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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Referencia : Expediente No. **06.008.335**
Asunto : Solicitud de patente para: **COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE TELMISARTANO O UNA DE SUS SALES EN COMBINACIÓN CON AMLODIPINA O NIFEDIPINA**
Solicitante : BOEHRINGER INGELHEIM INTERNATIONAL GMBH
Fecha solicitud : 30 de enero de 2006

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. **19409** notificado por fijación en lista del 15 de diciembre de 2011.

2. Mediante oficio No. **19409** 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:

2.1 De la solicitud de patente

2.1.1 Título

Señala el Examinador que el título de la solicitud no corresponde con el objeto de la misma porque la combinación reivindicada se refiere a una composición y no al uso de la misma el cual no es patentable.

2.1.2 Reivindicaciones

De manera resumida, el Examinador ha expuesto lo siguiente:

- Reivindicación 1: hace referencia a una composición con una combinación que no se encuentra soportada en la descripción
- Reivindicación 4: el grupo farmacológico “diurético” no caracteriza un compuesto específico, de manera que no se define la composición de manera correcta. Adicionalmente, no está soportada en la descripción.
- Reivindicaciones 5 y 6: carece de soporte en la descripción

2.2 Análisis de patentabilidad

2.2.1 Nivel inventivo

El Examinador cita el documento D12: WO0243807 titulado “Combination of Organic Compounds”. Sin embargo, hay apartes del análisis que hacen referencia a un documento D8 no referenciado. Por lo anterior, se asume que la comparación técnica y demás análisis y conclusiones hacen referencia al documento D12 y no al documento D8.

Se afirma que la composición reivindicada se diferencia de D12 en que dicho documento no menciona una composición específica que comprende los principios activos telmisartano o una de sus sales, en combinación con amlodipina o nifedipina y que debido a la falta de evidencia de un efecto técnico contribuido por la combinación reivindicada, un apersona del oficio normalmente versada en la materia podría lograr obviamente dicha combinación.

3. Respuesta a las objeciones

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

3.1 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 3 reivindicaciones, así como un nuevo título para la solicitud.

Así, siguiendo las amables observaciones del Examinador no se han incluido en esta oportunidad las reivindicaciones 4 a 5. Igualmente, se ha modificado la reivindicación 2 para indicar que la composición se presenta en un comprimido bicapa. Esta modificación está

soportada en la descripción, página 12, línea 25, página 14, línea 19 y en el ejemplo de la combinación de telmisartan con metformina.

Por otra parte, se ha modificado el título de la solicitud para que refleje mejor el título de la presente solicitud. El título ha sido modificado por el de:

COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE TELMISARTANO O UNA DE SUS SALES EN COMBINACIÓN CON AMLODIPINA O NIFEDIPINA

Se solicita tener en cuenta este nuevo pliego reivindicatorio, el cual presenta la materia reivindicada de manera más clara, por lo que las objeciones formuladas en este sentido por el Examinador se ven superadas.

3.2 De la reivindicación 1, soporte y nivel inventivo

El Examinador considera que la reivindicación 1 no se encuentra soportada en la descripción. Sin embargo, la descripción específicamente enseña en la página 10, líneas 16 a 20:

"También en el tratamiento de la hipertensión con inhibidores del sistema renina-angiotensina (RAS) en combinación con un antagonista de calcio como amlodipina o nifedipina o un antagonista de la aldosterona como espironolactona o eplerenona, el telmisartano debe ser considerado un inhibidor preferido de RAS".

[subrayado fuera del texto]

Dicha preferencia es debida a la activación pronunciada de los genes regulados por PPAR γ la cual es *"particularmente marcada para la sustancia activa telmisartano". "La inducción de la transcripción de los genes regulados por PPAR γ es conocida por las tiazolidindionas utilizadas como antidiabéticos (por ejemplo, rosiglitazonas) y activada por su unión con el receptor PPAR γ y su activación (ver descripción página 3, líneas 18 a 20 y 25). Este beneficio terapéutico del telmisartano bien sea solo o en combinación con otro agente activo no era obvio a partir del arte previo y ha sido confirmado en varias oportunidades. Como ejemplo de esto se adjunta al presente memorial una copia de Benson et al. en "Hypertension" 43: 993-1002 (2004).*

Adicionalmente, la combinación de telmisartano con amlodipina mejora considerablemente el evento adverso de edema periférico observado cuando se administra amlodipina de manera individual. En este contexto, se solicita atentamente tener en cuenta la

copia del documento Ahrens y Bramlage en Medicamentos en "Drugs of Today" 46(5): 339-359 (2010) que se presenta junto con el presente memorial y que indica en la segunda columna de la página 345: *"La combinación de telmisartan/amlodipina demostró ser efectiva y bien tolerada con menos edema periférico".* Igualmente la última rase de dicha página enseña *"la atenuación del edema no ha sido observada con otras combinaciones, tal como amlodipina y HCTZ".*

Por su parte, la sección de conclusión revela al final de la página 347 que *"el edema periférico es hasta 59% menor cuando se emplea 40 mg de telmisartano en combinación con 10 mg de amlodipina, comparado con 10 mg de monoterapia sola.*

Por lo anterior, se considera que la combinación reivindicada está soportada en la descripción y que los resultados experimentales prueban que la combinación reivindicada está asociada con un número de beneficios terapéuticos que no resultan predecibles en absoluto a partir del estado de la técnica. En consecuencia, la presente invención no sólo enseña una combinación novedosa sino también inventiva es decir, una combinación a la que la persona medianamente versada no llegaría de manera inevitable en vista de las enseñanzas de los documentos D1 y D2.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. Anexos

- Nuevo pliego reivindicatorio conformado por 3 reivindicaciones
- Formulario de modificaciones en solicitud pendiente
- Benson et al. en "Hypertension" 43: 993-1002 (2004)
- Ahrens y Bramlage en Medicamentos en "Drugs of Today" 46(5): 339-359 (2010)

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

 COLO-09255-264-005-1
COLO-09255-841-032-7
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No. M-2012-211521\JMS



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FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE:	
	☐ Corrección de Error Material ☒ Modificación a una solicitud	
2	SOLICITANTE Nombre: BOEHRINGER INTERNATIONAL GMBH Sociedad constituida y existente bajo las leyes de Alemania. Dirección: Binger Strasse 173, 55216 Ingelheim, Alemania Domicilio: Ingelheim, Alemania 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 PÁEZ Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax: 211 86 50 E-mail: clientes@cavelier.com Domicilio: Bogotá, Colombia.	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>35.456.344</u> T. P. <u>23.555</u>
4	Número de expediente: <u>06.008.335</u>	
5	Descripción de la corrección o modificación solicitada: <u>Presento nuevo capítulo reivindicatorio compuesto por 3 reivindicaciones con el fin de superar las</u> <u>objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que</u> <u>el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.</u>	
6	Comprobante de pago No. _____ Fecha: _____	
7	Anexos ☐ Comprobante de pago de la tasa por \$120.000, 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.	

on

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NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA:

Lea Clemencia Sobres

C.C. 35.456.344 de Usaquén T.P.A. 23.555

JMS

REIVINDICACIONES

- 1.** Composición farmacéutica que comprende telmisartano o una de sus sales en combinación con amlodipina ó nifedipina;
- 2.** La composición de la reivindicación 1, caracterizada porque contiene 20-200 mg de telmisartano en un comprimido bicapa.
- 3.** La composición de la reivindicación 2, caracterizada porque contiene 40, 80 o 160 mg de telmisartano.

