan was associated with lower all-cause mortality compared with losartan. The difference was significant even after adjustment for propensity scores and numerous clinical variables, including dose, potential interactions, and after stratification and quantification of potential residual confounding of a reasonable magnitude. The variables adjusted for included those that might affect choice of agent (selection bias) and outcome (confounders). However, we cannot eliminate the possibility that residual confounding explains some of the association. In prespecified subgroups, our findings persisted with both an LVEF of less than 40% and an LVEF of 40% or more.

There are mechanistic reasons to believe candesartan may be more effective than losartan. Angiotensin II receptor blockers competitively block the AT₁ receptor. Candesartan has 4 binding sites on the AT₁ receptor and losartan has 2 binding sites.²² In vitro studies have shown that losartan binds loosely and has a dissociation half-life of seconds to minutes, yielding "surmountable" antagonism. Candesartan binds tightly and has a dissociation half-life of 120 minutes, yielding "insurmountable" antagonism. Losartan has an active metabolite EXP3174, but even this has looser binding to the AT₁ receptor.^{11,23-25} A point mutation at Lys¹⁹⁰ decreases the affinity 45-fold for candesartan but only 5-fold for losartan.²⁶ Rat studies have shown candesartan to be 10 to 30 times more potent than losartan, and concentrations required for displacement of 50% radioligand were 0.9 nmol/L for candesartan and 8.9 nmol/L for losartan.¹²

Clinical studies in hypertension also suggest that candesartan may be more effective than losartan. Both candesartan (16 mg/d) and losartan (100 mg/d) improved endothelial function, measured by flow-mediated vasodilation, but only candesartan lowered plasma levels of plasminogen activator inhibitor 1 and monocyte chemoattractant

protein 1.²⁷ Candesartan inhibited the angiotensin II-induced increase in renal filtration fraction and the aldosterone secretion significantly more than losartan.²⁸ Candesartan (16 mg/d) compared with losartan (100 mg/d) was more effective at lowering blood pressure, and after a forced missed dose, patients receiving losartan but not candesartan returned to pretreatment blood pressure,²⁹ consistent with the affinity observations above. A meta-analysis suggests that candesartan is more effective at lowering blood pressure.¹³ In a registry study of hypertension, candesartan compared with losartan was associated with less de novo HF¹⁴ and, in a registry study of elderly patients with HF, losartan was associated with worse survival than irbesartan, valsartan, and candesartan.¹⁵

In HF, ARBs have not been compared head to head, but studies of candesartan are larger and more conclusively positive than studies of losartan. The CHARM program is the largest and most positive and conclusive set of studies.^{2,3,8,18} A meta-analysis of 38 080 patients from 24 trials revealed that most studies comparing ARB vs placebo were with candesartan and yielded a reduction in both mortality (odds ratio [OR], 0.83; 95% CI, 0.69-1.00) and HF hospitalization (OR, 0.64; 95% CI, 0.53-0.78); most studies comparing ARB vs ACE inhibitors were with losartan and yielded neutral effects (OR, 1.06; 95% CI, 0.90-1.26 for mortality and OR, 0.95; 95% CI, 0.80-1.13 for HF hospitalization); and most studies of ARB on top of ACE inhibitors were with candesartan and were overall neutral with respect to mortality (OR, 0.97; 95% CI, 0.87-1.08) but beneficial with respect to HF hospitalization (OR, 0.77; 95% CI, 0.69-0.87).¹

Registry studies have advantages compared with RCTs. Inherent to RCTs are strict inclusion/exclusion criteria that limits applicability to many patient groups (eg, elderly patients). Patients are carefully monitored, which may dilute any differences between therapies had they played out under normal clinical follow-up. Strict inclu-

sion criteria and careful monitoring also yield good prognosis. Indeed, RCTs of ARBs have attempted to augment risk by requiring hospitalization before inclusion but have still mainly demonstrated reductions in disease-specific morbidity such as HF hospitalization rather than all-cause mortality.³⁰ In contrast, our registry study provides information useful for every day clinical care of a broad unselected HF population,

Figure 1. Kaplan-Meier Estimates of Survival of Patients Receiving Candesartan and Losartan

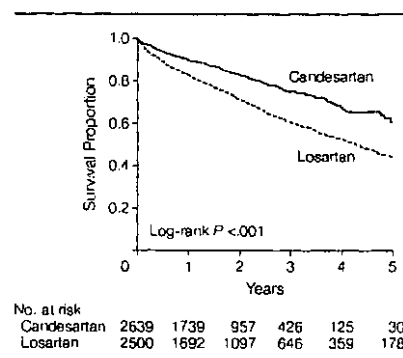


Table 3. Proportional Hazard Regression Models for All-Cause Mortality for Losartan vs Candesartan^a

Losartan vs Candesartan	Hazard Ratio (95% CI)
Univariate model	1.77 (1.58-1.99)
Multivariate model	
Adjusted for age and sex	1.56 (1.39-1.75)
Adjusted for duration of heart failure	1.71 (1.52-1.92)
Adjusted for hypertension	1.77 (1.58-1.99)
Adjusted dose of 50 mg/d ^b	2.53 (2.22-2.88)
Adjusted dose of 150 mg/d ^c	1.91 (1.67-2.18)
Adjusted for ACE inhibitor, β -blocker, and aldosterone antagonist	1.71 (1.52-1.93)
Multivariate final model	
Final	1.43 (1.23-1.65)
With propensity scores, covariate	1.41 (1.22-1.64)
With propensity scores strata	1.43 (1.23-1.65)

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval.

^a $P < .001$ for all univariate and multivariate models.

^b Target dose of 50 mg/d for losartan and 32 mg/d for candesartan.

^c Target dose of 150 mg/d for losartan and 32 mg/d for candesartan.

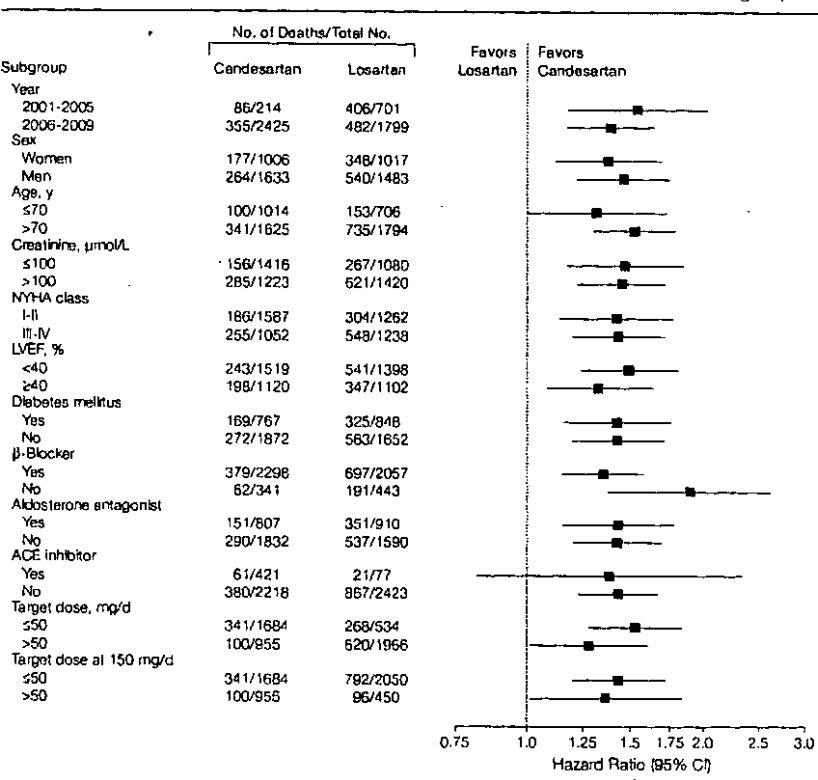
and our findings of reduced mortality with candesartan interacted statistically only with β -blocker therapy but no other parameters, making them broadly applicable. The reasons for this interaction are not readily apparent.

Table 4. Multivariate Final Analysis With Propensity Score Strata and Interaction for Losartan vs Candesartan

Multivariate Final Analysis	Hazard Ratio (95% CI)	P Value	
		Main Effect	Interaction
β -Blocker			
No	1.90 (1.39-2.60)	<.001	.04
Yes	1.35 (1.15-1.57)	<.001	.04
Cardiac resynchronization therapy			
No	1.45 (1.25-1.68)	<.001	.09
Yes	0.82 (0.42-1.58)	.55	.09
Duration of heart failure, mo			
<6	1.72 (1.35-2.20)	<.001	.05
≥ 6	1.33 (1.12-1.56)	<.001	.05
Creatinine ^a	1.51 (1.18-1.93)	<.001	.07
Lung disease			
No	1.52 (1.29-1.79)	<.001	.06
Yes	1.17 (0.90-1.51)	.24	.06

Abbreviation: CI, confidence interval.
^aFor creatinine = 100 μ mol/L (1.13 mg/dL).

Figure 2. Hazard Ratios for All-Cause Mortality for Losartan vs Candesartan From the Multivariate Model Stratified for Propensity Scores and Interaction With Selected Subgroups



ACE indicates angiotensin-converting enzyme; CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association. Continuous and categorical variables with more than 2 levels were dichotomized at clinically relevant cutoff for presentation purposes. For variables with missing data, this number is the mean of the 10 imputations.

The magnitude of the difference in association with mortality was large. The HR for all-cause mortality of losartan compared with candesartan was 1.43 (candesartan vs losartan, 0.70) overall and similar in the LVEF of less than 40% and the LVEF of 40% or more comparisons. In comparison, in the CHARM-Overall study,¹⁸ the adjusted HR for overall mortality was 0.90 ($P = .03$). The adjusted HRs for cardiovascular death and HF hospitalization was 0.70 ($P < .001$) in the CHARM-Alternative study,³ 0.85 ($P = .01$) in the CHARM-Added study,³ and 0.86 ($P = .051$) in the CHARM-Preserved study.⁸ The magnitude of our findings may be due to chance, but RCTs may understate “real world” differences, and it is conceivable that candesartan is better than losartan by a magnitude similar to placebo.

The survival in the overall population of our study was quite high. This may be explained by 54.5% of patients being registered as outpatients. Inpatient registration was indeed an independent predictor of mortality. However, inpatient vs outpatient registration did not affect the differences between losartan vs candesartan (location was included in all our models and there was no interaction between ARB agent and location).

Our study has limitations. First, the diagnosis of HF in the Swedish Heart Failure Registry is clinical and does not require objective evidence of HF. A majority of patients had echocardiography data (87%) but only 31% had (N-terminal pro) brain natriuretic peptide, and in patients with preserved LVEF, there were no formal diagnostic criteria. Indeed, a larger proportion of patients with preserved LVEF had concomitant lung disease and some of these may not have had HF. Nonetheless, ARBs are effective mainly in HF with reduced LVEF and, in our study, candesartan was associated with lower mortality than losartan in this subgroup. In a registry study, treatment may change over time and

adherence is not monitored, and our study reflects only agent, dose, and coexisting HF therapy at the time of inclusion. However, this is true in intention-to-treat randomized studies as well.

In addition, our study is limited by its nonrandomized character and there are potential biases and confounders that may be responsible for our findings. First, choice of ARB agent may be subject to selection bias and we cannot determine whether hypertension or HF or diabetes was the primary indication. The Swedish Heart Failure Registry contains clinical variables that may affect choice of agent, such as hypertension, diabetes, and duration of HF. These were accounted for in the derivation of a propensity score for each patient, adjusted for in multivariate regression and examined in tests for interaction with ARB agent (duration of HF was also stratified). Because losartan has been available longer than candesartan, earlier inclusion in the Swedish Heart Failure Registry may entail a higher likelihood of receiving losartan. Indeed, year of inclusion in the Swedish Heart Failure Registry was skewed toward later years for candesartan. However, year of inclusion was corrected for by the propensity score, did not interact with ARB agent, and was stratified for, and candesartan remained associated with lower mortality than losartan.

Second, the efficacy of different ARB agents is subject to confounding. The Swedish Heart Failure Registry contains numerous variables that may affect outcomes independent of ARB agent, such as age, LVEF, NYHA class, renal function, dose of ARB, and treatment with other HF drugs, and patients treated with losartan were less healthy (except for better LVEF). However, these were included in propensity scores and multivariate analysis and examined for interactions with ARB agent. Also, important variables were examined in stratifications, without

changing the results. Earlier inclusion may also entail less utilization of evidence-based therapies. However, concomitant HF therapies were included in the propensity score and multivariate analysis. In addition, the importance of up-titration of doses is well known. Indeed, the HEAAL study⁶ showed that losartan dose of 150 mg/d compared with 50 mg/d was associated with less combined cardiovascular mortality and HF hospitalization. However, even after adjustment for a target dose of 150 mg/d, losartan remained associated with higher mortality than candesartan did in our study.

Nonetheless, we cannot rule out that the benefits with candesartan are due to potential unknown confounders. The quantification of residual confounding suggests that to invalidate the results, a potential confounder or combination of confounders would have to have both a strong association with all-cause mortality and also be considerably likely to affect the choice of losartan vs candesartan. We are unaware of any previously described variables and find it unlikely (but cannot rule out) that there exists unknown variables, which are not adjusted for in our analysis, have a relatively strong association with all-cause mortality, and would be likely to affect the choice of losartan vs candesartan.

In conclusion, our findings suggest that candesartan is associated with less all-cause mortality than losartan. However, clinical decision making should await supportive evidence of this observed association. Ideally, different ARB agents should be tested against each other in RCTs. It would also be important and perhaps more feasible to confirm our findings in other large HF registries.

Author Contributions: Dr Lund and Ms Benson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Eklind-Cervenka, Rosenqvist, Lund.

Acquisition of data: Eklind-Cervenka, Dahlström, Edner, Lund.

Analysis and interpretation of data: Eklind-Cervenka, Benson, Dahlström, Edner, Rosenqvist, Lund.

Drafting of the manuscript: Eklind-Cervenka, Edner, Lund.

Critical revision of the manuscript for important intellectual content: Benson, Dahlström, Edner, Rosenqvist, Lund.

Statistical analysis: Eklind-Cervenka, Benson, Edner, Lund.

Obtained funding: Lund.

Administrative, technical, or material support: Dahlström, Edner, Lund.

Study supervision: Edner, Rosenqvist, Lund.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Eklind-Cervenka reported receiving speaker's fees from Astra-Zeneca. Dr Dahlström reported receiving speaker's fees from Astra-Zeneca and research grants from Linköping University, Research Foundation SouthEastern Sweden, and Swedish Heart-Lung Foundation. Dr Edner reported receiving speaker's fees from Merck Sharp and Dohme, and research grants from Karolinska Institutet, Stockholm County Council, Medtronic, St Jude, Boston Scientific, and Merck Sharp and Dohme. Dr Rosenqvist reported receiving consulting fees from Merck Sharp and Dohme, speaker's fees from Astra-Zeneca and Merck Sharp and Dohme, and research grants from Karolinska Institutet, Stockholm County Council, Swedish Heart-Lung Foundation, Vinnova, Swedish Order of Free Mason, Sanofi-Aventis, and Boehringer Ingelheim. Dr Lund reported receiving consulting fees and speaker's fees from Astra-Zeneca, and research grants from Karolinska Institutet, Stockholm County Council, Swedish Heart-Lung Foundation, Astra-Zeneca, and Orion Pharma. Ms Benson reported no financial disclosures.

Funding/Support: This study received no specific funding. However, establishment of the Swedish Heart Failure Registry was supported by the Swedish National Board of Health and Welfare, the Swedish Association of Local Authorities and Regions, the Swedish Society of Cardiology, AstraZeneca, Roche, Merck, Orion Pharma, and ResMed.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

Online-Only Material: An eTable is available at <http://www.jama.com>.

REFERENCES

1. Lee VC, Rhew DC, Dylan M, et al. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *Ann Intern Med*. 2004;141(9):693-704.
2. Granger CB, McMurray JJ, Yusuf S, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362(9386):772-776.
3. McMurray JJ, Ostergren J, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362(9386):767-771.
4. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.
5. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355(9215):1582-1587.

6. Konstam MA, Neaton JD, Dickstein K, et al; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 2009;374(9704):1840-1848.
7. Massie BM, Carson PE, McMurray JJ, et al; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359(23):2456-2467.
8. Yusuf S, Pfeffer MA, Swedberg K, et al; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet*. 2003;362(9386):777-781.
9. Dickstein K, Cohen-Solal A, Filippatos G, et al; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. *Eur J Heart Fail*. 2008;10(10):933-989.
10. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2009;119(14):e391-e479.
11. Vanderheyden PM, Fierens FL, De Backer JP, Fraeyman N, Vauquelin G. Distinction between surmountable and insurmountable selective AT1 receptor antagonists by use of CHO-K1 cells expressing human angiotensin II AT1 receptors. *Br J Pharmacol*. 1999;126(4):1057-1065.
12. Fabiani ME, Dinh DT, Nassif L, Casley DJ, Johnston CI. In vivo inhibition of angiotensin receptors in the rat kidney by candesartan cilexetil: a comparison with losartan. *Am J Hypertens*. 2000;13(9):1005-1013.
13. Meredith PA, Murray LS, McInnes GT. Comparison of the efficacy of candesartan and losartan: a meta-analysis of trials in the treatment of hypertension. *J Hum Hypertens*. 2010;24(8):525-531.
14. Kjeldsen SE, Stålhammar J, Hasvold P, Bodegard J, Olsson U, Russell D. Effects of losartan vs candesartan in reducing cardiovascular events in the primary treatment of hypertension. *J Hum Hypertens*. 2010;24(4):263-273.
15. Hudson M, Humphries K, Tu JV, Behlouli H, Sheppard R, Pilote L. Angiotensin II receptor blockers for the treatment of heart failure: a class effect? *Pharmacotherapy*. 2007;27(4):526-534.
16. Jonsson A, Edner M, Alchagen U, Dahlström U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail*. 2010;12(1):25-31.
17. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.
18. Pfeffer MA, Swedberg K, Granger CB, et al; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362(9386):759-766.
19. Swedberg K, Cleland J, Dargie H, et al; Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26(11):1115-1140.
20. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Circulation*. 2005;112(12):e154-e235.
21. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics*. 1998;54(3):948-963.
22. Bhuiyan MA, Ishiguro M, Hossain M, et al. Binding sites of valsartan, candesartan and losartan with angiotensin II receptor 1 subtype by molecular modeling. *Life Sci*. 2009;85(3-4):136-140.
23. Van Liefde I, Vauquelin G. Sartan-AT1 receptor interactions: in vitro evidence for insurmountable antagonism and inverse agonism. *Mol Cell Endocrinol*. 2009;302(2):237-243.
24. Vauquelin G, Fierens F, Van Liefde I. Long-lasting angiotensin type 1 receptor binding and protection by candesartan: comparison with other biphenyl-tetrazole sartans. *J Hypertens Suppl*. 2006;24(1):S23-S30.
25. Fierens F, Vanderheyden PM, De Backer JP, Vauquelin G. Binding of the antagonist [3H]candesartan to angiotensin II AT1 receptor-transfected [correction of tranfected] Chinese hamster ovary cells. *Eur J Pharmacol*. 1999;367(2-3):413-422.
26. Fierens FL, Vanderheyden PM, Gáborik Z, et al. Lys(199) mutation of the human angiotensin type 1 receptor differentially affects the binding of surmountable and insurmountable non-peptide antagonists. *J Renin Angiotensin Aldosterone Syst*. 2000;1(3):283-288.
27. Koh KK, Han SH, Chung WJ, et al. Comparison of effects of losartan, irbesartan, and candesartan on flow-mediated brachial artery dilation and on inflammatory and thrombotic markers in patients with systemic hypertension. *Am J Cardiol*. 2004;93(11):1432-1435, A10.
28. Fridman KU, Elmfeldt D, Wysocki M, Friberg PR, Andersson OK. Influence of AT1 receptor blockade on blood pressure, renal haemodynamics and hormonal responses to intravenous angiotensin II infusion in hypertensive patients. *Blood Press*. 2002;11(4):244-252.
29. Lacourcière Y, Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. *Am J Hypertens*. 1999;12(12 pt 1-2):1181-1187.
30. McMurray JJ, Swedberg K. HEAAL: the final chapter in the story of angiotensin receptor blockers in heart failure—lessons learnt from a decade of trials. *Eur J Heart Fail*. 2010;12(2):99-103.

ANEXO III

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 10, 2008

VOL. 358 NO. 15

Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

The ONTARGET Investigators*

ABSTRACT

BACKGROUND

In patients who have vascular disease or high-risk diabetes without heart failure, angiotensin-converting-enzyme (ACE) inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers (ARBs) in such patients is unknown. We compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes.

METHODS

After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

RESULTS

Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, $P<0.001$) and angioedema (0.1% vs. 0.3%, $P=0.01$) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%, $P<0.001$); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92 to 1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, $P<0.001$), syncope (0.3% vs. 0.2%, $P=0.03$), and renal dysfunction (13.5% vs. 10.2%, $P<0.001$).

CONCLUSIONS

Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit. (ClinicalTrials.gov number, NCT00153101.)

The members of the writing committee (Salim Yusuf, D.Phil., Koon K. Teo, Ph.D., Janice Pogue, M.Sc., Leanne Dyal, M.Sc., and Ingrid Copland, Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada; Helmut Schumacher, Ph.D., Boehringer Ingelheim, Ingelheim, Germany; Gilles Dagenais, M.D., Laval University Heart and Lung Institute, Laval Hospital, Quebec, QC, Canada; Peter Sleight, D.M., Oxford University, Oxford, United Kingdom; and Craig Anderson, Ph.D., George Institute for International Health, University of Sydney, Sydney) assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Yusuf at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, 237 Barton St. East, Hamilton, ON L8L 2X2, Canada, or at yusufs@mcmaster.ca.

*The Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET) investigators are listed in the Appendix.

This article (10.1056/NEJMoa080317) was published at www.nejm.org on March 31, 2008.

N Engl J Med 2008;358:1547-59.
Copyright © 2008 Massachusetts Medical Society.

RANDOMIZED, CONTROLLED TRIALS INVOLVING about 150,000 patients have convincingly demonstrated that angiotensin-converting-enzyme (ACE) inhibitors reduce rates of death, myocardial infarction, stroke, and heart failure among patients with heart failure,¹ left ventricular dysfunction,²⁻⁴ previous vascular disease alone,⁵⁻⁷ or high-risk diabetes.⁸ ACE inhibitors do not block the production of all angiotensin II, so direct receptor blockade might be more effective. ACE inhibitors reduce bradykinin degradation, which enhances vasodilatation, but increase the rates of angioedema and cough. In patients with heart failure, angiotensin II levels may increase and symptoms worsen, despite the use of ACE inhibitors.⁹ The use of an angiotensin-receptor blocker (ARB), as compared with placebo, reduced the rate of death or hospitalization for heart failure in patients with a low ejection fraction and heart failure who either could not tolerate an ACE inhibitor¹⁰ or were already receiving one.^{11,12} As compared with beta-blockers, ARBs also reduced vascular events in high-risk patients with hypertension and left ventricular hypertrophy.¹³ Nevertheless, in other high-risk populations, the role of ARBs as an alternative or in addition to ACE inhibitors to prevent cardiovascular outcomes is not known.

We evaluated whether the ARB telmisartan was not inferior to the ACE inhibitor ramipril and whether a combination of the two drugs was superior to ramipril alone as a treatment to prevent vascular events in high-risk patients who had cardiovascular disease or diabetes mellitus but did not have heart failure. We used a dose of ramipril that had previously been shown to be effective for this outcome.

METHODS

STUDY DESIGN

The design of the study has been described previously.¹⁴ We enrolled patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. Patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo in a parallel trial.¹⁴ Detailed eligibility criteria have also been described previously¹⁴ (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The primary objectives of our study were to determine the effectiveness of 80 mg of telmisartan daily, as com-

pared with 10 mg of ramipril daily. If the noninferiority of telmisartan was demonstrated, we would test the superiority of telmisartan over ramipril. We would also determine whether the combination of the two drugs was more effective than ramipril alone in reducing the composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

The main secondary outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke, which was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.⁵ Other secondary outcomes were new heart failure, diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures. Other outcomes were death from any cause or from noncardiovascular causes, angina, transient ischemic attack, development of left ventricular hypertrophy, microvascular complications of diabetes, changes in blood pressure or in the ankle-to-arm ratio of blood pressure, and new cancers.

National coordinators and clinical monitors supervised the recruitment of patients at 733 centers in 40 countries. The trial was coordinated and data were gathered and analyzed by the Population Health Research Institute at McMaster University and Hamilton Health Sciences, with coordinating suboffices at Oxford University and the University of Auckland. The steering committee designed and oversaw the trial. An operations committee, with representatives from the three coordinating centers and the sponsor (Boehringer Ingelheim), met regularly to evaluate progress.

All main study outcomes (death according to any cause, myocardial infarction, stroke, and hospitalization for heart failure) were adjudicated by a central committee whose members were unaware of study-group assignments, with the use of standard criteria.¹⁴ All serious adverse events were reviewed by an independent data and safety monitoring board.

The initial draft of the manuscript was written by Dr. Yusuf and the writing committee, who vouch for the data, with input from the steering committee. The protocol was approved by regulatory authorities and the ethics review committee at each participating institution.

RUN-IN PERIOD AND RANDOMIZATION

After written informed consent was obtained, patients entered a single-blind run-in period in which

they received 2.5 mg of ramipril once daily for 3 days, followed by 40 mg of telmisartan and 2.5 mg of ramipril once daily for 7 days and then 5 mg of ramipril plus 40 mg of telmisartan for 11 to 18 days. Of the 29,019 patients who entered the run-in period, 3399 (11.7%) were excluded from the study: 1123 (3.9%) had poor compliance, 597 (2.1%) withdrew from the study, 492 (1.7%) had symptomatic hypotension, 223 (0.8%) had an elevated potassium level, 64 (0.2%) had an elevated creatinine level, 872 (3.0%) had other reasons for exclusion, and 27 (0.1%) died.

A total of 25,620 patients underwent randomization and were stratified according to site with the use of permuted blocks through a central automated telephone service. For the first 2 weeks after randomization, 8542 patients were assigned to receive 80 mg of telmisartan once daily, 8576 were assigned to receive 5 mg of ramipril once daily, and 8502 were assigned to receive a combination of the two drugs (combination therapy). After 2 weeks, the dose of ramipril was increased to 10 mg per day. Follow-up visits occurred at 6 weeks, at 6 months, and then every 6 months until the last scheduled visit.

INTERIM ANALYSIS AND DATA MONITORING

An independent data and safety monitoring board of cardiologists, statisticians, and clinical-trial experts met twice yearly; three formal interim analyses were conducted when 25%, 50%, and 75% of the events accrued. A modified Haybittle-Peto approach¹⁵ guided decisions (i.e., a boundary of 4 SD in the first half of the trial and 3 SD in the second half for efficacy; for safety, if boundaries of 3 SD and 2 SD, respectively, were crossed in a second analysis 4 to 6 months later, it would trigger consideration of stopping).

STATISTICAL ANALYSIS

The number of patients was based on the rate of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure associated with ramipril in the HOPE trial, in which the Kaplan-Meier estimate for the primary outcome was 0.0397 per year. A determination of noninferiority required a hazard ratio for telmisartan as compared with ramipril that was below a predefined margin, with most of ramipril's effect, as compared with placebo, retained by telmisartan.

The margin was determined by the results of the HOPE trial, in which the hazard ratio with

10 mg of ramipril, as compared with placebo, was 0.775 for a composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure; this was similar to the hazard ratios in other studies comparing ACE inhibitors with placebo.^{6,7} We chose the 40th percentile (0.794) as a more robust reference to describe the effect of ramipril. The relative risk was translated into an excess risk for placebo as compared with ramipril of 1.26. Thus, a margin of 1.13 ensured that telmisartan retained at least half the effect of ramipril, if the upper limit of the one-sided 97.5% confidence interval for the hazard ratio was less than this value. We also evaluated whether the combination of telmisartan plus ramipril was superior to ramipril alone.

We tested both hypotheses using group sequential tests with a one-sided type I error of 0.025, with three planned interim analyses. If one of the two comparisons did not reject the null hypothesis, the other comparison needed an alpha of 0.0125. The original planned sample size of 7800 patients who were followed for a mean of 4.5 years provided a power of 93% for the superiority hypothesis, if the hazard ratio was 0.87. For noninferiority, the expected power was 89%, for a hazard ratio of 1.00.

The primary analysis used a time-to-event approach, counting the first occurrence of any component of the composite outcome, and included all randomized patients. All reported P values (other than for noninferiority) are two-sided. Consistency of treatment effects in prespecified subgroups was explored by the Cox regression model, with tests for interaction.^{16,17} We performed a sensitivity analysis according to the protocol by censoring data from patients who took the study drugs for less than 50% of the study period.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Characteristics of the 25,620 patients who underwent randomization were similar in the three study groups (Table 1); 27% were women, 85% had cardiovascular disease, 69% had hypertension, and 38% had diabetes. A high proportion of patients had previously received proven therapies: statins (61.6% at baseline, increasing to 70.6% by the end of the study), antiplatelet therapy (80.9% and 77.5%, respectively), beta-blockers (56.9% and 56.9%), and diuretics (28.0% and 32.5%).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)
Age — yr	66.4±7.2	66.4±7.1	66.5±7.3
Blood pressure — mm Hg†	141.8±17.4/82.1±10.4	141.7±17.2/82.1±10.4	141.9±17.6/82.1±10.4
Heart rate — beats/min	67.9±12.2	68.0±12.3	67.7±12.2
Body-mass index‡	28.1±4.5	28.1±4.6	28.0±4.5
Cholesterol — mmol/liter			
Total	4.9±1.1	4.9±1.1	5.0±1.2
LDL	2.9±1.0	2.9±1.0	2.9±1.0
HDL	1.3±0.4	1.3±0.4	1.3±0.4
Triglycerides — mmol/liter	1.7±1.1	1.7±1.1	1.7±1.1
Glucose — mmol/liter	6.7±2.6	6.7±2.5	6.7±2.6
Creatinine — μmol/liter	93.5±22.8	93.8±22.8	93.8±22.8
Potassium — mmol/liter	4.4±0.4	4.4±0.4	4.4±0.5
Female sex — no. (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)
Ethnic group — no. (%)§			
Asian	1182 (13.8)	1172 (13.7)	1167 (13.7)
Arab	102 (1.2)	106 (1.2)	106 (1.2)
African	206 (2.4)	215 (2.5)	208 (2.4)
European	6273 (73.1)	6213 (72.7)	6222 (73.2)
Native or aboriginal	747 (8.7)	756 (8.9)	728 (8.6)
Other ethnic group	64 (0.7)	77 (0.9)	69 (0.8)
Missing data	2 (<0.1)	3 (<0.1)	2 (<0.1)
Clinical history — no. (%)			
Coronary artery disease	6382 (74.4)	6367 (74.5)	6353 (74.7)
Myocardial infarction	4146 (48.3)	4214 (49.3)	4189 (49.3)
Angina pectoris			
Stable	3039 (35.4)	2958 (34.6)	2960 (34.8)
Unstable	1257 (14.7)	1296 (15.2)	1264 (14.9)
Stroke or transient ischemic attacks	1805 (21.0)	1758 (20.6)	1779 (20.9)
Peripheral artery disease	1136 (13.2)	1161 (13.6)	1171 (13.8)
Hypertension	5918 (69.0)	5862 (68.6)	5827 (68.5)
Diabetes	3146 (36.7)	3246 (38.0)	3220 (37.9)
Left ventricular hypertrophy	1085 (12.7)	1120 (13.1)	1082 (12.7)
Microalbuminuria¶	929 (13.1)	923 (13.2)	929 (13.3)
Previous procedures — no. (%)			
Coronary-artery bypass grafting	1862 (21.7)	1920 (22.5)	1893 (22.3)
Percutaneous transluminal coronary angioplasty	2527 (29.5)	2476 (29.0)	2434 (28.6)
Smoking status — no. (%)			
Current smoker	1062 (12.4)	1062 (12.4)	1101 (12.9)
Past smoker	4463 (52.0)	4468 (52.3)	4345 (51.1)

Characteristic	Ramipril (N = 8576)	Telmisartan (N = 8542)	Combination Therapy (N = 8502)
Medication — no. (%)			
Statin	5234 (61.0)	5294 (62.0)	5255 (61.8)
Beta-blocker	4847 (56.5)	4860 (56.9)	4876 (57.4)
Aspirin	6473 (75.5)	6469 (75.7)	6461 (76.0)
Clopidogrel or ticlopidine	927 (10.8)	966 (11.3)	931 (11.0)
Antiplatelet agent	6903 (80.5)	6926 (81.1)	6898 (81.1)
Diuretic	2454 (28.6)	2359 (27.6)	2351 (27.7)
Calcium-channel blocker	2821 (32.9)	2787 (32.6)	2864 (33.7)

* Plus-minus values are means $\pm$ SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† A total of 13,386 patients had a systolic blood pressure of more than 140 mm Hg.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Ethnic group was self-reported.

¶ The percentage is based on 21,074 patients who underwent baseline urinary analysis: 7073 patients in the ramipril group, 7013 patients in the telmisartan group, and 6988 patients in the combination-therapy group.

FOLLOW-UP AND ADHERENCE

A total of 25,577 patients (99.8%) were followed until a primary event occurred or until the end of the study (median, 56 months). Among patients in the ramipril group, 92.2% were taking an ACE inhibitor and 1.0% were taking an ARB at 1 year, with respective proportions of 89.4% and 1.8% at 2 years, 87.5% and 2.0% at 3 years, 86.6% and 2.4% at 4 years, and 84.7% and 3.3% at the end of the study. Among patients in the telmisartan group, 93.9% were taking an ARB and 2.6% were taking an ACE inhibitor at 1 year, with respective proportions of 91.2% and 4.2% at 2 years, 89.3% and 4.6% at 3 years, 87.7% and 5.0% at 4 years, and 85.6% and 6.4% at the end of the study. Among patients in the combination-therapy group, 85.5% received both drugs, 2.8% received an ACE inhibitor only, and 3.5% received an ARB only at 1 year; the respective proportions were 81.5%, 4.2%, and 4.8% at 2 years; 78.7%, 4.5%, and 5.4% at 3 years; 76.8%, 4.7%, and 5.7% at 4 years; and 73.6%, 6.0%, and 6.4% at the end of the study.

The proportion of patients receiving the full dose of ramipril at 2 years was 81.7% in the ramipril group and 75.3% in the combination-therapy group. The proportion of patients receiving the full dose of telmisartan at 2 years was 88.6% in the telmisartan group and 84.3% in the combination-therapy group. The study drug was discontinued by 2029 patients (23.7%) in the ramipril group and 1796 (21.0%) in the telmisartan group. In the combination-therapy group, 1929

patients (22.7%) discontinued both drugs, and an additional 566 (6.7%) stopped taking one drug.

The most important reasons for permanent discontinuation of a study drug are summarized in Table 2. More patients discontinued ramipril (either as monotherapy or with telmisartan) because of cough or angioedema than discontinued telmisartan alone. In the combination-therapy group, an increased number of patients stopped taking a study drug because of hypotensive symptoms, syncope, diarrhea, or renal impairment, as compared with the ramipril groups.

BLOOD PRESSURE, POTASSIUM, AND CREATININE

Before the run-in period, the mean blood pressure was 141.8/82.1 mm Hg. At 6 weeks, the mean blood pressure was reduced by 6.4/4.3 mm Hg in the ramipril group, by 7.4/5.0 mm Hg in the telmisartan group, and by 9.8/6.3 mm Hg in the combination-therapy group. Patients in the telmisartan group and the combination-therapy group continued to have slightly lower blood-pressure levels throughout the study period (average reductions, 0.9/0.6 mm Hg and 2.4/1.4 mm Hg, respectively) than did patients in the ramipril group. The numbers of patients who had a doubling of the creatinine level were similar in the three groups (159 in the ramipril group, 170 in the telmisartan group, and 180 in the combination-therapy group). The numbers of patients who had an increase in the potassium level of more than 5.5 mmol per liter were similar in the ramipril group (283 pa-

Table 2. Discontinuation of Study Medications and Selected Reasons for Permanent Discontinuation.*

Variable	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril		Combination Therapy vs. Ramipril	
				Relative Risk	P Value	Relative Risk	P Value
	number (percent)						
Total no. of discontinuations†	2099 (24.5)	1962 (23.0)	2495 (29.3)	0.94	0.02	1.20	<0.001
Reason for permanent discontinuation							
Hypotensive symptoms	149 (1.7)	229 (2.7)	406 (4.8)	1.54	<0.001	2.75	<0.001
Syncope	15 (0.2)	19 (0.2)	29 (0.3)	1.27	0.49	1.95	0.03
Cough	360 (4.2)	93 (1.1)	392 (4.6)	0.26	<0.001	1.10	0.19
Diarrhea	12 (0.1)	19 (0.2)	39 (0.5)	1.59	0.20	3.28	<0.001
Angioedema	25 (0.3)	10 (0.1)	18 (0.2)	0.4	0.01	0.73	0.30
Renal impairment	60 (0.7)	68 (0.8)	94 (1.1)	1.14	0.46	1.58	<0.001

* There were no predefined criteria for discontinuation.