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Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



**Identification of Telmisartan as a Unique Angiotensin II Receptor Antagonist
With Selective PPAR γ -Modulating Activity**
Stephen C. Benson, Harrihar A. Pershadsingh, Christopher I. Ho, Amar Chittiboyina,
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Identification of Telmisartan as a Unique Angiotensin II Receptor Antagonist With Selective PPAR γ -Modulating Activity

Stephen C. Benson, Harrihar A. Pershadsingh, Christopher I. Ho, Amar Chittiboyina, Prashant Desai, Michal Pravenec, Nianning Qi, Jiaming Wang, Mitchell A. Avery, Theodore W. Kurtz

Abstract—The metabolic syndrome is a common precursor of cardiovascular disease and type 2 diabetes that is characterized by the clustering of insulin resistance, dyslipidemia, and increased blood pressure. In humans, mutations in the peroxisome proliferator-activated receptor- γ (PPAR γ) have been reported to cause the full-blown metabolic syndrome, and drugs that activate PPAR γ have proven to be effective agents for the prevention and treatment of insulin resistance and type 2 diabetes. Here we report that telmisartan, a structurally unique angiotensin II receptor antagonist used for the treatment of hypertension, can function as a partial agonist of PPAR γ ; influence the expression of PPAR γ target genes involved in carbohydrate and lipid metabolism; and reduce glucose, insulin, and triglyceride levels in rats fed a high-fat, high-carbohydrate diet. None of the other commercially available angiotensin II receptor antagonists appeared to activate PPAR γ when tested at concentrations typically achieved in plasma with conventional oral dosing. In contrast to ordinary antihypertensive and antidiabetic agents, molecules that can simultaneously block the angiotensin II receptor and activate PPAR γ have the potential to treat both hemodynamic and biochemical features of the metabolic syndrome and could provide unique opportunities for the prevention and treatment of diabetes and cardiovascular disease in high-risk populations. (*Hypertension*. 2004;43:993-1002.)

Key Words: receptors, angiotensin II ■ angiotensin II ■ renin-angiotensin system ■ insulin resistance ■ losartan

All currently available classes of antihypertensive drugs were developed before it was widely recognized that increased blood pressure is closely associated with insulin resistance and dyslipidemia and well before public health authorities established diagnostic criteria for the metabolic syndrome.¹⁻³ Thus, the antihypertensive drugs in use today were designed primarily to affect cellular and biochemical mechanisms contributing to increased blood pressure and not to address the disordered carbohydrate and lipid metabolism that often accompany hypertension as part of the metabolic syndrome. Given the major impact of the metabolic syndrome on cardiovascular disease morbidity and mortality,⁴⁻⁶ the availability of antihypertensive agents that also improve insulin resistance and dyslipidemia could be of considerable clinical value.

Numerous studies have demonstrated that the peroxisome proliferator-activated receptor- γ (PPAR γ) plays an important role in regulating carbohydrate and lipid metabolism and that ligands for PPAR γ can improve insulin sensitivity, reduce triglyceride levels, and decrease the risk for atherosclerosis.⁷⁻¹⁵ PPAR γ ligands also have modest antihypertensive effects re-

lated at least in part to their ability to promote peripheral vasodilation.¹⁶⁻¹⁹ Several thiazolidinedione ligands for PPAR γ have been approved for the treatment of type 2 diabetes; however, these agents have limited capacity to reduce blood pressure and can provoke fluid retention, weight gain, edema, and heart failure in a significant proportion of patients with diabetes.²⁰⁻²² Such side effects can also occur with nonthiazolidinedione ligands of PPAR γ and are unlikely to be related to the thiazolidinedione moiety per se.^{18,23,24} Thus, currently approved synthetic ligands for PPAR γ cannot be used to effectively treat the abnormal hemodynamic features of the metabolic syndrome and are associated with adverse effects that are of particular concern for diabetic individuals predisposed to impaired cardiac function.

Recently, we observed an interesting structural resemblance between telmisartan, an angiotensin II (Ang II) type 1 receptor antagonist approved for the treatment of hypertension, and pioglitazone, a PPAR γ ligand approved for the treatment of type 2 diabetes.²⁵ This discovery supported the possibility that certain molecules might have the capacity not

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only to block the Ang II receptor, a key cell surface receptor involved in the regulation of blood pressure,²⁶ but also to activate PPAR γ , an intracellular nuclear hormone receptor involved in the regulation of carbohydrate and lipid metabolism. Theoretically, such bifunctional molecules could treat both the hemodynamic and biochemical features of the metabolic syndrome and have greater potential for preventing atherosclerotic cardiovascular disease than conventional antihypertensive agents. Moreover, given that blockade of the renin-angiotensin system can inhibit renal sodium reabsorption and attenuate the fluid retention and edema associated with peripheral vasodilators,²⁷ such molecules could also lead to the development of new antidiabetic PPAR γ ligands with improved safety profiles.

Herein we report that the biphenyl, nontetrazole Ang II receptor blocker (ARB) telmisartan can act as a partial agonist of PPAR γ ; influence the expression of PPAR γ target genes involved in the regulation of carbohydrate and lipid metabolism; and reduce glucose, insulin, and triglyceride levels in an animal model of diet-induced insulin resistance. Molecular modeling studies suggest that telmisartan might influence PPAR γ activity by interacting with regions of the ligand-binding domain (LBD) that are not typically engaged by full agonists of the receptor. In contrast, molecular modeling and receptor transactivation studies indicate that other ARBs lack telmisartan's potential for receptor interaction and have relatively little or no effect on PPAR γ activity. These findings (1) demonstrate that at least one of the ARBs currently in clinical use has the capacity to activate PPAR γ and (2) suggest a number of interesting opportunities for developing improved therapeutic approaches to the metabolic syndrome as well as type 2 diabetes and other clinical disorders that might be influenced by activity of the renin-angiotensin system, PPAR γ , or both.

Methods

Experimental Compounds

Ang II receptor antagonists and thiazolidinedione ligands of PPAR γ were obtained from the pharmacy and purified by high-performance liquid chromatography. Candesartan cilexetil and olmesartan medoxomil were hydrolyzed to their active forms before high-performance liquid chromatography purification. Both losartan and its more active metabolite EXP 3174 were used in some studies.

PPAR Transactivation Assays

PPAR γ activity was determined by transactivation assays in CV-1 cells (CCL-70 line from the American Type Culture Collection [ATCC], Manassas, Va) transfected by use of the GenePorter transfection reagent (Gene Therapy Systems) delivering 200 ng of the murine PPAR γ expression plasmid pGAL4-mPPAR γ LBD, 1 μ g luciferase reporter plasmid pUAS-tk-luc (both courteously provided by P. Tontonoz, Howard Hughes Medical Institute and Department of Pathology, University of California, Los Angeles), and 400 ng of pCMVSPORT β -gal (Gibco) as an internal control. Twenty-four hours after transfection, cells were treated with varying concentrations of the test compounds and incubated for an additional 24 hours. Cell extracts were assayed for luciferase and β -galactosidase activity with Promega assay systems. All treatments were performed in triplicate and normalized for β -galactosidase activity. Assays for PPAR α and PPAR δ activity were performed in a similar fashion with pGAL-mPPAR α LBD and pGAL4-mPPAR δ LBD plasmids courteously supplied by R. Evans, Salk Institute for Biological Studies and Howard Hughes Medical Center. Agonist concentrations yielding half-maximal activation (EC₅₀ values) were calculated with Graph-

Pad Prism version 3.03 software (GraphPad Software, Inc). In some experiments, a range of concentrations of the ARBs was combined with a fixed concentration of rosiglitazone to test for receptor antagonist activity. To determine ligand effects on the full-length human PPAR γ receptor, we also used a cloned full-length human receptor (pDEST-hPPAR γ) obtained from Dr N. Takahashi (Kyoto University, Kyoto, Japan). The reporter was p3xPPRE-tk-luc, and transfections were performed with 400 ng of each plasmid.

Molecular Modeling in PPAR γ

Computational studies were performed on a Silicon Graphics Octane 2 workstation equipped with 2 parallel R12000 processors, V6 graphics board, and 512-MB memory. Energy minimization and molecular dynamics were accomplished in the DISCOVER module of InsightII (Accelrys Inc), whereas the AFFINITY module of InsightII was used for docking studies.²⁸ The crystal structure of the partial agonist GW0072 in the PPAR γ LBD was used for telmisartan docking studies (PDB code 4PRG).²⁹ Hydrogen atoms were added, and the structure was subjected to preliminary minimization, followed by molecular dynamics to relieve internal strain while heavy atoms were tethered to their original positions. Docking was performed with a previously described protocol.³⁰

Adipocyte Differentiation Assay

Differentiation assays were performed on murine 3T3-L1 preadipocytes (CCL-173 line from the ATCC) by a modification of the technique of Smith et al.³¹ After the cells reached confluence, they were incubated in Dulbecco's modified Eagle medium containing 1.0 μ mol/L dexamethasone, 5 μ g/mL insulin, and 0.5 mmol/L 1-methyl-3-isobutylxanthine with 5% calf serum for 32 hours, after which the cells were washed with phosphate-buffered saline and incubated in medium containing varying concentrations of test compounds or the vehicle dimethyl sulfoxide (DMSO). Five days after treatment, cells were fixed and stained with oil red O. Quantitative evaluation of adipogenesis was performed with a modified version of the method of Ramirez-Zacarias et al³² by measuring absorbance at 510 nm.

PPAR γ Target Gene Expression Assays

Expression levels of the PPAR γ target genes *AP2* and *CD36* were determined by real-time polymerase chain reaction (PCR) of cDNA prepared from 3T3-L1 preadipocytes incubated with the test compounds or DMSO vehicle control for 3 days. Additional studies were performed in adult human subcutaneous adipocytes (Cambrex, Walkersville, Md) to determine the effects of the test compounds on expression of *PCK1* that codes for phosphoenolpyruvate carboxykinase-1 (PEPCK-C). This gene was selected because PEPCK-C has been proposed to be a key mediator of the effects of PPAR γ ligands on fatty acid metabolism and insulin sensitivity.³³ Previous studies have also shown that acetyl coenzyme A carboxylase (ACC2) is a major regulator of muscle fatty acid metabolism.^{34,35} Therefore, we also tested the effects of rosiglitazone, telmisartan, irbesartan, and valsartan on the expression of ACC2 in murine muscle myotubes that had been derived by differentiation of the C2C12 myoblast cell line (CRL 1772 from the ATCC). Total RNA was isolated by standard methods, and cDNA was prepared and analyzed by real-time PCR testing with SYBR green reagents, as previously described.³⁶ The cyclophilin (peptidylprolyl isomerase A) gene was used as an internal control, with results being determined in triplicate by the preferred method of Muller et al^{37,38} and displayed as the amount of mRNA in drug-treated samples relative to that in the vehicle-treated control, which was arbitrarily defined as 1. Primer specificity was confirmed by melting point analysis for each primer pair. Primer sequences are available on request.

Dietary Model of Insulin Resistance

Male Sprague-Dawley rats were placed on a high-fat, high-carbohydrate diet (Teklad Diet TD03203 containing 60% fructose, 10% lard, and 0.06% magnesium) at 6 weeks of age. Two days after starting the diet, the rats were randomized into 3 different groups

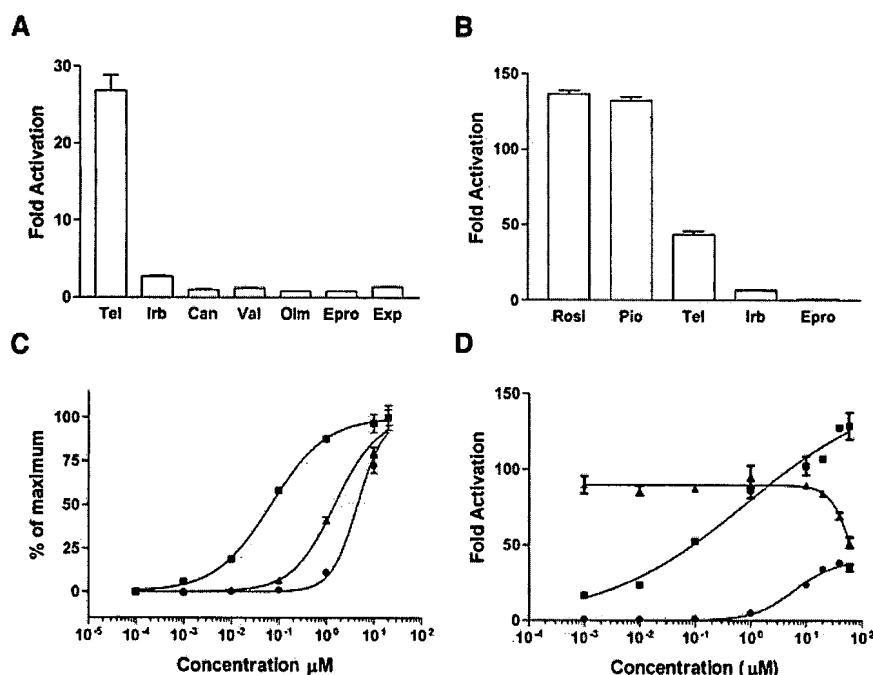


Figure 1. Telmisartan is a partial agonist of PPAR γ . A, Comparison of the ability of different ARBs to activate PPAR γ in a cell-based transient transfection assay. Cells were treated with 10 μ M/L telmisartan (Tel), irbesartan (Irb), candesartan (Can), valsartan (Val), olmesartan (Olm), eprosartan (Epro), or the EXP 3174 (Exp) active metabolite of losartan (Los). B, Comparison of the ability of different thiazolidinediones and ARBs to maximally activate PPAR γ . Cells were treated with 40 μ M/L rosiglitazone (Rosi), pioglitazone (Pio), telmisartan (Tel), irbesartan (Irb), or eprosartan (Epro). C, Dose-response curves comparing potency of Rosi (squares), Pio (triangles), and Tel (circles) in the transient transfection assay. D, Mixing experiment showing that high concentrations of Tel can antagonize the ability of Rosi to activate PPAR γ . Cells were treated with different concentrations of Rosi alone (squares), Tel alone (circles), or a mixture of 1 μ M/L Rosi with different concentrations of Tel (triangles).

($n=10$ rats per group): group 1, telmisartan dose ≈ 5 mg/kg body weight per day; group 2, losartan dose ≈ 5 mg/kg body weight per day; and group 3, controls (no drug). The drugs were administered by dissolving the commercially available medications in the drinking water at an initial concentration of 40 mg/L. Because fluid intake did not scale linearly with body weight, the drug intakes based on body weight tended to decline over time. Therefore, drug concentrations in the drinking water were increased during the course of the study to help maintain the scheduled dosing. Food and fluid intakes were measured each day, and a pair-feeding protocol was followed to ensure equivalent food intakes among the 3 groups. Rats in the losartan group and the control group were pair-fed the same amount of chow consumed by the telmisartan group the day before. This ensured that the telmisartan group consumed at least as much if not slightly more food than the other groups. The fluid intakes and therefore drug intakes were similar in the telmisartan and losartan groups. After 5 weeks, serum levels of glucose, insulin, and triglycerides were obtained in the semifasting state (the night before blood sampling the animals were given a restricted amount of chow equivalent to 3 g/100 g body weight at 5 PM, and blood was drawn the following morning through the tail vein in the unanesthetized state). The protocol was continued for an additional 9 weeks, at which time glucose tolerance testing (oral glucose tolerance test) was performed in conscious animals in the semifasting state by sampling blood for glucose and insulin measurements after oral administration of glucose, 100 mg/100 g body weight. Serum levels of glucose and triglycerides were measured by spectrophotometric methods, and insulin levels were measured by radioimmunoassay (Linco).

Statistical Analysis

Statistical analysis was performed by Student t test or ANOVA followed by Dunnett multiple comparison test or the Student-Newman-Keuls test for comparisons across multiple groups. Statistical significance was defined as $P<0.05$. Data are expressed as mean $\pm$ SEM.