*. There were no predefined criteria for each of the adverse events listed. Reasons listed are those provided by the investigator for the discontinuation of study drug.

† A patient could have multiple discontinuations, since patients were encouraged to restart study medications whenever possible after discontinuation.

tients) and the telmisartan group (287 patients), but the number was significantly higher in the combination-therapy group (480 patients, $P<0.001$ for the comparison between the combination-therapy group and the ramipril group).

PRIMARY OUTCOMES AND DEATH

The primary outcome occurred in 1412 patients (16.5%) in the ramipril group, in 1423 patients (16.7%) in the telmisartan group, and in 1386 patients (16.3%) in the combination-therapy group (Fig. 1 and 2 and Table 3). The upper boundary of the confidence interval (1.09) for the relative risk of the primary outcome in the telmisartan group as compared with the ramipril group was significantly lower than the predefined noninferiority boundary of 1.13 ($P=0.004$). However, the lower boundary of the confidence interval (0.94) indicates that telmisartan was not superior to ramipril. The secondary outcome — death from cardiovascular causes, myocardial infarction, or stroke — occurred in 1210 patients (14.1%) in the ramipril group and in 1190 patients (13.9%) in the telmisartan group (relative risk, 0.99; 95% confidence interval [CI], 0.91 to 1.07; $P=0.001$ for noninferiority). The results were consistent for all components of the primary outcome. Combination therapy was not significantly better than ramipril alone (relative risk, 0.99; 95% CI, 0.92 to 1.07). Adjustments for the small differences in

blood pressure did not materially alter the results for the primary outcome (relative risk for telmisartan vs. ramipril, 1.02; 95% CI, 0.95 to 1.10; relative risk for combination therapy vs. ramipril, 1.00; 95% CI, 0.93 to 1.07).

There was no significant difference in the total number of deaths between the ramipril group and the telmisartan group (1014 deaths and 989 deaths, respectively; relative risk in the telmisartan group, 0.98; 95% CI, 0.90 to 1.07); the number of deaths was higher in the combination-therapy group than in the ramipril group (1065 deaths vs. 1014 deaths; relative risk in the combination-therapy group, 1.07; 95% CI, 0.98 to 1.16), but the difference was not significant. Analyses of the cause of death did not indicate significant differences with respect to any particular cause (data not shown).

SECONDARY AND OTHER OUTCOMES

There were no significant differences in the rates of secondary outcomes (Table 4), except for renal dysfunction, which occurred in 871 patients (10.2%) in the ramipril group, 906 patients (10.6%) in the telmisartan group, and 1148 patients (13.5%) in the combination-therapy group. As compared with the ramipril group, the telmisartan group had a similar relative risk of renal impairment (1.04), whereas the combination-therapy group had a significant increase in the relative risk (1.33,

$P < 0.001$). The rate of renal dialysis was the same in the ramipril group and the telmisartan group, with 48 patients (0.6%) and 52 patients (0.6%), respectively, undergoing dialysis, whereas the rate was increased in the combination-therapy group, with 65 patients (0.8%) undergoing dialysis ($P = 0.10$ for the comparison with the ramipril group).

SUBGROUP ANALYSES

Comparisons of key subgroups showed similar results between the ramipril group and the telmisartan group (Fig. 3A) and between the ramipril group and the combination-therapy group (Fig. 3B). The results for both comparisons were also consistent in analyses that were adjusted for the patients' use of various concomitant drugs (e.g., statins, antiplatelet agents, beta-blockers, diuretics, and calcium-channel blockers) (data not shown).

PER-PROTOCOL ANALYSIS

For the primary outcome with telmisartan as compared with ramipril, the per-protocol analysis showed a relative risk of 1.00 (95% CI, 0.92 to 1.09; $P = 0.006$ for noninferiority). Analyses comparing combination therapy with ramipril showed results similar to those of the intention-to-treat analysis (relative risk, 0.98; 95% CI, 0.90 to 1.07).

DISCUSSION

ACE inhibitors have been convincingly shown to reduce rates of death, myocardial infarction, stroke, heart failure, and revascularization among patients with previous cardiovascular disease and high-risk diabetes. Therefore, to provide clinically relevant information, trials evaluating ARBs in these patients must include proven doses of an ACE inhibitor, either as background therapy or as a comparator.

In our study, we evaluated both approaches in a population similar to the one studied in the HOPE trial. Telmisartan was clearly not inferior to ramipril for both the prespecified primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure and for the primary outcome in the HOPE trial (death from cardiovascular causes, myocardial infarction, or stroke). Similarities in the telmisartan group and the ramipril group in the proportions of patients who had heart failure, underwent revascularization, or had renal dysfunction (outcomes that were reduced by

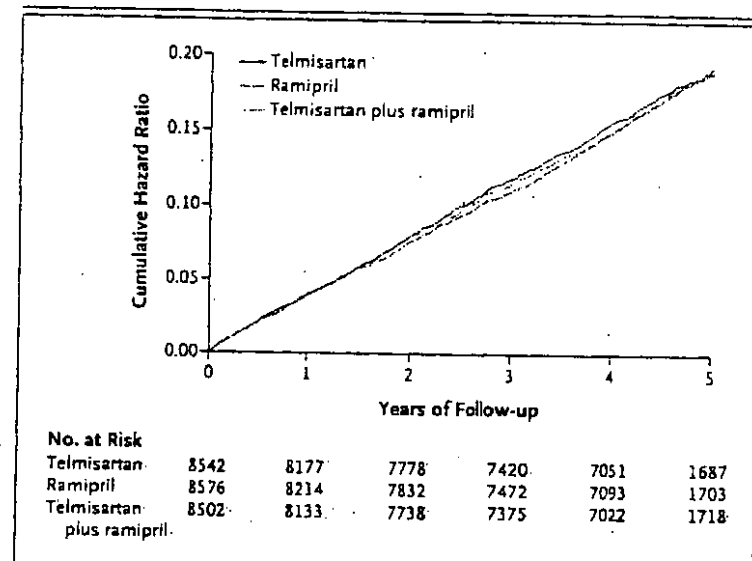


Figure 1. Kaplan-Meier Curves for the Primary Outcome in the Three Study Groups.

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

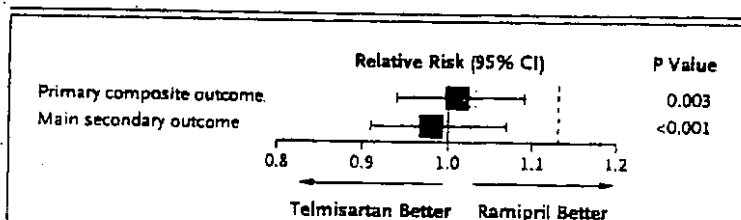


Figure 2. Relative Risk of the Primary Outcome and of the Main Secondary Outcome.

The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The main secondary outcome was death from cardiovascular causes, myocardial infarction, or stroke, which was used as the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.³ The P value is for the comparison with the noninferiority margins.

ramipril in the HOPE trial) and the high rates of adherence to both drug regimens provided additional confidence in establishing the noninferiority of telmisartan. As compared with the ramipril group, the telmisartan group had significantly fewer episodes of cough or angioedema, but this benefit was partially offset by higher rates of hypotensive symptoms (but not syncope). Higher rates of hypotension-related symptoms are consistent with the slightly lower blood-pressure levels associated with telmisartan, although the lower levels did not lead to further benefit. The

Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
	number (percent)			risk ratio (95% CI)	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Death from cardiovascular causes, myocardial infarction, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)

* Patients could have multiple events in this category. The numbers of events were 2058 (24.0%) in the ramipril group, 2042 (23.9%) in the telmisartan group, and 2000 (23.5%) in the combination-therapy group. The differences were not significant ($P=0.83$ for telmisartan vs. ramipril, and $P=0.38$ for combination therapy vs. ramipril).

† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.³

‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.

Table 4. Secondary and Other Outcomes.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
	number (percent)			relative risk (95% CI)	
Revascularization	1269 (14.8)	1290 (15.1)	1303 (15.3)	1.03 (0.95–1.11)	1.04 (0.97–1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95–1.14)	1.04 (0.95–1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84–1.07)	0.96 (0.85–1.08)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)
Renal impairment‡	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44)§
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)

* The numbers of patients included in this analysis were 5427 in the ramipril group, 5294 in the telmisartan group, and 5280 in the combination-therapy group.

† This category includes only patients who did not have atrial fibrillation at baseline: 8296 in the ramipril group, 8259 in the telmisartan group, and 8218 in the combination-therapy group.

‡ No specific definitions were used. A determination of renal impairment was based on the clinical investigator's report of an event that led to the discontinuation of a study drug.

§ $P<0.001$.

benefits of ARBs are being evaluated in three other placebo-controlled trials that are expected to be completed in 2008.^{14,18,19}

Our results parallel the findings of the Valsartan in Acute Myocardial Infarction Trial (VALIANT),²⁰ which established the noninferiority of valsartan, as compared with captopril, in

patients with left ventricular dysfunction or heart failure after myocardial infarction. The upper boundaries of the confidence intervals and the noninferiority margins were almost identical in the two studies, even though they enrolled different patient populations. The side effects in our study were similar to those in the VALIANT study,

which showed lower rates of cough and angioedema in the valsartan group than in the captopril group but higher rates of hypotension-related symptoms. There were more dose reductions (but not discontinuations) because of renal complications in the valsartan group than in the captopril group, an association that was not observed in our study.

In order to establish noninferiority, a rigorous trial design is required that includes a patient population similar to that in the reference trial, a similar drug regimen, high adherence rates, outcomes that the comparator is known to affect, and high statistical power to exclude clinically important differences. All these criteria were satisfied in our study. The entry criteria for our study and the event rates in the ramipril group were similar to those in the HOPE trial, with high follow-up rates in both trials. Moreover, the adherence rate was higher in the ramipril group (89.4% at 2 years and 84.7% at the end of the study among patients receiving either ramipril or an open-label ACE inhibitor) than that in the HOPE trial (85.0% and 78.8%, respectively). A sensitivity analysis that was restricted to patients who adhered to their allocated drug regimen for more than 50% of the study period showed the consistency of our results and confirmed the robustness of noninferiority.

In our study, we confirmed the statistical noninferiority of telmisartan, as compared with ramipril, since the upper boundary of the 97.5% confidence interval (1.09) was lower than the predefined margin of 1.13 for both the primary outcome ($P=0.004$) and the primary outcome used in the HOPE trial ($P=0.001$). Telmisartan preserved about 95% (95% CI, 83.2 to 106.3) of the benefits of ramipril over placebo with respect to the primary outcome and preserved 105% (95% CI, 91.6 to 119.0) of the benefits with respect to the outcome of death from cardiovascular causes, myocardial infarction, or stroke that were observed in the HOPE trial. Use of the method of Hasselblad and Kong²¹ to impute effects of telmisartan versus placebo (based on the benefits of ramipril over placebo in the HOPE trial) indicates a relative risk of 0.79 (95% CI, 0.70 to 0.89) for the primary outcome. The number of patients who discontinued therapy was significantly smaller in the telmisartan group than in the ramipril group, although the absolute difference in the discontinuation rate was modest, be-

cause we used an active run-in phase that selected patients for randomization only if they tolerated both medications. After randomization, we vigorously reinforced adherence and encouraged patients who stopped medications to restart them. In clinical practice, the rates of discontinuation might be higher.

We also evaluated whether the combination of telmisartan and ramipril (with both drugs targeted to the full dose) would be superior to ramipril alone. Surprisingly, despite a reduction in systolic blood pressure of 2 to 3 mm Hg in the combination-therapy group, as compared with the ramipril group — a decrease that should have translated into a risk reduction of 4 to 5% — no significant benefit was seen in the primary outcome among patients receiving the two-drug therapy. However, combination therapy significantly increased the risk of hypotension, syncope, renal dysfunction, and hyperkalemia, with a trend toward an increased risk of renal dysfunction requiring dialysis. These results are similar to the analysis of the combined effects of an ARB and an ACE inhibitor, as compared with an ACE inhibitor alone, in four previous trials.²² Therefore, even though combination therapy had a larger biologic effect (as suggested by greater blood-pressure lowering and changes in potassium), dual blockade did not produce any additional clinical benefit in this population.

In this regard, our results are also similar to those of the VALIANT study, in which the combination of a full dose of captopril plus valsartan (the latter at a dose of 80 mg per day, which was lower than the 160 mg per day used in the valsartan-only group) did not significantly reduce the occurrence of the primary outcome but did increase hypotension.²⁰ Taken together, these two studies showed no additive effect for an ARB in conjunction with a full dose of a proven ACE inhibitor.

However, our findings contrast with those of two other studies. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study,¹² which involved patients who had symptomatic heart failure and had been hospitalized in the previous 6 months, candesartan, when added to existing therapy with any ACE inhibitor used at variable doses (with less than half the patients receiving full doses), was superior to placebo in reducing death or hospitalization for heart failure. Similarly, a reduction

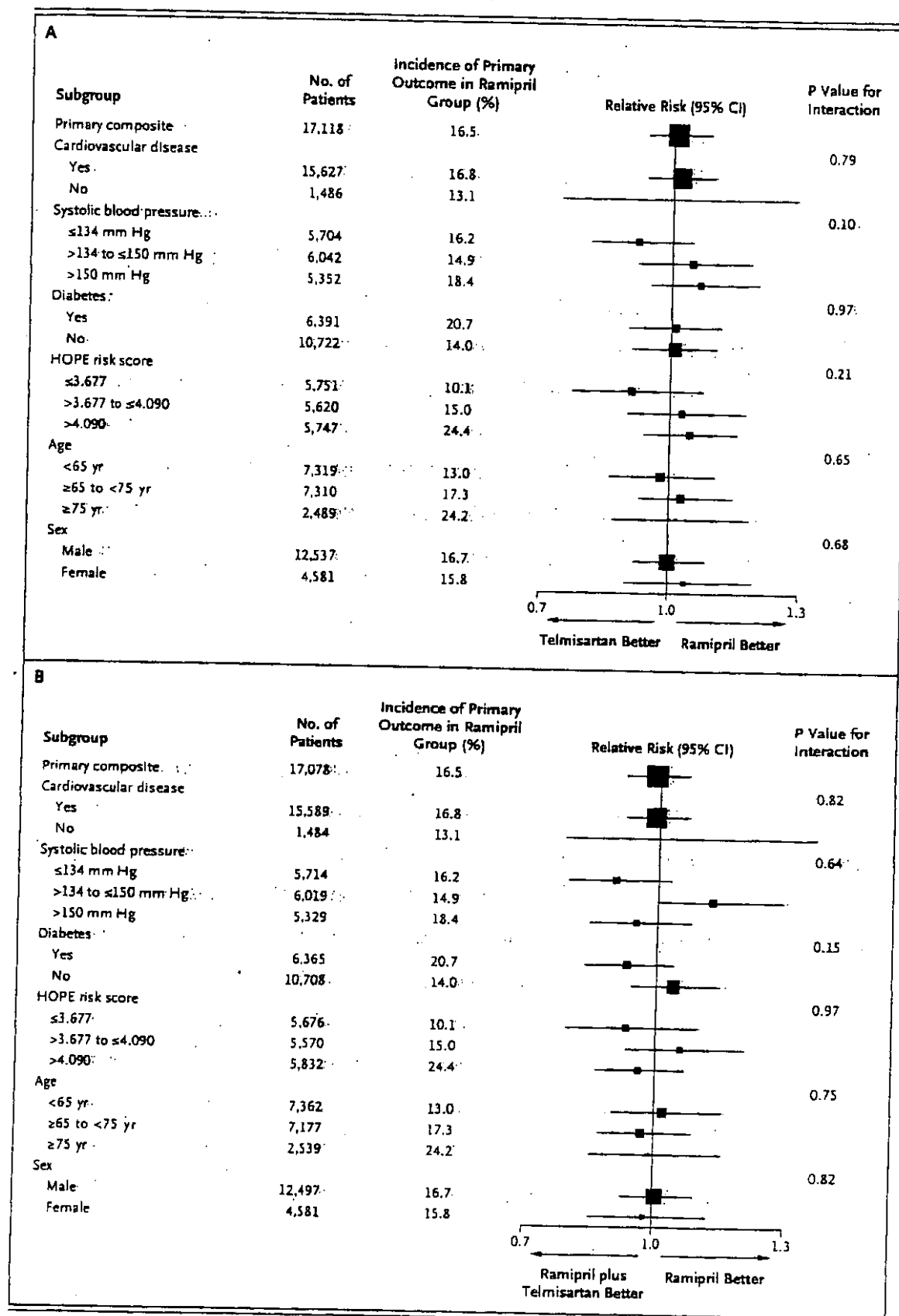


Figure 3 (facing page). Relative Risks in Prespecified Subgroups.

Shown are the comparisons between the telmisartan group and the ramipril group (Panel A) and between the combination therapy (telmisartan plus ramipril) group and the ramipril group (Panel B). The risk score from the Heart Outcomes Prevention Evaluation (HOPE) trial⁸ ranges from 2.350 to 5.928, with higher scores indicating higher risk. The sizes of the squares are proportioned to the numbers of events.

in hospitalization for heart failure was observed in the Valsartan Heart Failure Trial,¹¹ which compared valsartan with placebo in patients with heart failure, with about 90% of patients receiving background therapy with ACE inhibitors at variable doses. Both trials differed from both our study and the VALIANT study in that decisions regarding the dose and choice of an ACE inhibitor were left to individual physicians, and there was no attempt to titrate the ACE inhibitor to the maximum dose. Furthermore, patients had symptomatic heart failure despite receiving an ACE inhibitor.

The lack of an additional benefit of a substantial lowering of blood pressure is puzzling, both in our study and in the VALIANT study. These results may have been due to previous successful treatment of patients with other drugs so that little further clinical benefit was possible with the addition of full doses of multiple drugs that block the renin-angiotensin system. Alternatively, some harm from combined therapy with ACE inhibitors and ARBs used at full doses may offset

any potential gains. Further information is expected regarding the role of ARBs as compared with placebo in patients after stroke,¹² in high-risk patients with vascular disease who are unable to tolerate an ACE inhibitor,¹⁴ and in patients with atrial fibrillation.¹⁹

In conclusion, our data show that in patients who have vascular disease or high-risk diabetes but do not have heart failure, telmisartan is an equally effective alternative to ramipril and is less likely to cause angioedema. The choice between the two agents will depend on the preferences of patients and physicians and the individual patient's susceptibility to specific adverse events. There is no additional advantage (and there is some harm) from the combination of telmisartan and ramipril used in full doses in this population, as compared with ramipril alone.

Supported by a grant from Boehringer Ingelheim, the Heart and Stroke Foundation of Ontario, and a Senior Scientist Award from the Canadian Institutes of Health Research (to Dr. Yusuf).

Dr. Yusuf reports receiving consulting and lecture fees and research grants from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, Servier, Bristol-Myers Squibb, and GlaxoSmith-Kline; Dr. Teo, receiving consulting and lecture fees and grant support from Boehringer Ingelheim; Dr. Schumacher, being an employee of Boehringer Ingelheim; Dr. Dagenais, receiving consulting and lecture fees from Boehringer Ingelheim and Sanofi-Aventis and grant support from Sanofi-Aventis; Dr. Sleight, receiving consulting and lecture fees from Boehringer Ingelheim and lecture fees from AstraZeneca and Sanofi-Aventis; and Dr. Anderson, receiving consulting fees from Boehringer Ingelheim, Servier, Novo Nordisk, and AstraZeneca, lecture fees from Boehringer Ingelheim, Servier, AstraZeneca, and Sanofi-Aventis, and grant support from Boehringer Ingelheim. No other potential conflict of interest relevant to this article was reported.

We thank Judy Lindeman for her secretarial assistance.

APPENDIX

Current members of the Operations Committee are denoted by an asterisk. Previous members of the Operations Committee are denoted by a dagger. NC denotes National Coordinator, and NL National Leader. Steering Committee: S. Yusuf (Chair and Principal Investigator),* P. Sleight,* C. Anderson,* K. Teo,* I. Copland,* B. Ramos,† L. Richardson,* J. Murphy,* M. Haehl,* L. Hilbrich,† R. Svaerd,* K. Martin,† D. Murwin,* T. Meinicke,† A. Schlosser,* G. Schmidt,† R. Creek,* H. Schumacher,* M. Distel,† B. Aubert, J. Pogue, L. Dyal, R. Schmieder, T. Unger, R. Asmar, G. Mancía, R. Díaz, E. Paolasso, L. Piegas, A. Avezum, G. Dagenais, E. Cardona Munoz, J. Probstfield, M. Weber, J. Young, R. Fagard, P. Jansky, J. Mallion, J. Mann, M. Böhm, B. Eber, N.B. Karatzas, M. Keltai, B. Trimarco, P. Verdecchia, A. Maggioni, F.W.A. Verheugt, N.J. Holwerda, L. Ceremuzynski, A. Budaj, R. Ferreira, I. Chazova, L. Rydén, T.L. Svendsen, K. Metsärinne, K. Dickstein, G. Fodor, P. Commerford, J. Redon, T.R. Luescher, A. Oto, A. Binbrek, A. Parkhomenko, G. Jennings, L.S. Liu, C.M. Yu, A.L. Dans, R. Shah, J.-H. Kim, J.-H. Chen, S. Chaitiraphan. Data and Safety Monitoring Board: J. Cairns (Chair), L. Wilhelmsen, J. Chalmers, J. Wittes, M. Gent, C.H. Hennekens. Adjudication Committee: G. Dagenais (Chair), N. Anderson, A. Avezum, A. Budaj, G. Fodor, M. Keltai, A. Maggioni, J. Mann, A. Parkhomenko, K. Yusoff, P. Auger, V. Bernstein, E. Lonn, A. Panju, I. Anand, J.T. Bigger, P. Linz, J. Healey, C. Held, C. McGorrian, M. Rokoss, J. Villar. Substudies/Publication Committee: P. Sleight (Chair), C. Anderson, R. Creek, A. Dans, R. Díaz, R. Fagard, J. Probstfield, R. Svaerd, K. Teo, T. Unger, S. Yusuf. Coordinating Centers: Hamilton — K. Teo, I. Copland, B. Ramos, A. McDonald, J. Pogue, L. Dyal, R. Afzal, F. Zhao, S. Yusuf; Oxford — P. Sleight, L. Richardson; Auckland — C. Anderson, J. Murphy. Sites and Principal Investigators by Country: Argentina — R. Díaz (NC), E. Paolasso (NL), R.A. Ahuad Guerrero, M. Amuchastegui, H.P. Baglivo, M. Bendersky, J. Bono, B. Bustos, A. Caccavo, L.R. Cartasegna, C.R. Castellanos, M.A. Cipullo, P. Crunger, C.A. Cuneo, M. Focaccia, J.J. Fuselli, E. Hasbani, M.A. Hominal, J. Humphreys, F. Insera, C.R. Killinger, E. Kuschner, C.R. Majul, O.D. Manuale, G. Martinez, E.M. Marzetti, R. Nordaby, A.D. Orlandini, J.C. Pomposiello, G.M. Rodriguez, J. Salas, O.A. Salomone, R.A. Sanchez, C. Serra, M.L. Vico; Australia — G.L.R. Jennings (NC), J.V. Amerena, L.F. Arnolda, G.M. Aroney, P.E. Aylward, C.F. Bladin, J.C. Bridgeman, B.R. Chambers, A.J. Corbett, D.S. Crimmins, D.B. Cross, L. Davies, S.M.

- Davis, G.A. Donnan, D.S. Eccleston, J.H. Frayne, R. Hendriks, G.K. Herkes, A.T. Hill, I.M. Jeffery, J.A. Karrasch, G. Koshy, T.H. Marwick, D.A. Owensby, M.W. Parsons, D.M. Rees, A. Russell, R. Schwartz, B. Singh, P.L. Thompson, J.H. Waites, W.F. Walsh, D.L. Walters, R.W. Watts, A.P. Whelan; Austria — M. Böhm (NC), B.E. Eber (NL), J.B. Bonelli, P. Dolliner, J.H. Hohenacker, G.S. Steurer, W.W. Weihs; Belgium — R. Fagard (NC), I. Bekaert, C. Brohet, P. Chaumont, P. Cheron, V. Crasset, J.-P. Degaute, P. Dendale, K. Du-jardin, S. Elshot, S. Hellemans, M. Herssens, G. Heyndrickx, P. Laloux, H. Lesseliers, P. Noyens, M. Quinonez, F. Stammen, H. Strie-
 kwold, J. Thoeng, W. Van Mieghem, G. Vanhooren, G. Vervoort, M. Vrolix, B. Wollaert; Brazil — L. Piegas (NC), A. Avezum (NL), J. A.M. Abrantes, D. Armaganijan, J.C. Ayoub, L.C. Bodanese, A.C. Carvalho, M. Coutinho, J.P. Esteves, R.J.S. Franco, P.C.B.V. Jardim, J.F. Kerr Saraiva, P.E. Leães, L.N. Maia, J.A. Marin-Neto, R.L. Marino, D. Mion, Jr., J.R. Moreira, Jr., W. Oigman, R.C. Pedrosa, E.A. Pelloso, F.L. Plavnik, C.A. Polanczyk, A. Rabelo, Jr., S. Rassi, G. Reis, A.B. Ribeiro, J.M. Ribeiro, J.C. Rocha, P.R.F. Rossi, R.D. Santos, J.C.E. Taraschuk, M.N. Villalón; Canada — K. Teo (NC), G. Dagenais (NC), B. Abramson, M. Arnold, T. Ashton, P. Auger, I. Batz, K. Bayly, J. Beauchef, A. Bélanger, V. Bernstein, R. Bhargava, A.W. Booth, S. Bose, M. Boulianne, M. Cameron, Y.K. Chan, C. Constance, P. Costi, D. Dion, J. Doukakis, D. Fell, J.P. Giannoccaro, A. Glanz, G. Gosselin, D. Gould, S. Goulet, F. Grondin, M. Gupta, G. Gyenes, J.W. Heath, V.A. Heath, A. Hess, J.G. Hiscock, G. Hoag, G. Honos, J. Imrie, R. Kuritzky, C. Lai, A. Lalani, A. Lamy, P. LeBouthillier, H. Lochnan, E. Lonn, B. Lubelsky, A. Mackey, M. Meunier, A. Milot, L.B. Mitchell, S. Nawaz, M. Omichinski, A. Panju, C. Pilon, D. Pilon, P. Polasek, G. Proulx, T. Rebane, A.J. Ricci, D.W. Rupka, É. Sabbah, D. Savard, N.K. Sharma, D. Shu, R. St. Hilaire, F. St. Mau-
 rice, R. Starra, B. Sussex, T. Szaky, P. Talbot, K.-W. Tan, T.B. To, S. Tobe, R. Tytus, R. Vexler, P. Whitsitt, V. Woo; China — L. Liu (NC), X. Bai, X. Chen, J. Feng, S. Fu, Y. Ge, L. Gong, Z. He, J. Huang, Y. Jiang, L. Li, Q.H. Li, Y. Liao, Z. Lu, F. Lu, S. Ma, F. Niu, C. Pan, F. Qian, X. Shi, N. Sun, M. Sun, G. Sun, J. Wang, S. Wang, Y. Wang, Z. Wu, X. Yan, X. Yang, H. Yang, X. Ye, S. Yuan, T. Zhang, C. Zhang, F. Zhang, S. Zhang, D. Zhao, B. Zheng, H.Y. Zhou, S. Zhou, J. Zhu; Czech Republic — P. Janský (NC), V. Dedek, J. Dvorský, R. Holaj, J. Kotouš, E. Pederzoliová, M. Polák, J. Povolný, K. Smetana, J. Špác; Denmark — T.L. Svendsen (NC), L. Götzsche, H.F. Juhl, K. Koelendorf, P. Lund, F. Pedersen, O.L. Pedersen, T. Pindborg, L.H. Rasmussen, S.L. Rasmussen, K. Thygesen, C. Tuxen; Finland — K. Metsärinne (NL), R. Antti-
 kainen, M. Jääskivi, I. Kantola, M. Katarinen, P. Kohonen-Jalonen, A. Koistinen, E. Lehmus, R. Nuuttila, M.-L. Tuominen, H. Ylihärsilä; France — J. Mallion (NC), N. Abenham, J. Allix, L. Boucher, M. Bourgoïn, A. Boye, N. Breton, D. Cadot, A. Campagne, J. Churet, G. Constantin, E. De Sainte Lorette, A. El Sawy, G. Etchegarray, S. Farhat, F. Lacoïn, T. Latte, C. Magnani, D. Pineau-Valenciennes, M. Pithon, A. Quéguiner, J. Sicard, G. Sorbe, D. Taminiau, H. Vilarem, J.Y. Vogel; Germany — H.H. Ebert, S. Genth-Zott, N. Hermanns, C. Holzer, J. Minnich, D. Schimkus, M. Boehm (NC), J. Mann (NC), B. Brado, G. Claus, U. Dietz, R. Griebenow, T. Haak, K. Hahn, R. Hampel, H. Heitzer, G. Holle, T. Horzcek, J. Jordan, C. Klein, R. Kolloch, S. Ludewig, W. Motz, T. Muenzel, H.P. Nast, M. Nauck, H. Nebelsieck, K. Rybak, H. Samer, T. Schaefer, J. Scholze, B. Schulze, Schleppinghoff, R. Schmieder, B. Schwaab, U. Sechtem, W. Sehnert, E. Steinhagen-
 Thiessen, G. Stenzel, P. Trenkwalder, B. Wedler, J. Zippel; Greece — N. Karatzas (NC), A. Achimastos, E. Diamantopoulos, A. Efstratopou-
 los, M. Elisaf, H. Karvounis, D. Mentzikof, D. Mytas, D. Papadogiannis, V. Pyrgakis, C. Stefanadis, D. Symeonidis, A. Tsoukas, I. Vogiatzis, S. Voyaki, C. Zamboulis; Hong Kong — C.-M. Yu (NC), C.K.H. Chan, L. Lam, Y.K. Lau, J. Sanderson, J. Wong, E.B. Wu, C.S. Yue; Hungary — M. Keltai (NC), I. Czurgai, I. Édes, C.S. Farsang, A. Kalina, K. Keltai, M. Kozma, Z. László, V. Nagy, A. Papp, G.Y. Polák, I. Préda, A. Rónaszéki, M. Sereg, K. Simon, S. Sonkodi, J. Szegedi, S. Timár, K. Tóth, G.Y. Vándorfi, A. Vértés; Ireland — J. Feeley, V.M.G. Maher, A.V. Stanton, P. Sullivan; Italy — B. Trimarco (NC), P. Verdecchia (NC), A. Maggioni (NL), E. Agabiti Rosei, G.B. Ambrosio, M. Benivoglio, A. Branzi, P. Cavallo Perin, M. Chiariello, V. Cirrione, R. Ferrari, R. Gattobigio, E. Giovannini, D. Giugliano, A. Lacchè, R. Lauro, G. Lembo, G. Marchetti, L. Moretti, L. Pancaldi, L. Pantemi, S. Pede, G. Pettinati, G. Reboldi, R. Ricci, G. Rosiello, F. Rozza, M.G. Sardone, E.V. Scabbia, G. Selvenella, L. Tavazzi, P. Terrosu, A. Venco, A. Vetrano, M. Volpe, G. Zilio; Malaysia — T. Ismail, R.P. Shah, M. Singaraveloo, W.A. Wan Ahmad, Z. Yusof, K. Yusoff, I. Zainal Abidin, R. Zambahari; Mexico — E. Cardona Munoz (NC), L. Alcocer Diaz, S. Pascoe-Gonzalez, R. Arriaga Nava, G. De La Peña Topete, L.A. Elizondo Sifuentes, H.R. Hernández García, J. Illescas-Diaz, M.A. Macías
 Islas, J.A. Noriega Arellano, R. Olvera Ruiz, J.Z. Parra Carrillo, G. Velasco Sánchez, M. Vidrio Velásquez; the Netherlands — F.W.A. Verheugt
 (NC), N.J. Holwerda (NL), D.C.G. Basart, A.J.M. Boermans, H.A. Bosker, C.P. Bouter, C.P. Buiks, W.A. de Backer, J. J. de Graaf, J.H.M. Deppenbroek, F.D. Eefting, F.C.N.M. Gunnégweg, H.R. Michels, D. Poldermans, G. Schrijver, M.I. Sedney, T. Slagboom, J.G. Smilde, G.E.M.G. Storms, R.M. Tjon, P.F.M.M. van Bergen, G.J.M. van Doesburg, L.H.J. van Kempen, H.F.C.M. van Mierlo, A. Veerman, F.A.A.M. Vermetten, A. Wester; New Zealand — W. Bagg, J. Benatar, R.J. Coxon, R.N. Doughy, D.H. Friedlander, R.A. Luke, P.L. Nairn, Y. Ramasa-
 bapathy, A.M. Richards, G.P. Singh, R.A.H. Stewart, R.W. Troughton, H.D. White, M. Williams, S.P. Wong; Norway — K. Dickstein (NL), N. Bogale, J.O. Lier, J.E. Otterstad, P.K. Rønnevik, S. Skeie, P.O. Walløe; Philippines — A.L. Dans (NC), M.T.B. Abola, J.C. Afonuevo, J.M. Jaro, D.R. Marahon, V.L. Mendoza, D.R. Morales, E.P. Pacheco, E.B. Reyes, A.A. Roxas, M.B. Sedurante; Poland — L. Ceremuzynski (NC), A. Budaj (NC), Z. Binio, M. Bronisz, P. Buszman, T. Czerski, M. Dalkowski, J. Gessek, A. Gieroba, K. Janik, M. Janion, T. Kawka-Urbanek, R. Klabisz, M. Krauze-Wielicka, S. Malinowski, P. Miekus, J. Mornul, M. Ogorek, G. Opolski, M. Skura, M. Szpajer, M. Tendera, T. Waszyrowski, M. Wierzchowiecki, B. Zalska; Portugal — R. Ferreira (NC), R. Capucho, C. Correia, L. Cunha, J.M. Ferro, V. Gama Ribeiro, V. Gil, P. Marques da Silva, M. Oliveira Carrageta, R. Sebra Gomes, M. Veloso Gomes; Russia — I. Chazova (NC), F. Ageev, Y. Belenkov, A. Ivleva, Y. Karpov, M. Shestakova, E. Shlyakhto, S. Shustov, B. Sidorenko; Singapore — H.M. Chang, B. Kwok; Slovakia — G. Fodor (NC), A. Dukát, J. Gonsorcik, M. Hranai, J. Lietava, D. Pella, R. Rybar, L. Ruffini; South Africa — P. Commerford (NC), F. Bonnici, B. Brown, A.J. Dalby, G.J. Gibson, L. Herbst, J. King, E. Klug, M. Middle, D. P. Naidoo, M. Pretorius, G. Podgorski, N. Ranjith, K. Süwa-Hahle, H. Theron; South Korea — J.H. Kim (NC), S.C. Chae, N.S. Chung, K.P. Hong, M.H. Jeong, H.J. Kang, J.J. Kim, M.H. Kim, H.S. Seo, E.K. Shini; Spain — J. Redón (NC), J. Abellán, P. Aranda, V. Barrios, C. Calvo, M. De La Figuera, E. De Teresa, R. Durá, F. Escobar, F. Fernandez-Cruz, E. Galve, J. Garcia-Puig, B. Gil-Extremera, R. Gomis, O. Gonzalez-Albarán, J.R. González-Juanatey, A. Llacer, L. López-Bescós, J. Oliván, A. Picó, A. Pose, A. Roca-Cusachs, L.M. Ruilope; Sweden — L. Rydén (NC), A. Alvång, P.-Å. Bostrom, M. Dellborg, U.-B. Ericsson, J. Her-
 litz, T. Juhlin, K. Pedersen, B. Ström, B. Sundqvist, B.-O. Tengmark, G. Ulvenstam, B. Westerdahl, L. Winberg; Switzerland — T.R. Luescher
 (NC), I. Baumgartner, P. Dubach, A. Gallino, T. Moccetti, G. Noll, A. Nordmann, H. Rickli, H. Schläpfer, K. Weber; Taiwan — J.-H. Chen
 (NC), T.H. Chao, C.Y. Chen, J.J. Cheng, H.C. Chiou, C.C. Fu, M. Fu, W.T. Lai, Y.H. Li, L.M. Lien, C.D. Tsai, J.H. Wang, P.S. Yeh; Thailand — S. Chaithiraphan (NC), T. Chantadansuwan, K. Jirasitrojjanakorn, R. Kritayaphong, P. Laothavara, N. Mahanonda, S. Sithisook, S. Tanomsup, S. Tansuphaswadikul, P. Tatsanavivat, S. Yamwong; Turkey — A. Oto (NC), M. Akın, N.T. Caglar, A. Ergin, H. Müderrisoğlu, A. Oguz, Z. Ongen, V. Sansoy, T. Tetiker, A. Uysal; Ukraine — A. Parkhomenko (NC), E. Amosova, O. Cherkasova, Y. Dykun, G. Dzyak, A. Galystska, O. Grishyna, O. Jazemko, L. Kononenko, E. Koval, V. Kovalenko, V. Netyazhenko, T. Petseva, A. Prokhorov, G. Radchenko, Y.U. Rudyk, Y. Sirenko, A. Skarzhevsky; United Arab Emirates — A.S. Binbrek (NC), A.A.R. Al Hajiri, E. Al Hatou, A.A.S. Al-Sousi, M. Alo-
 mairi, I. Maqsood Wajib; United Kingdom — P. Sleight (NC), A.A.J. Adgey, R. Andrews, S.G. Ball, D.H. Barer, A.H. Barnett, A.B. Bridges, V. Bryson, A.S. Cowie, A.J. De Belder, R. Donnelly, C.M. Francis, J. Furnace, S.K. Glen, N. Gough, A.M. Heagerty, P.R. Jackson, S.H.D. Jackson, E. Joyce, D.J. McEneaney, A.J. Moriarty, D.L. Murdoch, J.P. O'Hare, W.J. Penny, C.J. Reid, J. Tilley, J.P. Vora, J. Webster, B. Wil-

liams; United States — J. Probstfield (NC), M. Weber (NC), J. Young (NC), I. Ahmed, I.S. Anand, J.L. Anderson, J.S. Aponte Pagin, J. Barzilay, J.N. Basile, P.F. Bass III, S.S. Blumenthal, W.J. Bommer, D.F. Brautigam, C.D. Brown, N. Brown, J.D. Byrum, A.A. Carr, J. Chinn, D. Chiu, N.R. Cho, J.O. Ciocon, P.J. Colón-Ortiz, J.B. Cruz, W.D. Dachman, G.M. Dolson, S.G. Dorfman, W. Drummond, C. East, F. Eelani, H.S. Ellison, J.V. Felicetta, M.H. Fishbach, R.W. Force, S.I. Giddings, M.C. Goldberg, S. Goldman, R. Gomez Adrover, S.L. Goss, S.P. Graham, C.B. Granger, M.M. Greenspan, R.H. Grimm, G.B. Habib, M.R. Hagen, P.D. Hart, T.J. Hartney, M.A. Henriquez, J.I. Holland, B.I. Hoogwerf, M. Hossfeld, A.K. Jacobson, M.J. Jelley, T.V. Jones, R.A. Kaplan, D.G. Karalis, L.A. Katz, D.J. Kereiakes, M. Khan, R.M. Kipperman, M.J. Kozinn, J.G. Kozlowski, E.W. Lader, C. Landau, J.S. Landzberg, D. Lughrun, S.J. Lewis, C.S. Liang, M.C. Limacher, P.E. Linz, T.S. Lo, F. Lopez-Arostegui, R.R. Maddox, P.R. Mahrer, M.S. Maurer, D.K. McGuire, A.D. Mercado, J.H. Mersey, M. Meyer, A.N. Mooss, P. Narayan, S. Oparil, D.N. Padhiar, A.L. Phillips, M. Prisant, N. Qureshi, M.P. Raghuvanshi, R.R. Randall, T.M. Retta, R.E. Ringrose, A.A. Rizvi, M.D. Rjzvi, M.G. Saklayen, S. Sastrasinh, I.K. Savani, A. Schlaue, H.S. Schultz, M.J. Schweiger, R.D. Smith, M. Sosa-Padilla, D. Streja, T.P. Stuver, D.C. Subich, F.C. Sulak, W.A. Swagler III, M. Taitano, J.A. Tavaréz-Valle, E.M. Taylor, M.L. Tuck, W.B. White, W.J. Wickemeyer, T.B. Wiegmann, P.A. Zee, X.Q. Zhao.