Results

Telmisartan Is a Partial Agonist of PPAR γ

We tested the ability of different ARBs to activate PPAR γ in a heterologous transactivation assay that eliminates interference from endogenous nuclear receptors (Figure 1A).⁹ Thus, exogenously added drugs including rosiglitazone and telmisartan do

not cause any activation of the reporter gene in the absence of the PPAR construct (data not shown). In the full assay system including the PPAR γ construct, we found that telmisartan was the only ARB that caused substantial activation of PPAR γ (Figure 1A). Although irbesartan appeared to cause slight activation of PPAR γ (2- to 3-fold activation) when tested at 10 μ M/L, none of the other ARBs, including the active metabolite of losartan, increased PPAR γ activity when tested at this concentration (Figure 1A). Moreover, telmisartan was the only ARB that activated PPAR γ when tested at lower concentrations (1 to 5 μ M/L) that can be achieved in plasma with conventional oral dosing (data not shown).³⁹ Telmisartan concentrations of <10 μ M/L did not significantly affect the activity of PPAR α or PPAR δ , although 25 μ M/L telmisartan appeared to cause a modest activation (4-fold) of PPAR α (data not shown).

Telmisartan functioned as a moderately potent ($EC_{50}=4.5$ μ M/L), selective PPAR γ partial agonist, activating the receptor to 25% to 30% of the maximum level achieved by the full agonists pioglitazone and rosiglitazone (Figure 1B and 1C). Corresponding EC_{50} values for rosiglitazone and pioglitazone were 0.066 and 1.5 μ M/L, respectively. As expected for a partial agonist, high concentrations of telmisartan (>10 to 20 μ M/L) in the presence of the full agonist rosiglitazone (1 μ M/L) attenuated the level of receptor activation otherwise achieved by the full agonist alone (Figure 1D). It should be noted that under normal circumstances, plasma concentrations of telmisartan do not reach 10 to 20 μ M/L. Thus, in patients with diabetes, administration of telmisartan is unlikely to interfere with the therapeutic effects of a simultaneously administered thiazolidinedione. We also tested telmisartan for its ability to activate full-length human PPAR γ by using the full-length receptor and the luciferase reporter gene fused to the tandemly repeated PPAR γ DNA response element. At 10 and 1 μ M/L, rosiglitazone achieved activation levels of 16-fold, whereas the values for telmisartan were 6-fold and 3-fold, respectively. Other sartans were inactive up to 40 μ M/L.

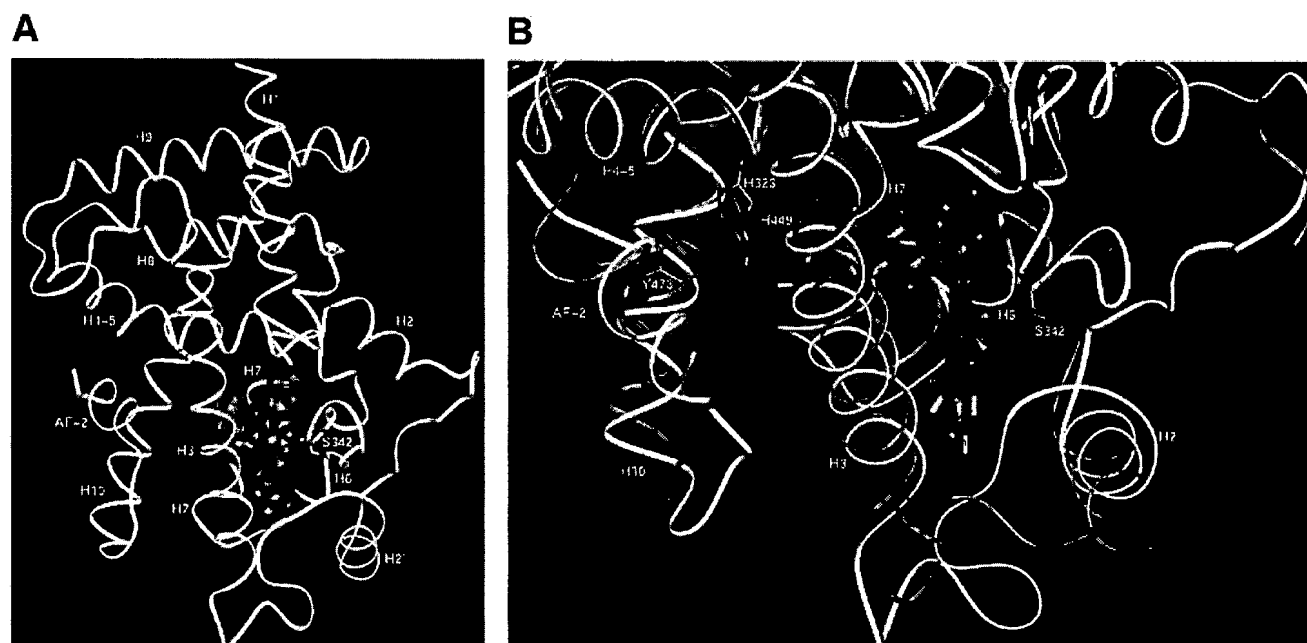


Figure 2. Binding mode of telmisartan in the PPAR γ LBD. A, The protein backbone is illustrated as a yellow ribbon with telmisartan shown as a Van der Waals space-filling representation in blue. Ser342 is colored by atom types. B, Superimposition of telmisartan bound to the PPAR γ LBD (extracted from PDB structure 4PRG) on the cocrystal structure of rosiglitazone and the PPAR γ LBD (PDB structure 2PRG). The protein bound to telmisartan is shown as a yellow ribbon; the protein bound to rosiglitazone is shown as a magenta ribbon. Telmisartan and rosiglitazone are represented as sticks in blue and orange, respectively. Residues His323, His449, and Tyr473 of the rosiglitazone-bound protein and Ser342 of the telmisartan-bound protein are shown as sticks colored by atom types. Hydrogen bonding interactions are shown as dashed white lines.

Molecular Modeling of Telmisartan in the PPAR γ LBD

Docking studies of the molecular binding mode in PPAR γ revealed that telmisartan is surrounded by helices H3, H6, and H7 (Figure 2A). The region of the LBD occupied by telmisartan is similar to that occupied by other partial agonists of PPAR γ , including GW0072 and nTZDpa (data not shown).^{29,40} The interaction of telmisartan with PPAR γ might be explained by strong hydrophobic interactions with many of the residues forming the H3 and H7 helices. Additionally, the hydrogen bond between the 1'-benzimidazole nitrogen and the amide proton of Ser342 might also contribute toward stabilization of this interaction (Figure 2A), particularly given that the partial agonists GW0072 and nTZDpa also form hydrogen bonds with the same serine residue.

The superimposition of telmisartan bound to PPAR γ on the cocrystal structure of rosiglitazone and PPAR γ is shown in Figure 2B. In contrast to the binding of full agonists such as rosiglitazone,⁴¹ telmisartan, like other partial agonists including GW0072 and nTZDpa, does not appear to make direct contact with the activation function helix (AF-2) or with the adjacent histidine residues (Figure 2B). Interaction with the AF-2 helix has been shown to be responsible for receptor stabilization and activation by full agonists of PPAR γ .^{9,41} The lack of interaction of telmisartan with the AF-2 helix likely explains its inability to fully activate the receptor.