REFERENCES

1. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
2. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med* 1992;327:669-77.
3. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003;361:1843-8.
4. Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;355:1575-81.
5. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53. [Errata, *N Engl J Med* 2000;342:784, 1376.]
6. Fox KM. EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
7. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;368:581-8.
8. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE sub-study. *Lancet* 2000;355:253-9. [Erratum, *Lancet* 2000;356:860.]
9. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. *Circulation* 1999;100:1056-64.
10. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772-6.
11. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
12. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.
13. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003.
14. Teo K, Yusuf S, Sleight P, et al. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J* 2004;148:52-61.
15. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
16. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
17. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall, 1984.
18. Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS). *Cerebrovasc Dis* 2007;23:368-80.
19. The ACTIVE Steering Committee. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. *Am Heart J* 2006;151:1187-93.
20. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906. [Erratum, *N Engl J Med* 2004;350:203.]
21. Hasselblad V, Kong DF. Statistical methods for comparison to placebo in active-control trials. *Drug Inf J* 2001;35:435-49.
22. Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials. *Arch Intern Med* 2007;167:1930-6.

Copyright © 2008 Massachusetts Medical Society.

ANEXO IV



[About Us](#) [Health Information](#) [Kids/Teens Zone](#) [Funded Research](#) [Advocate](#) [News](#) [Events](#) [Volunteer](#) [Multicultural Resources](#)

[Home](#) > [News](#) > [Press Releases](#)

PRESS RELEASES

Guideline alert for blood pressure patients as treatment combo fails

Toronto, Jan. 16, 2009 – Thousands of Canadians with high blood pressure (hypertension) are being treated with a drug combination that increases the risk of kidney disease and the likelihood of dialysis, warns the Heart and Stroke Foundation.

New guidelines from Canadian Hypertension Education Program (CHEP) based on international research funded in part by the Foundation will urge patients who have been prescribed a combination of ACE inhibitors and Angiotensin II Receptor Blockers (ARBs) to see their family physicians as soon as possible for a treatment change.

"These two popular categories of hypertension medication are each safe and effective treatments – but not together," says Dr. Sheldon Tobe, spokesperson for the Heart and Stroke Foundation and CHEP executive member.

As many as 175,000 Canadians with high blood pressure may be currently treated with this combination of medications.

Angiotensin Converting Enzyme (ACE) inhibitors are a type of blood pressure medication that helps widens blood vessels, making it easier for blood to flow through. Angiotensin II Receptor Blockers (ARBs) inhibit the action of a peptide called angiotensin, which causes blood vessels to narrow, helping to relax the blood vessels and lower blood pressure.

According to CHEP, most people who develop hypertension will require treatment with two or more medications plus lifestyle modifications. Treating these patients with combinations of drugs will remain a widespread and highly effective practice.

But problems surfaced earlier this year in the ONTARGET study carried out by Heart and Stroke Foundation researchers and published in the New England Journal of Medicine.

In this major international clinical trial of 25,620 patients, the drug combination of an ACE inhibitor and an ARB was found to be only marginally more effective at lowering blood pressure than either of the drugs taken alone. In addition, patients on this combination experienced more side effects such as kidney problems than those on only one of the drugs. Patients were age 55 and over and had vascular disease or high-risk diabetes.

"This trial is a landmark study that helps healthcare providers better understand and more safely prescribe drug combinations for hypertension," says Margaret Moy Lum-Kwong, director of the High Blood Pressure AIM Strategy of the Heart and Stroke Foundation of Ontario. "If you are on this particular combination treatment for high blood pressure do not stop taking your medication. Instead go directly to your doctor for an alternative treatment."

There is a synergy that happens when you use this particular drug combination but, unfortunately, it is not a synergy that benefits

patients," says Dr. Tobe who is also a nephrologist at Sunnybrook Health Sciences Centre in Toronto. "When you put the two drugs together, you don't get any additional protection against heart attacks and strokes and you get more negative side effects."

ACE inhibitors and ARBs both lower blood pressure through their action on the renin-angiotensin system – a group of hormones regulated by the kidneys that control long-term blood pressure.

"The combined action of these two drugs is a source of major stress on the kidneys," says Dr. Tobe.

"They don't give any additional benefit in combination but each is associated with side effects so all you do is double up the side effect but you don't double up the benefits."

Side effects can include fainting, diarrhea, and dangerously elevated potassium levels which could result in the need for dialysis.

Margaret Moy Lum-Kwong has some advice for Canadians with high blood pressure: "Be aware of your medications – know what you are taking and why."

"Sometimes more is not better," says Dr. Tobe. "The good news is that patients who are experiencing side effects recover as soon as they get off the combination of medications," he says. The recommendations also describe how to combine blood pressure medications appropriately to lower blood pressure in people with diabetes.

The Heart and Stroke Foundation and CHEP have translated the professional blood pressure management guidelines and they are available at www.heartandstroke.ca. For more information on hypertension medications go to www.hypertension.ca.

The Heart and Stroke Foundation's Blood Pressure Action Plan™ offers realistic strategies and on-going support to help individuals prevent and control high blood pressure. Canadians can get a free, confidential risk assessment by going to www.heartandstroke.ca.

ANEXO V

AMLODIPINE/ARB FIXED-DOSE COMBINATIONS FOR THE TREATMENT OF HYPERTENSION: FOCUS ON AMLODIPINE/OLMESARTAN COMBINATION

Steven G. Chrysant

Oklahoma Cardiovascular and Hypertension Center and The University of Oklahoma School of Medicine,
 Oklahoma City, OK, USA

CONTENTS

Summary	443
Introduction	444
History of fixed-dose combination therapy of hypertension	444
Rationale for fixed-dose combination therapy	444
Clinical trials of fixed-dose combination therapies	446
Discussion	450
References	451

Summary

The incidence of hypertension continues to increase worldwide and, according to recent estimates, its incidence is approximately 30% of the U.S. population. However, the control of blood pressure (BP) to recommended levels of < 140/90 mmHg for uncomplicated hypertension, recommended in the 7th Report of the Joint National Committee (JNC-7) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, remains low at 36.8%. Because the level of BP is

directly related to cardiovascular and stroke morbidity and mortality, aggressive treatment and control of hypertension are strongly indicated. Since monotherapy alone is not effective for the control of stage 2 hypertension, fixed-dose combination therapy with two complementary drugs has been recommended by the JNC-7 guidelines as initial therapy for subjects with diastolic BP $\geq$ 100 mmHg and systolic BP $\geq$ 160 mmHg. There are several fixed-dose combination preparations already available, each with its individual indications. The recently FDA-approved fixed-dose combinations of amlodipine with either olmesartan or valsartan are very effective in treating hypertension and are safe and well tolerated. In addition to reducing BP, these new fixed-dose combinations have also demonstrated significant reductions in the inci-

Correspondence: Steven G. Chrysant, M.D., Ph.D.,
 5850 W. Wilshire Blvd., Oklahoma City, OK 73132,
 USA. Tel.: +1-405-721-8662; Fax: +1-405-721-8417;
 E-mail: schrysant@yahoo.com

dance of edema associated with amlodipine monotherapy, which makes them more acceptable to patients. In addition, due to the metabolic neutrality of both component drugs, these preparations are preferable for the treatment of hypertensive patients with diabetes or the metabolic syndrome, in addition to other cardiovascular risk factors. Copyright 2008 Prous Science, S.A.U. or its licensors. All rights reserved.

Introduction

The hypertensive population in the U.S. is increasing but blood pressure (BP) control remains low (1). At present, of the approximately estimated 88 million hypertensive patients, only 36.8% are controlled (BP < 140/90 mmHg) as recommended by the 7th Report of the Joint National Committee (JNC-7) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (1, 2). Several clinical trials have shown that monotherapy of hypertension is only effective in approximately 50% of patients in achieving BP goals (3) and that the majority of patients will require at least two antihypertensive drugs to achieve their BP goal (3-5). The need for the use of more than one drug for the successful control of BP is due to the multifactorial causes of hypertension and the involvement of two or more pathological mechanisms. In addition, the administration of one drug initiates counterregulatory mechanisms which interfere with its antihypertensive effectiveness. In such cases, the addition of a second drug with a complementary mechanism of action may antagonize the counterregulatory effects of the first drug and lead to a greater reduction of BP, and it may also modify the side effects caused by the first drug (6-9). In the case of dihydropyridine calcium channel blockers (CCBs), the leg edema caused by these agents is ameliorated by their combination with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), as has been demonstrated in several clinical trials (10-15). Among all fixed-dose drug combinations, the dihydropyridine CCB/ACEI and CCB/ARB combinations have been very effective for the treatment of hypertension and are metabolically neutral. In this concise review, I will focus on the fixed-dose combination of amlodipine besylate/olmesartan medoxomil for the treatment of stage 1 and stage 2 hypertension.

History of fixed-dose combination therapy of hypertension

The principle of using more than one different drug with complementary mechanisms of action for the treatment of hypertension has been well accepted by physicians and has been used for many years. However, the fixed-dose combination of two or more complementary drugs has been slow to gain widespread acceptance. Historically, the first fixed-dose drug combination approved by the FDA for the treatment of hypertension was Ser-AP-Es (16), a combination of reserpine, hydralazine and hydrochlorothiazide. Since then, several fixed-dose combinations, most with a low-dose diuretic, have been approved by the FDA and marketed for the treatment of hypertension. Recently, nondiuretic fixed-dose drug combinations have been shown to be effective, safe and well tolerated and have been approved by the FDA for the treatment of hypertension. These include combinations of either ACEIs with CCBs (10, 13, 17-19) or ARBs with CCBs (20, 21).

Rationale for fixed-dose combination therapy

The goal of antihypertensive treatment is to maximize therapeutic efficacy without significant side effects. The old approach was to initiate treatment with a low dose of a single drug and titrate the dose upward as needed to achieve a better therapeutic effect (22). However, this approach did not necessarily lead to greater efficacy, since most drugs reach an early plateau phase of their dose-response effect and higher doses may lead to a greater incidence and severity of side effects (23), as illustrated in Figure 1. This figure shows that within the linear relationship of the dose-response curve, a 10-fold increase in the dose of the drug will be required to achieve a doubling of the effect (moving from A to B). However, it will also increase the toxic effects of the drug (moving from A₁ to B₁), with the exception of ARBs and ACEIs, which have not shown dose-dependent side effects. Using a low-dose combination therapy, we avoid the toxic effects of the high-dose monotherapy and at the same time achieve a better BP control (6, 8).

The benefits of fixed-dose drug combinations are listed in Table 1. By combining two drugs with complementary mechanisms of action, we use a lower dose of the component drugs, avoid the development of serious clinical and metabolic side effects, and at the same time, achieve a greater BP-lowering effect through synergism. We also en-

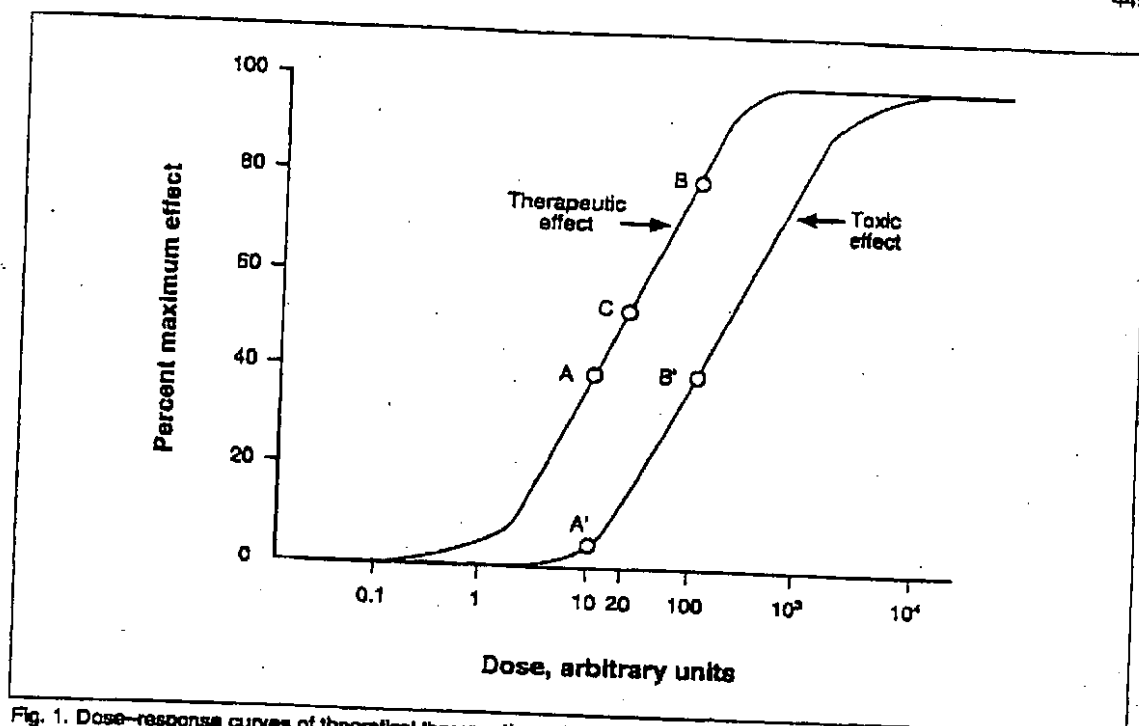


Fig. 1. Dose-response curves of theoretical therapeutic and toxic drug effects. The horizontal axis is a logarithmic scale of arbitrary dose units. The vertical axis is a linear scale showing the possible maximum therapeutic effect of a hypothetical drug and its associated toxic effects. (Reproduced with permission from Fagan, T.C. *Remembering the lessons of basic pharmacology*. Arch Intern Med 1994, 154(13): 1430-1. Copyright 1994, American Medical Association. All rights reserved.)

Table 1: Benefits of fixed-dose combination therapy for hypertension.

- Uses lower doses of component drugs
- Minimizes drug side effects
- Enhances drug efficacy
- Prolongs duration of action
- Enhances effect on cardiovascular remodeling
- Drug dosing flexibility is not lost
- Improves patient satisfaction and compliance
- Lowers the cost of care

hance the efficacy of each drug by interfering with the counterregulatory mechanisms set in motion with the administration of each component drug. In addition, the duration of action of the combined drug preparation may be prolonged due to different half-lives of the component drugs (6), providing greater protection of target organs and enhancing patient compliance. Due to the existence of sever-

al fixed-dose combinations of the component drugs, the dosing flexibility is not lost in the majority of cases (8). In addition, the cost of patient care is decreased through fewer titration visits and lower drug costs, because the cost of the combined drug preparation is frequently equal to the cost of just one of the component drugs (6, 8).

With respect to the combination of dihydropyridine CCBs with ACEIs or ARBs, their complementary action results from arteriolar dilatation, some diuretic action produced by the CCBs and interference with the counteraction of angiotensin II (Ang II), either through interference with its generation (ACEIs) or through its blockade at the receptor site (ARBs). The vasodilatation and diuresis produced by the CCBs stimulate renin release from the kidney, leading to increased generation of Ang II, which in turn causes vasoconstriction and counterbalances the BP-lowering effects of CCBs. The addition of either ACEIs or ARBs interferes with the action of Ang II and adds to the BP-lowering effects of CCBs. An additional benefit of this combi-

nation is the alleviation of pedal edema associated with the CCBs (10, 15). The generation of pedal edema from the CCBs results from their preferential arteriolar vasodilatation, which causes a pressure gradient between the arteriolar and venular capillaries of the circulation, leading to exudation of fluid into the interstitial tissue, which is accentuated by the gravity of the orthostatic posture and is greater during the day. The addition of ACEIs or ARBs causes both arteriolar and venodilatation, which diminishes the pressure gradient, enhances the absorption of interstitial fluid and alleviates the edema (10, 13, 17, 21).

Clinical trials of fixed-dose combination therapies

The antihypertensive effectiveness and safety of various doses of amlodipine besylate (AB) and olmesartan medoxomil (OM) alone and in fixed combination were evaluated in a large multicenter trial in patients with mild to severe hypertension (21). The objectives of this study were to assess the degree of BP-lowering effect and the incidence and magnitude of leg edema with the two drugs alone and in combination. For this study, 4,234 patients were screened in 172 investigational centers and 1,940 patients with sitting diastolic BP (SDBP) of 95–120 mmHg or sitting systolic BP (SSBP) of < 180 mmHg were randomized to 12 treatment groups: amlodipine besylate 5 or 10 mg/day, olmesartan medoxomil (OM) 10, 20 or 40 mg/day, their combination AB/OM 5/10, 5/20, 5/40, 10/10, 10/20 or 10/40 mg/day, or placebo (PL); they were followed for 8 weeks. Of the 1,940 randomized patients, 1,689 completed the study. The number of patients who participated in this study and their response to treatment are shown in Table II. All treatment groups showed a significantly greater reduction in BP compared to placebo ($P < 0.001$) and the BP-lowering effects of combination therapy were greater than the monotherapies ($P < 0.001$). In addition, a greater number of patients treated with the combination therapy reached BP goals (< 140/90 mmHg) than those receiving monotherapy (Fig. 2). All treatment regimens were well tolerated and side effects were not significantly greater than on placebo, with the exception of edema (Table III). Edema occurred in 36.6% of patients on the high dose (10 mg/day) of amlodipine, which was reduced to 23.5% when olmesartan 40 mg/day was added to amlodipine 10 mg/day, for a 36.1% decrease ($P < 0.001$). The relatively higher

incidence of edema with amlodipine monotherapy in this study compared to previous studies (12, 13) was considered to be due to greater alertness of the investigators, as the assessment of edema was one of the objectives of this study, and the greater weight of these patients (body mass index [BMI] = 33.0 kg/m²), making edema more difficult to discern.

Two other similar studies evaluated the antihypertensive effectiveness of monotherapy with valsartan or amlodipine and their combination compared to placebo in 3,161 patients with a mean SDBP of ≥ 95 and < 110 mmHg (20). Although the protocols were slightly different, the results were similar for the two studies (Table II). The results for this combination in these two studies compare well with those for three other marketed fixed combinations of CCBs with ACEIs (10, 13, 17, 19).

In the study by Gradman *et al.* (10), different doses of an extended-release felodipine (felodipine-ER)/enalapril combination were tested in 707 patients with a mean SDBP of 95–115 mmHg, followed for 8 weeks. In this study, all doses of felodipine-ER and enalapril produced significant BP reductions compared to placebo ($P < 0.001$) and the drug combinations were more effective than monotherapy ($P < 0.05$) (Table II).

In the study by Dequattro *et al.* (18), different doses of sustained-release verapamil (verapamil-SR) were combined with different doses oftrandolapril. In this study, 746 patients with stage 1–3 hypertension were randomized to different drug combinations and followed for 8 weeks. All treatment regimens reduced BP more than placebo ($P < 0.01$), except the low-dose combination oftrandolapril/verapamil-SR 0.5/120 mg/day. Combination therapy was better than monotherapy ($P < 0.005$) in reducing the mean SDBP (Table II).

In the studies by Chrysant and Bakris (13) and Chrysant *et al.* (19), different dose combinations of amlodipine were studied in patients with stage 1 and 2 hypertension. In one study (13), 329 patients whose SDBP was ≥ 95 mmHg after 4 weeks of treatment with benazepril 40 mg/day were randomized to continued treatment with benazepril 40 mg/day for 8 additional weeks, or a combination of benazepril/amlodipine 40/5 mg/day for 4 weeks and then forced titrated to benazepril/amlodipine 40/10 mg/day for an additional 4 weeks. In the second study (19), 812 patients whose SDBP was ≥ 95 mmHg after 4 weeks of treatment with amlodipine 10 mg/day were randomized to continued

Table II: Blood pressure decrease from baseline on the various treatment regimens.

Chrysant (21)							
Patient no.: 1940	Age: 54.0 years		Duration: 8 weeks				
Monotherapy							
Treatment	PL	AB	AB	OM	OM	OM	
Dose (mg/day)	0	5	10	10	20	40	
SDBP (mmHg)	-3.1	9.4	12.7	8.3	9.2	10.2	
SSBP (mmHg)	-4.8	14.8	19.7	11.5	13.8	16.1	
Combination therapy							
Treatment	AB/OM	AB/OM	AB/OM	AB/OM	AB/OM	AB/OM	
Dose (mg/day)	5/10	5/20	5/40	10/10	10/20	10/40	
SDBP (mmHg)	-13.8	14.0	15.5	16.0	17.0	19.0	
SSBP (mmHg)	-24.2	23.8	25.4	25.3	29.2	30.1	
Philipp (20)							
Patient no.: 3161	Age: 55.5 years		Duration: 8 weeks				
Monotherapy							
Treatment	PL	AB	AB	VH	VH	VH	VH
Dose (mg/day)	0	5	10	40	80	160	320
SDBP (mmHg)	-6.5	11.5	15.6	10.1	9.7	11.0	13.4
SSBP (mmHg)	-6.2	15.1	24.1	11.8	12.9	15.1	15.7
Combination therapy							
Treatment	AB/VH	AB/VH	AB/VH	AB/VH	AB/VH	AB/VH	
Dose (mg/day)	5/40	5/80	5/160	5/320	10/160	10/320	
SDBP (mmHg)	-14.6	14.5	14.2	15.9	17.6	18.6	
SSBP (mmHg)	-18.6	20.8	19.5	22.7	27.8	28.4	
Gradman (10)							
Patient no.: 707	Age: 54 ± 11 years		Duration: 8 weeks				
Monotherapy							
Treatment	PL	FEL	FEL	FEL	EN	EN	
Dose (mg/day)	0	2.5	5	10	5	20	
SDBP (mmHg)	-4.4	7.3	9.2	11.7	6.0	6.1	
SSBP (mmHg)	-4.0	8.0	10.1	15.0	5.9	10.0	
Combination therapy							
Treatment	FEL/EN	FEL/EN	FEL/EN	FEL/EN	FEL/EN	FEL/EN	
Dose (mg/day)	2.5/5	2.5/20	5/5	5/20	10/5	10/20	
SDBP (mmHg)	-6.9	11.0	10.6	13.0	12.8	15.4	
SSBP (mmHg)	-18.8	20.8	19.5	22.7	27.8	28.4	
DeQuattro (18)							
Patient no.: 726	Age: 55 ± 11 years		Duration: 6 weeks				
Monotherapy							
Treatment	PL	TRA	TRA	TRA	VER	VER	VER
Dose (mg/day)	0	0.5	2.0	8.0	80	120	240
SDBP (mmHg)	-2.0	3.0	6.0	6.0	2.0	4.0	4.0
SSBP (mmHg)	-3.5	3.8	5.8	6.5	3.0	3.5	5.4

Continued

Table II (Cont.): Blood pressure decrease from baseline on the various treatment regimens.

Combination therapy									
Treatment	TRA/VER	TRA/VER	TRA/VER	TRA/VER	TRA/VER	TRA/VER	TRA/VER	TRA/VER	TRA/VER
Dose (mg/day)	0.5/120	0.5/180	0.5/240	2/120	2/180	2/240	8/120	8/180	8/240
*SDBP (mmHg)	-4.0	3.0	4.0	3.0	6.0	7.0	6.0	7.0	8.0
*SSBP (mmHg)	-4.8	5.7	1.9	4.9	8.3	10.2	8.9	8.4	9.5

Chrysant (19)

Patient no.: 812	Age: 51 ± 11 years	Duration: 6 weeks
------------------	--------------------	-------------------

Monotherapy		Combination therapy	
Treatment	AB	AB/BEN	AB/BEN
Dose (mg/day)	10	10/20	10/40
SDBP (mmHg)	-8.5	11.6	12.9
SSBP (mmHg)	-6.6	12.1	13.3

Chrysant (13)

Patient no.: 329	Age: 53 ± 10 years	Duration: 6-8 weeks
------------------	--------------------	---------------------

Monotherapy		Combination therapy	
Treatment	BEN	BEN/AB	BEN/AB
Dose (mg/day)	40	40/5	40/10
SDBP (mmHg)	-7.4	11.0	14.7
SSBP (mmHg)	-5.8	13.3	18.2

Fogari (14)

Patient no.: 80	Age: 59 ± 9.2 years	Duration: 6 weeks
-----------------	---------------------	-------------------

Monotherapy		Combination therapy	
Treatment	AB	VH	AB/VH
Dose (mg/day)	10	160	10/160
SDBP (mmHg)	-12.9	10.2	16.8
SSBP (mmHg)	-15.9	14.5	22.9

*BP changes were subtracted from placebo. PL, placebo; AB, amlodipine besylate; OM, olmesartan medoxomil; VH, valsartan hydrochloride; FEL, felodipine; EN, enalapril; TRA,trandolopril; VER, verapamil.

treatment with amlodipine 10 mg/day for an additional 6 weeks, or a combination of amlodipine/benazepril 10/20 mg/day for 6 weeks, or a combination of amlodipine/benazepril 10/20 mg/day for 2 weeks and then 10/40 mg/day for an additional 4 weeks. The results are shown in Table II. In both studies, monotherapy and combination therapy significantly reduced BP compared to baseline ($P < 0.001$), and combination therapy was more effective than monotherapy ($P < 0.05$). In all of the above studies, the incidence of edema was greater with CCB monotherapy and was reduced with the addition of an ACEI.

In another study, Chrysant *et al.* (17) randomized 93 patients with stage 3-4 essential hyper-

tension to fixed combinations of enalapril/diltiazem-ER 5/120 and 5/180 mg/day and followed them for 12 weeks. Both drug combinations produced similar reductions in SSBP and SDBP of 15.0/14.5 mmHg ($P < 0.001$). This study was extended into a 40-week, open-label extension phase where other drugs were added for better BP control. With the addition of other drugs, the SSBP and SDBP were decreased by 27.0 and 15.0 mmHg, respectively, from baseline ($P < 0.001$).

In a study by Fogari *et al.* (14), 130 patients with stage 1-2 hypertension (SBP/DBP of 161/98 mmHg) were treated with amlodipine 10 mg/day, valsartan 160 mg/day or their combination and were followed for 8 weeks. Amlodipine and valsar-

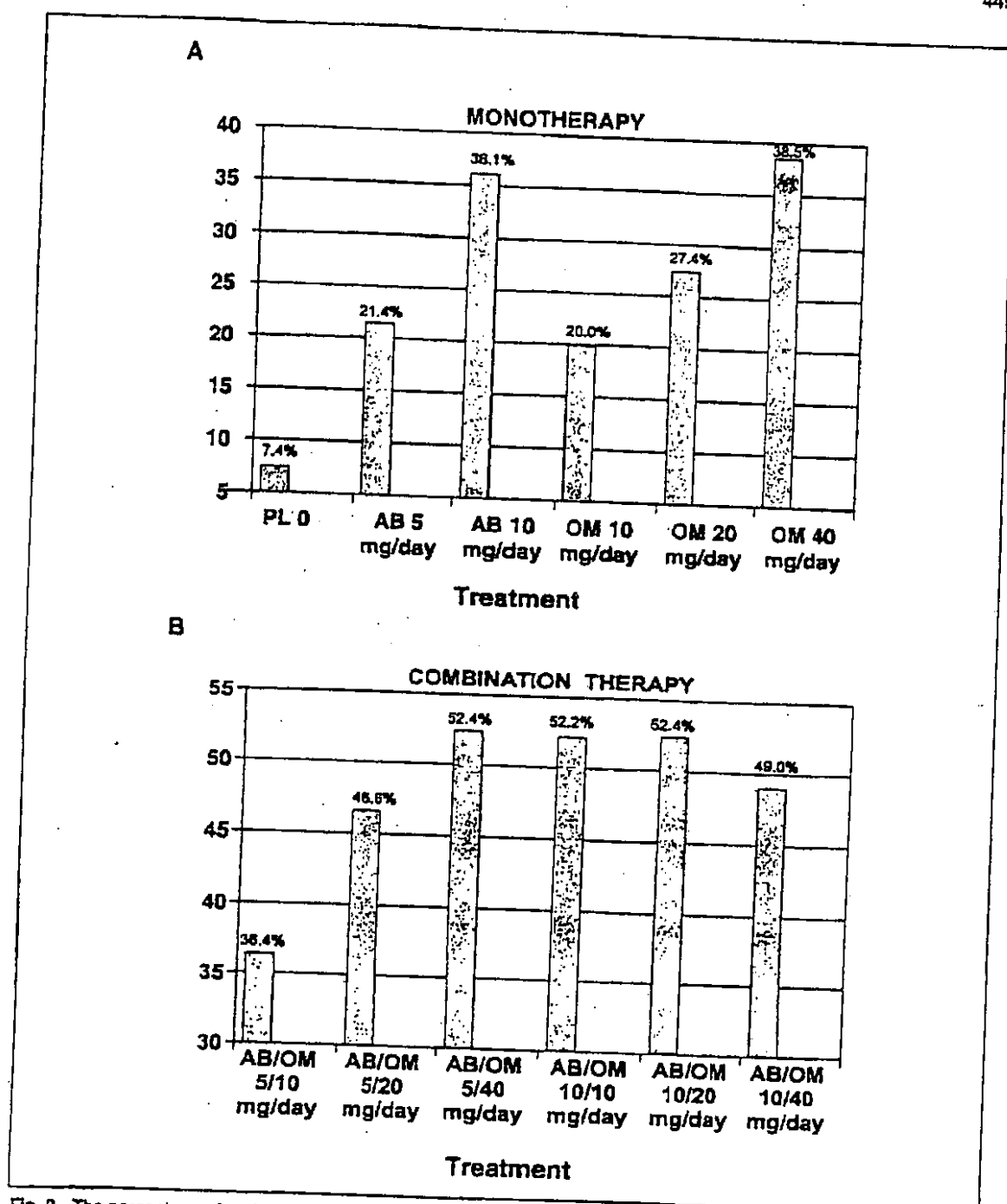


Fig. 2. The percentage of patients achieving BP control (< 140/90 mmHg) with monotherapy (A) or combination therapy (B). PL, placebo; AB, amlodipine besylate; OM, olmesartan medoxomil. Adapted with permission from Table III of Chrysant, S.G., Melino, M., Karki, S., Lee, J., Heyman, R. *The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8 week factorial efficacy and safety study.* Clin Ther 2008, 30(4): 587-604. Copyright 2008, Excerpta Medica Inc.

Table III: Most common treatment-related adverse events ($\geq 3\%$).

	PL	AB	AB	OM	OM	OM	AB/OM	AB/OM	AB/OM	AB/OM	AB/OM	AB/OM
TEAE (%)	0	5	10	10	20	40	5/10	5/20	5/40	10/10	10/20	10/40
Dizziness	5.6	3.1	2.5	3.1	6.2	4.9	1.8	5.2	4.3	3.7	3.1	3.7
Edema	12.6	13.0	36.8	14.3	9.9	18.5	20.9	18.0	18.5	26.5	25.6	23.5
Fatigue	3.7	3.1	1.8	4.3	1.8	1.9	1.8	3.1	4.9	1.2	8.8	1.9
Headache	14.2	8.1	4.9	5.8	8.7	8.6	2.5	5.6	3.7	6.2	6.9	5.8
Hypertension	8.0	2.5	1.2	4.3	5.0	3.7	0.8	1.9	1.2	0.8	0.6	0
Infections	8.0	11.2	11.7	9.3	9.9	6.8	9.8	8.7	10.5	11.1	7.5	7.4
Musculoskeletal	9.3	9.3	9.2	9.9	7.5	9.6	7.4	10.6	8.0	3.7	10.8	9.9
SAE	1.9	0	0.6	0.6	2.5	0.6	0.6	1.2	1.2	1.9	1.9	3.1
D/C	13.0	6.2	6.1	8.1	10.6	6.2	0	2.5	3.7	6.8	1.9	5.6

TEAE, treatment-emergent adverse events; SAE, serious adverse events; D/C, discontinuations; PL, placebo; AB, amlodipine besylate; OM, olmesartan medoxomil.

tan monotherapy reduced SBP/DBP by 14.5/12.9 and 16.9/10.2 mmHg from baseline, respectively ($P < 0.01$). As in the other studies, combination therapy was more effective than monotherapy ($P < 0.001$), reducing SBP/DBP by 22.9/16.8 mmHg from baseline (Table II). In this study, in which leg edema was the main objective, combination therapy resulted in a significant reduction of pedal edema compared to amlodipine monotherapy ($P < 0.001$).

Discussion

The incidence of hypertension continues to rise in the U.S., occurring in 30% of the population according to the latest National Health and Nutrition Examination Survey (1). However, BP control to $< 140/90$ mmHg, as recommended by the JNC-7 (2), remains low at 36.8% (1). The reasons for the low control of BP are multiple, but the most important is the lack of aggressive treatment of hypertension by physicians (24, 25). The JNC-7 has recommended that when SBP/DBP is 20/10 mmHg above target, treatment with a two-drug combination therapy should be begun (26). Such combinations should include drugs with complementary mechanisms of action. This allows for the use of lower doses of the component drugs, resulting in better BP control and avoiding the side effects of the higher doses of a single drug for a similar control of BP (see Fig. 1). Fixed-dose combinations have the additional advantage of lowering the cost of patient care, since the price of the combined drug preparation is the same as one of the component drugs and, in addition, decrease patient

titration visits to the doctor and increase patient compliance (6, 8).

Good BP control is very important, as a large meta-analysis of one million hypertensive patients showed that a 2-mmHg reduction of SBP was associated with a 7% and 10% risk reduction for cardiovascular and stroke deaths, respectively (26). The combination of olmesartan medoxomil with amlodipine besylate was very effective in lowering both systolic and diastolic BP and achieving target BP levels in a pivotal study in 1,940 patients with stage 1 and 2 hypertension (21), as shown in Table II and Figure 2, and was well tolerated. The only side effect of clinical importance was leg edema, which was higher with the higher dose of amlodipine and was significantly decreased with the addition of high-dose olmesartan, as shown in Table III. The incidence of edema in this study was higher than in other studies of treatment with CCBs, alone and in combination with other ARBs or ACEIs (10, 14, 18, 20). The higher incidence of leg edema in this study was most likely due to two factors: the higher incidence of obesity in this study, where the presence of edema is more difficult to discern, and the greater awareness of investigators, since the incidence of edema was one of the objectives of the study. However, the incidence of leg edema was similar to or even lower than that reported by Fogari *et al.* (14), where the incidence of edema was the main objective of the study. It appears that when the incidence of edema with dihydropyridine CCBs is not specifically mandated by the study protocol, its incidence is underestimated.