To further understand the structural changes in the protein induced by binding of ligands with different biologic profiles (full agonists vs partial agonists), we analyzed the crystal structures of the PPAR γ LBD in its native form (PDB code

1PRG), the PPAR γ LBD bound to the full agonist rosiglitazone (PDB code 2PRG), and the PPAR γ LBD bound to the partial agonist GW0072 (PDB code 4PRG). As previously noted, the crystallographically determined structure of PPAR γ bound to a partial agonist (GW0072) was more similar to the native (apo) structure than the crystallographically determined conformation of the protein bound to the full agonist rosiglitazone.²⁹ This was evidenced by the root mean square deviation (RMSD) of the backbone atoms that, for the partial agonist versus the apo protein, was 0.87, whereas this difference for the full agonist was 2.58. It is interesting to note that the shift in the structure of the native receptor induced by binding of GW0072 appears primarily to be a result of changes in the backbone conformation of helices H3 and H7. The RMSD for the backbone atoms of helices H3 and H7 in the 2 structures was found to be 0.79. Although binding of the full agonist resulted in a significant structural change in the native protein (RMSD 2.60 for the backbone atoms), the conformation of helices H3 and H7 in this case did not differ significantly from the native protein (RMSD 0.44 for the backbone atoms). Based on these comparisons and the observation that protein-bound complexes of partial agonists like telmisartan, nTZDpa, and GW0072 are mainly stabilized by hydrophobic interactions with helices H3 and H7, an alteration in the conformation of these helices induced by partial agonists might contribute to the differences in receptor activation and target gene expression caused by such ligands compared with full agonists. In preliminary studies, high concentrations of telmisartan did not displace radiolabeled rosiglitazone from a recombinant form of the LBD (data not shown), further suggesting that telmisartan does not

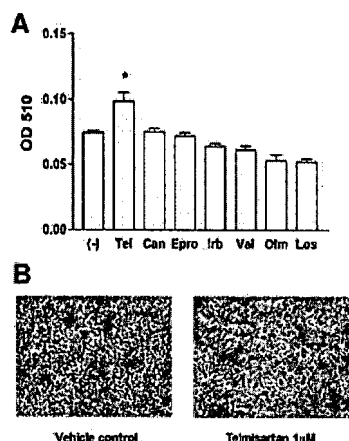


Figure 3. Telmisartan induces adipocyte differentiation in 3T3-L1 cells. A, Comparison of the effects of different ARBs on adipogenesis and lipid accumulation in 3T3-L1 cells as measured by the absorbance at 510 nm of oil red O eluted from stained cells. Cells were treated with 5 μ mol/L of the indicated compounds or DMSO vehicle (-) for 5 days. * P <0.01 compared with all other groups by ANOVA and Dunnett multiple comparison test. Drug abbreviations are as in the legend to Figure 1. B, Oil red O staining of 3T3-L1 cells treated with 1 μ mol/L telmisartan or DMSO vehicle control for 5 days.

interact with the receptor in the same fashion as conventional agonists of PPAR γ .

Docking studies of several tetrazole-containing ARBs, including losartan, EXP 3174, irbesartan, olmesartan, and candesartan, in the PPAR γ LBD revealed a different binding mode than for telmisartan. These tetrazole-containing ARBs made contacts with residues of helix H3 but not H7. Eprosartan, a nontetrazole ARB, was seen to interact with residues of helix H7 but not H3. None of these ARBs revealed a hydrogen bond with the binding domain or any interaction with the AF-2 helix. Thus, insufficient interaction with the PPAR γ LBD might explain the inability or poor ability of these other ARBs to activate the protein.

Telmisartan Induces Adipocyte Differentiation

PPAR γ plays a critical role in adipogenesis and has been shown to be necessary and sufficient for fat cell differentiation in cultured cells and in mice.^{8,42} Therefore, we compared the ability of telmisartan and other ARBs to induce adipocyte differentiation of 3T3-L1 cells, a well-known characteristic of PPAR γ ligands.^{7,9} Telmisartan but none of the other ARBs clearly induced adipogenesis when tested at a concentration of 1 to 5 μ mol/L (Figure 3 and data not shown). Although a higher concentration of irbesartan (10 μ mol/L) induced adipocyte differentiation, none of the other ARBs, including the active metabolite of losartan, induced adipogenesis even when tested at concentrations of up to 25 μ mol/L. In other experiments (data not shown), we found that the level of adipogenesis induced by rosiglitazone was $\approx$ 2 to 3 times greater than that induced by telmisartan. The relatively modest effect of telmisartan on adipogenesis is not surprising, given that other partial agonists of PPAR γ have also been found to be relatively weak stimulators, or even inhibitors, of adipogenesis compared with full agonists such as rosiglitazone.^{29,40,43}

Telmisartan Selectively Modulates the Expression of PPAR γ Target Genes

PPAR γ ligands influence the expression of multiple genes in differentiating preadipocytes and in mature adipocytes, such as *AP2* (*FABP4*) and *CD36*.^{44–46} When tested at a concentration of 5 μ mol/L, only telmisartan and irbesartan caused a substantial (>2-fold) increase in the expression of *AP2* and *CD36* in 3T3-L1 preadipocytes (Figure 4A and 4B). Whereas telmisartan and irbesartan both increased the expression of *AP2* and *CD36*, they appeared to have different effects on the expression of 2 other important genes related to lipid metabolism. In differentiated human adipocytes, telmisartan was the only ARB at concentrations of 2.5 to 5.0 μ mol/L that clearly increased the expression of the *PCK1* gene encoding

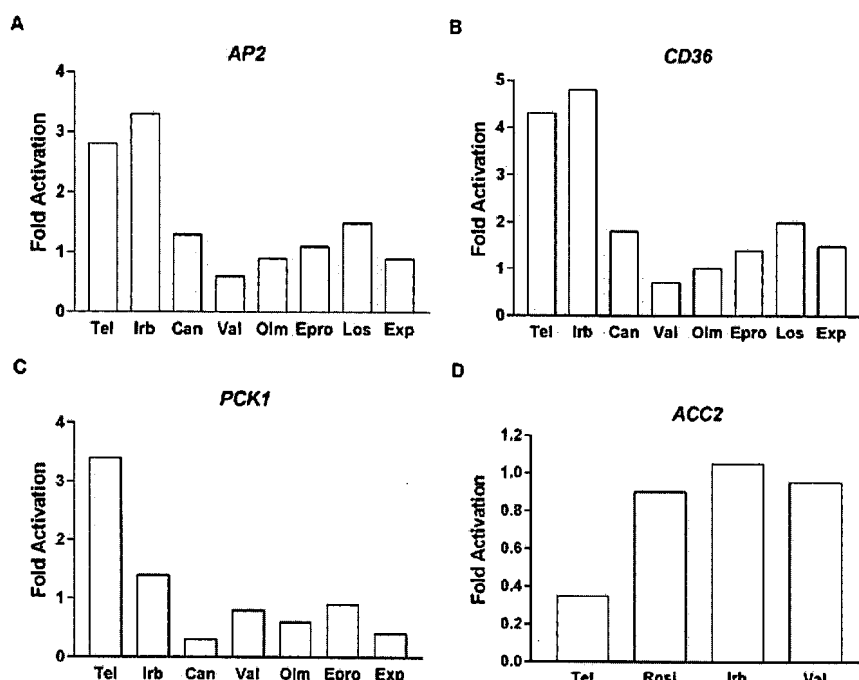


Figure 4. Telmisartan influences the expression of PPAR γ target genes in differentiating 3T3-L1 cells, mature human adipocytes, and murine myotubes, as measured by real-time PCR. A, Comparison of the effects of different ARBs on *AP2* expression in 3T3-L1 cells. B, Comparison of the effects of different ARBs on *CD36* expression in 3T3-L1 cells. C, Comparison of the effects of different ARBs on expression of the *PCK1* target gene encoding PEPCK in mature human subcutaneous adipocytes. D, Comparison of the effects of telmisartan, rosiglitazone, irbesartan, and valsartan on *ACC2* expression in differentiated C2C12 murine myotubes. For studies of *AP2*, *CD36*, and *ACC2*, cells were treated with 5 μ mol/L of the indicated compounds or DMSO vehicle control for 3 days. For studies of *PCK1*, human adipocytes were treated with 2.5 μ mol/L of the indicated compounds or DMSO vehicle control for 3 days. The real-time PCR assays were performed in triplicate, and in all panels each value represents the amount of mRNA in drug-treated samples relative to that in the vehicle-treated control, which was arbitrarily defined as 1. Drug abbreviations are as in the legend to Figure 1.