The major finding of this study was the significant decrease of BP with the addition of olmesartan 40 mg to amlodipine 10 mg/day (21). This decrease was greater than that associated with the addition of equivalent doses of valsartan to the same dose of amlodipine (14, 20), but since no head-to-head comparisons were performed, superiority can not be claimed. However, olmesartan is a potent antihypertensive agent and, in comparison with equivalent doses of losartan, valsartan and irbesartan, provided greater BP reduction than the other ARBs according to both office and ambulatory EP measurements (27).

Besides their potent antihypertensive effects, CCBs and ARBs have shown benefits beyond BP control in the reduction of cardiovascular and stroke risk and the onset of new diabetes (27-37). The beneficial effects of CCBs on stroke reduction are possibly attributed to stimulation of renin release leading to higher Ang II levels (37), and those of the ARBs could be due to their dual effect in the brain, blocking the action of Ang II at the AT₁ receptor level and at the same time allowing Ang II to stimulate the unoccupied AT₂ receptors, causing local vasodilatation and preventing the extension of stroke (32-38). Additional beneficial effects of ARBs on stroke prevention could be generated from their pleiotropic effects, i.e., their ability to prevent platelet adhesion and atrial fibrillation (39).

The data presented in this review strongly indicate that the fixed-dose combination of amlodipine besylate with olmesartan medoxomil is very effective in lowering BP regardless of age, sex or race. It is also safe and well tolerated. Due to its significant antihypertensive effects and metabolic neutrality, this fixed-dose drug combination could be particularly useful for the treatment of high-risk hypertensive patients, such as the elderly, black patients, diabetic patients and those with the metabolic syndrome.

References

- Ong, K.L., Cheung, B.M., Man, Y.B. et al. Prevalence, awareness, treatment and control of hypertension among United States adults 1999-2004. *Hypertension* 2007, 49(1): 69-75.
- Chobanian, A.V., Bakris, G.L., Black, H.R. et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC7 report. *Hypertension* 2003, 42(6): 1206-52.
- Materson, B.J., Reda, D.J., Cushman, W.C. et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med* 1993, 328(13): 914-21.
- Mancia, G., DeBaker, G., Dominiczak, A. et al. 2007 ESH-ESC Practice guidelines for the management of arterial hypertension. *J Hypertens* 2007, 25(9): 1751-82.
- Ram, C.V. Antihypertensive efficacy of the angiotensin receptor blockers in combination with hydrochlorothiazide: A review of the factorial-design studies. *J Clin Hypertens (Greenwich)* 2004, 6(10): 569-77.
- Chrysant, S.G. Fixed low-dose drug combination for the treatment of hypertension. *Arch Fam Med* 1998, 7(4): 370-6.
- Messerli, F.H. Combination therapy in hypertension. *J Hum Hypertens* 1992, 6(Suppl. 2): S19-21.
- Epstein, M., Bakris, G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med* 1996, 156(17): 1869-78.
- Sica, D.A. Fixed-dose combination anti-hypertensive drugs. Do they have a role in rational therapy? *Drugs* 1994, 48(1): 16-24.
- Gradman, A.H., Cutler, N.R., Davis, P.J. et al. Combined enalapril and felodipine extended release (ER) for systemic hypertension. Enalapril - Felodipine ER Factorial Study Group. *Am J Cardiol* 1997, 79(4): 431-5.
- Chrysant, S.G., Cohen, M. Sustained blood pressure control with controlled release isradipine. *Am J Hypertens* 1995, 8(1): 87-9.
- Chrysant, S.G., Marbury, T.C., Robinson, T.D. Antihypertensive efficacy and safety of olmesartan medoxomil compared to amlodipine for mild-to-moderate hypertension. *J Hum Hypertens* 2003, 17(6): 425-32.
- Chrysant, S.G., Bakris, G.L. Amlodipine/benazepril monotherapy. *Am J Hypertens* 2004, 17(7): 590-6.
- Fogari, R., Zappi, A., Derosa, G. et al. Effect of valsartan addition to amlodipine on ankle edema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens* 2007, 21(3): 220-4.
- Messerli, F.H. Vasodilatory edema: A common side effect of antihypertensive therapy. *Am J Hypertens* 2001, 14(9, Pt. 1): 978-9.

16. Ausubel, H., Levine, M.L. Treatment of hypertension with Ser-Ap-Es. *Curr Ther Clin Exp* 1967, 9(1): 29-35.
17. Chrysant, S.G., Gavras, H., Niederman, A.I. et al. Clinical utility of long-term enalapril/diltiazem ER in stage 3-4 essential hypertension. *J Clin Pharmacol* 1997, 37(9): 810-5.
18. Dequattro, V., Lee, D., Messerli, F.H. Fixed-dose combination therapy with trandolapril and verapamil SR in primary hypertension: A 4x4 trial design. *The Trandolapril Study Group. Clin Exp Hypertens* 1999, 19(3): 373-87.
19. Chrysant, S.G., Sugimoto, D.H., Lefkowitz, M. et al. The effects of high-dose amlodipine/benazepril combination therapies on blood pressure reduction in patients not adequately controlled with amlodipine monotherapy. *Blood Press* 2007, 16(Suppl. 1): 10-7.
20. Philipp, T., Smith, T.R., Glazer, R. et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther* 2007, 29(4): 563-80.
21. Chrysant, S.G., Melino, M., Kark, S., Lee, J., Heyman, R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8 week factorial efficacy and safety study. *Clin Ther* 2008, 30(4): 587-604.
22. Moser, M. From JNC1 to JNC7. What have we learned? *Prog Cardiovasc Dis* 2006, 48(5): 303-15.
23. Fagan, T.C. Remembering the lessons of basic pharmacology. *Arch Intern Med* 1994, 154(13): 1430-1.
24. Okonofua, E.C., Simpson, K.N., Jesri, A. et al. Therapeutic inertia is an impediment to achieving the healthy people 2010 blood pressure control goals. *Hypertension* 2006, 47(3): 345-51.
25. Rose, A.J., Berlowitz, D.R., Omer, M.B. et al. Understanding uncontrolled hypertension: Is it the patient or the provider? *J Clin Hypertens* 2007, 9(12): 937-43.
26. Lewington, S., Clarke, R., Qizibash, N., Peto, R., Collins, R.; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data from one million adults in 61 prospective studies. *Lancet* 2002, 360(9349): 1903-13.
27. Oparil, S., Williams, D., Chrysant, S.G. et al. Comparison of efficacy of olmesartan, losartan, valsartan and irbesartan in the control of essential hypertension. *J Clin Hypertens* 2001, 3(5): 283-91.
28. Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002, 288(23): 2981-97.
29. Julius, S., Kjeldsen, S.E., Weber, M.A. et al. Outcomes in hypertensive patients at high risk treated with regimens based on valsartan or amlodipine: The VALUE randomized trial. *Lancet* 2004, 363(9426): 2022-31.
30. Chrysant, S.G., Dimas, B., Shiraz, M. Treatment of hypertension with olmesartan medoxomil, alone and in combination with a diuretic: An update. *J Hum Hypertens* 2007, 21(9): 699-708.
31. Chrysant, S.G., Chrysant, G.S. Clinical experience with angiotensin receptor blockers with particular reference to valsartan. *J Clin Hypertens* 2004, 6(8): 445-51.
32. Dahlöf, B., Devereux, R.B., Kjeldsen, S.E. et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint (LIFE) reduction hypertension study: A randomized trial against atenolol. *Lancet* 2002, 359(9311): 995-1003.
33. Kjeldsen, S.E., Dahlöf, B., Devereux, R.B. et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: A Losartan Intervention For Endpoint (LIFE) sub-study. *JAMA* 2002, 288(12): 1491-8.
34. Lithell, H., Hansson, L., Skoog, I. et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): Principal results of a randomized double-blind intervention trial. *J Hypertens* 2003, 21(5): 875-86.
35. Papademetriou, V., Farsang, C., Elmfeldt, D. et al. Stroke prevention with the angiotensin-II

- type 1 receptor blocker candesartan in elderly patients with isolated systolic hypertension: The Study on Cognition and Prognosis in the Elderly (SCOPE). J Am Coll Cardiol* 2004, 44(6): 1775-80.
36. Schrader, J., Luder, S., Kulschewski, A. et al. *Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: Principal results of a prospective randomized control study (MOSES). Stroke* 2005, 36(6): 1218-26.
37. Chrysant, S.G. *Stroke prevention with losartan in the context of other antihypertensive drugs. Drugs Today (Barc)* 2004, 40(9): 791-801.
38. Chrysant, S.G. *Possible pathophysiologic mechanisms supporting the superior stroke protection of angiotensin receptor blockers compared to angiotensin-converting enzyme inhibitors: Clinical and experimental evidence. J Hum Hypertens* 2005, 19(12): 923-31.
39. Chrysant, S.G., Chrysant, G.S. *The pleiotropic effects of angiotensin receptor blockers. J Clin Hypertens* 2006, 8(4): 261-8.

ANEXO VI

The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure: COACH, a Randomized, Double-Blind, Placebo-Controlled, 8-Week Factorial Efficacy and Safety Study

Steven G. Chrysant, MD, PhD¹; Michael Melino, PhD²; Sulekha Karki, BAMS²; James Lee, PhD²; and Reinilde Heyrman, MD²

¹Oklahoma Cardiovascular Hypertension Center, Oklahoma City, Oklahoma; and ²Daiichi Sankyo, Inc., Parsippany, New Jersey

ABSTRACT

Background: Hypertension guidelines recommend the use of 2 agents having complementary mechanisms of action when >1 agent is needed to achieve blood pressure (BP) goals.

Objective: The aim of this study was to compare the efficacy and tolerability of combinations of olmesartan medoxomil (OM) and amlodipine besylate with those of the component monotherapies in patients with mild to severe hypertension.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, factorial study. Patients who were naive to antihypertensive therapy or who underwent a washout of previous antihypertensive therapy for up to 2 weeks and had a seated diastolic BP (SeDBP) of 95 to 120 mm Hg were randomized to receive 1 of the following for 8 weeks: OM 10, 20, or 40 mg; amlodipine (AML) 5 or 10 mg; each possible combination of OM and AML; or placebo. The primary end point was the change from baseline in SeDBP at week 8, with secondary end points including the change in seated systolic blood pressure (SeSBP), the proportion of patients reaching the BP goal (<140/90 mm Hg; <130/80 mm Hg for patients with diabetes), and the proportions of the intention-to-treat population reaching BP thresholds of <120/80, <130/80, <130/85, and <140/90 mm Hg. Safety and tolerability were also evaluated, with a particular focus on the incidence and severity of edema.

Results: Of the 1940 randomized patients, 54.3% were male. The mean age of the study population was 54.0 years and 19.8% were aged ≥65 years. The mean baseline BP was 164/102 mm Hg, and 79.3% of patients had stage 2 hypertension. Combination therapy with OM and AML was associated with dose-dependent reductions in SeDBP (from -13.8 mm Hg

with OM/AML 10/5 mg to -19.0 mm Hg with OM/AML 40/10 mg) and SeSBP (from -23.6 mm Hg with OM/AML 20/5 mg to -30.1 mm Hg with OM/AML 40/10 mg) that were significantly greater than the reductions with the corresponding component monotherapies ($P < 0.001$). At week 8, the number of patients achieving the BP goal ranged from 57 of 163 (35.0%) to 84 of 158 (53.2%) in the combination-therapy groups, from 32 of 160 (20.0%) to 58 of 160 (36.3%) in the OM monotherapy groups, and from 34 of 161 (21.1%) to 53 of 163 (32.5%) in the AML monotherapy groups ($P < 0.005$, combination therapies vs component monotherapies), compared with 14 of 160 (8.8%) in the placebo group. Achievement of the BP thresholds was highest in the combination-therapy groups, with 56.3% and 54.0% of patients achieving a BP <140/90 mm Hg with OM/AML 20/10 and 40/10 mg, respectively. Combination therapy was generally well tolerated, and no unexpected safety concerns emerged in the course of the study. The most common adverse events were edema (ranging from 9.9% [OM 20 mg] to 36.8% [AML 10 mg], compared with 12.3% with placebo) and headache (ranging from 2.5% [OM/AML 10/5 mg] to 8.7% [OM 20 mg], compared with 14.2% with placebo).

Conclusion: The combination of OM and AML was effective and well tolerated in this adult population with hypertension. (*Clin Ther.* 2008;30:587-604) © 2008 Excerpta Medica Inc.

Accepted for publication February 26, 2008.

Express Track online publication April 7, 2008.

doi:10.1016/j.clinthera.2008.04.002

0149-2918/\$32.00

© 2008 Excerpta Medica Inc. All rights reserved.

Key words: hypertension, olmesartan medoxomil, amlodipine besylate, fixed-dose combination, edema.

INTRODUCTION

According to data from the most recent National Health and Nutrition Examination Survey (2003–2004),¹ the age-adjusted prevalence of hypertension in the US population is 30% and increasing. Although improved from the previous survey (2001–2002), attainment of blood pressure (BP) control (BP <140/90 mm Hg) remains low (36.8%).¹ The increased prevalence of hypertension appeared to be driven by a disproportionate increase in prevalence and poor BP control among women² and Mexican Americans.¹ A meta-analysis of 61 prospective, observational studies enrolling a total of 1 million adults indicated that for every 2-mm Hg decrease in systolic BP (SBP), there was a 7% reduction in the risk of cardiovascular mortality and a 10% reduction in the risk of stroke mortality.³ Moreover, it has been estimated that controlling BP to the levels recommended in current guidelines would prevent 370,000 coronary events in men and 150,000 coronary events in women over 10 years.⁴

One of the main reasons for poor BP control has been the reluctance of physicians to intensify antihypertensive therapy in patients who have not reached their BP goal.⁵ Large trials have found that BP goals can be achieved in most patients with hypertension; however, the majority of patients will require ≥ 2 antihypertensive agents.^{6–10} Both US and European guidelines recommend that physicians consider starting therapy with 2 agents in patients who are at high cardiovascular risk or who have a BP $>20/10$ mm Hg above goal.^{11,12} The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure¹¹ (JNC 7) recommends that drug combinations be used, if indicated, as initial therapy for most patients with stage 2 hypertension (SBP ≥ 160 mm Hg or diastolic BP [DBP] ≥ 100 mm Hg) to accelerate achievement of BP targets, as well as to avoid multiple drug-titration steps and multiple patient visits.

When contemplating combination therapy, the use of antihypertensive agents having different mechanisms of action may augment overall BP-lowering effects.¹¹ Furthermore, the actions of one agent may ameliorate the adverse effects of another. For example, dihydropyridine calcium channel blockers (CCBs) are

potent vasodilators and are intrinsically natriuretic, inducing a state of negative sodium balance¹³ and leading to stimulation of the renin–angiotensin–aldosterone system (RAAS); on the other hand, drugs such as angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors block the RAAS and, when used in combination with a CCB, reinforce the antihypertensive effects of the CCB.¹⁴ Peripheral edema, one of the adverse events most commonly associated with dihydropyridine CCBs, is likely to result from preferential arteriolar vasodilatation and an increase in the pressure gradient between the arteriolar and venular capillaries, leading to exudation of interstitial fluid.^{15,16} This effect may be ameliorated by concomitant administration of ARBs or ACE inhibitors, which lower precapillary resistance, normalize intracapillary pressure, and reduce fluid exudation.^{15–18}

Among newer antihypertensive combinations to become available are fixed-dose combinations of an ARB and a dihydropyridine CCB. The combination of olmesartan medoxomil (OM) and amlodipine is indicated for use when initial treatments are ineffective in achieving the BP goal. Combination therapies are often evaluated in studies having a factorial design, in which each dose of monotherapy is compared with each possible combination of these doses. This allows comparison of the efficacy of the combination with that of the individual monotherapy components, with the monotherapies compared with placebo for internal validity.¹⁹

The Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) study was an 8-week factorial study with the objective of assessing the antihypertensive efficacy of the combination of OM and amlodipine (AML) at various doses compared with the respective monotherapy components in patients with mild to severe hypertension. Another objective was to evaluate the safety profile of the combinations relative to monotherapy, with a particular focus on the incidence and severity of edema.

PATIENTS AND METHODS

Study Population

Study participants were recruited from patients presenting to the research sites (primary care practices, specialist practices, hospitals, or research centers). Patients were eligible for randomization if they were aged ≥ 18 years, had a mean seated DBP (SeDBP) of

95 to 120 mm Hg at both the visit before randomization and the randomization visit, and had a difference of ≤ 10 mm Hg between the 2 mean SeDBP measurements. Patients with a history of cardiovascular disease or uncontrolled diabetes or who smoked >1 pack of cigarettes per day were excluded. Patients also were excluded if they had an SeDBP >120 mm Hg, had laboratory values or systemic disease considered clinically significant by the investigator, or were taking any medication that could interfere with the objectives of the study.

Study Design

This was an 8-week, randomized, double-blind, factorial study conducted at 172 clinical sites in the United States. The study was conducted in accordance with institutional review board (IRB) regulations, the Declaration of Helsinki, and good clinical practice guidelines. All patients provided written informed consent at screening. All medications were provided to patients free of charge; patients were compensated for travel expenses and time, as approved by the IRB, but received no other compensation.

After the screening visit, eligible patients who had not been taking antihypertensive medications for at least 2 weeks before screening were immediately randomized to receive 1 of the following for 8 weeks: OM monotherapy (10, 20, or 40 mg), AML monotherapy (5 or 10 mg), combination therapy (including all possible combinations of the monotherapy doses of OM and AML), or placebo. Patients who were taking antihypertensive medications at the screening visit entered a washout phase of up to 2 weeks, during which all antihypertensive medications were withdrawn. If patients met the criteria for inclusion after withdrawal of antihypertensive medications, they were randomized to 1 of the 12 groups. Randomization was accomplished by assigning each patient a unique 4-digit number via an interactive voice-response system.

Patients were given 2 weeks' worth of medication at each visit and were instructed to take their medication at the same time each day (± 2 hours), except on the day of a visit. Clinic visits were scheduled for 2, 4, 6, and 8 weeks after randomization. Patients who did not return for a scheduled clinic visit received telephone and mail follow-ups, including certified letters. The case-report forms of all patients who were lost to follow-up were reviewed to ensure that the withdrawal was not the result of an adverse event.

Patients with an SeDBP >120 mm Hg or a seated systolic BP (SeSBP) <90 mm Hg at any time during the study (including the washout phase) were removed at that time, and their original antihypertensive regimen was reinstituted or appropriate therapy initiated. The maximum allowable SeSBP was left to the discretion of the investigator. Efficacy and safety were evaluated after 2, 4, 6, and 8 weeks of blinded treatment.

A physical examination was performed at screening, and vital signs, including BP and heart rate, were obtained at all scheduled visits. A 12-lead electrocardiogram was performed at screening, randomization, and week 8, and was analyzed by eResearch Technology (Philadelphia, Pennsylvania). BP was measured using a validated automated BP-monitoring device (Model HEM-705CP, Omron Healthcare, Inc., Bannockburn, Illinois) with a cuff of an appropriate size. After the patient had rested for 5 minutes, 3 separate seated BP (SeBP) measurements were obtained at least 1 minute apart, and the mean of the 3 measurements was recorded.

Standardization across investigator sites was maintained through establishment of a detailed clinical protocol and through monitoring for adherence to the protocol by Medpace Inc., Cincinnati, Ohio.

Efficacy Variables

The primary efficacy variable was the change from baseline in mean SeDBP at week 8, using last-observation-carried-forward (LOCF) methodology for patients who did not complete the study protocol. Secondary efficacy variables included the change from baseline in mean SeSBP at week 8 (LOCF); the mean change from baseline in SeDBP and SeSBP at weeks 2, 4, 6, and 8 without LOCF; and the proportion of patients achieving the JNC 7-recommended BP goal ($<140/90$ mm Hg; $<130/80$ mm Hg for patients with diabetes¹¹) at weeks 2, 4, 6, and 8 without LOCF and at week 8 with LOCF. In addition, the proportions of patients in the intention-to-treat (ITT) population (including those with diabetes) achieving BP thresholds of $<120/80$, $<130/80$, $<130/85$, and $<140/90$ mm Hg at week 8 (LOCF) was examined.

Safety Assessments and Evaluation of Edema

Safety was monitored by assessing the incidence of adverse events at each visit and by performing laboratory tests (standard serum chemistry and hematology panel, and dipstick urinalysis [with microscopy when

results were abnormal)) at the randomization visit and at week 8. Laboratory tests were conducted at a single certified central laboratory (Pharmaceutical Product Development Global Central Laboratory, Highland Heights, Kentucky), which used flow cytometry for hematology variables (Coulter SKTS or LH 750, Beckman Coulter Inc., Fullerton, California), spectrophotometry for chemistry variables (Hitachi 747 [Hitachi High Technologies America Inc., San Jose, California] or Roche Modular Analyzer [Roche Diagnostics Corp., Indianapolis, Indiana]), high-performance liquid chromatography for glycosylated hemoglobin (Tosoh 2.2 Plus, Tosoh Bioscience Inc., South San Francisco, California), and reflectance photometry for urinalysis (Atlas Urine Chemistry Analyzer, Siemens Healthcare Diagnostics Inc., Tarrytown, New York). Tests performed on different analyzers were extensively cross-validated for comparability. Investigators received the results and evaluated the clinical significance of findings that were outside the laboratory's reference ranges while still blinded to patients' treatment allocation.

An *adverse event* was defined as any untoward occurrence in study subjects from the time they signed the informed-consent form until 14 days after the last intake of study medication. All adverse events, whether detected by the investigator or reported by the patient, were recorded on the case-report form, with the date of occurrence, time of onset, duration, likely relationship to study medication, action taken, patient outcome, and whether the event met US Food and Drug Administration criteria for a serious adverse event. A *treatment-emergent adverse event* (TEAE) was defined as any event occurring after the first dose of randomized treatment or that occurred before the randomized-treatment phase but worsened after randomization. The likelihood of an adverse event being related to study medication was assessed by investigators as either *definitely related* (TEAE follows a reasonable temporal sequence from study-product administration, abates on discontinuation of the study product, and is confirmed by reappearance of the reaction on repeat exposure [rechallenge]); *probably related* (TEAE follows a reasonable temporal sequence from study-product administration, abates on discontinuation of the study product, and cannot reasonably be explained by the known characteristics of the patient's clinical state); *possibly related* (TEAE follows a reasonable temporal sequence from study-product ad-

ministration and could have been produced by the patient's state or by other types of therapy administered to the patient); *unlikely to be related* (the temporal relationship between the TEAE and study-product administration is such that the drug is not likely to have had any reasonable association with the observed event and could have been produced by the patient's clinical condition or by other types of therapy administered to the patient); or *unrelated* (TEAE is definitely produced by the patient's clinical condition or by other types of therapy administered to the patient and does not follow a temporal sequence from study-product administration).

If the investigator found that the assigned study medication was not efficacious (ie, BP was not controlled or worsened during the randomized-treatment phase), she or he was required to report this as an adverse event. The terms used for this reporting could include *hypertension*, *systolic hypertension*, *diastolic hypertension*, *accelerated hypertension*, *blood pressure increased*, *diastolic blood pressure increased*, and *blood pressure inadequately controlled*. As noted earlier, patients with an SeDBP >120 mm Hg were removed from the trial.

The occurrence and severity of peripheral edema were assessed at all scheduled clinic visits. If peripheral edema (including the terms *edema*, *edema*, *peripheral*, *pitting edema*, *generalized edema*, and *localized edema*) was present, the investigators rated its severity on a case-report form using the following 5-point scale: 0 = no edema; 1 = mild pitting edema/slight indentation; 2 = moderate pitting edema/moderate indentation; 3 = deep pitting edema/indentation remains; and 4 = leg remains swollen. When an increase in edema category occurred after randomization, investigators were encouraged to report this as an adverse event. The methods used to evaluate peripheral edema were not validated but were consistent with those used in clinical practice.

Statistical Analysis

It was estimated that 158 patients per treatment group would be needed (total population, 1894) to detect a 3-mm Hg difference in DBP between monotherapy and combination therapy with 80% power at a 1-sided level of $P < 0.01$, assuming a common SD of 7.5 mm Hg. To achieve even distribution among treatment groups, the randomization process included stratification factors for age group (≥ 65 years,

<65 years) and diabetic status. Approximately 20% of randomized patients were to be aged ≥ 65 years.

ITT analysis was used for the efficacy evaluations and included all patients who took ≥ 1 dose of randomized, double-blind study medication, had a baseline BP measurement, and had ≥ 1 BP measurement after taking randomized, double-blind study medication. The population for the safety assessments consisted of all patients who took ≥ 1 dose of randomized, double-blind study medication, including both active treatment and placebo.

Baseline characteristics that were continuous variables were summarized using mean (SD), and categorical variables were summarized using frequency counts and percentages. Differences between treatment groups in baseline demographic characteristics were evaluated using an analysis-of-variance model for continuous variables and a χ^2 test for categorical variables.

Hommel's procedure²⁰ was used to adjust *P* values for testing the null hypotheses that there would be no difference between the 6 combination-therapy regimens and their respective monotherapy components in the change from baseline in SeDBP at week 8, LOCF (primary), and the change from baseline in SeSBP at week 8, LOCF (secondary), and to control the overall 1-sided type I error rate at 0.025. One-sided *P* values for testing the null hypotheses were obtained from an analysis-of-covariance (ANCOVA) model with fixed effects for treatment group, diabetic status (with or without diabetes), and age group (≥ 65 years or <65 years), and baseline BP as a covariate. The least squares mean (LSM) and corresponding SE and 2-sided 95% CI, as well as the differences in LSM, SE, and 2-sided 95% CI, were derived for continuous end-point variables from the ANCOVA model. The ANCOVA model was also used to compare each monotherapy with placebo. For categorical variables (eg, the proportion of patients achieving the BP goal at weeks 2, 4, 6, and 8), a χ^2 test was used to test for significant differences between treatment groups. Other categorical variables (proportion of patients achieving BP thresholds) were summarized using frequency counts and percentages (statistical comparisons were not performed).

The study was not powered to detect differences in the incidence of adverse events between treatment groups. However, when an apparent difference was identified in the incidence of edema between the amlodipine 10-mg monotherapy and combination-

therapy groups, the incidences were compared retrospectively using the Fisher exact test. In addition, a post hoc Cochran-Armitage trend analysis²¹ was undertaken to evaluate whether the differential edema rates were dose related.

RESULTS

Study Population

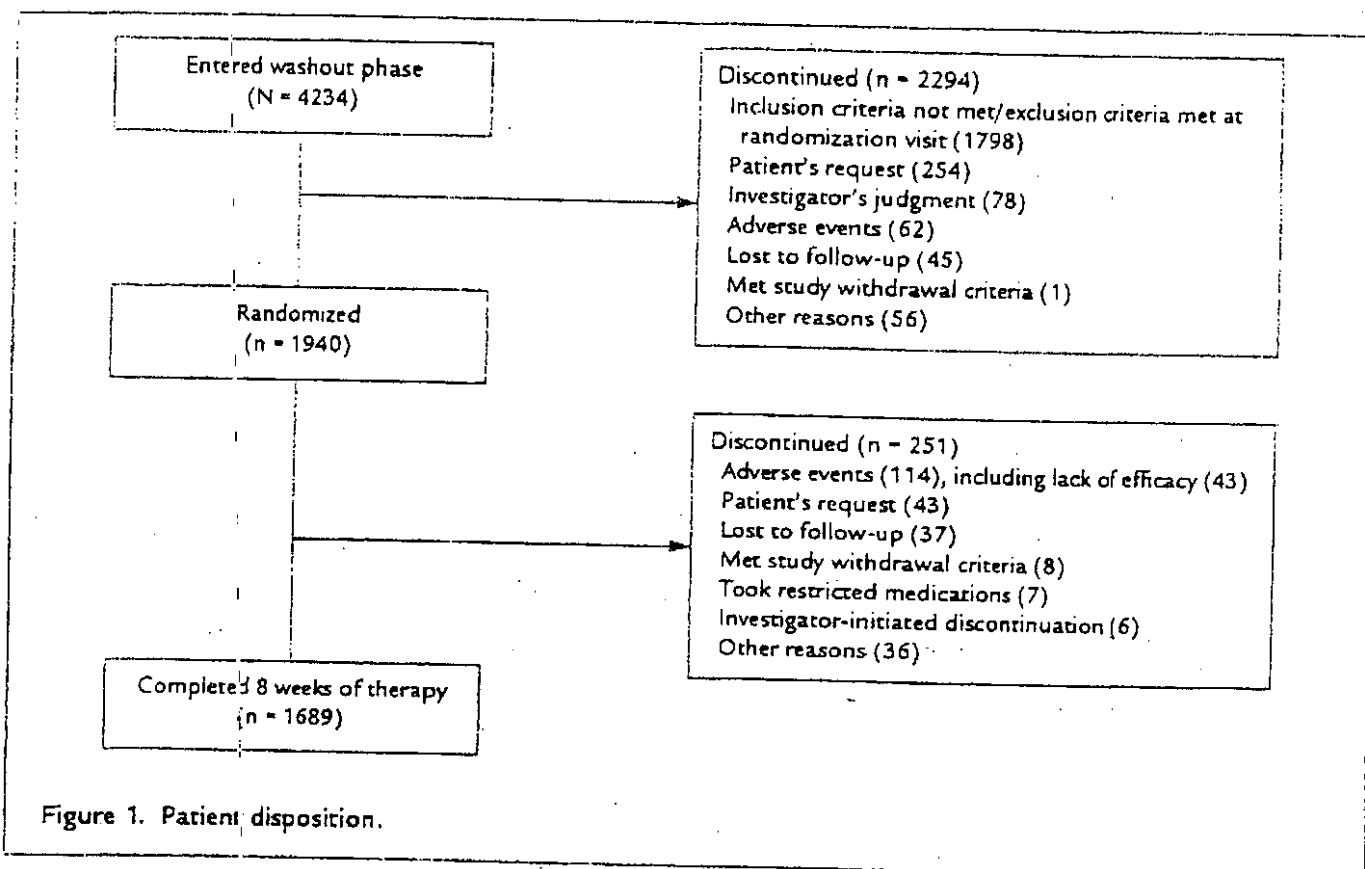
Of 4234 patients who entered the washout phase, 1940 were randomized and 1689 completed the study (Figure 1). The most common reasons for withdrawal during the randomized-treatment phase were adverse events (114 patients), including lack of efficacy (43 patients). The mean number of patients enrolled at each site was 13.

Among the 1940 randomized patients, 1054 (54.3%) were male, 1385 (71.4%) were white, and 481 (24.8%) were black. The mean age of randomized patients was 54.0 years, and the mean baseline SeBP was 164/102 mm Hg. At baseline, 1538 patients (79.3%) had stage 2 hypertension (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg). Three hundred eighty-four patients (19.8%) were aged ≥ 65 years, 261 (13.5%) had diabetes, 1254 (64.6%) were overweight or obese (body mass index ≥ 30 kg/m²), and 1274 (65.7%) had been receiving antihypertensive therapy. There were no statistically significant differences in demographic or other baseline characteristics between treatment groups (Table I).

At baseline, 264 of the 1940 randomized patients (13.6%) had peripheral edema. Edema was graded as mild in 215 patients (11.1%), moderate in 38 (2.0%), and deep pitting edema with minor leg swelling in 11 (0.6%). No patient had deep pitting edema with major leg swelling at baseline.

Efficacy

All active treatments and placebo were associated with significant reductions in SeDBP from baseline ($P < 0.001$), with the greatest reductions occurring in the groups that received combination therapy (Figure 2). Combination therapy was associated with dose-related changes in mean (SD) SeDBP at week 8 that ranged from -13.8 (7.48) mm Hg with OM/AML 10/5 mg to -19.0 (8.90) mm Hg with OM/AML 40/10 mg. For monotherapy, the changes in SeDBP were -8.3 (9.28), -9.2 (9.73), and -10.2 (10.69) mm Hg with OM 10, 20, and 40 mg, respectively; -9.4 (8.25) and -12.7 (8.25) mm Hg with AML 5 and 10 mg, respectively;



and -3.1 (10.67) mm Hg for placebo (Table II). All SeDBP reductions in the combination-therapy groups were significantly greater than those in the corresponding monotherapy groups ($P < 0.001$) (Table II).

The changes in mean SeSBP at week 8 followed a similar pattern to the changes in mean SeDBP, with significant reductions from baseline in all active-treatment groups ($P < 0.001$) and the placebo group ($P = 0.024$). The combinations were associated with dose-dependent mean (SD) changes ranging from -24.2 (13.96) mm Hg with OM/AML 10/5 mg to -30.1 (15.91) mm Hg with OM/AML 40/10 mg (Table II). For monotherapy, the mean changes in SeSBP were -11.5 (15.23), -13.8 (15.90), and -16.1 (16.58) mm Hg with OM 10, 20, and 40 mg, respectively; -14.9 (14.95) and -19.7 (16.52) mm Hg with AML 5 mg and 10 mg, respectively; and -4.8 (18.70) mm Hg with placebo. The mean reductions in SeSBP were significantly greater for all combination-therapy groups than for the component monotherapy groups ($P < 0.001$). The LSM (SE) changes in SeSBP are summarized in Table II. In all active-treatment groups, the greatest mean reduction in SeBP occurred between

baseline and week 2. The reductions in SeDBP and SeSBP plateaued by week 4 and were maintained across all treatment groups, but with no further marked reductions.

The BP goal ($<140/90$ mm Hg; $<130/80$ mm Hg for patients with diabetes) was achieved by week 8 (LOCF) in 20.0% to 36.3% of patients receiving OM monotherapy (10 and 40 mg, respectively) and 21.1% to 32.5% of patients receiving AML monotherapy (5 and 10 mg, respectively), compared with 8.8% of patients in the placebo group (Table III). Rates of goal achievement at week 8 (LOCF) were greatest in the combination-therapy arms, ranging from 35.0% with OM/AML 10/5 mg to 53.2% with OM/AML 20/10 mg. Differences in rates of achievement of the BP goal between treatment groups were statistically significant at all time points ($P < 0.001$) and were consistently higher with combination therapy than with the component monotherapies ($P < 0.005$) (Table III).

The proportions of patients achieving the predefined BP thresholds at week 8 (LOCF) reflected a similar pattern; overall, the proportion of patients achieving each threshold was highest in the groups

Table 1. Demographic and other baseline characteristics. There were no significant differences between groups.

Variable	Olmesartan			Amlodipine		Olmesartan/Amlodipine						Placebo
	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	
Age, mean (SD), y	53.8 (11.0)	53.6 (10.8)	53.9 (10.6)	53.4 (11.4)	54.1 (10.6)	53.7 (11.8)	54.3 (10.9)	53.7 (11.3)	54.3 (10.5)	54.3 (11.6)	54.1 (12.2)	54.7 (10.9)
Sex, no. (%)												
Male	87 (54.0)	90 (55.9)	82 (50.6)	87 (54.0)	98 (60.1)	84 (51.5)	83 (51.6)	97 (59.9)	94 (58.0)	71 (44.4)	88 (54.3)	93 (57.4)
Female	74 (46.0)	71 (44.1)	80 (49.4)	74 (46.0)	65 (39.9)	79 (48.5)	78 (48.4)	65 (40.1)	68 (42.0)	89 (55.6)	74 (45.7)	69 (42.6)
Race,* no. (%)												
White	119 (73.9)	118 (73.3)	111 (68.5)	113 (70.2)	120 (73.6)	121 (74.2)	111 (68.9)	115 (71.0)	113 (69.8)	107 (66.9)	123 (75.9)	114 (70.4)
Black	32 (19.9)	36 (22.4)	44 (27.2)	42 (26.1)	39 (23.9)	34 (20.9)	43 (26.7)	40 (24.7)	44 (27.2)	47 (29.4)	35 (21.6)	45 (27.8)
Other†	10 (6.2)	8 (5.0)	7 (4.3)	7 (4.3)	5 (3.1)	10 (6.1)	9 (5.6)	7 (4.3)	6 (3.7)	6 (3.8)	6 (3.7)	3 (1.9)
Ethnicity, no. %												
Hispanic	23 (14.3)	23 (14.3)	23 (14.2)	20 (12.4)	20 (12.3)	21 (12.9)	21 (13.0)	20 (12.3)	16 (9.9)	25 (15.6)	20 (12.3)	13 (8.0)
Weight, kg												
Mean (SD)	95.5 (22.3)	95.4 (22.0)	94.3 (21.9)	95.8 (21.5)	96.2 (21.5)	94.3 (21.0)	95.6 (21.1)	93.4 (20.1)	95.9 (22.8)	94.1 (22.4)	94.6 (24.1)	96.3 (22.6)
Range	52-173	45-175	43-188	45-172	48-172	45-151	51-171	54-174	55-185	57-147	46-172	52-181
Body mass index, mean (SD), kg/m ²	33.5 (6.8)	32.9 (6.8)	33.6 (6.9)	34.1 (7.8)	33.3 (7.4)	33.3 (6.5)	34.0 (7.2)	32.5 (6.4)	33.2 (7.0)	33.9 (7.2)	33.2 (7.3)	33.9 (7.6)
Diabetes, no. (%)	20 (12.4)	22 (13.7)	22 (13.6)	22 (13.7)	23 (14.1)	23 (14.1)	22 (13.7)	18 (11.1)	20 (12.3)	22 (13.8)	24 (14.8)	23 (14.2)

(continued)

Table I. (Continued)

Variable	Olmesartan			Amlodipine		Olmesartan/Amlodipine						Placebo
	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	
Previously treated for hypertension, no. (%)	101 (62.7)	108 (67.1)	109 (67.3)	106 (65.8)	102 (62.6)	115 (70.6)	102 (63.4)	100 (61.7)	108 (66.7)	104 (65.0)	109 (67.3)	110 (67.9)
Seated blood pressure, mean (SD), mm Hg												
SeSBP	162.9 (16.7)	164.1 (16.5)	162.8 (15.7)	162.6 (17.2)	163.5 (15.9)	165.5 (15.6)	163.8 (14.9)	161.7 (14.8)	162.5 (15.6)	164.1 (14.9)	165.7 (16.7)	166.5 (17.6)
SeDBP	101.8 (5.9)	101.5 (4.6)	101.2 (5.1)	101.5 (5.2)	101.6 (4.8)	102.1 (5.4)	101.7 (5.1)	100.9 (4.8)	101.4 (5.5)	101.2 (4.7)	102.4 (5.8)	102.3 (4.8)
Edema present, no. (%)	19 (11.8)	20 (12.4)	32 (19.8)	18 (11.2)	22 (13.5)	20 (12.3)	29 (18.0)	17 (10.5)	24 (14.8)	18 (11.3)	25 (15.4)	20 (12.3)

SeSBP = seated systolic blood pressure; SeDBP = seated diastolic blood pressure.

* Race and ethnicity were separate questions. Patients could choose >1 race, so total of numbers may exceed 100%.

† Other included Asian (n = 36), Native American/Alaskan (n = 11), Native Hawaiian/Pacific Islander (n = 1), and other race not defined (n = 36).

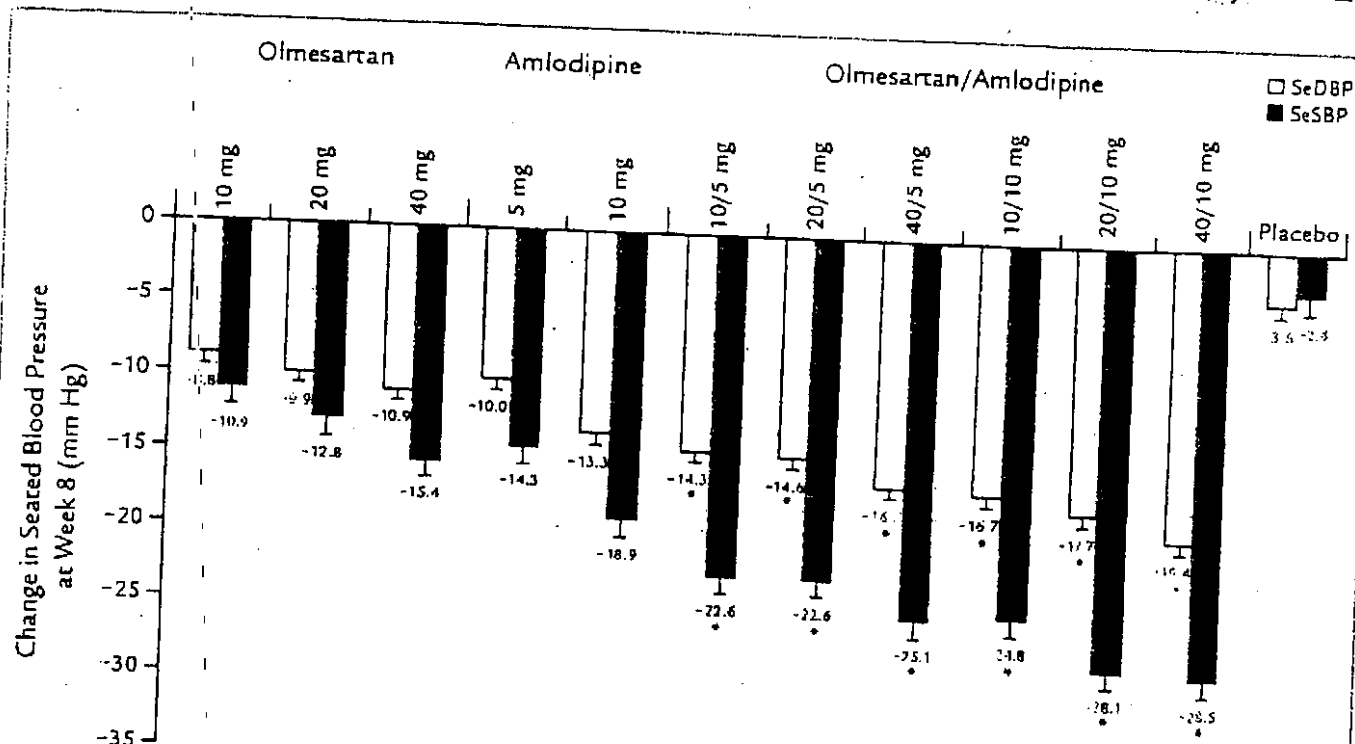


Figure 2. Least squares mean (SE) reduction from baseline in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) after 8 weeks of treatment with olmesartan medoxomil or amlodipine, alone and in combination (last observation carried forward). * $P < 0.001$ versus monotherapy with either component at the same dosage.

receiving OM/AML 20/10 mg or 40/10 mg (Figure 3). The proportions of all patients (including those with diabetes) achieving the BP threshold of $<140/90$ mm Hg with the highest doses of monotherapy and combination therapy were 38.1% for OM 40 mg, 35.0% for AML 10 mg, and 54.0% for OM/AML 40/10 mg, compared with 10.0% for placebo. Similarly, the proportions of patients achieving the BP threshold of $<130/80$ mm Hg were 13.8% for OM 40 mg, 7.4% for AML 10 mg, 23.0% for OM/AML 40/10 mg, and 2.5% for placebo. In addition, 77.6% of patients receiving OM/AML 40/10 mg achieved an SeDBP <90 mm Hg, compared with 18.1% of those receiving placebo.

Safety and Tolerability

One thousand twenty patients (52.6%) experienced an adverse event during treatment, with an overall incidence of 45.3% to 58.9% across active-treatment groups and 56.2% for placebo (Table IV). Approximately half of these adverse events were considered by the investigator to be definitely, probably, or possibly

related to study medication. Five hundred twenty-one patients (26.9%) experienced a drug-related TEAE, with an incidence of 19.6% to 33.1% across active-treatment groups and 29.6% for placebo. There were no apparent differences in the overall incidence of TEAEs across treatment groups, and the majority of adverse events were considered mild in severity.

Edema was the most common TEAE, occurring in 385 of 1940 patients (19.8%) (Table IV). The frequency of edema was greatest among patients receiving AML 10-mg monotherapy (60/163 [36.8%]). The frequency of edema was lower in the groups in which AML 10 mg was combined with OM 10 mg (43/162 [26.5%]), 20 mg (41/160 [25.6%]), or 40 mg (38/162 [23.5%]), reaching statistical significance relative to AML 10 mg in the groups that received OM/AML 20/10 mg ($P = 0.032$) and 40/10 mg ($P = 0.011$). The frequency of edema was lowest in the OM monotherapy groups (10 mg: 23/161 [14.3%]; 20 mg: 16/161 [9.9%]; 40 mg: 30/162 [18.5%]), the AML 5-mg monotherapy group (21/161 [13.0%]), and the pla-

Table II. Change in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) from baseline to week 8 in the intention-to-treat population (last observation carried forward).

Group	No. of Patients	Change in SeDBP, mm Hg		Change in SeSBP, mm Hg	
		Mean (SD)	LS Mean (SE)	Mean (SD)	LS Mean (SE)
Olmesartan					
10 mg	160	-8.3 (9.28)*	-8.8 (0.75)*	-11.5 (15.23)*	-10.9 (1.24)*
20 mg	159	-9.2 (9.73)*	-9.9 (0.75)*	-13.8 (15.90)*	-12.8 (1.25)*
40 mg	160	-10.2 (10.69)*	-10.9 (0.75)*	-16.1 (16.58)*	-15.4 (1.24)*
Amlodipine					
5 mg	161	-9.4 (8.25)*	-10.0 (0.75)*	-14.9 (14.95)*	-14.3 (1.24)*
10 mg	163	-12.7 (8.25)*	-13.3 (0.74)*	-19.7 (16.52)*	-18.9 (1.23)*
Olmesartan/amlodipine					
10/5 mg	163	-13.8 (7.48)*	-14.3 (0.74)*	-24.2 (13.96)*	-22.6 (1.23)*
20/5 mg	160	-14.0 (9.07)*	-14.6 (0.75)*	-23.6 (14.86)*	-22.6 (1.24)*
40/5 mg	157	-15.5 (8.15)*	-16.3 (0.76)*	-25.4 (14.70)*	-25.1 (1.26)*
10/10 mg	161	-16.0 (8.62)*	-16.7 (0.75)*	-25.3 (14.88)*	-24.8 (1.24)*
20/10 mg	158	-17.0 (8.04)*	-17.7 (0.75)*	-29.2 (16.72)*	-28.1 (1.25)*
40/10 mg	161	-19.0 (8.90)*	-19.4 (0.74)*	-30.1 (15.91)*	-28.5 (1.24)*
Placebo	160	-3.1 (10.67)*	-3.5 (0.75)*	-4.8 (18.70)†	-2.8 (1.25)†

LS = least squares.

* $P < 0.001$.

† $P < 0.05$.

cebo group (20/162 [12.3%]). Rates of edema in the groups receiving OM 10 to 40 mg in combination with AML 5 mg ranged from 18.0% to 20.9% (OM/AML 10/5 mg: 34/163 [20.9%]; OM/AML 20/5 mg: 29/161 [18.0%]; OM/AML 40/5 mg: 30/162 [18.5%]). A retrospective Cochran-Armitage trend analysis of the AML 10-mg, OM/AML 10/10-mg, OM/AML 20/10-mg, and OM/AML 40/10-mg groups indicated a statistically significant reduction in the incidence of edema with increasingly higher doses of OM combined with AML 10 mg ($P = 0.003$). Most occurrences of edema in all treatment groups were mild to moderate in severity. Severe edema occurred in 5 of 1940 (0.3%) patients: 1 of 161 patients (0.6%) in the AML 5-mg group, 2 of 163 patients (1.2%) in the AML 10-mg group, 1 of 162 patients (0.6%) in the OM/AML 10/10-mg group, and 1 of 162 patients (0.6%) in the OM/AML 40/10-mg group.

Other common adverse events included headache (130/1940 [6.7%]), dizziness (76/1940 [3.9%]), and

fatigue (62/1940 [3.2%]), with no consistent differences between active-treatment groups (Table IV). The incidence of headache was highest in the placebo group (23/162 [14.2%]).

Lack of efficacy, as previously defined, was reported as an adverse event in 48 patients (2.5%): 7 of 161 (4.3%) in the OM 10-mg monotherapy group, 8 of 161 (5.0%) in the OM 20-mg monotherapy group, 6 of 162 (3.7%) in the OM 40-mg monotherapy group, 4 of 161 (2.5%) in the AML 5-mg monotherapy group, 2 of 163 (1.2%) in the AML 10-mg monotherapy group, 1 of 163 (0.6%) in the OM/AML 10/5-mg group, 3 of 161 (1.9%) in the OM/AML 20/5-mg group, 2 of 162 (1.2%) in the OM/AML 40/5-mg group, 1 of 162 (0.6%) in the OM/AML 10/10-mg group, 1 of 160 (0.6%) in the OM/AML 20/10-mg group, and 13 of 162 (8.0%) in the placebo group. None of the patients receiving OM/AML 40/10 mg had uncontrolled BP during treatment.

Nine of 1940 patients (0.5%) experienced hypotension: 1 patient (0.6%) each in the OM 10-mg ($n =$

Table III. Patients achieving the blood pressure goal (<140/90 mm Hg for patients with uncomplicated hypertension; <130/80 mm Hg for patients with diabetes) after 8 weeks of treatment with olmesartan or amlodipine, alone and in combination (last observation carried forward).

Treatment Group	No. (%)
Olmesartan	
10 mg (n = 160)	32 (20.0)
20 mg (n = 159)	42 (26.4)
40 mg (n = 160)	58 (36.3)
Amlodipine	
5 mg (n = 161)	34 (21.1)
10 mg (n = 163)	53 (32.5)
Olmesartan/amlodipine	
10/5 mg (n = 163)	57 (35.0)*†
20/5 mg (n = 160)	68 (42.5)*‡
40/5 mg (n = 157)	80 (51.0)§
10/10 mg (n = 161)	79 (49.1)*†
20/10 mg (n = 158)	84 (53.2)*‡
40/10 mg (n = 161)	79 (49.1)§
Placebo (n = 160)	14 (8.8)

*P < 0.001 versus monotherapy with olmesartan at the same dosage.
†P = 0.003 versus monotherapy with amlodipine at the same dosage.
‡P < 0.001 versus monotherapy with amlodipine at the same dosage.
§P < 0.005 versus monotherapy with olmesartan at the same dosage.

161), AML 10-mg (n = 163), and OM/AML 40/5-mg groups (n = 162), and 2 patients (1.2%–1.3%) each in the OM/AML 10/10-mg (n = 162), 20/10-mg (n = 160), and 40/10-mg groups (n = 162). Of the 7 patients with drug-related hypotension, 1 each in the OM/AML 10/10-mg and 40/10-mg groups were removed from the study because of moderate or severe hypotension.

Serious TEAEs occurred in 25 of 1940 patients (1.3%). Only 1 of these was considered drug related (Table IV): a patient receiving OM 20 mg had a non-fatal cerebrovascular accident (CVA) that the investigator considered probably related to study medication, as the patient's BP was not fully controlled.

Two patients died during the study: 1 had a fatal CVA during the washout phase and the other (a placebo recipient) was a victim of homicide during the randomized-treatment phase. Neither death was considered treatment related. The patient who died during the washout phase had a BP of 155/87 mm Hg at the assessment 10 days before the CVA. Of the 1940 randomized patients, 114 (5.9%) discontinued treatment due to any adverse event (Table IV): 40 of 484 (8.3%) in the 3 OM-monotherapy groups, 20 of 324 (6.2%) in the 2 AML-monotherapy groups, 33 of 970 (3.4%) in the 6 combination-therapy groups, and 21 of 162 (13.0%) in the placebo group. The adverse events leading to study discontinuation were considered treatment related in 74 patients (3.8% of the total study group; 64.9% of patients discontinuing treatment because of an adverse event).

Although small mean changes were observed in serum chemistry, hematology, and urinalysis parameters, there was no consistent pattern and no apparent relationship to dose or compound. None of the mean changes were considered clinically significant. Although there were statistically significant increases from baseline in mean platelet count with AML 5-mg monotherapy (P = 0.002) and 10-mg monotherapy (P < 0.001) and all doses of the combination (P < 0.001), the magnitude of the increase was <10% in all groups and was not considered clinically meaningful (the highest increase was 22.08 × 10³/mm³ with AML 10 mg). A small number of patients developed laboratory abnormalities outside the prespecified safety ranges (Table V), but only 1 patient (receiving AML 10-mg monotherapy) was removed from the study because of increases in alkaline phosphatase and γ-glutamyltransferase. No differences in serum chemistry, hematology, or urinalysis parameters between treatment groups were considered clinically relevant by the investigators.

DISCUSSION

This 8-week study found that all doses of the combination of OM and AML were significantly more effective than the component monotherapies in reducing both SeDBP and SeSBP (P < 0.001). In addition, the proportion of patients achieving the BP goal (<140/90 mm Hg; <130/80 mm Hg in patients with diabetes) was greatest in the combination-therapy arms, with ~50% of patients achieving BP control with the higher doses of combination therapy. In addition, 54.0% of patients receiving the highest dose of OM/AML

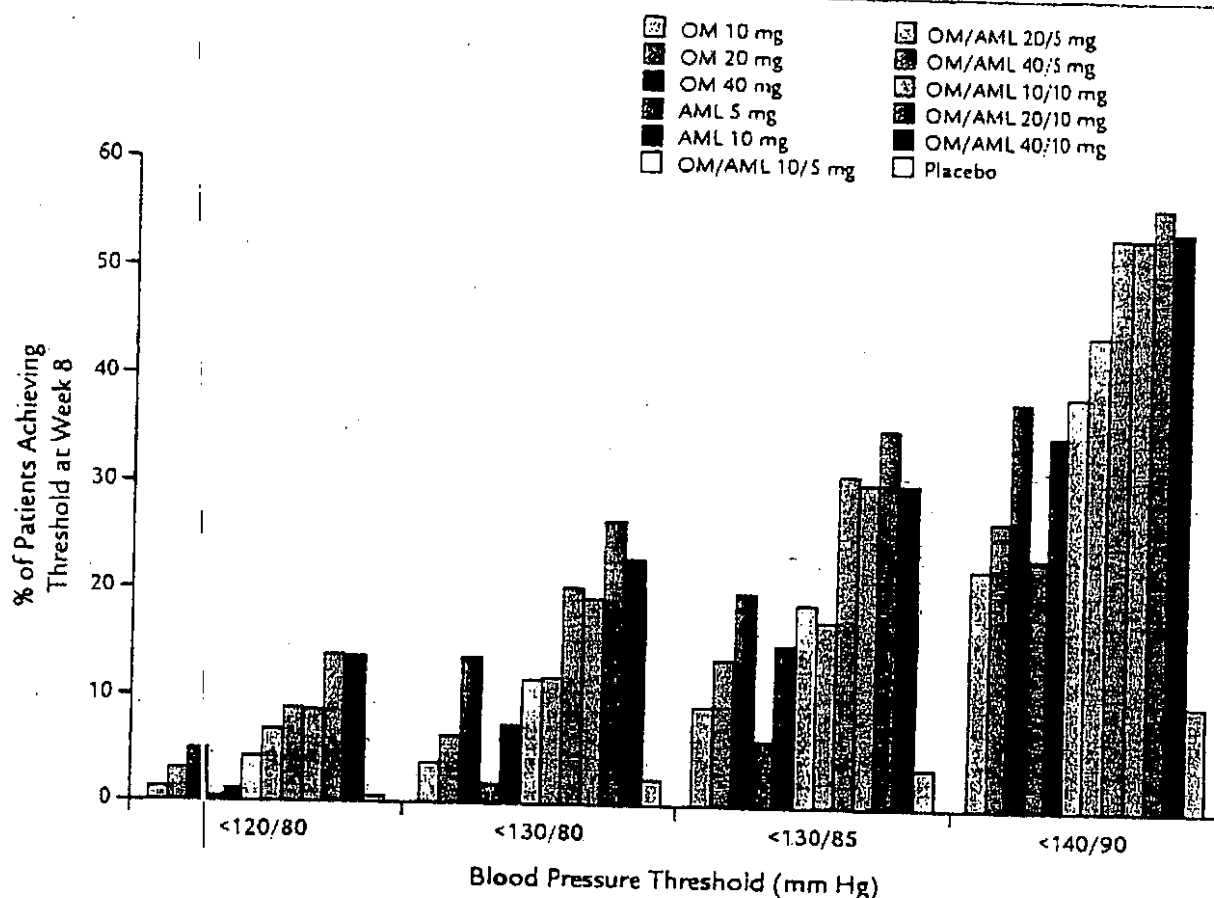


Figure 3. Proportions of patients in the intention-to-treat population achieving blood pressure thresholds at week 8 (last observation carried forward). OM = olmesartan medoxomil; AML = amlodipine; OM/AML = olmesartan/amlodipine.

achieved a BP <140/90 mm Hg at week 8. All OM and AML monotherapy and combination regimens were well tolerated, and no unexpected safety concerns were identified.

The finding of dose-dependent efficacy with the combination of OM/AML is consistent with results from similar studies of other fixed-dose combinations,²²⁻²⁸ as well as from studies that specifically examined the combination of another ARB, valsartan, with AML.^{29,30} As in the present trial, these studies found higher BP reductions and greater proportions of patients achieving BP targets with the combination therapy than with the component monotherapies.

A number of fixed-dose antihypertensive combinations are available in the United States, including ARBs combined with a diuretic (hydrochlorothiazide) and ACE inhibitors combined with a diuretic or CCB. The

treatment approach underlying these combinations is consistent with the JNC 7 recommendation that combination agents should consist of drugs that act through different antihypertensive pathways to maximize the therapeutic benefit.¹¹

OM and AML have complementary mechanisms of action, accounting for their additive antihypertensive effects. The vasodilatory action of CCBs stimulates counterregulatory mechanisms such as sympathetic activation and activation of the RAAS.¹³ These mechanisms reduce the BP-lowering effects of CCBs. However, an added ARB or ACE inhibitor counteracts RAAS activation, thereby maximizing the BP-lowering effect of the CCB while having an antihypertensive effect of its own.

Both European and US guidelines for the management of hypertension have noted the importance of

Table IV. Number (%) of patients having treatment-emergent adverse events (TEAEs) occurring in $\geq 3\%$ of patients in any group during 8 weeks of treatment with olmesartan or amlodipine, alone and in combination.

Variable	Olmesartan			Amlodipine			Olmesartan/Amlodipine						Placebo
	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)	(n = 162)	
Any TEAE	88 (54.7)	83 (51.6)	78 (48.1)	73 (45.3)	96 (58.9)	74 (45.4)	90 (55.9)	83 (51.2)	92 (56.8)	85 (53.1)	87 (53.7)	91 (56.2)	
Any discontinuations due to a TEAE	13 (8.1)	17 (10.6)	10 (6.2)	10 (6.2)	10 (6.1)	0	4 (2.5)	6 (3.7)	11 (6.8)	3 (1.9)	9 (5.6)	21 (13.0)	
Any drug-related TEAE	43 (26.7)	36 (22.4)	40 (24.7)	32 (19.9)	54 (33.1)	32 (19.6)	44 (27.3)	46 (28.4)	51 (31.5)	48 (30.0)	47 (29.0)	48 (29.6)	
Serious drug-related TEAE	0	1 (0.6)	0	0	0	0	0	0	0	0	0	0	
Discontinuations due to a drug-related TEAE	10 (6.2)	11 (6.8)	7 (4.3)	4 (2.5)	6 (3.7)	0	3 (1.9)	4 (2.5)	9 (5.6)	1 (0.6)	8 (4.9)	11 (6.8)	
Specific TEAEs													
Edema*	23 (14.3)	16 (9.9)	30 (18.5)	21 (13.0)	60 (36.8)	34 (20.9)	29 (18.0)	30 (18.5)	43 (26.5)	41 (25.6)	38 (23.5)	20 (12.3)	
Headache	9 (5.6)	14 (8.7)	14 (8.6)	13 (8.1)	8 (4.9)	4 (2.5)	9 (5.6)	6 (3.7)	10 (6.2)	11 (6.9)	9 (5.6)	23 (14.2)	
Fatigue	7 (4.3)	3 (1.9)	3 (1.9)	5 (3.1)	3 (1.8)	3 (1.8)	5 (3.1)	8 (4.9)	2 (1.2)	14 (8.8)	3 (1.9)	6 (3.7)	
Dizziness	5 (3.1)	10 (6.2)	8 (4.9)	5 (3.1)	4 (2.5)	3 (1.8)	8 (5.0)	7 (4.3)	6 (3.7)	5 (3.1)	6 (3.7)	9 (5.6)	
Hypertension†	7 (4.3)	8 (5.0)	6 (3.7)	4 (2.5)	2 (1.2)	1 (0.6)	3 (1.9)	2 (1.2)	1 (0.6)	1 (0.6)	0	13 (8.0)	
Nausea	2 (1.2)	3 (1.9)	2 (1.2)	2 (1.2)	2 (1.2)	1 (0.6)	5 (3.1)	3 (1.9)	2 (1.2)	2 (1.3)	5 (3.1)	5 (3.1)	
Rash	0	0	1 (0.6)	1 (0.6)	5 (3.1)	2 (1.2)	1 (0.6)	3 (1.9)	1 (0.6)	2 (1.3)	1 (0.6)	2 (1.2)	

* Combines the terms edema, peripheral edema, pitting edema, generalized edema, and localized edema. Patients were counted once for any instance of any of these terms.
† Combines the terms hypertension, systolic hypertension, diastolic hypertension, accelerated hypertension, blood pressure increased, diastolic blood pressure increased, and blood pressure inadequately controlled. Patients were counted once for any instance of any of these terms.

Table V. Number (%) of patients in the safety population developing laboratory abnormalities (values outside the predefined safety thresholds).

Parameter (Threshold)	Olmesartan			Amlodipine		Olmesartan/Amlodipine							Placebo (n = 162)
	10 mg (n = 161)	20 mg (n = 161)	40 mg (n = 162)	5 mg (n = 161)	10 mg (n = 163)	10/5 mg (n = 163)	20/5 mg (n = 161)	40/5 mg (n = 162)	10/10 mg (n = 162)	20/10 mg (n = 160)	40/10 mg (n = 162)		
Serum chemistry													
AST (>66 mU/mL)	1 (0.6)	2 (1.2)	0	1 (0.6)	0	0	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)	0	
ALT (>75 mU/mL)	2 (1.2)	1 (0.6)	0	1 (0.6)	0	1 (0.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	
GGT (>87 mU/mL)	6 (3.7)	6 (3.7)	5 (3.1)	5 (3.1)	4 (2.5)*	6 (3.7)	13 (8.1)	5 (3.1)	9 (5.6)	2 (1.3)	4 (2.5)	6 (3.7)	
Alkaline phosphatase (>216 mU/mL)	0	0	0	0	1 (0.6)*	0	0	0	0	0	0	1 (0.6)	
Total bilirubin (>1.65 mg/dL)	0	0	0	0	1 (0.6)	0	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)	
Potassium (>5.0 mEq/L)	11 (6.8)	6 (3.7)	9 (5.6)	3 (1.9)	4 (2.5)	3 (1.8)	8 (5.0)	17 (10.5)	8 (4.9)	9 (5.6)	9 (5.6)	6 (3.7)	
Hematology													
Hematocrit (<30%)	0	0	1 (0.6)	0	0	0	1 (0.6)	0	0	0	1 (0.6)	0	
Platelet count (<100 × 10 ³ /mm ³)	0	0	0	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	0	0	0	0	0	
AST = aspartate aminotransferase													

AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = γ glutamyltransferase.

*One patient receiving this dosage developed an increase in both alkaline phosphatase and GGT and was withdrawn from the study.

combination therapy in accelerating progress toward BP goals.^{11,12} In addition, these guidelines advocate use of combination therapy, when indicated, as initial treatment for patients who require reductions of >20/10 mm Hg to achieve the BP goal. However, the combination of OM and AML is not approved for the initial treatment for hypertension.

In addition to having improved BP-lowering efficacy, fixed-dose combinations may offer patient convenience compared with 2 agents taken separately. A recent meta-analysis reported that patient compliance was significantly better with fixed-dose antihypertensive combinations than with the same 2 agents administered concomitantly ($P < 0.001$).³¹

The combination of OM and AML was well tolerated in this study. The incidence of TEAEs, serious adverse events, and discontinuations due to adverse events was comparable among treatment groups, and the frequency of TEAE-related discontinuations was lower in the combination-treatment groups than in the placebo group. Edema was the only adverse event that showed a meaningful dose-response relationship. Most occurrences of edema were mild in severity, with moderate or severe edema most commonly seen in the groups receiving AML 10 mg, alone or in combination with OM. Although the incidence of edema was high in the group that received AML 10-mg monotherapy, both the incidence and severity of edema were reduced when AML 10 mg was combined with increasing doses of OM. In fact, the placebo-subtracted incidence of treatment-emergent edema was reduced by 54% when OM 40 mg was added to AML 10 mg. As expected, AML 5-mg monotherapy was associated with a lower incidence of edema than AML 10-mg monotherapy.

The reduction in edema when the higher dose of AML was combined with increasing doses of OM in this study is consistent with other reports indicating that the use of a RAAS blocker in combination with AML reduced the likelihood of AML-induced edema.^{29,32,33} The present study is one of the few trials of an antihypertensive combination to actively seek out occurrences of edema and grade its severity. As a result, the incidence of edema reported here is higher than in other trials that have relied on passive reporting. For example, a factorial study of valsartan and AML that used a passive-reporting system (adverse events were volunteered by patients, elicited by general questioning, or detected on physical examination)

reported edema rates of 8.7% with AML monotherapy and 3.0% with placebo,²⁹ compared with 13.0% to 36.8% with AML monotherapy and 12.3% with placebo in the present study. However, our findings are consistent with the incidence of edema in trials that used active edema surveillance, including studies of AML monotherapy. For example, Leonetti et al³⁴ reported a 19% rate of edema with AML 5 or 10 mg when symptoms were actively elicited using a patient questionnaire. Furthermore, in the Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE),³⁵ which used a proactive monitoring system, 22.1% of patients receiving AML 5 or 10 mg were reported to have edema. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE),³⁶ which also used a proactive monitoring system, 32.9% of patients receiving AML 5 or 10 mg with or without hydrochlorothiazide developed edema. The incidence of edema with the ARBs used in the foregoing studies was 8.9% for candesartan and 14.9% for valsartan, comparable to the incidence with OM in the present study (9.9%–18.5%).

The factorial design of this study provides important dose-response information about the BP-lowering effects of the combination of OM and AML. However, the study was of short duration (8 weeks) and thus had limited ability to predict long-term effectiveness or tolerability. Finally, the results of this study are applicable to the population studied (adults with mild to severe hypertension) and may not be generalizable to other populations with different characteristics.

CONCLUSIONS

In this population of adult patients with mild to severe hypertension, the OM/AML combinations were significantly better than their monotherapy components and placebo in lowering BP and achieving JNC 7 BP goals. Combination therapy was well tolerated and was associated with a lower incidence of edema relative to monotherapy with high-dose AML (10 mg).

ACKNOWLEDGMENTS

Research funds for this study and preparation of the manuscript were provided by Daiichi Sankyo, Inc., Parsippany, New Jersey. The trial was designed by Daiichi Sankyo in conjunction with the investigators. Data were collected by Medpace Inc., Cincinnati, Ohio, a contract clinical research organization, and analyzed by Medpace in collaboration with Daiichi

Sankyo. Investigators were compensated for their participation. Dr. Chrysant has received research grants from Daiichi Sankyo. The authors thank Catherine Rees and Wolters Kluwer Health Medical Communications for their editorial assistance.

The study investigators were: Mohammed Allaw, MD; Odilon Alvarado, MD; Lawrence Alwine, DO; Nabil Andrawis, MD; Luis Angles, MD; Michael Azort, MD; George Bakris, MD; Neville Bittar, MD; Kenneth Blaze, MD; Steven Bowman, MD; Dennis Breen, MD; Cristian Breton, MD; Paul Bristol, MD; Robert Broker, MD; Patricia Buchanan, MD; Rafael Canadas, MD; James Capo, Jr., MD; Dave Chamberlain, MD; Christopher Chappel, MD; Richard Cherlin, MD; Deanna Cheung, MD; Shane Christensen, MD; Steven Chrysant, MD; Anthony Ciulla, MD; Timothy Cleary, MD; Kenneth Cohen, MD; Lisa Cohen, MD; Selwyn Cohen, MD; Marc Comianos, MD; Wajdi Ali Dbouk, MD; Charles DeBusk, MD; Waymon Drummond, MD; Steven Duckor, MD; Hugh Durrence, MD; Robert Eads, MD; Gordon Eckerling, MD; John Ervin, MD; Cecil Farrington, MD; Michael Feldman, MD; David Ferrera, MD; Paul Fiocco, MD; Ritchard Fishman, MD; Darrell Fiske, MD; Alan Forker, MD; Neil Fraser, MD; Melissa Gamponia, MD; Raul Gaona, MD; Ralph Geiger, MD; William George, MD; C. Allen Goetsch, MD; G. Murthy Gollapudi, MD; Alan Graff, MD; Gary Greenwald, MD; Michael Guice, MD; Frank Hampel, MD; Wayne Harper, MD; Terence Hart, MD; David Hassman, DO; James Heaton, MD; Carlos Hernandez, MD; Charles Herring, MD; Darrell Herrington, DO; James Herron, MD; Robert Hippert, DO; C. Scott Horn, MD; Barry Horowitz, MD; Timothy Howard, MD; Randall Huling, MD; Terence Isakov, MD; William Jennings, MD; John Joseph, MD; James Judd, MD; Jeffrey Kaladas, MD; Adam Karns, MD; David Kayne, MD; Dean Keriakes, MD; Thomas Kinstry, MD; Eric Klein, MD; Lauro Lapuz, MD; Wayne Larson, MD; David Laughlin, MD; Gilbert Ledesma, MD; Derek Lewis, MD; Robert Lipetz, DO; Thomas Littlejohn, MD; Norman Lunde, MD; Robert Maddler, DO; Frank Maggiacomo, DO; Thomas Marbury, MD; Richard Marple, MD; Dennis McCluskey, MD; Stefano Mion-Bet, MD; Manuel Modiano, MD; Martin Mollen, MD; David Morin, MD; Kenneth Morris, DO; Julie Mullen, DO; Linda Murray, DO; Pundit Narayan, MD; John Nardandrea, MD; Julio Navarro, MD; Joel Neutel, MD; Harlan Nevin, MD; Michael Noss, MD; Mandeep

Oberoi, MD; Stephen Ong, MD; Suzanne Oparil, MD; Barry Packman, MD; Jorg Pahl, MD; E. David Pampe, MD; Sridhar Patnam, MD; Andres Patron, DO; John Peniston, DO; Monica Perlman, MD; Jon Peterson, MD; Frank Pettyjohn, MD; Keith Pierce, MD; Sanford Plevin, MD; Bryan Pogue, MD; Mark Radbill, DO; Ramon Ramirez, MD; David Ramstad, MD; Paul Ratner, MD; Albert Razzetti, MD; Harvey Resnick, MD; James Rhyne, MD; Dean Rider, MD; Dennis Riff, MD; Lee Rocamora, MD; Jeffrey Rosen, MD; Jonathan Rosen, MD; Eli Roth, MD; John Rubino, MD; George Ryckman, DO; Mario Salgado, MD; Mercedes Samson, MD; Jaime Sandoval, MD; Jay Schmidt, MD; Steven Schmidt, DO; Robert Schulman, MD; Douglas Schumacher, MD; David Schwartz, MD; Sherwyn Schwartz, MD; William Seger, MD; Michael Seidner, MD; Gregory Serfer, DO; Stephen Sharp, MD; Mandy Shaw, MD; Tanna Shaw, MD; Dirk Smith, MD; William Smith, MD; Philip Snell, MD; Malcolm Sperling, MD; Cynthia Strout, MD; Danny H. Sugimoto, MD; Francisco Tejada, MD; Melvin Tonkon, MD; Philip Torh, MD; Gabriel Uwaifo, MD; Robert Venuti, DO; Brian Walls, MD; Jeffrey Wayne, MD; Mervyn Weerasinghe, MD; Richard Weinstein, MD; Robert Weiss, MD; David Williams, MD; Peter Winkle, MD; Duane Wombolt, MD; Lisa Wright, MD; Douglas Young, MD; Franklin Zieve, MD; and Douglas Zmolek, MD.

REFERENCES

1. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension*. 2007;49: 69-75.
2. Kim JK, Alley D, Seeman T, et al. Recent changes in cardiovascular risk factors among women and men. *J Womens Health (Larchmt)*. 2006;15:734-746.
3. Lewington S, Clarke R, Qizilbash N, et al, for the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies [published correction appears in *Lancet*. 2003;361: 1060]. *Lancet*. 2002;360:1903-1913.
4. Lopez VA, Franklin SS, Tang S, Wong ND. Coronary heart disease events preventable by control of blood pressure and lipids in US adults with hypertension. *J Clin Hypertens (Greenwich)*. 2007;9:436-443.
5. Okonofua EC, Simpson KN, Jesri A, et al. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. *Hypertension*. 2006;47: 345-351.

6. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published corrections appear in *JAMA*. 2003;289:173 and *JAMA*. 2004;291:2196]. *JAMA*. 2002;288:2981-2997.
7. Brenner BM, Cooper ME, de Zeeuw D, et al, for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
8. Dahlöf B, Devereux RB, Kjeldsen SE, et al, for the LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet*. 2002;359:995-1003.
9. Dahlöf B, Sever PS, Poulter NR, et al, for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet*. 2005;366:895-906.
10. Hansson L, Zanchetti A, Carruthers SG, et al, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351:1755-1762.
11. Chobanian AV, Bakris GL, Black HR, et al, for the National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report [published correction appears in *JAMA*. 2003;290:197]. *JAMA*. 2003;289:2560-2572.
12. Mancia G, De Backer G, Dominiczak A, et al, for the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension; the Task Force for the Management of Arterial Hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2007;28:1462-1536.
13. Cappuccio FP, Markandu ND, Sagnella GA, et al. Effects of amlodipine on urinary sodium excretion, renin-angiotensin-aldosterone system, atrial natriuretic peptide and blood pressure in essential hypertension. *J Hum Hypertens*. 1991;5:115-119.
14. Osswald H, Mühlbauer B. The pharmacological basis for the combination of calcium channel antagonists and angiotensin converting enzyme inhibitors in the treatment of hypertension. *J Hypertens Suppl*. 1995;13:S21-S28.
15. Pedrinelli R, Dell'Omo G, Mariani M. Calcium channel blockers, postural vasoconstriction and dependent oedema in essential hypertension. *J Hum Hypertens*. 2001;15:455-461.
16. Messerli FH. Vasodilatory edema: A common side effect of antihypertensive therapy. *Curr Cardiol Rep*. 2002;4:479-482.
17. Chrysant SG, Bakris GL. Amlodipine/benazepril combination therapy for hypertensive patients nonresponsive to benazepril monotherapy. *Am J Hypertens*. 2004;17:590-596.
18. Weir MR. Incidence of pedal edema formation with dihydropyridine calcium channel blockers: Issues and practical significance. *J Clin Hypertens (Greenwich)*. 2003;5:330-335.
19. Chow SC, Liu JP. Combination trials. In: *Design and Analysis of Clinical Trials: Concepts and Methodologies*. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2004:270-283.
20. Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika*. 1988;75:383-386.
21. Gad SC. Trend analysis. In: *Statistics and Experimental Design for Toxicologists*. 3rd ed. Boca Raton, Fla: CRC Press; 1999:125-130.
22. Benz JR, Black HR, Graff A, et al. Valsartan and hydrochlorothiazide in patients with essential hypertension. A multiple dose, double-blind, placebo controlled trial comparing combination therapy with monotherapy. *J Hum Hypertens*. 1998;12:861-866.
23. DeQuattro V, Lee D, Messerli F, for the Trandolapril Study Group. Efficacy of combination therapy with trandolapril and verapamil SR in primary hypertension: A 4 x 4 trial design. *Clin Exp Hypertens*. 1997;19:373-387.
24. Fogari R, Corea L, Cardoni O, et al. Combined therapy with benazepril and amlodipine in the treatment of hypertension inadequately controlled by an ACE inhibitor alone. *J Cardiovasc Pharmacol*. 1997;30:497-503.
25. Gradman AH, Brady WE, Gazdick LP, et al. A multicenter, randomized, double-blind, placebo-controlled, 8-week trial of the efficacy and tolerability of once-daily losartan 100 mg/hydrochlorothiazide 25 mg and losartan 50 mg/hydrochlorothiazide 12.5 mg in the treatment of moderate-

- to-severe essential hypertension. *Clin Ther*. 2002;24:1049-1061.
26. Kochar M, Guthrie R, Triscari J, et al. Matrix study of irbesartan with hydrochlorothiazide in mild-to-moderate hypertension. *Am J Hypertens*. 1999;12:797-805.
27. McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: A multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *Clin Ther*. 2001;23:833-850.
28. Chrysant SG, Weber MA, Wang AC, Hinman DJ. Evaluation of antihypertensive therapy with the combination of olmesartan medoxomil and hydrochlorothiazide. *Am J Hypertens*. 2004;17:252-259.
29. Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle edema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens*. 2007;21:220-224.
30. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther*. 2007;29:563-580.
31. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: A meta-analysis. *Am J Med*. 2007;120:713-719.
32. Fogari R, Malamani GD, Zoppi A, et al. Effect of benazepril addition to amlodipine on ankle edema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens*. 2003;17:207-212.
33. Neutel JM, Smith DH, Weber MA, et al. Efficacy of combination therapy for systolic blood pressure in patients with severe systolic hypertension: The Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study. *J Clin Hypertens (Greenwich)*. 2005;7:641-646.
34. Leonetti G, Magnani B, Pessina AC, et al. Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. *Am J Hypertens*. 2002;15:932-940.
35. Kloner RA, Weinberger M, Pool JL, et al, for the Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. *Am J Cardiol*. 2001;87:727-731.
36. Julius S, Kjeldsen SE, Weber M, et al, for the VALUE Trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet*. 2004;363:2022-2031.

Address correspondence to: Steven G. Chrysant, MD, PhD, Oklahoma Cardiovascular Hypertension Center, 5850 W. Wilshire Blvd, Oklahoma City, OK 73132-4904. E-mail: schrysant@yahoo.com

ANEXO VII

Articles

Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies

Prospective Studies Collaboration*

Summary

Background The age-specific relevance of blood pressure to cause-specific mortality is best assessed by collaborative meta-analysis of individual participant data from the separate prospective studies.

Methods Information was obtained on each of one million adults with no previous vascular disease recorded at baseline in 61 prospective observational studies of blood pressure and mortality. During 12.7 million person-years at risk, there were about 56 000 vascular deaths (12 000 stroke, 34 000 ischaemic heart disease [IHD], 10 000 other vascular) and 66 000 other deaths at ages 40–89 years. Meta-analyses, involving “time-dependent” correction for regression dilution, related mortality during each decade of age at death to the estimated usual blood pressure at the start of that decade.

Findings Within each decade of age at death, the proportional difference in the risk of vascular death associated with a given absolute difference in usual blood pressure is about the same down to at least 115 mm Hg usual systolic blood pressure (SBP) and 75 mm Hg usual diastolic blood pressure (DBP), below which there is little evidence. At ages 40–69 years, each difference of 20 mm Hg usual SBP (or, approximately equivalently, 10 mm Hg usual DBP) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from IHD and from other vascular causes. All of these proportional differences in vascular mortality are about half as extreme at ages 30–39 years as at ages 40–49 years, but the annual absolute differences in risk are greater in old age. The age-specific associations are similar for men and women, and for cerebral haemorrhage and cerebral ischaemia. For predicting vascular mortality from a single blood pressure measurement, the average of SBP and DBP is slightly more informative than either alone, and pulse pressure is much less informative.

Interpretation Throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mm Hg.

Lancet 2002; **360**: 1903–13

*Collaborators listed at end of paper

Correspondence to: PSC Secretariat, CTSU, Radcliffe Infirmary, Oxford OX2 6HE, UK
(e-mail: psc@cts.ox.ac.uk)

Introduction

Meta-analysis of individual participant data

The observed relationships between blood pressure and vascular disease mortality in particular epidemiological studies are subject to appreciable random error, especially at lower blood pressure levels, for which the mortality rates are relatively low. As a consequence, different studies may produce apparently very different results, and unduly selective emphasis on some and not on others could introduce substantial biases. Hence, both to limit purely random errors and to minimise selective biases, meta-analyses of the observational studies of these relations are needed. By combining data from many studies, such meta-analyses can assess reliably the relevance of blood pressure to disease risk in a wide range of circumstances (including the extremes of the usual blood pressure distribution, and different ages). The present collaborative meta-analysis¹ differs from previous meta-analyses^{2–4} in several ways that increase its reliability and informativeness: (i) it is large, involving 120 000 deaths among one million participants in 61 cohorts (with parallel analyses of the Multiple Risk Factor Intervention Trial [MRFIT] observational study⁵ that involve a further 17 000 vascular deaths); (ii) individual records are available for each of the participants in each study, allowing detailed analyses; (iii) individuals with pre-existing vascular disease recorded were excluded, limiting any effects of disease on blood pressure (ie, avoiding “reverse causality”); (iv) cause-specific mortality data, together with age at death, are generally available; and (v) information on 286 000 repeat measurements made during prolonged follow-up allows appropriate time-dependent correction for “regression dilution”.^{6,7}

Time-dependent correction for regression dilution

Typically in prospective studies of the relevance to disease of risk factors such as blood pressure, various characteristics of a cohort are recorded at an initial baseline survey and these baseline characteristics of individuals who subsequently develop a particular disease are then compared with those of individuals who do not. But, because of fluctuations in the measured values of a risk factor at baseline, such comparisons often substantially underestimate the strength of the real association between the “usual” (ie, long-term average) level of that risk factor during a particular exposure period and the disease rate during that same, or a later, period.⁸ This regression dilution effect may be caused by measurement error, by short-term biological variability (including both transient fluctuations and any diurnal or seasonal variation), or by longer-term within-person fluctuations or trends in risk factor values (which may occur for several reasons, including physical activity, diet, treatment, disease, or age). Information from repeat measurements of the risk factor after just a year or two in a reasonably representative sample of individuals can be used to correct for the effects not only of random measurement error but also of short-

term variability in risk factor levels.² If, however, the aim is to estimate the usual risk factor levels 5, 10, or 15 years later then corrections based on remeasurements made relatively soon after baseline may not allow properly for the effects of longer-term within-person variability or trends. Moreover, since the interval between the baseline survey and the occurrence of an event in prospective studies is typically longer among those who suffer events at older ages, such underestimation may well be greater in the elderly. In order to make appropriate time-dependent corrections for these effects of regression dilution, remeasurements during prolonged follow-up can be used to estimate the usual risk factor levels at some particular fixed interval prior to death in each decade of age.⁴

Hence, by combination of individual participant data from many prospective observational studies in a systematic meta-analysis that is appropriately corrected for time-dependent regression dilution, the present report characterises, with greater precision and less bias than has previously been possible, the age-specific and sex-specific relevance of the usual blood pressure to the subsequent rates of death from stroke, ischaemic heart disease (IHD), other vascular causes, and the aggregate of all non-vascular causes.

Methods

Study selection criteria and data collection

As described previously,¹ collaboration was sought from the investigators of all prospective observational studies in which data on blood pressure, blood cholesterol, date of birth (or age), and sex had been recorded at a baseline screening visit, and in which cause and date of death (or age at death) had been routinely sought for all screenees during more than 5000 person-years of follow-up (see appendix A; <http://image.thelancet.com/extras/01art8300webappendixA.pdf>). Relevant studies were identified through computer searches of Medline and Embase, by hand-searches of meeting abstracts, and by extensive discussions with investigators. To minimise the effects of reverse causality (whereby established disease could change the usual blood pressure), studies were excluded if they had selected participants on the basis of a positive history of stroke or heart disease, and individuals from contributing studies were excluded from the present analyses if they had such a history recorded at baseline.

The primary risk factors for the present meta-analysis are age, and the systolic and diastolic blood pressures (SBP and DBP). Blood pressure was variously measured in different studies using standard or random-zero sphygmomanometers (but, similar results were found with these different methods; data not shown), typically with participants seated and DBP recorded at the disappearance of arterial flow sounds (phase V). Three US studies among doctors, nurses, or other health professionals involved self-reported blood pressure (see footnote to table A1 in appendix A); in aggregate, however, these three studies and the other 58 studies yielded similar results (data not shown). In some studies there was a strong preference for recording blood pressures that ended in zero (eg, 120 mm Hg); hence, the present analyses mostly use categories of baseline blood pressure that are centred on such values (eg, 115–124). Total blood cholesterol and, where available, lipid fractions (HDL and non-HDL cholesterol), diabetes, weight, alcohol consumption, and smoking at baseline were also assessed (but, controlling for these factors did not materially alter the estimated hazard ratios for the effects of blood pressure; data not shown). Information was sought not

SBP (mm Hg): baseline categories and values			Estimated "usual" SBP (mm Hg) at average of 5 years before death for deaths at ages				
Group	Range	Mean	40–49	50–59	60–69	70–79	80–89
i	<115	107.7	113.4	115.0	116.6	118.3	119.9
ii	115–124	120.0	123.4	124.7	126.0	127.3	128.7
iii	125–134	129.7	130.9	132.0	133.1	134.1	135.2
iv	135–144	139.4	138.1	138.9	139.7	140.5	141.3
v	145–154	149.4	145.2	145.6	146.0	146.4	146.9
vi	155–164	159.4	152.0	152.0	152.1	152.1	152.2
vii	165–174	169.4	158.6	158.1	157.7	157.3	157.0
viii	175–184	179.5	164.8	163.9	163.0	162.1	161.2
ix	185–194	189.6	170.7	169.2	167.8	166.4	165.0
x	≥195	210.0	181.8	179.6	177.6	174.6	171.7
Difference (x–i)		102.3	68.4	64.6	60.5	56.3	51.8
Regression dilution ratio*		..	0.67	0.62	0.58	0.54	0.49
Years from baseline†		..	2	4	6	8	10

*Ratio of the cited difference (x–i) in usual SBP at the start of each decade to that in baseline SBP. †Mean years from baseline to start of age range, for those who died in it (estimated as 5 years less than mean years from baseline to death). Hence, regression dilution ratios for usual blood pressure at an average of about 1 year before death in each decade are equivalent to those for years from baseline to start of age range plus 4 years (eg, 0.58, rather than 0.67, for usual SBP at age 40–49 years).

Table 1: Mean baseline values and estimated usual values of systolic blood pressure (SBP)

only from the baseline examination but also from any subsequent examinations during follow-up in order to devise appropriate general formulae for time-dependent correction of regression dilution (see below).⁶

Cause-specific mortality was sought in the greatest detail available, down to three-digit International Classification of Diseases (ICD) coding. In most studies the cause of death was initially taken from the death certificate, but in many cases confirmation was then sought from medical records, autopsy findings, or other sources. Information was provided on stroke deaths (with, for about half, attribution of probable stroke type: cerebral ischaemia, cerebral haemorrhage, or subarachnoid haemorrhage) and on IHD deaths in all but one study (ie, for 99.8% of the 12.7 million person-years at risk). Vascular causes of death other than stroke and IHD could be further subdivided, according to a predefined list,¹ in all but seven studies (ie, for 76% of the person-years at risk; see footnote to table A1 in appendix A).

Statistical methods

The main analyses are age-specific, and are of cause-specific death rates during five decades of age at risk (40–49, 50–59, . . . , 80–89 years), ignoring the few deaths outside the age range 40–89 years.

Age at risk (years)	Person-years at risk (×10 ⁶)	Number of deaths by attributed cause					
		Stroke	IHD	Other vascular	Non-vascular	Unknown cause	All causes
<40	2020	74	98	57	1302	91	1622
40–49	3269	414	1322	386	4386	265	6773
50–59	3843	1372	5594	1377	12 228	847	21 418
60–69	2482	2939	10 450	2549	18 771	1686	36 395
70–79	913	4327	10 852	3227	16 112	1716	36 234
80–89	177	2636	5649	2251	7436	895	18 867
≥90	7	198	318	245	562	84	1407
Total*	12 711	11 960	34 283	10 092	60 797	5584	122 716

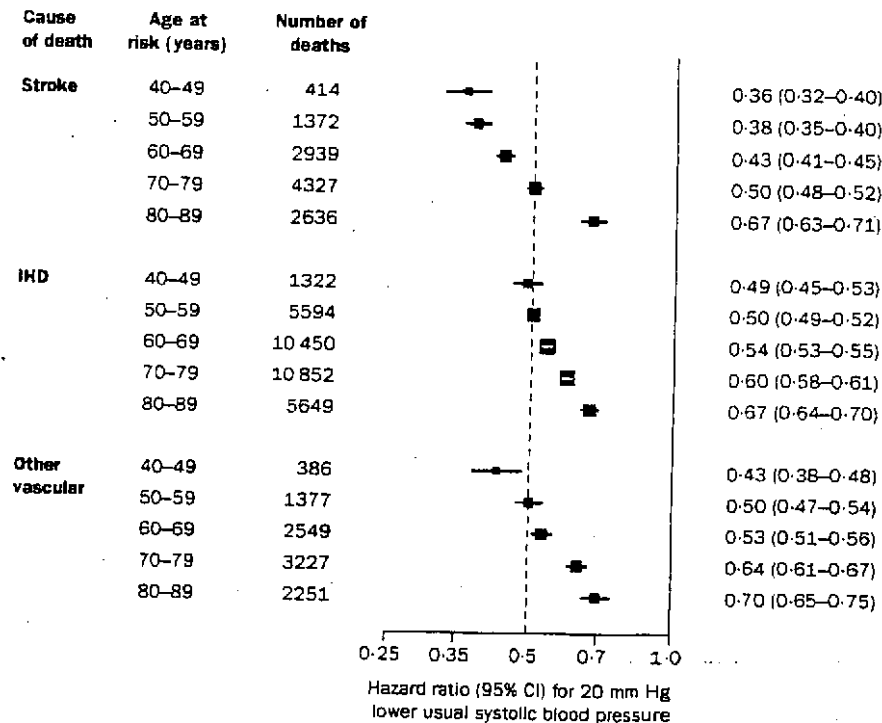
*For parallel analyses of the MRFIT study, which involved men dying only at ages 40–49, 50–59, and 60–69 years, respectively, there were 107, 461, and 717 stroke deaths; 1084, 4597, and 5679 IHD deaths; and 296, 1484, and 2359 other vascular deaths.

Table 2: Numbers of deaths attributed to stroke, ischaemic heart disease (IHD), other vascular causes, and non-vascular causes, by age at risk

Correction for time-dependent regression dilution—For SBP, the baseline measurement was used to divide people into ten categories (<115, 115–124, . . . , ≥195 mm Hg at baseline; table 1). The analyses relate the risk of death during each particular decade of age to the estimated “usual” blood pressure at the start of that decade (eg, age 40 years for death at ages 40–49 years). The mean intervals from the baseline survey until death (from any cause) varied with age at death, being 7, 9, 11, 13, and 15 years for those dying at ages 40–49, 50–59, 60–69, 70–79, and 80–89 years, respectively, in these studies. For those who die in a particular decade of age, the mean age at death is about the middle of that decade (ie, an average of about 5 years after the start of the decade). Hence, the mean intervals from the time of the baseline survey to the start of the decade of age in which death occurred were 2, 4, 6, 8, and 10 years, respectively (table 1). Information on a total of 286 000 blood pressure remeasurements in the different studies (see footnote to table A1 in appendix A) was used to provide estimates of age-specific usual SBP after these particular intervals for each category of baseline SBP (details in appendix B; <http://image.thelancet.com/extras/01art8300webappendixB.pdf>).

Estimation of hazard ratios for given differences in usual blood pressure—The five age ranges and ten SBP categories yielded a total of 50 different groups, one of which was taken as the reference group with a hazard ratio of 1.0. Relative to this, the other 49 hazard ratios for SBP were estimated simultaneously by Cox’s method,⁷ stratified for sex and study (with an additional term that allowed the hazard ratio in each decade of age to be estimated as the geometric mean of the hazard ratios in the first and second half of that decade). Fitting each of these 50 separate values avoids any assumptions as to whether the proportional relationships of risk to usual SBP are similar in different decades of age. Collectively, the 50 hazard ratios are “floating” (ie, all are related to the absolute death rates in a particular population by some common constant of proportionality), and so they are presented as “floating absolute risks”. This does not change their estimated values, but it does mean that an “effective variance” can be assigned to each log risk (including that for the reference group), which reflects the

A: Usual systolic blood pressure (≥115 mm Hg)



B: Usual diastolic blood pressure (≥75 mm Hg)

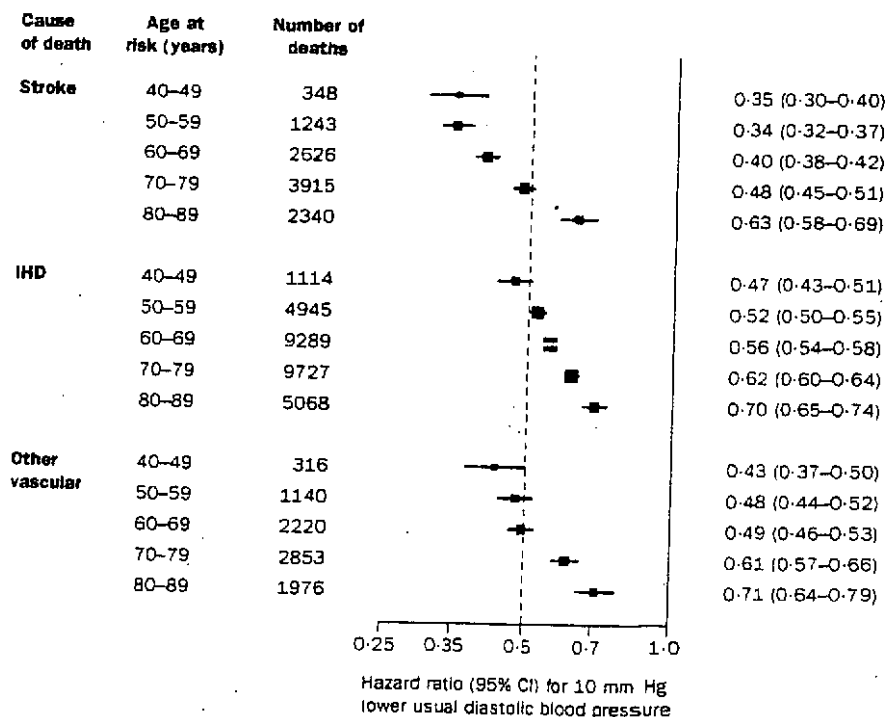


Figure 1: Stroke, ischaemic heart disease (IHD), and other vascular mortality: age-specific hazard ratios for given differences in usual blood pressure
The values plotted are the hazard ratios in each decade of age associated with (A) 20 mm Hg lower usual systolic blood pressure (SBP); and (B) 10 mm Hg lower usual diastolic blood pressure (DBP) at the start of that decade. Each square has area inversely proportional to the effective variance of the log hazard ratio, with the vertical broken line indicating a hazard ratio of 0.5. In parallel analyses of the large MRFIT study, a 20 mm Hg lower usual SBP at the start of the decade for deaths at ages 40–49, 50–59, and 60–69 years, respectively, was associated with hazard ratios of (i) stroke: 0.30 (95% CI 0.23–0.40), 0.33 (0.29–0.38), and 0.35 (0.31–0.40); (ii) IHD: 0.42 (0.38–0.47), 0.44 (0.42–0.46), and 0.46 (0.44–0.48); and (iii) other vascular: 0.35 (0.30–0.42), 0.42 (0.39–0.46), and 0.44 (0.41–0.48).

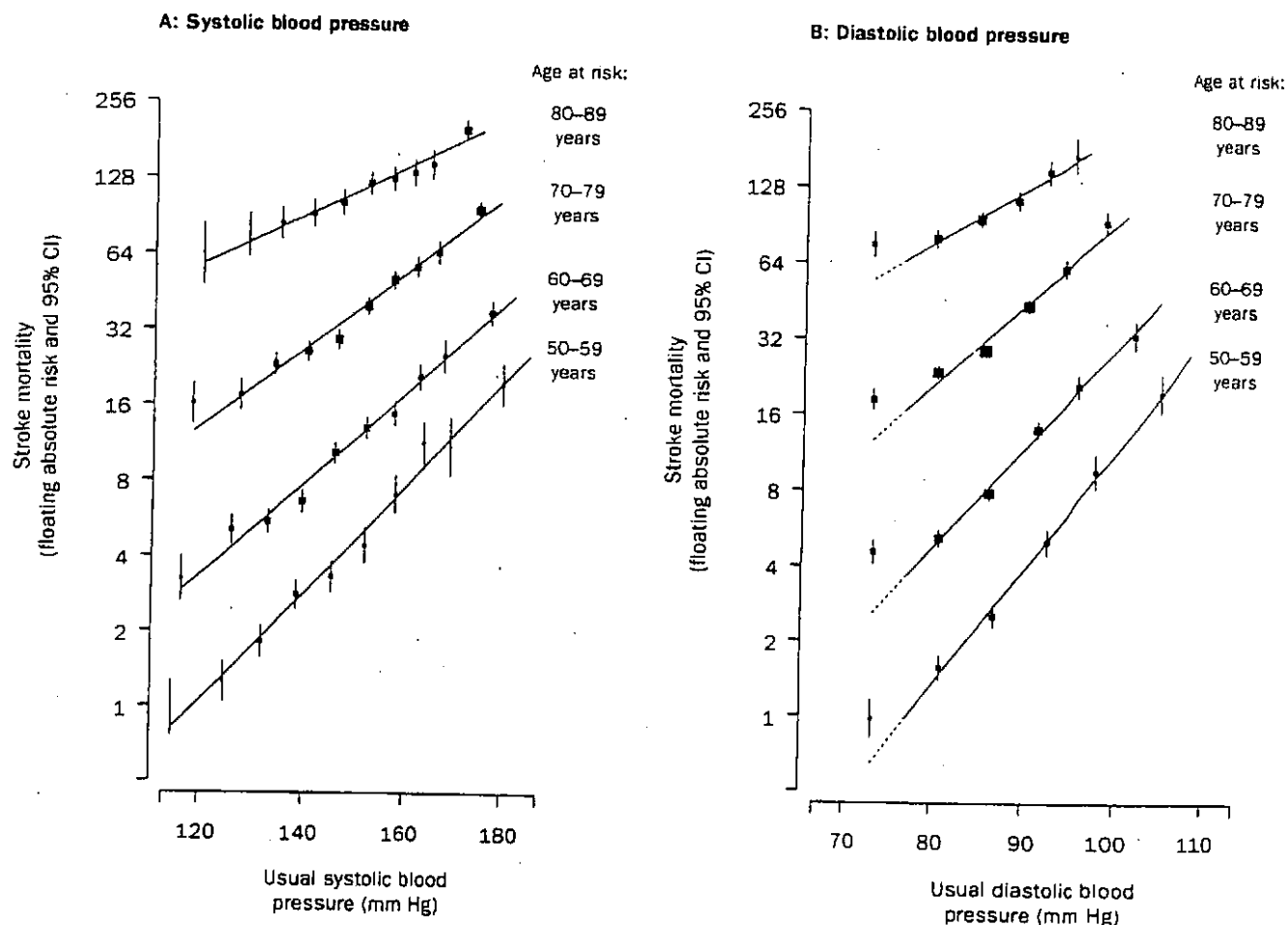


Figure 2: Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade

Rates are plotted on a floating absolute scale, and each square has area inversely proportional to the effective variance of the log mortality rate. For diastolic blood pressure, each age-specific regression line ignores the left-hand point (ie, at slightly less than 75 mm Hg), for which the risk lies significantly above the fitted regression line (as indicated by the broken line below 75 mm Hg).

amount of information underlying that particular group (details in appendix C; <http://image.thelancet.com/extras/01art8300webappendixC.pdf>). The statistical comparisons between groups then take the 50 log risks for SBP to be mutually independent with these 50 variances. The analyses for DBP were similar to those for SBP, except that the baseline DBP measurement was used to divide people into only six categories, reflecting the narrower range of values (see table B2 in appendix B).

The present report describes the hazard ratios (and 95% CIs) that are associated with 20 mm Hg lower usual SBP, and with 10 mm Hg lower usual DBP. If the slope of log risk against usual SBP (calculated as in appendix C) is x , then the hazard ratio for a 20 mm Hg lower usual SBP is $\exp(-20x)$. Hence, for example, to obtain the hazard ratio for a 10 mm Hg lower usual SBP, one would raise the hazard ratio for a 20 mm Hg lower usual SBP to the power $10/20$ (ie, take its square root).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study populations

Individual records for each of 958 074 participants in 61 studies were included in this meta-analysis, with 70% of the participants from Europe, 20% from North America

or Australia, and the remainder from Japan or China (table A1 in appendix A). During 12.7 million person-years at risk (mean of 12 years to death), there were 11 960 deaths attributed to stroke, 34 283 attributed to IHD, 10 092 attributed to other vascular causes, and 60 797 attributed to non-vascular causes (while a further 5584 deaths were of unknown cause: table 2 and table A1 in appendix A). Of the deaths from a specified type of stroke, one-sixth of those at ages 40–59 years, one-third of those at 60–69 years, and half those at 70–89 years were attributed to cerebral ischaemia. Individual records were not available for inclusion in the meta-analysis from participants in the MRFIT study, which involved 16 784 vascular deaths at ages 40–69 years among 353 168 men (see footnote to table 2). But parallel analyses using the same methods of that one large study yielded similar findings, and these are given separately.

Age-specific hazard ratios

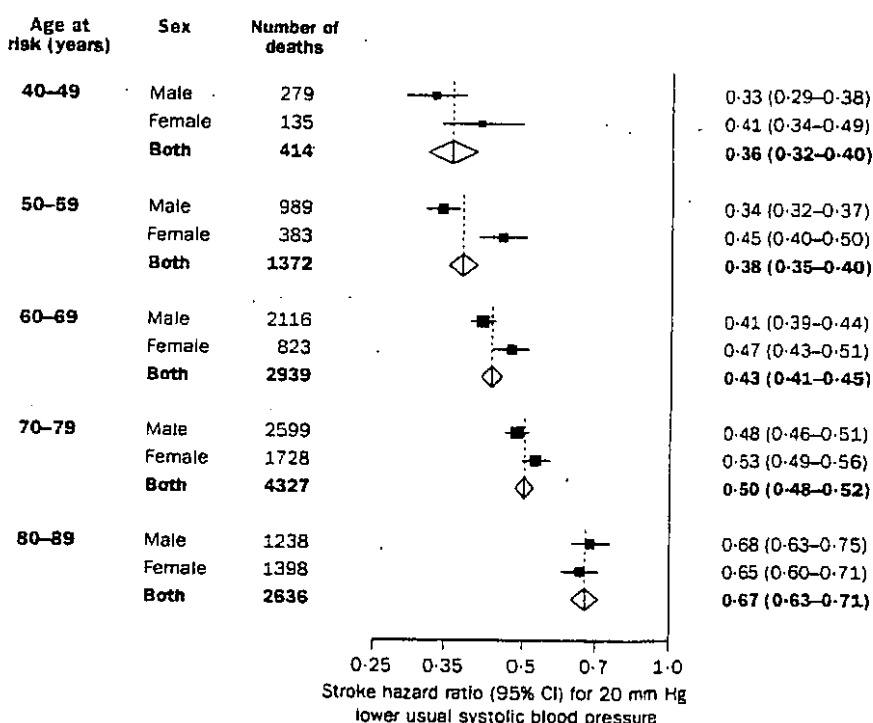
Figure 1 summarises the age-specific hazard ratios for death from stroke (top), from IHD (middle), and from other vascular causes (bottom) that are associated with a 20 mm Hg lower usual SBP throughout the range down to 115 mm Hg (figure 1A); or, approximately equivalently, with a 10 mm Hg lower usual DBP throughout the range down to 75 mm Hg (figure 1B). At ages 60–69 years, such differences in usual blood pressure are associated with slightly more than a twofold difference in the risk of stroke death and with almost a

twofold difference in death from IHD and from other vascular causes. (In figure 1, this twofold difference in risk is represented by the vertical broken line through a hazard ratio of 0.5.) The hazard ratios are about twice as extreme for vascular deaths at ages 40–49 years as at ages 80–89 years, but the associations with each of these three categories of vascular mortality remain strong even in old age. Thus, although a 20 mm Hg lower usual SBP is associated with more than a twofold difference in vascular mortality at ages 40–49 years (hazard ratios of 0.36 for stroke, 0.49 for IHD, and 0.43 for other vascular mortality), it is still associated with about one-third less vascular mortality at ages 80–89 years (hazard ratios of 0.67, 0.67, and 0.70, respectively). Parallel analyses of the MRFIT study yield similar age-specific results for the relevance of usual SBP to vascular mortality (see legend to figure 1).

Stroke mortality and usual blood pressure

Figure 2 shows that the relationship of stroke mortality to usual blood pressure is strong and direct at all ages, with no good evidence of a threshold at any age in the range of usual SBP above 115 mm Hg or of usual DBP above 75 mm Hg. A “doubling” (ie, proportional, or log) scale has been used for mortality rates, with a 95% CI for each point that reflects the amount of information underlying each risk estimate (see Methods). Because these mortality rates are collectively “floating”, multiplication of all of them by some constant appropriate for a particular population would allow prediction of the absolute rates in that population. For usual SBP, all ten points within each age-group are well fitted by the age-specific regression lines plotted (figure 2A). These approximately “log-linear” relationships imply that the proportional difference in the age-specific risk of stroke death associated with a given absolute difference in usual blood pressure is about the same at all levels of usual SBP down to at least 115 mm Hg. For usual DBP, the age-specific regression lines were fitted to five points only, ignoring the left-hand point (corresponding to slightly less than 75 mm Hg) for which the risk lies significantly above the fitted regression line but still below that of the adjacent point (figure 2B). The slopes of these regression lines were used to calculate the age-specific hazard ratios for stroke death associated with a 20 mm Hg lower usual SBP, or 10 mm Hg lower usual DBP, that were given in figure 1. Throughout middle age, such differences in usual blood pressure are associated with more than a twofold difference in the risk

A: Sex



B: Type of stroke

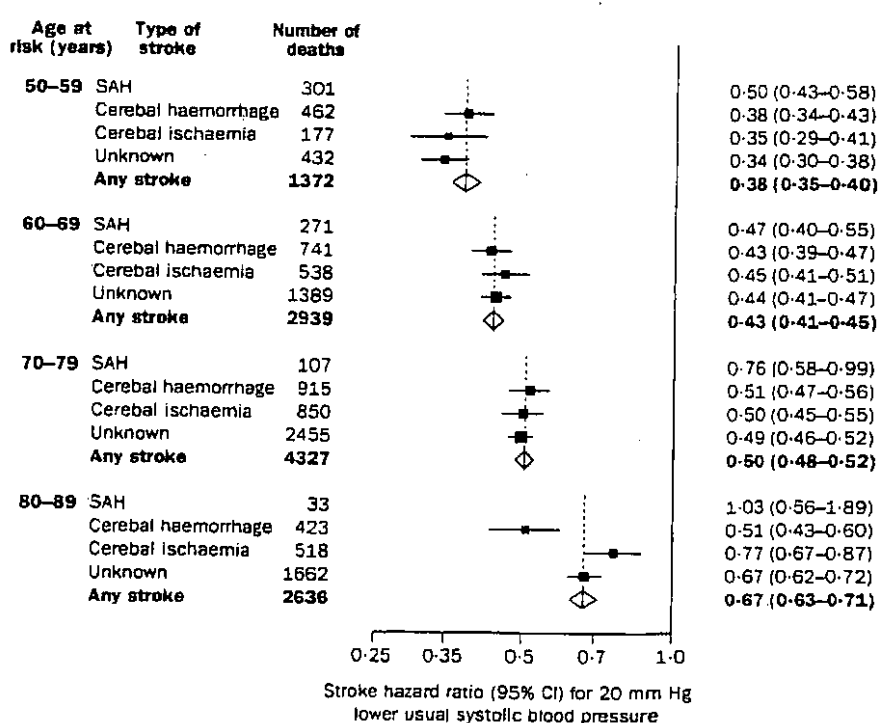


Figure 3: Stroke mortality: sex-specific and type-specific hazard ratios for 20 mm Hg lower usual systolic blood pressure

Conventions as in figure 1. Hazard ratios (95% CIs) for subarachnoid haemorrhage (SAH) are given numerically but are not plotted.

of stroke death. Although the strength of the association between the proportional risk of stroke death and usual blood pressure declines to some extent with increasing age at death, stroke is so much more common in old age than in middle age that the absolute annual difference in stroke death associated with a given difference in blood pressure increases with increasing age. For example, the

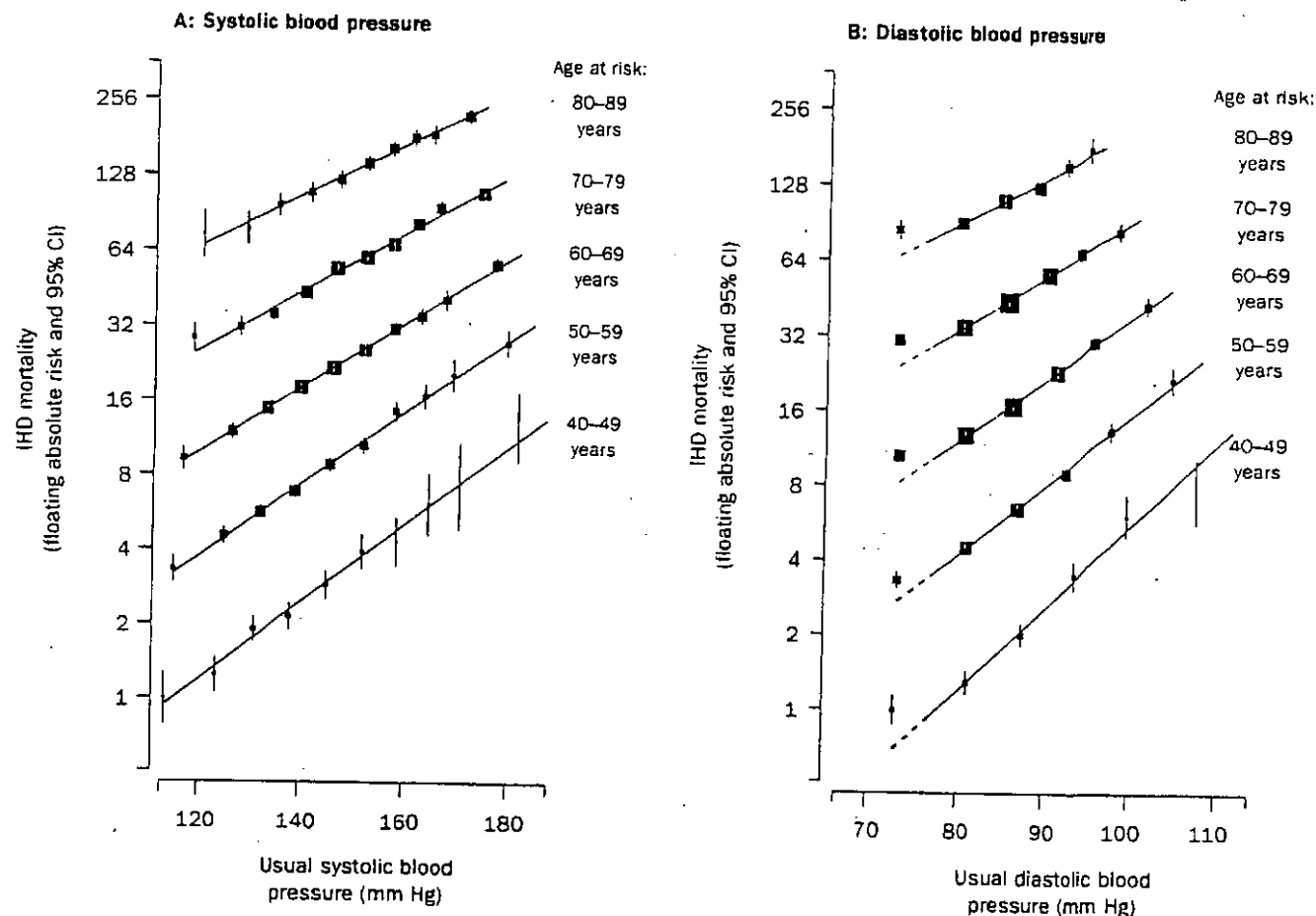


Figure 4: Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade. Conventions as in figure 2.