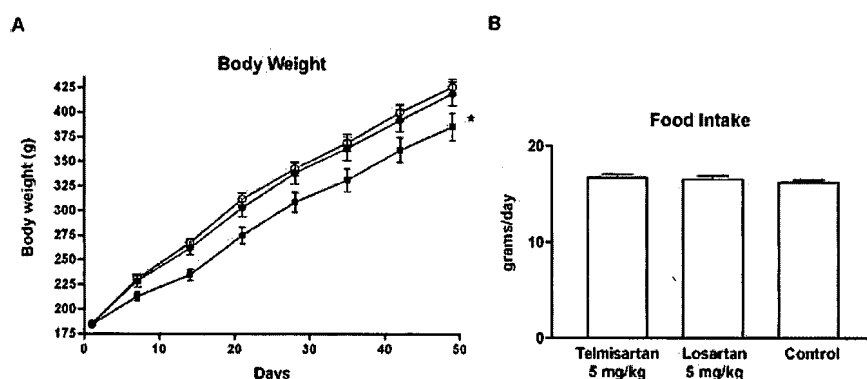


Figure 5. Telmisartan attenuates weight gain in rats fed a high-fat, high-carbohydrate diet. A, Mean body weights in rats given telmisartan, 5 mg/kg body weight per day (solid squares); losartan, 5 mg/kg body weight per day (solid circles); and in controls not given any drugs (open circles). B, Mean daily food intakes in rats treated with telmisartan or losartan and in untreated controls. Drug treatment groups and initial daily drug doses are listed below each bar graph. * $P < 0.01$ for effects of drug, time, and drug-time interaction on body weight by 2-way ANOVA.

PEPCK-C (Figure 4C). This is noteworthy because the induction of PEPCK-C activity in adipocytes and the resultant increases in glycerooneogenesis and fatty acid reesterification have been proposed to play an essential role in the antidiabetic actions of PPAR γ ligands.³³ In murine muscle myotubes, 5.0 $\mu\text{mol/L}$ telmisartan caused a 60% to 70% decrease in the expression of *ACC2*, whereas rosiglitazone, irbesartan, and valsartan had little or no effect on *ACC2* expression (Figure 4D). *ACC2* is a major regulator of muscle fatty acid metabolism, because this enzyme generates malonyl coenzyme A, a potent inhibitor of muscle carnitine palmitoyltransferase-1, which is a critical enzyme involved in fatty acid uptake in mitochondria. Accordingly, decreases in *ACC2* expression might be expected to promote increased fatty acid oxidation in skeletal muscle.³⁵

Telmisartan Improves Glucose, Insulin, and Triglyceride Levels

Figure 5A shows body weights in control rats and in rats given either telmisartan or losartan. The 2-way ANOVA showed a significant effect of the drug ($P < 0.01$), time ($P < 0.01$), and a drug-time interaction ($P < 0.01$) on body weight. Telmisartan administration caused a significant attenuation of weight gain compared with losartan and control groups ($\approx 10\%$), whereas losartan appeared to have little or no effect on body weight compared with controls. Remarkably, the telmisartan-induced attenuation of weight gain could not be attributed to reduced energy intake, because daily food consumption was nearly identical in all groups as a result of the pair-feeding protocol (Figure 5B). Fluid intakes were similar among all 3 groups (data not shown).

Serum glucose levels measured after 5 weeks of treatment were significantly decreased in the telmisartan group compared with both the losartan group ($P < 0.01$) and the control group ($P < 0.001$) by ANOVA and Student-Newman-Keuls testing (Figure 6). Serum insulin levels also tended to be lower in the telmisartan-treated animals (Figure 6). Although overall ANOVA testing did not achieve statistical significance ($P = 0.09$), the results of individual comparisons were consistent with lower insulin levels in the telmisartan group compared with the losartan group and the control group (both $P = 0.025$ by 1-tailed t testing and $P < 0.10$ by Student-Newman-Keuls testing; Figure 6B). Serum triglycerides were significantly decreased in the telmisartan treated group compared with both the losartan group ($P < 0.05$) and the control

group ($P < 0.01$) by ANOVA and Student-Newman-Keuls testing; Figure 6).

During the oral glucose tolerance test, serum levels of glucose were similar among all 3 groups (Figure 7). However, serum insulin levels were significantly lower in the telmisartan group compared with both the losartan group and control group throughout the glucose tolerance test (Figure 7). The area under the curve for insulin in the telmisartan-treated rats, $3.7 \pm 0.3 \text{ ng} \cdot \text{mL}^{-1} \cdot 2 \text{ h}^{-1}$, was significantly lower than in the losartan-treated rats ($6.0 \pm 0.7 \text{ ng} \cdot \text{mL}^{-1} \cdot 2 \text{ h}^{-1}$) and the control rats ($5.3 \pm 0.7 \text{ ng} \cdot \text{mL}^{-1} \cdot 2 \text{ h}^{-1}$; $P < 0.05$ by ANOVA and Student-Newman-Keuls testing). Compared with controls, losartan did not have significant effects on any of the parameters measured.

Discussion

On the basis of cellular assays of PPAR γ activation, we have found that the Ang II receptor antagonist telmisartan is also a partial agonist of PPAR γ , a well-known target of insulin-sensitizing drugs used to treat type 2 diabetes. In contrast, none of the other ARBs affected PPAR γ activity with the possible exception of irbesartan, which appeared to cause a modest activation of the receptor when tested at a concentration of 10 $\mu\text{mol/L}$. In addition to activating PPAR γ in cell-based transactivation assays, telmisartan increased the expression of known PPAR γ target genes in both murine preadipocyte fibroblasts and human subcutaneous adipocytes and induced adipogenesis in 3T3-L1 preadipocyte fibroblasts, as expected for a PPAR γ activator. Finally, in rats fed a high-fat, high-carbohydrate diet, orally administered telmisartan reduced glucose, insulin, and triglyceride levels, whereas losartan did not. In preliminary studies in obese Zucker rats that harbor mutant leptin receptors (data not shown), telmisartan did not appear to affect glucose, insulin, or triglyceride levels, suggesting that at least some of the beneficial metabolic effects of telmisartan might depend on the presence of an intact leptin signaling system.

The mechanism whereby telmisartan activates PPAR γ remains to be determined; however, given the substantial chemical structural differences between telmisartan and all of the other commercially available ARBs, it is not surprising that telmisartan has unique biologic properties. There are a number of possible mechanisms that could theoretically mediate the effects of telmisartan on PPAR γ activity, including but not limited to effects on the conformation or phos-