20 mm Hg difference in usual SBP between 120 and 140 mm Hg (or between 140 and 160 mm Hg) is associated with an annual difference in absolute risk that is nearly ten times larger at ages 80-89 years than that at ages 50-59 years (figure 2A).

Reverting to proportional risks, the age-specific associations of stroke mortality with blood pressure appear to be slightly less extreme for women than for men (figure 3A). Comparing different regions of the world, a 20 mm Hg difference in usual SBP is associated with age-standardised hazard ratios for stroke mortality at ages 40-89 years of 0.49 (95% CI 0.48-0.51) in the studies conducted in Europe, 0.50 (0.47-0.53) in the USA or Australia, and 0.42 (0.39-0.46) in Asia. Overall, the probable nature of about half of these fatal strokes was reported, with the remainder being of unknown type. Among people of the same age (at least up to age 80 years), the hazard ratios for death attributed to cerebral haemorrhage and to cerebral ischaemia appear similar (figure 3B). The proportion of stroke deaths considered to be due to cerebral haemorrhage was greater at younger ages, when the strength of the

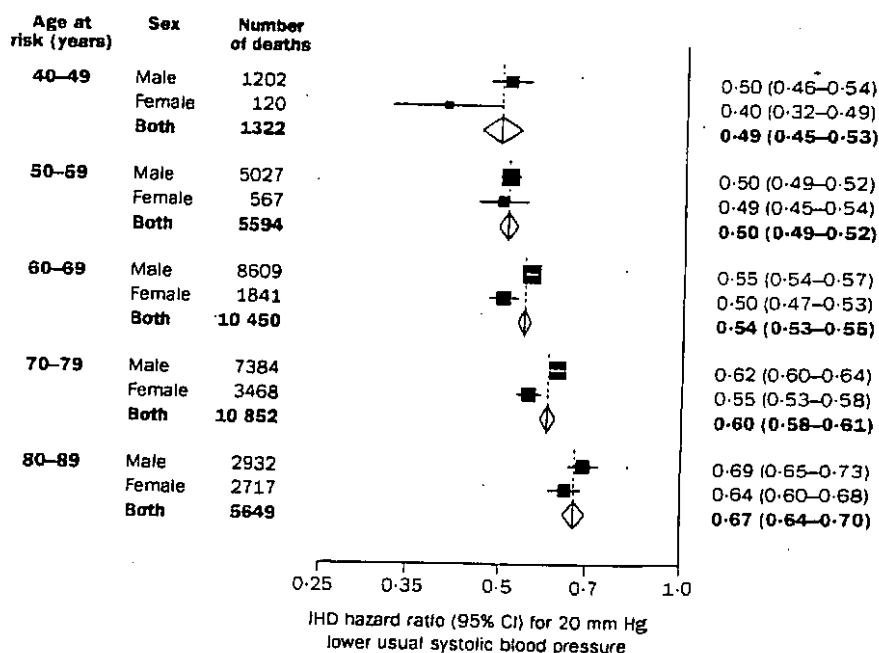


Figure 5: Ischaemic heart disease (IHD) mortality: sex-specific hazard ratios for 20 mm Hg lower usual systolic blood pressure. Conventions as in figure 1.

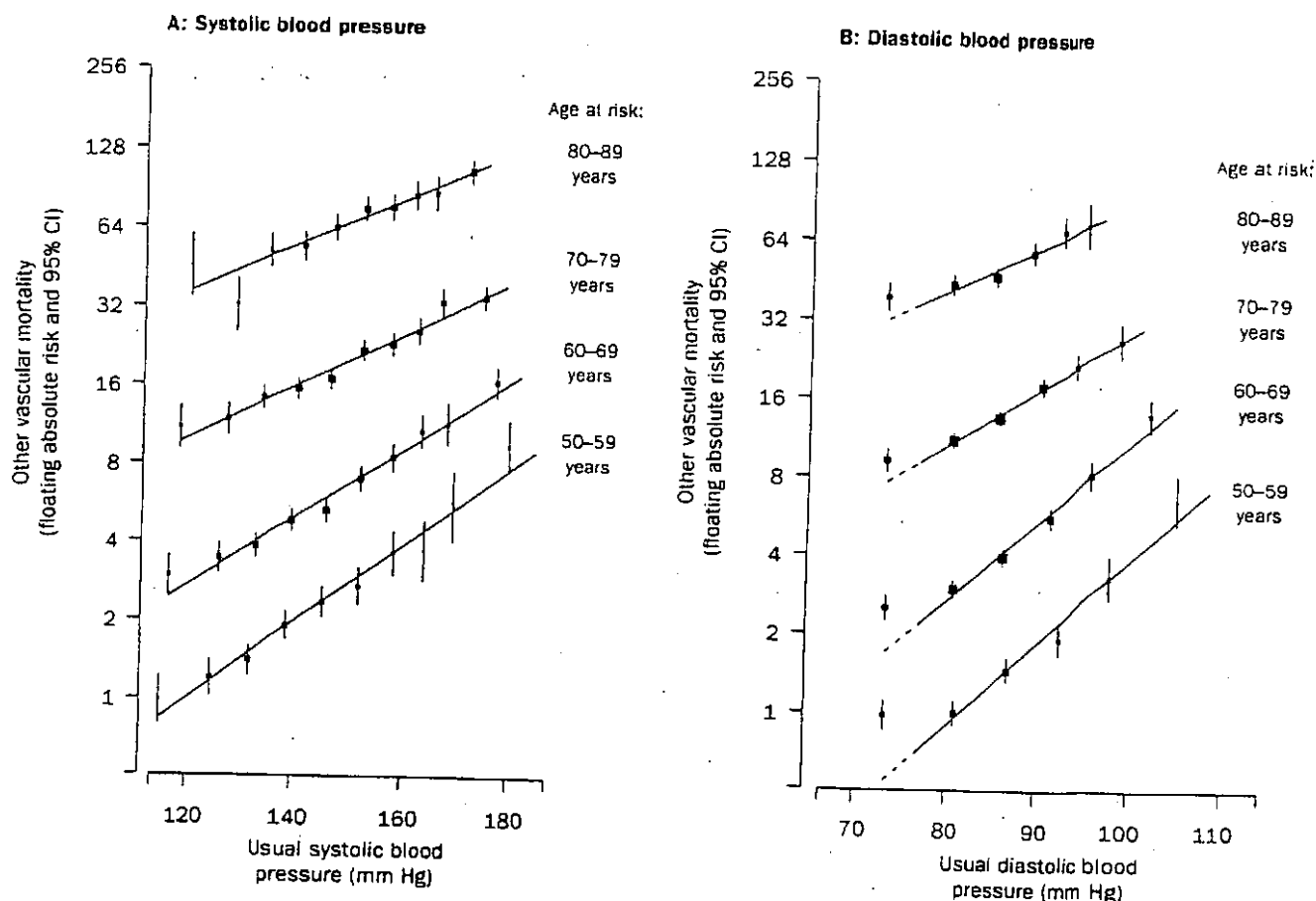


Figure 6: Other vascular (not stroke or ischaemic heart disease) mortality rate in each decade of age versus usual blood pressure at the start of that decade
Conventions as in figure 2.

association with stroke is stronger (and misclassification of the type of fatal stroke is less likely). Hence, analyses that are not stratified appropriately by age might suggest that the associations with blood pressure are stronger for deaths due to cerebral haemorrhage than for those due to cerebral ischaemia,⁴ even though the age-specific associations are actually about the same for strokes attributed to each cause.

Relatively few deaths were attributed to subarachnoid haemorrhage and, at all ages, the associations of mortality with blood pressure appear to be weaker for this outcome than for other types of stroke (figure 3B). Even so, throughout middle age (ie, at ages 40–69 years), a difference of 20 mm Hg in usual SBP is associated with about a twofold difference in the mortality rate from subarachnoid haemorrhage. (Note that the hazard ratios for subarachnoid haemorrhage are given in figure 3B, but they are not plotted in order that their wide CIs do not dominate the figure.)

IHD mortality and usual blood pressure

Usual blood pressure levels are also strongly and directly associated with IHD mortality at all ages (figure 4), although the relative strength of the association in middle age is somewhat weaker for IHD than for stroke mortality (figure 1). Throughout the range of usual SBP that was studied (ie, down to at least 115 mm Hg), the slope of the association between IHD mortality, plotted on a doubling scale, and the usual level of SBP is approximately constant within each age range (figure 4A). The same also appears to be true for the relationship between IHD mortality and usual DBP down to at least 75 mm Hg (figure 4B), and

within this range the age-specific hazard ratios associated with 10 mm Hg differences in usual DBP are similar to those associated with 20 mm Hg differences in usual SBP (figure 1). Throughout middle age, such differences in usual blood pressure are associated with about a twofold difference in IHD mortality. Although the strength of the association between the proportional risk of IHD death and usual blood pressure declines to some extent with increasing age (but not as markedly as for stroke: figure 1), the absolute annual difference in IHD death associated with a given difference in blood pressure increases with increasing age.

Reverting to proportional risks, the age-specific associations of IHD mortality with blood pressure appear to be slightly more extreme for women than for men (figure 5). This is the opposite of the slight trend seen for stroke (figure 3A), but in neither case are the effects of sex substantial. Hence, for vascular mortality as a whole (data not shown), sex is of little relevance to the age-specific hazard ratios associated with a given difference in usual blood pressure. Comparing different regions, a 20 mm Hg difference in usual SBP is associated with age-standardised hazard ratios for IHD mortality at ages 40–89 years of 0.57 (95% CI 0.56–0.58) in the studies conducted in Europe, 0.54 (0.51–0.56) in the USA or Australia, and 0.55 (0.48–0.63) in Asia.

Other vascular mortality and usual blood pressure

Likewise, for the aggregate of all vascular causes of death other than stroke or IHD, both SBP and DBP are strongly and directly associated with mortality in each age range. As is the case for stroke and IHD, there appears to

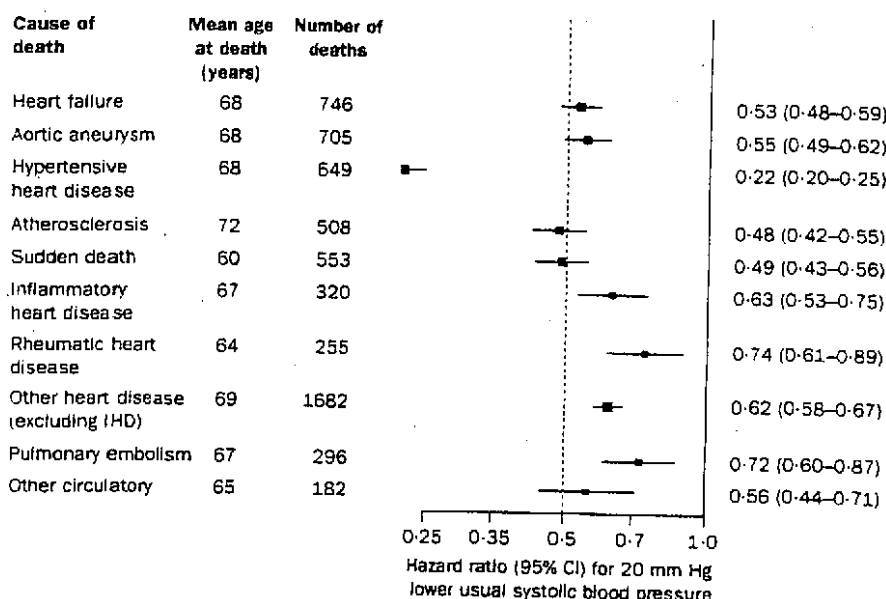


Figure 7: Mortality from other vascular causes (not stroke or ischaemic heart disease): hazard ratios for 20 mm Hg lower usual systolic blood pressure
Conventions as in figure 1. Only 54 of the studies subdivided these other vascular causes (see table A1 in appendix A).

be an approximately log-linear relationship between usual blood pressure and mortality from these other vascular causes (and, indeed, with mortality from the aggregate of all vascular causes; data not shown), with no evidence of a threshold down to at least 115/75 mm Hg (figure 6). Again, the strength of the association between the proportional risk of such deaths and the usual blood pressure declines to some extent with increasing age at death (figure 1). Three large, and four small, studies did not provide any subdivision of these other vascular causes of death (table A1 in appendix A), but the 5896 such deaths at ages 40–89 years in the remaining studies can be further subdivided by cause (figure 7). In these age-standardised analyses, a 20 mm Hg difference in usual SBP is associated with about a fourfold difference in mortality from hypertensive heart disease, with about a twofold difference in mortality from each of heart failure, aortic aneurysm, atherosclerosis, and sudden death, and with differences that were less extreme, although still significant (each $p<0.01$), in mortality from inflammatory heart disease, rheumatic heart disease, and pulmonary embolism.

Non-vascular mortality and usual blood pressure

Of the 120 000 deaths at ages 40–89 years, about 60 000 were attributed to non-vascular causes (table 2) and 5000

Blood pressure index	Informativeness* for prediction of	
	Stroke	IHD
Systolic blood pressure (SBP)	89%	93%
Diastolic blood pressure (DBP)	83%	73%
Pulse pressure (SBP–DBP)	37%	43%
Mean arterial pressure (2/3DBP+1/3SBP)	100%	97%
Mid blood pressure (1/2SBP+1/2DBP)	100%	100%

*Informativeness of the given index (as indicated by the age-stratified χ^2 statistic relating it to cause-specific mortality), as a percentage of the informativeness of the mid blood pressure. Age-specific values are provided in appendix D (<http://image.thelancet.com/extras/01art8300webappendixD.pdf>).

Table 3: Relative ability of different blood pressure indices (measured once only) to predict stroke and ischaemic heart disease (IHD) mortality rates

to an unknown cause (presumably about half vascular and half not). Throughout the range of usual blood pressures down to 115/75 mm Hg, mortality from the aggregate of all non-vascular causes is also positively related to blood pressure, although the relationship is much shallower than that for vascular mortality, with each 20 mm Hg lower usual SBP corresponding to an age-standardised hazard ratio for non-vascular mortality of 0.88 (95% CI 0.87–0.89). If the deaths from an unknown cause are included then this relationship becomes slightly steeper (data not shown). A separate report will describe the associations of blood pressure with deaths attributed to specific non-vascular causes (some of which, such as renal and hepatic diseases, may be partially related to vascular disease). But, at least down to about 115/75 mm Hg, there is no good evidence of any net hazard attributable to lower blood pressure.

Predictive power of different blood pressure indices

Using just the blood pressure measurements recorded in these studies at baseline (ie, without any allowance for regression dilution), the relative abilities of a single SBP measurement, of a single DBP measurement, or of some combination of them to predict subsequent mortality from stroke or IHD at different ages were assessed (table 3). This relative “informativeness” of a given blood pressure index was estimated from the age-stratified χ^2 statistic relating it to cause-specific mortality. For, within each particular age range, the more informative a particular blood pressure index is about a particular risk the larger the corresponding χ^2 statistic will tend to be.

Of the indices considered, the most informative about stroke mortality is “mid blood pressure” (defined as $1/2\text{SBP}+1/2\text{DBP}$), partly because any random measurement errors that just affect SBP or that just affect DBP are halved in calculating the average. By comparison, measurements of SBP and of DBP are, respectively, only 89% and 83% as informative about stroke mortality as is mid blood pressure, and pulse pressure is only 37% as informative. Mean arterial pressure ($2/3\text{DBP}+1/3\text{SBP}$) is highly correlated with mid blood pressure, and is about as informative. For IHD mortality, a similar pattern is seen, although the superiority of a single measurement of SBP over a single measurement of DBP is more definite. Again, mid blood pressure is the most informative of these measurements, with SBP 93% as informative, DBP 73% as informative, and pulse pressure only 43% as informative. If each decade of age at death is considered separately, then SBP is still a much more informative index of stroke or IHD risk than is pulse pressure, and again mid blood pressure is slightly better than SBP (details in appendix D; <http://image.thelancet.com/extras/01art8300webappendixD.pdf>). For, at a given measured value of SBP, the measured value of DBP is still very significantly positively related (as in mid blood pressure), rather than negatively related (as in pulse pressure), to stroke and to IHD mortality.

Discussion

Continuous positive associations between blood pressure and disease risk

In the present meta-analysis of data from 61 prospective observational studies on deaths from vascular disease among individuals without known vascular disease at baseline (and in parallel analyses of the large MRFTT study), blood pressure is associated strongly with the age-specific mortality rates from stroke, almost as strongly with the mortality rates from IHD and with those from other vascular causes, and much less strongly (although still positively) with the age-specific mortality rates from the aggregate of all non-vascular causes. In general, a 20 mm Hg difference in usual SBP is approximately equivalent in its hazards to a 10 mm Hg difference in usual DBP. These relationships with vascular mortality continue steeply down at least as far as a usual SBP of 115 mm Hg and a usual DBP of 75 mm Hg, below which there is little evidence. (Note that a single measurement of 110/70 mm Hg would, in these populations, indicate a usual blood pressure of just over 115/75 mm Hg [table 1 and appendix B], which lies within the range of the steep dose-response relationship.) Throughout this blood pressure range, the proportional difference in risk associated with a given absolute difference in usual blood pressure is similar at all blood pressure levels (ie, the relationship is approximately log-linear). This refutes the recent suggestion that there might be a threshold level of SBP at about 140–160 mm Hg (depending on age),⁹ below which lower blood pressure levels are not associated with lower disease risks. Indeed, the vascular mortality rates are only about half as great at 120 as at 140 mm Hg usual SBP, with no apparent net adverse effect on non-vascular mortality.

The present analyses of the relevance of usual blood pressure to cause-specific mortality show that the strengths of these age-specific associations with particular causes of death differ. By contrast, analyses of the association of usual blood pressure with the aggregate of all causes of death⁹ would tend to obscure both the continuous log-linear associations with particular vascular causes of death and the much weaker associations with non-vascular mortality. Consequently, although misclassification of causes of death may have some impact on the observed associations, such cause-specific analyses are more informative than analyses of all-cause mortality. Moreover, these analyses of cause-specific mortality can be generalised more reliably to different circumstances in which the proportions of deaths due to particular causes differ from those in the studies contributing to the present analyses.

Strength of associations after time-dependent correction for regression dilution

After making time-dependent corrections for regression dilution in these prospective studies, usual blood pressure has been found to be more strongly related to vascular disease risk than previously estimated,¹⁴ particularly for deaths at older ages. The proportional differences in vascular mortality associated with a given difference in blood pressure remain greater in middle than in old age, but the absolute annual differences in vascular mortality are greater at older ages than in middle age because the underlying rates of vascular disease are higher. The age-specific proportional differences in vascular mortality are also about the same for men and for women, and (in contrast with analyses that combine information from widely different ages⁹)

are similar for haemorrhagic stroke and for ischaemic stroke. Moreover, other risk factors (such as blood cholesterol, diabetes, smoking, and weight) were not found to have any material influence on the proportional differences in vascular mortality associated with a given absolute difference in usual blood pressure.

These analyses related the risks of death during a particular decade of age to the estimated usual systolic and diastolic blood pressure levels at the start of that decade. The choice of which exposure period is most appropriate depends on the rapidity with which a change in the usual blood pressure would change the mortality rates. If blood pressure levels over the previous decade or so are all of comparable relevance then it might be appropriate (as in the present analyses) to relate risk to the usual blood pressure about 5 years before death. At least for stroke, however, the main changes in risk may well occur quite rapidly after a change in the usual blood pressure (to judge from the substantial reductions in risk observed within just a few years in randomised trials of blood pressure lowering^{10–13}). If so, then the present analyses should perhaps have related stroke mortality to estimates of what the usual blood pressure levels would have been (in the absence of any effects of disease) shortly before death. In that case, the associations of blood pressure with risk would be about one-sixth stronger for usual SBP and one-third stronger for usual DBP than in the present report (as indicated by comparison of the regression dilution ratios at the start of each age range with those at the middle of each age range; see footnotes to table 1 and to table B2 in appendix B).

If just one single measurement of blood pressure is to be used to predict risk then, irrespective of age, the measured SBP is slightly more informative than the measured DBP, their average (ie, the mid blood pressure) is slightly more informative than either alone, and their difference (ie, the pulse pressure) is much less informative, contrary to the findings of some much smaller studies.^{14,15} Indeed, among people of a given age whose measured SBP is the same, the pulse pressure is actually inversely correlated with risk (because the measured DBP is positively correlated with risk).

Implications for disease prevention

Among people with no previous vascular disease recorded, the usual blood pressure is positively related to the risks of death from vascular disease not only among individuals who might be considered hypertensive, but also among those who would usually be considered normotensive (at least down to usual blood pressure levels of 115/75 mm Hg). Moreover, throughout this range, lower blood pressure is also associated with a slightly lower overall risk of death from non-vascular causes, although some of this may represent reverse causality (eg, renal disease exacerbating hypertension) or misclassification of deaths caused (at least in part) by vascular disease. Given the continuous relationship observed between blood pressure and risk of death from vascular disease, the absolute benefits of a lower blood pressure level are likely to be greatest for those at greatest absolute risk of vascular disease, largely irrespective of their blood pressure level (except insofar as it is one of the factors that influences this risk). So, even though the present meta-analysis did not include people who already had some history of vascular disease recorded at baseline (in order to avoid reverse causality, whereby established disease reduces or increases the blood pressure), it may

well be that those who are at high risk because of pre-existing disease (or age, or other factors) would gain particular benefit from lowering blood pressure, even if they would currently be classified as normotensive. This is supported by the limited evidence available from subgroups within meta-analyses of randomised trials of blood-pressure-lowering treatment^{10,16,17} and by the large-scale randomised evidence that is now emerging in higher-risk settings.^{18,19} Hence, blood-pressure-lowering treatment should be considered for a wide range of patients with evidence of occlusive vascular disease, largely irrespective of their current blood pressure or the use of other medication.

Not only do the present analyses confirm that there is a continuous relationship with risk throughout the normal range of usual blood pressure (down at least as far as 115/75 mm Hg), but they also demonstrate that within this range the usual blood pressure is even more strongly related to vascular mortality than had previously been supposed.²⁻⁴ Randomised trials (which typically last only a few years) have shown that blood-pressure lowering can produce rapid reductions in vascular disease risk,¹⁰⁻¹³ and this meta-analysis of observational studies provides complementary evidence of the even greater differences in risk that are likely to be produced by really prolonged differences in blood pressure. For example, a 10 mm Hg lower usual SBP or 5 mm Hg lower usual DBP (as have typically been assessed in previous randomised trials of just a few years of blood pressure lowering¹⁰⁻¹³) would, in the long term, be associated with about 40% lower risk of stroke death and about 30% lower risk of death from IHD or other vascular causes throughout middle age (and with only slightly smaller proportional differences at older ages). Indeed, even a 2 mm Hg lower usual SBP would involve about 10% lower stroke mortality and about 7% lower mortality from IHD or other vascular causes in middle age. So, for the general normotensive population, producing persistent reductions in average blood pressure of just a few mm Hg by some widely practicable methods (such as, perhaps, reducing sodium intake in manufactured foods²⁰⁻²²) should avoid large absolute numbers of premature deaths and disabling strokes,²³ especially in places that, perhaps for other reasons, have relatively high stroke rates (such as Northern China^{24,25}) or high IHD rates (such as Eastern Europe²⁶).

Prospective Studies Collaboration

Writing Committee—Sarah Lewington, Robert Clarke, Nawab Qizilbash, Richard Peto, Rory Collins.

Steering Committee—S Lewington (coordinator), S MacMahon (chairman), R Peto (statistician), A Aromaa, C Baigent, J Carstensen, Z Chen, R Clarke, R Collins, S Duffy, D Kromhout, J Neaton, N Qizilbash, A Rodgers, S Tominaga, S Törnberg, H Tunstall-Pedoe, G Whitlock.

Studies and Collaborators—Atherosclerosis Risk in Communities (ARIC): L Chambless; Belgian Interuniversity Research on Nutrition and Health (BIRNH): G De Backer, D De Bacquer, M Kornitzer; British Regional Heart Study (BRHS): S Ebrahim, P Whincup, G Wannamethee; British United Provident Association (BUPA): N Wald, J Morris, M Law; Buskellton: M Knuiman, H Bartholomew; Caerphilly and Speedwell: G Davey Smith, P Sweetnam, P Elwood, J Yarnell; Cardiovascular Health Study (CHS): R Kronmal; CB project: D Kromhout; Charleston: S Sutherland, J Keil; Copenhagen City Heart Study (CCHS): G Jensen, P Schnohr; Evans County: G Haines; Finnish Mobile Clinic Survey (FMCS): A Aromaa, P Knekt, A Reunanen; Finnish: J Tuomilehto, P Jousilahti, E Vartiainen, R Antikainen; Glostrup Population Studies (GPS): T Thomsen; Gothenburg Women: C Bengtsson; Honolulu: D Sharp; Ikawa, Noichi and Kyowa: H Iso, S Sato, A Kitamura, Y Naito; Centre d'Investigations Préventives et Cliniques (IPC), Paris: A Benetos, L Guize; Israeli Ischaemic Heart Disease Study (IHDS): U Goldbourt, S Yaari; Japan Railways: M Tomita, Y Nishimoto, T Murayama; Leuven: J Staessen; Lipid Research Clinics (LRC): M Criqui, C Davis; Minnesota Heart Health Project (MHHP) and Minnesota Heart Survey (MHS): D Jacobs, H Blackburn, R Luepker; Multiple Risk Factor

Intervention Trial (MRFIT): J Neaton, L Eberly; First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS): C Cox; NHLBI Framingham Heart Study: D Levy, R D'Agostino, H Silbershatz; Norwegian: A Tverdal, R Selmer; Northwick Park Heart Study (NPHS): T Meade, K Garrow, J Cooper; Occupational Groups (OG), Rome: A Menotti, A Spagnolo; Ohasama: I Tsuji, Y Imai, T Ohkubo, S Hisamichi; Oslo: L Haheim, I Holme, I Hjermann, P Leren; Paris: P Ducimetiere, M Zureik; Perth: K Jamrozik, R Broadhurst; Prospective Cardiovascular Munster Study (PROCAM): G Assmann, H Schulte; Puerto Rico Health Heart Program (PRHHP): P Sorlie, M Garcia-Palmieri; Rancho Bernardo: E Barrett-Connor, R Langer; Renfrew/Paisley: C Hart, D Hole, G Watt, C Gillis; Saitama: K Nakachi, K Imai; Seven Cities China: X Fang, S Li; Seven Countries (SC) Croatia: R Buzina; SC Finland: P Kivinen, A Nissinen; SC Greece: C Aravanis, A Dontas; SC Italy: A Menotti; SC Japan: H Toshima, H Adachi, T Imaizumi; SC Netherlands: D Kromhout; SC Serbia: S Nedeljkovic, N Vojvodic, C Ostojic; Shanghai: Z Chen; Scottish Heart Health Study (SHHS): H Tunstall-Pedoe, R A'Brook, Shibata: T Nakayama, N Yoshiike, T Yokoyama; Tecumseh: J Keller; Tromsø: K Bonaa, E Arnesen; United Kingdom Heart Disease Prevention Project (UKHDPP): H Tunstall-Pedoe, C Brown; US Health Professionals: E Rimm; US Nurses: F Speizer, M Stampfer; US Physicians: C Hennekens, J Buring; Värmland: S Törnberg, J Carstensen; West of Scotland: C Hart, G Davey Smith, D Hole, C Gillis; Whitehall: M Shipley, D Leon, M Marmot; Clinical Trial Service Unit (CTSU): R Clarke, R Collins, A Donald, S Lewington, A Palmer, S Parish, R Peto, P Sherliker, G Whidock, L Youngman, W Zhang.

Conflict of interest statement
None declared.

Acknowledgments

The Prospective Studies Collaboration (PSC) has been supported by the UK Medical Research Council, British Heart Foundation, EU Biomed programme, NIA/NIH grant PO1 AG17625-01, and CTSU overheads. Merck (F Walker) helped support the 1996 meeting of collaborators. S Lewington had a British Heart Foundation Fellowship to coordinate the project. Gale Mead (1943-2001) and Cathy Harwood typed the many versions of the manuscript.

References

- 1 Prospective Studies Collaboration. Collaborative overview ("meta-analysis") of prospective observational studies of the associations of usual blood pressure and usual cholesterol levels with common causes of death: protocol for the second cycle of the Prospective Studies Collaboration. *J Cardiovasc Risk* 1999; 6: 315-29.
- 2 MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335: 765-74.
- 3 Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995; 346: 647-53.
- 4 Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998; 352: 1801-07.
- 5 Martin MJ, Browner WS, Hulley SB, Kuller LH, Wentworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361 662 men. *Lancet* 1986; 2: 933-36.
- 6 Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999; 150: 341-54.
- 7 Cox DR. Regression models and life tables. *J R Stat Soc* 1972; 34: 187-220.
- 8 Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991; 10: 1025-35.
- 9 Port S, Demer L, Jennrich R, Walter D, Garfinkel A. Systolic blood pressure and mortality. *Lancet* 2000; 355: 175-80.
- 10 Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990; 335: 827-38.
- 11 Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994; 50: 272-98.
- 12 Gueyffier F, Bouillon F, Boissel J-P, et al, for the INDANA Investigators. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men: a meta-analysis of individual patient data from randomised controlled trials. *Ann Intern Med* 1997; 126: 761-67.

- 13 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; 355: 1955-64.
- 14 White WB. The systolic blood pressure versus pulse pressure controversy. *Am J Cardiol* 2001; 87: 1278-81.
- 15 Franklin SS, Larsen MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001; 103: 1245-49.
- 16 Gueyffier F, Boissel JP, Bouillon F, et al, on behalf of the INDANA (individual data analysis of antihypertensive intervention trials) Project Collaborators. Effect of antihypertensive treatment in patients having already suffered from stroke: gathering the evidence. *Stroke* 1997; 28: 2557-62.
- 17 Staessen JA, Gusowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; 355: 865-72.
- 18 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358: 1033-41.
- 19 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145-53.
- 20 Graudal NA, Gailoe AM, Anders M, Gørdt P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterol and triglyceride: a meta-analysis. *JAMA* 1998; 279: 1383-91.
- 21 Sacks FM, Svetkey LP, Vollmer WM, et al, for the DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001; 344: 3-10.
- 22 Tuomilehto J, Jousilahti P, Rastenyte D, et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 2001; 357: 848-51.
- 23 Murray CJ, Lopez AD. Global pattern of cause of death and burden of disease in 1990, with projections to 2020—investing in health research and development: report of the ad hoc committee on health research relating to future intervention options. Geneva: WHO, 1996.
- 24 Chen J, Campbell TC, Li J, Peto R. Diet, lifestyle and mortality in China: a study of the characteristics of 65 Chinese counties. Oxford: Oxford University Press, 1990 (updated at www.ctsu.ox.ac.uk).
- 25 Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas A-M, Schroll M, for the WHO MONICA Project. Stroke incidence, case fatality, and mortality in the WHO MONICA Project. *Stroke* 1995; 26: 361-67.
- 26 Kuulasmaa K, Tunstall-Pedoe H, Dobson A, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. *Lancet* 2000; 355: 675-87.

Uses of error

Brugada syndrome

S R Vavricka, A Himmelmann, A Schaffner

A 50-year-old white man in previously good health was found unresponsive on the street by a bystander. Lay cardiopulmonary resuscitation was started and paramedics were called. The squad found the patient in ventricular fibrillation.

Defibrillation was successful without neurological sequelae. In hospital serum electrolytes were normal. At cardiac catheterisation a normal ventriculography and normal coronary arteries were found. The ECG demonstrated normal sinus rhythm with normal PR, QT, and QTc intervals. However, we suspected Brugada syndrome because of ST-segment elevation in V1 and V2 and an incomplete right bundle-branch block. Furthermore left-axis deviation was present. Therefore, we implanted a cardioverter defibrillator (ICD) on the sixth day of hospitalisation. Because of oxygenation problems computed tomography was done on the fourth day of hospitalisation which showed a paracentral embolism in the right pulmonary artery originating from a deep venous thrombosis. We started treatment with low molecular weight heparin. ECG on day five showed disappearance of the ST-segment elevation and the incomplete right bundle-branch block. 20 months after implantation of the ICD the patient feels fine and there

has been no discharge of the ICD to the present day. A thrombophilia screen including APC-resistance, protein C and S deficiency, and fibrinogen mutation were negative.

Brugada syndrome is a recognised cause of ventricular fibrillation in the absence of structural heart disease, for which there are no stringent diagnostic criteria. Typical ECG findings are ST-segment elevation in the right precordial leads and a right bundle branch block. Other causes must be ruled out before implanting an ICD. As with the long QT syndrome, prevalence is estimated to be 1 per 5000. Currently, an ICD is the only effective therapy to prevent sudden death. Therefore, not least because of cost-effectiveness, an unequivocal diagnostic definition of this life-threatening syndrome is needed. Nevertheless, Brugada syndrome is currently a diagnosis of exclusion and the possibility of structural or coronary heart disease, or pulmonary embolism should first be pursued. Pulmonary embolism can lead to ECG-changes such as ST-segment elevation and right bundle branch block and thus mimic Brugada syndrome.

Our case also demonstrates that the focus of over-specialisation sometimes results in dramatic increases in health-care costs.

Department of Internal Medicine, University Hospital 8091, Zurich, Switzerland (S R Vavricka MD, A Himmelmann MD, A Schaffner MD)

8

ANEXO VIII

Antihypertensive efficacy of olmesartan medoxomil or valsartan in combination with amlodipine: A review of factorial-design studies

C. Venkata S. Ram

Dallas Nephrology Associates, Dallas, TX, USA

Address for correspondence: C. Venkata S. Ram, MD, Dallas Nephrology Associates, University of Texas, Southwestern Medical Center, 13154 Coit Road, Suite 100, Dallas, TX 75249, USA.
Tel.: +1 214 366 6412; E-mail: ramv@DNEPH.COM

Key words: Amlodipine – Factorial design – Hypertension – Olmesartan medoxomil – Valsartan

ABSTRACT

Background: Most patients with hypertension require more than one drug to attain recommended blood pressure (BP) targets. Initiating therapy with two agents is recommended for patients at high risk of a cardiovascular event or with a BP > 20/10 mmHg above goal. Combination therapy is effective when comprised of agents with complementary mechanisms of action, such as calcium channel blockers (CCBs) and angiotensin II-receptor blockers (ARBs). Two fixed-dose CCB/ARB combinations are approved in the US: amlodipine/valsartan (AML/VAL) and amlodipine/olmesartan medoxomil (AML/OM).

Objectives: To review and describe the efficacy of AML/VAL and AML/OM combinations by discussing similarly designed clinical trials.

Methods: Three 8-week, randomized, double-blind, placebo-controlled, parallel-group factorial-design studies were examined (two AML/VAL; one AML/OM). The study endpoints presented in this review were: change from baseline in least-squares mean seated diastolic BP (SeDBP) and least-squares mean seated systolic BP (SeSBP). In addition to the efficacies of AML/VAL and AML/OM combinations, the efficacies of AML, VAL and OM administered as monotherapy are presented. Placebo-subtracted BP reductions were calculated for this review.

Results: Patient demographics were similar but mean baseline SeBP was higher in the OM study

(163.8/101.6 mmHg) than in the VAL studies (152.8/99.3 and 156.7/99.1 mmHg), possibly suggesting that the OM study included a more difficult-to-treat patient population. AML/ARB combinations consistently produced greater mean SeBP reductions than monotherapy. Least squares (LS) mean SeDBP reductions were 19.4 mmHg (AML/OM 10/40 mg; placebo-corrected: 15.9 mmHg) and 18.6 mmHg (AML/VAL 10/320 mg; placebo-corrected: 9.8 mmHg). LS mean SeSBP reductions were 28.5 mmHg (AML/OM 10/40 mg; placebo-corrected: 25.7 mmHg) and 28.4 mmHg (AML/VAL 10/320 mg; placebo-corrected: 15.5 mmHg).

Conclusions: This review of published factorial-design studies showed that the maximal marketed doses of an amlodipine/olmesartan medoxomil combination (10/40 mg) and an amlodipine/valsartan combination (10/320 mg) produced large reductions in BP from baseline. Limitations of this review include the small number of studies analyzed and the inherent heterogeneity between patient populations. Further research is warranted to directly compare the efficacy of these combinations in a randomized, controlled trial, or additional published clinical trials are required to provide larger data sets for robust meta-analyses and to overcome heterogeneity observed within these studies.

Introduction

Poorly controlled hypertension is associated with an increased risk of cardiovascular events including

stroke, renal failure, and coronary artery disease¹⁻³. Cardiovascular mortality risk has been shown to double with every 20/10 mmHg increase in blood pressure (BP) above 115/75 mmHg¹. Despite the

availability of effective antihypertensive agents, high BP remains poorly controlled and the prevalence of hypertension continues to be unacceptably high⁴. Current practice guidelines recommend a goal BP of <140/90 mmHg for the general population with hypertension and <130/80 mmHg for patients at high cardiovascular risk, including those with diabetes^{2,5}.

The majority of patients with hypertension will require at least two antihypertensive agents to achieve recommended BP goals². For patients at high risk of a cardiovascular event or those with BP >20/10 mmHg above goal, practice guidelines advise initiating therapy with two agents^{2,5}. To obtain the best possible results, in terms of both maximization of BP lowering and minimization of adverse events, combination therapy should, in principle, be comprised of agents with complementary mechanisms of action^{2,5-8}. Angiotensin receptor blockers (ARBs) and dihydropyridine calcium channel blockers (CCBs) are effective classes of antihypertensive agents with distinct and complementary mechanisms of action^{5,8-10}. CCB/ARB fixed-dose combinations are, therefore, emerging as a rational treatment option. Two such combinations, an amlodipine/valsartan fixed-dose combination and an amlodipine/olmesartan medoxomil fixed-dose combination, are available and approved in the US.

To date, three factorial-design studies have been undertaken in relation to CCBs in combination with an ARB^{11,12}. Two of these studies investigated amlodipine and valsartan¹², and the other investigated amlodipine and olmesartan medoxomil¹¹. Factorial studies are designed to evaluate whether a specific combination therapy is more effective than either of the individual components used as monotherapy. These studies have confirmed that combination CCB/ARB therapy is more effective than either agent alone. To derive information about the relative efficacy of CCB/ARB combinations and their constituent components, in the absence of direct head-to-head trials and given the similar design of factorial studies and the comparable patient population, we conducted a comparative review of results from the available factorial studies.

Methods

The primary efficacy endpoint in all studies was the change from baseline in mean seated diastolic blood pressure (SeDBP) at week 8. Change from baseline in mean seated systolic blood pressure (SeSBP) was a secondary endpoint. The combined goal BP in the olmesartan medoxomil study was <140/90 mmHg for most patients or <130/80 mmHg for patients with diabetes. In the valsartan studies, BP response rate was defined

as SeDBP <90 mmHg or a ≥ 10 -mmHg decrease from baseline. In all three studies, BP measurements were taken after the patient had been sitting for 5 minutes. Safety profiles were assessed via monitoring of adverse events, hematology and biochemistry parameters, vital signs, physical examinations, and 12-lead electrocardiography. The olmesartan medoxomil study was unique in that the protocol specified that the occurrence and severity of peripheral edema be proactively assessed at each visit on a 5-point severity scale (no edema=0; mild pitting/slight indentation=1; moderate pitting/moderate indentation=2; deep pitting/indentation remains=3; deep pitting/leg remains swollen=4)¹¹. In the valsartan studies, the severity of peripheral edema was not proactively assessed or specifically reported¹².

Results

Study design

All three studies were randomized, double-blind, placebo-controlled, parallel-group trials of 8 weeks' duration (Table 1). The olmesartan medoxomil study was a multicenter US study. Valsartan study 1 was a multinational study (Belgium, Canada, France, Germany, Mexico and the US), as was valsartan study 2 (Egypt, France, Germany, Korea, Malaysia, Norway, Peru, Portugal, Spain and Taiwan). All studies were conducted according to good clinical practice guidelines and in compliance with the Declaration of Helsinki. Each study received institutional review board or ethical review committee approval, and all patients followed procedures ensuring written informed consent.

Inclusion criteria were the same for both valsartan studies: patients aged ≥ 18 years with mean SeDBP ≥ 95 and <110 mmHg. Patients included in the olmesartan medoxomil study were permitted to have a higher grade of hypertension (allowable SeDBP range of 95–120 mmHg) than those in the valsartan studies. Patients with mean SeSBP ≥ 180 mmHg were excluded from the valsartan studies. SeSBP <90 mmHg was not permitted at any point throughout the olmesartan medoxomil study, but maximum allowable SeSBP was left to the discretion of the investigator. Patients with a history of cardiovascular disease or diabetes requiring insulin treatment or poorly controlled type 2 diabetes (fasting glycosylated hemoglobin > 8% at visit 1) were excluded from all of the studies.

All three studies had a 2-week washout phase during which patients discontinued any antihypertensive agents. The two valsartan studies also included a 2- to 4-week single-blind placebo run-in period before the double-blind active treatment phase. The olmesartan

Table 1. Design and methodology of the amlodipine/ARB factorial studies

Drug combination	Study design	Entry criteria	Treatment arms/drug doses	Primary efficacy endpoint
Amlodipine/olmesartan medoxomil ¹¹	Multicenter, randomized, double-blind, placebo-controlled 4 × 3 factorial design	SeDBP 95–120 mmHg	Placebo AML 5 or 10 mg OM 10, 20, or 40 mg AML/OM 5/10, 5/20, 5/40, 10/10, 10/20, or 10/40 mg	Change from baseline in mean SeDBP at week 8
Amlodipine/valsartan ¹² (study 1)	Multicenter, randomized, double-blind, placebo-controlled 5 × 3 factorial design	SeDBP ≥ 95 and < 110 mmHg	Placebo AML 2.5 or 5 mg VAL 40, 80, 160, or 320 mg AML/VAL 2.5/40, 2.5/80, 2.5/320, 5/40, 5/80, 5/160, or 2.5/160 (1 week) → 5/320 mg	Change from baseline in mean SeDBP at week 8
Amlodipine/valsartan ¹² (study 2)	Multicenter, randomized, double-blind, placebo-controlled 3 × 2 factorial design	SeDBP ≥ 95 and < 110 mmHg	Placebo AML 10 mg VAL 160 or 320 mg AML/VAL 10/160, 5/160 (1 week) → 10/320 mg	Change from baseline in mean SeDBP at week 8

AML, amlodipine; ARB, angiotensin receptor blocker; OM, olmesartan medoxomil; SeDBP, seated diastolic blood pressure; VAL, valsartan

medoxomil study employed a 4 × 3 factorial design in which 1940 patients were randomized to one of 12 treatment groups: placebo, olmesartan medoxomil 10, 20, or 40 mg/day, amlodipine 5 or 10 mg/day, or combination therapy with one of the six possible combinations of active drug. Valsartan study 1 employed a 5 × 3 factorial design in which 1911 patients were randomized to one of 15 groups: placebo, valsartan 40, 80, 160, or 320 mg/day, amlodipine 2.5 or 5 mg/day, or combination therapy with one of the eight possible combinations of active drug. Valsartan study 2 employed a 3 × 2 factorial design in which 1250 patients were randomized to one of six treatment groups: placebo, valsartan 160 or 320 mg/day, amlodipine 10 mg/day, or combination therapy with one of the two possible active drug combinations. To minimize the potential for orthostatic adverse events, patients randomized to receive amlodipine 5 or 10 mg/day plus valsartan 320 mg/day underwent forced titration after 1 week of treatment with amlodipine 2.5 or 5 mg/day plus valsartan 160 mg/day.

Patients

A total of 1940 patients were randomized to treatment in the olmesartan medoxomil study and 1911 and 1250

patients in valsartan studies 1 and 2, respectively. Demographic characteristics of patients in the three studies are shown in Table 2. In light of the BP inclusion criteria, not surprisingly, the mean SeBP was highest in the olmesartan medoxomil study (163.8/101.6 mmHg vs. 152.8/99.3 and 156.7/99.1 mmHg in the two valsartan studies). Although the patients in the olmesartan medoxomil study would be predominantly described as a stage 2 hypertension population (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg) and patients in the valsartan studies would be predominantly described as a stage 1 hypertension population (SBP 140–159 mmHg or DBP 90–99 mmHg) standard deviations for these values were not provided and substantial heterogeneity is likely to exist.

The gender ratios were similar among the studies with the proportion of men ranging from 50.3% in the valsartan study 2 to 54.3% in the olmesartan medoxomil study. The mean age ranged from 54 in the olmesartan medoxomil study and valsartan study 1 to 57 in valsartan study 2. Patients aged ≥ 65 years comprised 18.2% and 28.6% of patients in the valsartan studies 1 and 2, respectively, and 19.8% of patients in the olmesartan medoxomil study. The mean weight of patients was highest in the olmesartan medoxomil study (95.1 kg vs. 88.8–79.7 kg in the valsartan studies).

Table 2. Demographic and baseline characteristics of patients in the amlodipine/ARB factorial studies

Treatment group	Mean age (years)	% ≥ age 65	Mean weight (kg/m ²)	Mean BMI	Sex (%)		Race (%)			Mean sitting BP (mmHg)		
					Male	Female	White	Black	Other	Diastolic	Systolic	
AML/OM	54.0	19.8	95.1	33.5	54.3	45.7	71.4	24.8	4.4	101.6	163.8	
AML/VAL (study 1)	54.4	18.2	88.8	29.8*	53.5	46.5	79.5	10.4	10.1	99.3	152.8	
AML/VAL (study 2)	56.9	28.6	79.7	29.8*	50.3	49.7	79.4	0.4	20.3	99.1	156.7	

*Mean BMI (kg/m²) for combination of study 1 and study 2

AML, amlodipine; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; OM, olmesartan medoxomil; VAL, valsartan

Two-thirds of patients in the olmesartan medoxomil study were overweight or obese (body mass index [BMI] ≥ 30 kg/m²) with a mean BMI of approximately 33.5 kg/m² and the combined mean BMI for the two valsartan studies was 29.8 kg/m². The proportion of white patients ranged from 71.4% in the olmesartan medoxomil study to 79% in the valsartan studies with the olmesartan medoxomil study having the highest proportion of black patients (24.8 vs. 10.4% in valsartan study 1 and 0.4% in valsartan study 2). Patients with diabetes comprised 13.5% of patients in the olmesartan medoxomil study. The proportion of patients with diabetes was not reported in either of the valsartan studies. At baseline, 13.6% of patients in the olmesartan medoxomil study had peripheral edema. Edema was not reported at baseline as part of the valsartan studies.

Review of the evidence of efficacy

The primary population for analysis in both studies was the intent-to-treat (ITT) population (all randomized patients who had a baseline BP measurement and ≥ 1 post-baseline BP measurement after taking double-blind study medication). Standard errors of the mean (SE) were reported individually for each dosage in the olmesartan-based study and were pooled for SeDBP and SeSBP reductions in the valsartan-based studies.

SeDBP

Placebo was associated with least squares (LS) mean reductions in SeDBP that ranged from 3.5 mmHg (SE 0.75) in the olmesartan medoxomil study (Figure 1) to 6.8 (SE 0.65–0.67) and 8.8 mmHg (SE 0.62–0.63) in valsartan studies 1 and 2, respectively (Figures 2 and 3)¹².

All active treatments produced greater LS mean SeDBP reductions than placebo. For the purposes of this overview, placebo-corrected values were calculated and presented. For monotherapy with amlodipine 5 mg, the LS mean reduction in SeDBP was 10.0 mmHg (SE 0.75) in the olmesartan study and 11.5 mmHg in the valsartan study 1 (SE 0.65–0.67) (placebo-corrected values of 6.5 and 4.7 mmHg, respectively). For monotherapy with amlodipine 10 mg, the LS mean reduction in SeDBP was 13.3 mmHg (SE 0.74) in the olmesartan study and 15.6 mmHg (SE 0.62–0.63) in the valsartan study 2 (placebo-corrected values of 9.8 and 6.8 mmHg, respectively) (Table 3). Olmesartan medoxomil produced LS mean reductions ranging from 8.8 mmHg (SE 0.75) with the 10-mg dose to 10.9 mmHg (SE 0.75) with the 40-mg dose (placebo-corrected values of 5.3–7.4 mmHg), and valsartan produced LS mean reductions ranging from 10.1 mmHg (SE 0.65–0.67)

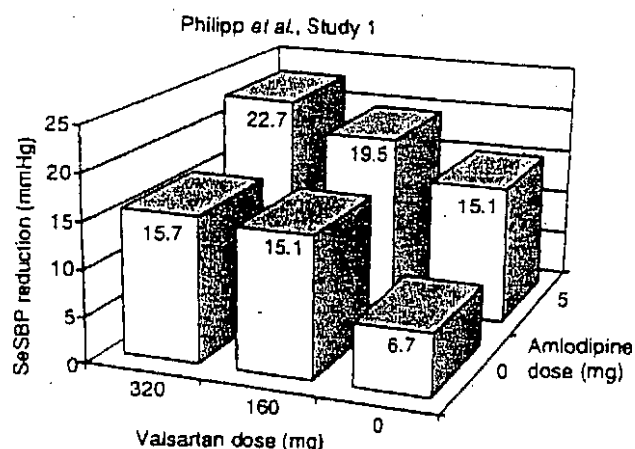
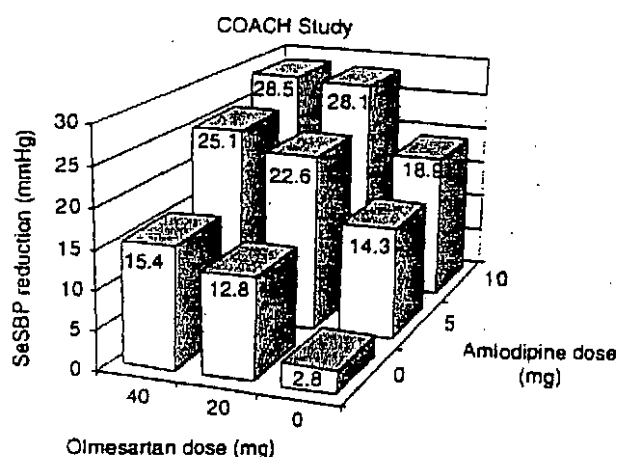
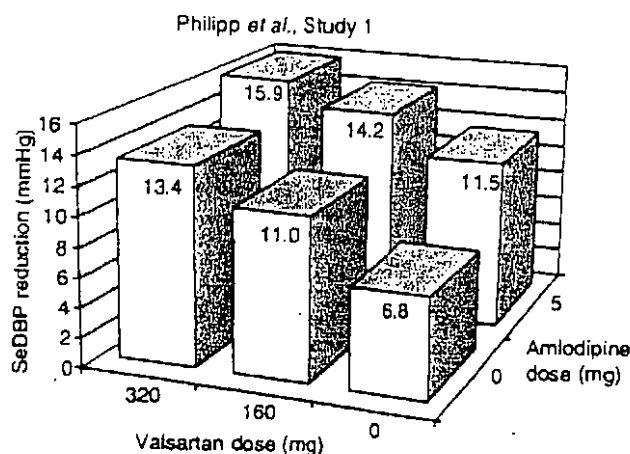
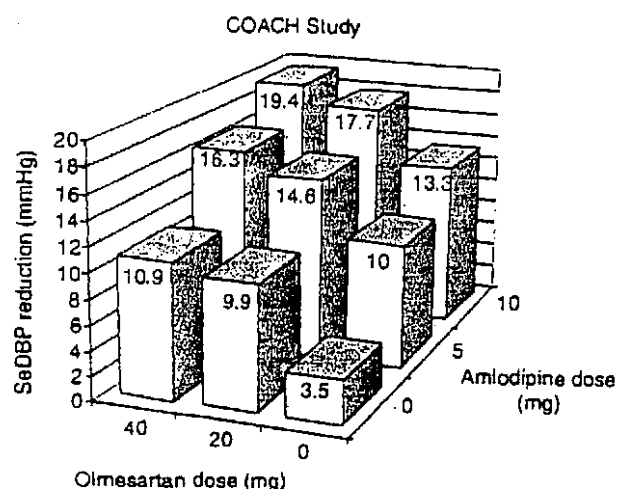


Figure 1. LS mean reductions in SeDBP and SeSBP in patients treated with marketed dosages of amlodipine + olmesartan medoxomil¹¹

Figure 2. LS mean reductions in SeDBP and SeSBP in patients treated with marketed dosages of amlodipine + valsartan (study 1)¹²

with the 40-mg dose to 13.4 mmHg (SE 0.62–0.63) with the 320-mg dose (placebo-corrected values of 3.3–6.6 mmHg) (Table 4).

With the exception of the lowest amlodipine/valsartan (2.5 mg/40 mg) dose pairing, all the amlodipine/ARB combinations consistently produced greater lowering of SeDBP than monotherapy with component agents. In relation to combination therapy in the olmesartan medoxomil study, LS mean SeDBP reductions ranged from 14.3 mmHg (SE 0.74) with amlodipine 5 mg/olmesartan 10 mg to 19.4 mmHg (SE 0.74) with amlodipine 10 mg/olmesartan medoxomil 40 mg (placebo-corrected values of 10.8–15.9 mmHg) (Table 5). In the valsartan studies, LS mean reductions ranged from 10.8 mmHg (SE 0.65–0.67) with amlodipine 2.5 mg/valsartan 40 mg to 18.6 mmHg (SE 0.62–0.63) with amlodipine 10 mg/valsartan 320 mg (placebo-corrected values of 4.0–9.8 mmHg).

SeSBP

LS mean reductions in SeSBP associated with placebo ranged from 2.8 mmHg (SE 1.25) in the olmesartan

medoxomil study (Figure 1) to 6.7 mmHg (SE 1.03–1.06) in valsartan study 1 and 12.9 mmHg (SE 0.96–0.97) in valsartan study 2 (Figures 2 and 3). For monotherapy with amlodipine, the LS mean reduction was 14.3 mmHg (SE 1.24) in the olmesartan medoxomil study and 15.1 mmHg (SE 1.03–1.06) in valsartan study 1 (placebo-corrected values of 11.5 and 8.4 mmHg) for the 5-mg dose and from 18.9 mmHg (SE 1.23) in the olmesartan medoxomil study to 24.1 mmHg (SE 0.96–0.97) in valsartan study 2 (placebo-corrected values of 16.1 and 11.2 mmHg) for the 10-mg dose (Table 3).

Olmesartan medoxomil produced LS mean SBP reductions of 10.9 mmHg (SE 1.24) with the 10-mg dose and 15.4 mmHg (SE 1.24) with the 40-mg dose (placebo-corrected values of 8.1–12.6 mmHg), and valsartan produced reductions of 11.8 mmHg (SE 1.03–1.06) with the 40-mg dose and 19.8 mmHg (SE 0.96–0.97) with the 320-mg dose (placebo-corrected values of 5.1–6.9 mmHg) (Table 4). LS mean reductions in SeSBP were greater with combination therapy than with any agent given alone. In relation to combination therapy in the olmesartan medoxomil study, LS mean SeSBP reductions ranged

from 22.6 mmHg (SE 1.24) with amlodipine 5 mg/olmesartan medoxomil 20 mg to 28.5 mmHg (SE 1.24) with amlodipine 10 mg/olmesartan medoxomil 40 mg (placebo-corrected values of 19.8–25.7 mmHg) (Table 5). In the valsartan studies, LS mean reductions ranged from 15.5 mmHg (SE 1.03–1.06) with amlodipine 2.5 mg/valsartan 40 mg to 28.4 mmHg (SE 0.96–0.97) with amlodipine 10 mg/valsartan 320 mg (placebo-corrected values of 8.8–15.5 mmHg).

Attainment of BP goals

As with reductions in SeBP, goal BP (<140/90 mmHg or <130/80 mmHg for patients with diabetes in the

olmesartan medoxomil study) was achieved to the greatest extent in the combination therapy arms. At week 8, approximately 49.1–53.2% of patients treated with the higher dose amlodipine and olmesartan combination therapies reached their BP goal^{11,12}. Bearing in mind the relatively stringent definition of BP control in the olmesartan medoxomil study, the proportion of patients achieving goal DBP (<90 mmHg) was 77.6% with amlodipine/olmesartan medoxomil 10/40 mg and 84.1% with amlodipine/valsartan 10/320 mg^{11,12}.

Review of the evidence of the safety profiles of the two combinations

The amlodipine/ARB combinations were well-tolerated, with no unexpected safety concerns. The incidence of peripheral edema (the most common adverse event in all studies) was lower with combination therapy than with amlodipine monotherapy. The incidence of peripheral edema significantly decreased from 36.8% with amlodipine 10 mg monotherapy to 23.5% when combined with olmesartan medoxomil 40 mg ($p=0.011$). Most occurrences of edema were of mild-to-moderate severity. The incidence of peripheral edema in valsartan studies was not broken down into dosage groups and was not as rigorously examined as in the olmesartan medoxomil study (overall incidence decreased from 8.7% with amlodipine monotherapy to 5.4% with combination amlodipine/valsartan, $p<0.05$).

Other common adverse events in the olmesartan medoxomil study included headache (6.7%), dizziness (3.9%), and fatigue (3.2%), none of which showed consistent differences among active treatment groups. Other common adverse events in the valsartan studies included headache (5.1%); nasopharyngitis (3.8%), upper respiratory tract infection (2.3%), and dizziness (2.0%). The incidence of headache was significantly lower in the amlodipine/valsartan combination therapy arm compared with amlodipine monotherapy (4.3 vs. 7.6%, respectively; $p<0.05$). The overall incidence of orthostatic hypotension was low in all studies (0.3–0.5%). With regard to laboratory parameters,

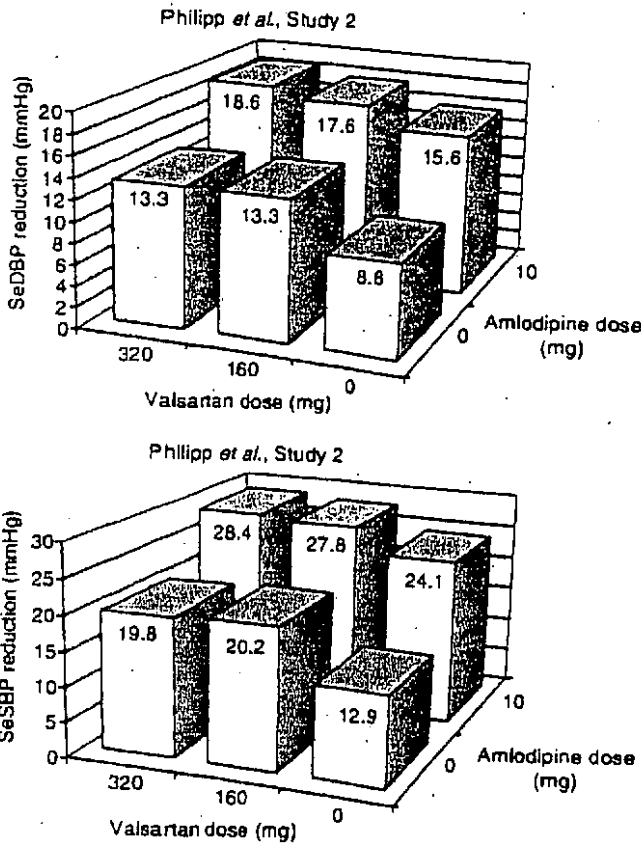


Figure 3. LS mean reductions in SeDBP and SeSBP in patients treated with marketed dosages of amlodipine + valsartan (study 2)¹²

Table 3. LS mean reductions in SeDBP and SeSBP after 8 weeks of treatment with amlodipine monotherapy in factorial studies

Amlodipine doses	SeDBP, mmHg (placebo-corrected)			SeSBP, mmHg (placebo-corrected)		
	Chrysant et al. ¹¹	Philipp et al. study 1 ¹²	Philipp et al. study 2 ¹²	Chrysant et al. ¹¹	Philipp et al. study 1 ¹²	Philipp et al. study 2 ¹²
2.5 mg	NA	−9.3 (−2.5)	NA	NA	−12.4 (−5.7)	NA
5 mg	−10.0 (−6.5)	−11.5 (−4.7)	NA	−14.3 (−11.5)	−15.1 (−8.4)	NA
10 mg	−13.3 (−9.8)	NA	−15.6 (−6.8)	−18.9 (−16.1)	NA	−24.1 (−11.2)

LS, least squares; NA, not applicable; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure

Table 4. LS mean reductions in SeDBP and SeSBP after 8 weeks of treatment with ARB monotherapy in factorial studies

ARB	SeDBP, mmHg (placebo-corrected)			SeSBP, mmHg (placebo-corrected)		
	Chrysant <i>et al.</i> ¹¹	Philipp <i>et al.</i> study 1 ¹²	Philipp <i>et al.</i> study 2 ¹²	Chrysant <i>et al.</i> ¹¹	Philipp <i>et al.</i> study 1 ¹²	Philipp <i>et al.</i> study 2 ¹²
Olmesartan						
10 mg	-8.8 (-5.3)	—		-10.9 (-8.1)	—	—
20 mg	-9.9 (-6.4)	—	—	-12.8 (-10.0)	—	—
40 mg	-10.9 (-7.4)	—	—	-15.4 (-12.6)	—	—
Valsartan						
40 mg	-	-10.1 (-3.3)	NA	—	-11.8 (-5.1)	NA
80 mg	-	-9.7 (-2.9)	NA	—	-12.9 (-6.2)	NA
160 mg	-	-11.0 (-4.2)	-13.3 (-4.5)	—	-15.1 (-8.4)	-20.2 (-7.3)
320 mg	-	-13.4 (-6.6)	-13.3 (-4.5)	—	-15.7 (-9.0)	-19.8 (-6.9)

ARB, angiotensin receptor blocker; LS, least squares; NA, not applicable; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure

Table 5. LS mean reductions in SeDBP and SeSBP after 8 weeks of treatment with amlodipine/ARB in factorial studies

	SeDBP, mmHg (placebo-corrected)	SeSBP, mmHg (placebo-corrected)
Amlodipine/olmesartan medoxomil		
5 mg/10 mg	-14.3 (-10.8)	-22.6 (-19.8)
10 mg/10 mg	-16.7 (-13.2)	-24.8 (-22.0)
5 mg/20 mg	-14.6 (-11.1)	-22.6 (-19.8)
10 mg/20 mg	-17.7 (-14.2)	-28.1 (-25.3)
5 mg/40 mg	-16.3 (-12.8)	-25.1 (-22.3)
10 mg/40 mg	-19.4 (-15.9)	-28.5 (-25.7)
Amlodipine/valsartan		
2.5 mg/40 mg	-10.8 (-4.0)	-15.5 (-8.8)
5 mg/40 mg	-14.6 (-7.8)	-19.6 (-12.9)
2.5 mg/80 mg	-13.4 (-6.6)	-17.0 (-10.3)
5 mg/80 mg	-14.5 (-7.7)	-20.8 (-14.1)
2.5 mg/160 mg	-13.3 (-6.5)	-16.7 (-10.0)
5 mg/160 mg	-14.2 (-7.4)	-19.5 (-12.8)
10 mg/160 mg	-17.6 (-8.8)	-27.8 (-14.9)
2.5 mg/320 mg	-14.2 (-7.4)	-18.3 (-11.6)
5 mg/320 mg	-15.9 (-9.1)	-22.7 (-16.0)
10 mg/320 mg	-18.6 (-9.8)	-28.4 (-15.5)

ARB, angiotensin receptor blocker; LS, least squares; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure

there were no clinically significant differences between treatment groups.

Discussion

A notable difference between the studies was the inclusion criteria, which led to a patient population

with more severe systolic hypertension in the olmesartan medoxomil study compared with the valsartan studies (mean baseline SeSBP 163.8 mmHg vs. 152.8–156.7 mmHg). Note that, relative to DBP, goal SBP is particularly difficult to obtain, requiring drug doses and combinations that go beyond those necessary for control of DBP¹³. Mean baseline SeSBP was relatively high in the olmesartan medoxomil study, and SBP was included in the definition of goal BP (<140/90 mmHg or <130/80 mmHg for patients with diabetes), whereas the only goal-related results reported in the valsartan studies were response rates defined as DBP <90 mmHg or a ≥ 10 mmHg reduction from baseline and control rates defined as DBP <90 mmHg.

The mean baseline DBP was 99.3 and 99.1 mmHg in the valsartan study 1 and study 2, respectively. Olmesartan medoxomil study patients started with a higher baseline mean DBP of 101.6 mmHg. Consequently, a greater reduction in DBP was necessary in the olmesartan medoxomil study population in order to achieve a DBP goal of <90 mmHg. As would be expected from these discrepancies, proportions of patients achieving their target DBP were relatively high with amlodipine/valsartan versus the proportions of patients achieving target SBP/DBP with amlodipine/olmesartan medoxomil.

Placebo response was greater in the valsartan studies (LS mean SBP reduction of 6.7 and 12.9 mmHg in study 1 and 2, respectively; and LS mean DBP reduction of 6.8 and 8.8 mmHg in study 1 and 2, respectively) compared with the olmesartan medoxomil study (LS mean SBP reduction of 2.8 mmHg and LS mean DBP reduction of 3.5 mmHg). In the valsartan studies, patients randomized to the maximum dose combination were started with 1 week of amlodipine 2.5 mg (study 1) or amlodipine 5 mg (study 2) and

valsartan 160 mg, then up-titrated. In contrast, patients in the olmesartan medoxomil study were immediately randomized to the maximum dose combination. This variation in treatment administration, and differences in washout protocols prior to study entry, may be a source of heterogeneity between the studies and in the patients' responses to therapy.

The demographics of patients differed substantially in the racial composition and BMI status between studies. These differences between study populations may potentially have had an impact upon BP-lowering efficacy due to the increased preponderance of difficult-to-treat patients in the olmesartan study as opposed to the valsartan studies. For example, hypertension management in obese individuals, who were greater in number in the olmesartan medoxomil study, is complicated by poorer response to treatment, and the increased need for multiple medications¹⁴.

The differences in patient demographics should be considered when interpreting the observation that BP lowering in the olmesartan study was remarkably similar to that seen in the valsartan studies. Differences in demographics may also have accounted for the larger BP decreases in patients receiving placebo in the valsartan studies. The studies also recruited patients from different geographical areas, and lifestyle or dietary factors may also have contributed to heterogeneity between the studies. Inclusion and exclusion criteria were also different between the studies. For example, consumption of more than one pack of cigarettes per day was a criterion for exclusion from the olmesartan study but apparently not the valsartan studies.

However, generally the results of this analysis show that the BP-lowering efficacy of low- and high-dose combination amlodipine/olmesartan medoxomil and amlodipine/valsartan are at least comparable. At the maximal dose, amlodipine 10 mg/olmesartan medoxomil 40 mg provided the largest placebo-corrected reductions in both LS mean SeDBP and SeSBP (15.9 and 25.7 mmHg, respectively, as opposed to 9.8 and 15.5 mmHg, respectively, with maximal dose amlodipine 10 mg/valsartan 320 mg).

At lower doses, reductions in SeSBP tended to be greater with amlodipine/olmesartan medoxomil versus amlodipine/valsartan. As opposed to increasing the dose of a single agent, administering a combination of agents with complementary modes of action may result in better BP-lowering efficacy and improved adverse events profile⁹. CCBs can stimulate release of renin and increased sympathetic outflow, which is blunted by the addition of a renin-angiotensin-blocking agent, such as an ARB⁹. As opposed to monotherapy, efficacy was enhanced by CCB/ARB combination therapy in these factorial studies (additive activity consistent with the complementary

mechanisms described above). Note, however, that combined therapy with valsartan 160 mg in combination with amlodipine 10 mg has been reported to be unable to attenuate amlodipine-induced sympathetic activation¹⁵. It is not clear whether differences between the ARBs with respect to attenuation of amlodipine-induced sympathetic activation could help to explain the difference in BP-lowering efficacy between different amlodipine/ARB combinations. Such a hypothesis requires prospective validation.

In terms of complementary mechanisms in relation to ARBs, thiazide diuretics represent another rational add-on class of antihypertensive^{5,9}. Administration of a diuretic potentiates a similar cascade of events to that of a CCB⁹. In the same way that the current review of factorial-design amlodipine/ARB studies supports the rational use of this combination therapy for patients with hypertension, a previously conducted review of factorial-design ARB/HCTZ (hydrochlorothiazide) studies supports the rational use of ARB/HCTZ combination therapy¹⁶. Note that, in the review of ARB/HCTZ combinations, high-dose olmesartan 40 mg/HCTZ 25 mg was associated with the greatest placebo-corrected reduction in BP as opposed to other ARB/HCTZ combinations involving irbesartan, telmisartan or valsartan¹⁶. This finding is consistent with findings related to amlodipine/olmesartan medoxomil versus amlodipine/valsartan in the current review.

Differences between placebo-corrected BP changes in amlodipine monotherapy-treated patients may be due in part to the higher mean baseline BP of patients entering the olmesartan study (Table 2). As well as reviewing the antihypertensive effects of different amlodipine/ARB combination therapies, this comparison also provided information on the comparative efficacy of ARB monotherapies. For example, olmesartan medoxomil 40 mg produced a placebo-corrected LS mean reduction in SeDBP of 7.4 mmHg, and valsartan 320 mg produced placebo-corrected LS mean reductions of 6.6 and 4.5 mmHg in valsartan studies 1 and 2. As well as improving efficacy, administering a combination of agents with complementary modes of action may also result in an improved adverse events profile⁹. Risk of edema with CCBs can be ascribed to potent unopposed arterial vasodilation¹⁷, but this can be counterbalanced by dilation of the venous circulation with renin-angiotensin system blockade⁹. In the amlodipine/olmesartan medoxomil and amlodipine/valsartan factorial studies, safety profiles of both combination therapies were consistent with the known pharmacologic properties of each of their components, and amlodipine-induced peripheral edema was partially reduced by combining with an ARB at some dose combinations.

Conclusions

This comparison of findings from the literature supports the rational use of amlodipine/ARB combination therapy for patients with hypertension. Contextual comparison of the combinations of amlodipine/olmesartan medoxomil and amlodipine/valsartan evaluated in similarly designed factorial studies revealed that BP was effectively reduced at the maximal marketed doses of 10 mg/40 mg and 10 mg/320 mg, respectively. This comparison of findings is limited by the small number of studies analyzed and differences between patient populations. Determination of which of the two combinations is more efficacious could be achieved by a meta-analysis comprising further published studies. Such an analysis would negate many of the sources of heterogeneity inherent within the three studies compared here. Due to the current unavailability of additional study data, an alternative would be a clinical study encompassing a direct head-to-head trial of amlodipine 10 mg/olmesartan medoxomil 40 mg with the maximal marketed dose of amlodipine 10 mg/valsartan 320 mg in order to eliminate potentially confounding aspects of the current analysis.

Acknowledgments

Declaration of interest: Funding for editorial assistance was provided by Daiichi Sankyo, Inc. The authors thank Jennifer M. Kulak, PhD, and Christopher J. Jones, PhD, Wolters Kluwer Health, for their editorial assistance in the preparation of this manuscript. Figures 2 and 3 reprinted from Clin Ther, 29(4), Philipp T, et al, Two multicenter, 8-week, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension, 563-580, Copyright (2007), with permission from Excerpta Medica, Inc.

References

- Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13
- Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72
- Rosendorff C, Black HR, Cannon CP, et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 2007;115:2761-88
- Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007;49:69-75
- Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105-87
- Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. *Drugs* 2002; 62:443-62
- Weber MA. Creating a combination antihypertensive regimen: what does the research show? *J Clin Hypertens (Greenwich)* 2003;5:12-20
- Weir MR. Targeting mechanisms of hypertensive vascular disease with dual calcium channel and renin-angiotensin system blockade. *J Hum Hypertens* 2007;21:770-9
- Epstein BJ, Vogel K, Palmer BF. Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs* 2007;67:1309-27
- Swales P, Williams B. Calcium channel blockade in combination with angiotensin-converting enzyme inhibition or angiotensin II (AT(1)-receptor) antagonism in hypertensive diabetics and patients with renal disease and hypertension. *J Renin Angiotensin Aldosterone Syst* 2002;3:79-89
- Chrysant SG, Melino M, Kariki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther* 2008;30:587-604
- Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther* 2007;29:563-80
- Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002;20:1461-4
- Chrostowska M, Szczeh R, Narkiewicz K. Antihypertensive therapy in the obese hypertensive patient. *Curr Opin Nephrol Hypertens* 2006;15:487-92
- de Champlain J, Karas M, Assouline L, et al. Effects of valsartan or amlodipine alone or in combination on plasma catecholamine levels at rest and during standing in hypertensive patients. *J Clin Hypertens (Greenwich)* 2007;9:168-78
- Ram CV. Antihypertensive efficacy of angiotensin receptor blockers in combination with hydrochlorothiazide: a review of the factorial-design studies. *J Clin Hypertens (Greenwich)* 2004;6:569-77
- Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. *Curr Cardiol Rep* 2002;4:479-82

CrossRef links are available in the online published version of this paper:
<http://www.cmrojournal.com>
 Paper CMRO-4776_4, Accepted for publication: 4 November 2008
 Published Online: 8 December 2008
 doi:10.1185/03007990802597456