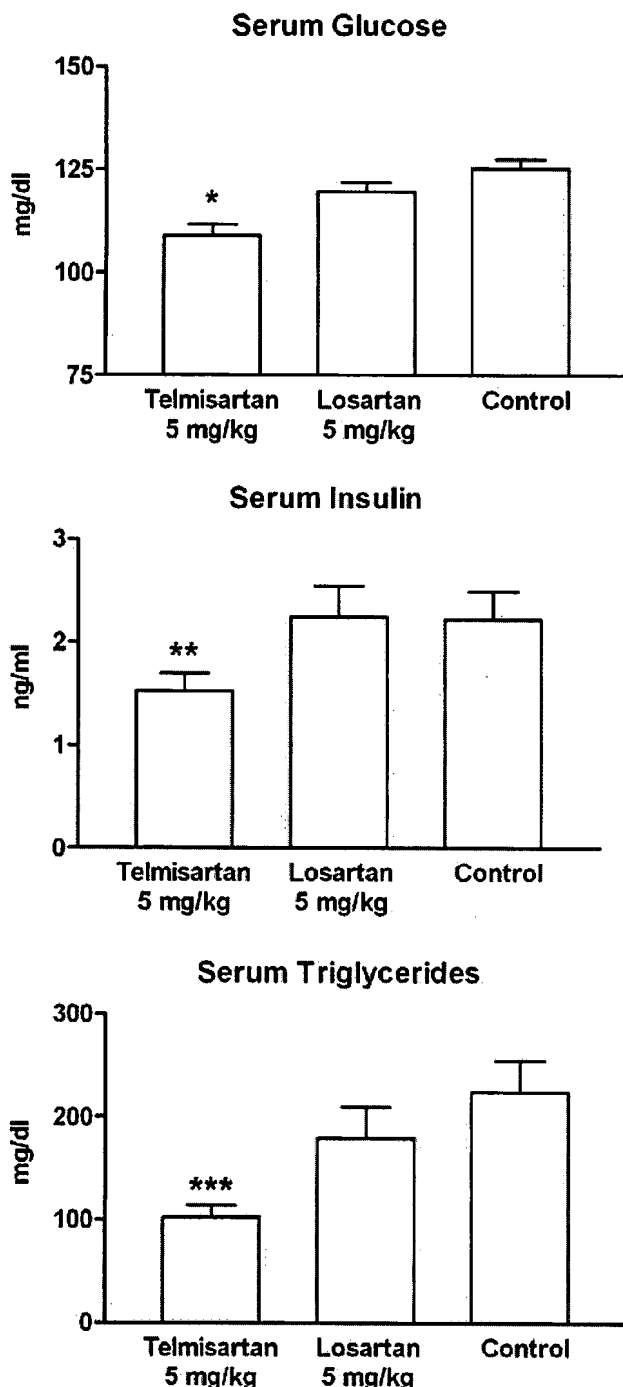


Figure 6. Telmisartan reduces serum levels of glucose, insulin, and triglycerides. Drug treatment groups and initial daily drug doses are listed below each bar graph. * $P < 0.001$ by ANOVA, $P < 0.001$ compared with control group, and $P < 0.01$ compared with losartan group by Student-Newman-Keuls testing. ** $P = 0.09$ by ANOVA, $P = 0.025$ compared with control group and losartan group by 1-tailed t testing, and $P = 0.09$ compared with control group and losartan group by Student-Newman-Keuls testing. *** $P < 0.01$ by ANOVA, $P < 0.01$ compared with control group, and $P < 0.05$ compared with losartan group by Student-Newman-Keuls testing.

phorylation status of the receptor, effects on the activity of coactivators or corepressors that modulate the transcriptional effects of PPAR γ , or even effects on endogenous ligands of PPAR γ . For example, molecular modeling studies suggest that telmisartan might fit within the LBD of PPAR γ in a

complex that is stabilized by hydrophobic interactions with helices H3 and H7, as well as by a hydrogen bond with the amide proton of Ser342. This binding mode is similar to that observed for the partial agonist GW0072.²⁹ In contrast, the other ARBs do not appear to have the same potential for interaction with the receptor like telmisartan. Although it remains to be determined whether the unusual ability of telmisartan to activate PPAR γ is indeed related to the receptor interactions identified in the modeling studies, it is clear that substantial differences exist between the chemical structures of telmisartan and the other ARBs.

Although telmisartan was developed with the goal of selectively blocking the Ang II type 1 receptor to treat hypertension, the finding that this molecule can also activate PPAR γ has potentially important therapeutic implications for pharmacological treatment of the metabolic syndrome, type 2 diabetes, and other clinical disorders that might be responsive to PPAR γ activators.⁴⁷ Because hypertension frequently occurs together with insulin resistance and dyslipidemia,⁴⁸ the availability of multifunctional molecules that treat more than just increased blood pressure or the associated metabolic disturbances could be of considerable clinical value. It is widely believed that the currently available ARBs are metabolically neutral and have little or no impact on carbohydrate and lipid metabolism when administered in conventional doses used to treat hypertension.²⁶ However, the current findings suggest that telmisartan might be an exception in this regard and provide insight into new strategies for developing molecules that could improve many if not all of the biochemical and blood pressure disturbances that compose the metabolic syndrome.⁴⁷

It should be emphasized that telmisartan is a partial agonist of PPAR γ and appears to function as a selective PPAR modulator with different effects on gene expression than a full agonist of PPAR γ like rosiglitazone. It is well known that partial agonists of PPAR γ can exert different effects on gene expression patterns than do full agonists and that even full agonists might differ among themselves with respect to their precise effects on gene expression profiles.^{40,49} Thus, it is not surprising that telmisartan, but not rosiglitazone, affected the expression of *ACC2*, a key gene involved in the regulation of muscle fatty acid metabolism. In fact, intense interest exists in the development of selective PPAR γ modulators that can exert beneficial effects on the expression of genes that regulate carbohydrate and lipid metabolism without causing changes in gene expression that promote weight gain, fluid retention, or the other adverse effects associated with administration of conventional PPAR γ activators.^{29,40,43,50} In the current study, it is noteworthy that telmisartan attenuated weight gain despite the use of a pair-feeding protocol that ensured comparable food intakes among all of the experimental groups. Other partial agonists of PPAR γ have also been shown to attenuate the weight gain ordinarily induced by a high-fat diet.^{40,49} The current observations raise the intriguing possibility that telmisartan might have the capacity to influence genes that regulate energy metabolism in vivo and should motivate future studies on the ability of telmisartan to attenuate weight gain in humans consuming high-fat, high-carbohydrate diets.

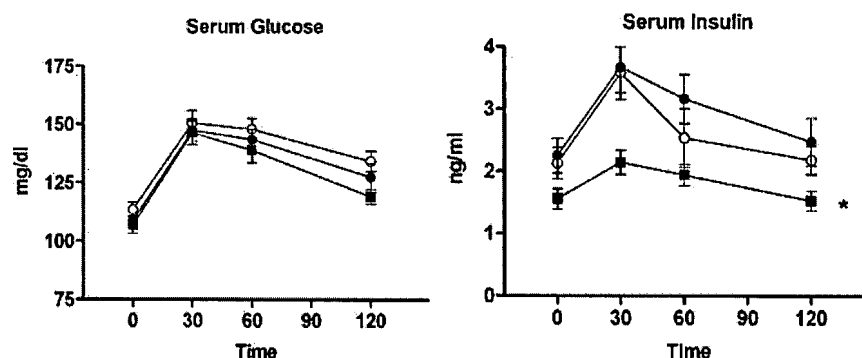


Figure 7. Telmisartan reduces insulin levels during oral glucose tolerance testing in rats fed a high-fat, high-carbohydrate diet. Serum glucose and insulin levels after oral administration of glucose, 100 mg/100 g body weight, to rats treated with telmisartan (solid squares), losartan (solid circles), or controls (open circles). *Area under the curve for insulin in the telmisartan-treated rats, $3.7 \pm 0.3 \text{ ng} \cdot \text{mL}^{-1} \cdot 2 \text{ h}^{-1}$, was significantly lower than in the losartan-treated rats ($6.0 \pm 0.7 \text{ ng} \cdot \text{mL}^{-1}$) and control rats ($5.3 \pm 0.7 \text{ ng} \cdot \text{mL}^{-1} \cdot 2 \text{ h}^{-1}$; $P < 0.05$ by ANOVA and Student Newman-Keuls testing).

In light of a number of clinical and experimental studies suggesting that angiotensin-converting enzyme (ACE) inhibitors can improve insulin sensitivity and decrease the incidence of new-onset type 2 diabetes in patients with hypertension,^{51–54} the question arises as to whether pharmacologic interruption of the renin-angiotensin system per se should be expected to lead to improvements in carbohydrate and lipid metabolism. However, recent studies have indicated that the insulin-sensitizing effects of ACE inhibitors might be more closely related to their effects on kinin metabolism rather than their effects on the renin-angiotensin system.^{54–56} Thus, based on the results of studies with ACE inhibitors, it could not have been predicted that any of the existing ARBs would activate PPAR γ and improve the disturbances in carbohydrate and lipid metabolism that are characteristic of the metabolic syndrome.

Although it is generally believed that ARBs do not exert significant effects on carbohydrate and lipid metabolism, such views are based largely on the results of clinical trials and experimental studies that have been conducted with ARBs that are structurally quite different from telmisartan. For example, measurements of systemic insulin action with the euglycemic clamp technique have failed to reveal any consistent effect of losartan on insulin sensitivity.⁵⁴ In the recent LIFE trial, the incidence of new-onset type 2 diabetes was reported to be significantly lower in hypertensive subjects treated with losartan than in those treated with atenolol, suggesting potential antidiabetic effects of angiotensin receptor blockade.⁵⁷ However, given the known diabetogenic effects of β -adrenergic blockers, it is possible that the lower incidence of new-onset diabetes in the losartan arm of the trial was related to a prodiabetic effect of atenolol rather than an antidiabetic effect of ARB. In the CHARM Preserved trial, the incidence of new-onset type 2 diabetes was significantly lower in subjects given candesartan than in those given placebo.⁵⁸ However, in other trials including CHARM Added, CHARM Alternative, and SCOPE, there was no significant difference in the incidence of new-onset diabetes in subjects given candesartan compared with controls.^{59–61} In the ALPINE and CROSS studies, candesartan appeared to have little or no effect on serum levels of insulin, glucose, or triglycerides.^{62,63} Although candesartan administration ap-

peared to improve an indirect estimate of insulin action in the CROSS study, it failed to show any effect on the HOMA (homeostasis model assessment) index of insulin resistance in the ALPINE study.^{62,63} Finally, in the obese Zucker rat, Henriksen et al⁶⁴ found that oral administration of an extremely high dose of irbesartan (50 mg/kg) improved insulin sensitivity but apparently failed to improve lipid levels. Thus, although the results of Henriksen et al are consistent with our finding of a weak effect of high concentrations of irbesartan on PPAR γ activity, they do not imply that conventional doses of irbesartan or any other ARB could be used to activate PPAR γ in vivo or treat the metabolic syndrome.

Recently, Janke and colleagues⁶⁵ have reported that very high concentrations of Ang II can inhibit differentiation of human preadipocytes and that high concentrations of irbesartan can enhance adipogenesis. On the basis of these findings and recent evidence showing that a lack of adipose tissue can promote diabetes by causing excess storage of fat in muscle, liver, and pancreas,⁶⁶ Sharma and colleagues⁶⁷ have proposed that blockade of the renin-angiotensin system per se might prevent diabetes by promoting the recruitment and differentiation of adipocytes. In the current studies, we found that moderate concentrations of telmisartan and high concentrations of irbesartan could activate PPAR γ and promote adipogenesis; however, other ARBs failed to show any effects on PPAR γ activity or adipogenesis. PPAR γ is known to play a pivotal role in adipogenesis, whereas the effect of the renin-angiotensin system on fat cell differentiation is much less clear, particularly given that very high concentrations of Ang II are typically required to observe effects on adipogenesis. If the adipogenic effects of telmisartan and irbesartan were related to blockade of the renin-angiotensin system in the cells we tested, one would have expected other ARBs also to induce adipogenesis. Moreover, the concentrations of telmisartan and irbesartan required to induce adipogenesis are far greater than the concentrations required to block the Ang II type 1 receptor, further suggesting that the in vitro effects of telmisartan or other ARBs on adipogenesis in the cells that we tested are unlikely to be related to Ang II receptor blockade. Thus, although our findings are consistent with the results of Sharma and colleagues, we believe that at least in the cell line we studied, the effects of telmisartan and

irbesartan on adipocyte differentiation are more likely related to their ability to activate PPAR γ rather than their ability to block Ang II receptors.

Perspectives

Aside from the potential use of telmisartan for the prevention and treatment of diabetes and the metabolic syndrome, the discovery that telmisartan can activate PPAR γ has a number of implications for the development of next-generation molecules for treating clinical disorders that are influenced by activity of the renin-angiotensin system and PPAR γ . Notwithstanding the results of the recent ALLHAT trial,⁵³ drugs that interrupt the renin-angiotensin system are considered by many to be superior for preventing hypertension-related target-organ damage than are antihypertensive agents that were not designed to interrupt the renin-angiotensin system.^{68–70} The development of novel ARBs that ameliorate insulin resistance and dyslipidemia as well as hypertension could provide even more effective options for preventing target-organ damage and cardiovascular disease in patients with hypertension, diabetes, or both. Such agents, either alone or in combination with ACE inhibitors, could also be useful for the prevention of new-onset diabetes in patients with hypertension or in other high-risk populations. Finally, given the known inhibitory effects of Ang II receptor blockade on renal sodium reabsorption, the current findings could provide new opportunities for developing antidiabetic PPAR γ ligands without the adverse effects of fluid retention, peripheral edema, and heart failure associated with conventional agonists of PPAR γ , like rosiglitazone and pioglitazone.^{20–22}

Acknowledgments

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IMPORTANCE OF A FIXED COMBINATION OF TELMISARTAN AND AMLODIPINE FOR THE TREATMENT OF HYPERTENSION

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SUMMARY

Patients with moderate to severe hypertension frequently require ≥ 2 antihypertensives to achieve blood pressure (BP) control. The combination telmisartan/amlodipine is especially suitable for the treatment of severely hypertensive, high-risk patients, because it offers a substantial and sustained 24-h BP-lowering effect and is well tolerated in a range of patients with hypertension, who are at risk for cardiovascular events. ACCOMPLISH was the first trial to test two fixed-dose combinations (the angiotensin-converting

enzyme inhibitor [ACEi] benazepril in combination with either the diuretic hydrochlorothiazide [HCTZ] or the calcium channel blocker amlodipine). It was shown that a combination including amlodipine was superior to that including HCTZ in reducing the risk of cardiovascular events and death among high-risk patients. Results of the ONTARGET study comparing telmisartan with ramipril showed that telmisartan was an equally effective alternative to ramipril and less likely to cause angioedema. The telmisartan/amlodipine combination is therefore a particularly attractive choice for difficult-to-control hypertensive patients at cardiovascular risk, including those with diabetes, or those who are obese, elderly, not controlled by amlodipine monotherapy, or who are intolerant to ACEi.

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INTRODUCTION

Hypertension is a highly prevalent risk factor for coronary heart disease (CHD), stroke, heart failure (HF), renal disease and recurrent cardiovascular events. It is estimated that nearly 1 billion people are affected by hypertension worldwide, and this figure is predicted to increase to 1.5 billion by 2025 (1). In its 2009 reappraisal of the guidelines, the European Society of Hypertension (ESH) Task Force recommended that, in general, systolic blood pressure (SBP) should be below 140 mmHg and diastolic blood pressure (DBP) below 90 mm Hg (2).

The combination of two drugs is recommended by the ESH/European Society of Cardiology (ESC) guidelines for initial treatment whenever hypertensive patients either have a high initial BP or are classified as being at high/very high cardiovascular risk because of the pres-

ence of organ damage, diabetes, renal disease or a history of cardiovascular disease (CVD) (3). Both thiazide diuretics such as hydrochlorothiazide (HCTZ) and calcium channel blockers (CCB) are recommended by the recent ESH/ESC guidelines as preferred agents for combination antihypertensive treatment together with renin angiotensin system (RAS)-blocking agents (3) (Fig. 1). Besides being highly effective in lowering BP, available fixed-dose combinations offer the advantage of easy, once-daily dosing, which has been shown to improve patient compliance. The choice of either combination is based on compelling indications for either component and in many cases is left up to the treating physician.

There are a number of reasons why combination therapy is becoming more widely available and prescribed. Firstly, data from a number of trials indicate that two or more drugs are needed to lower BP to the target of <

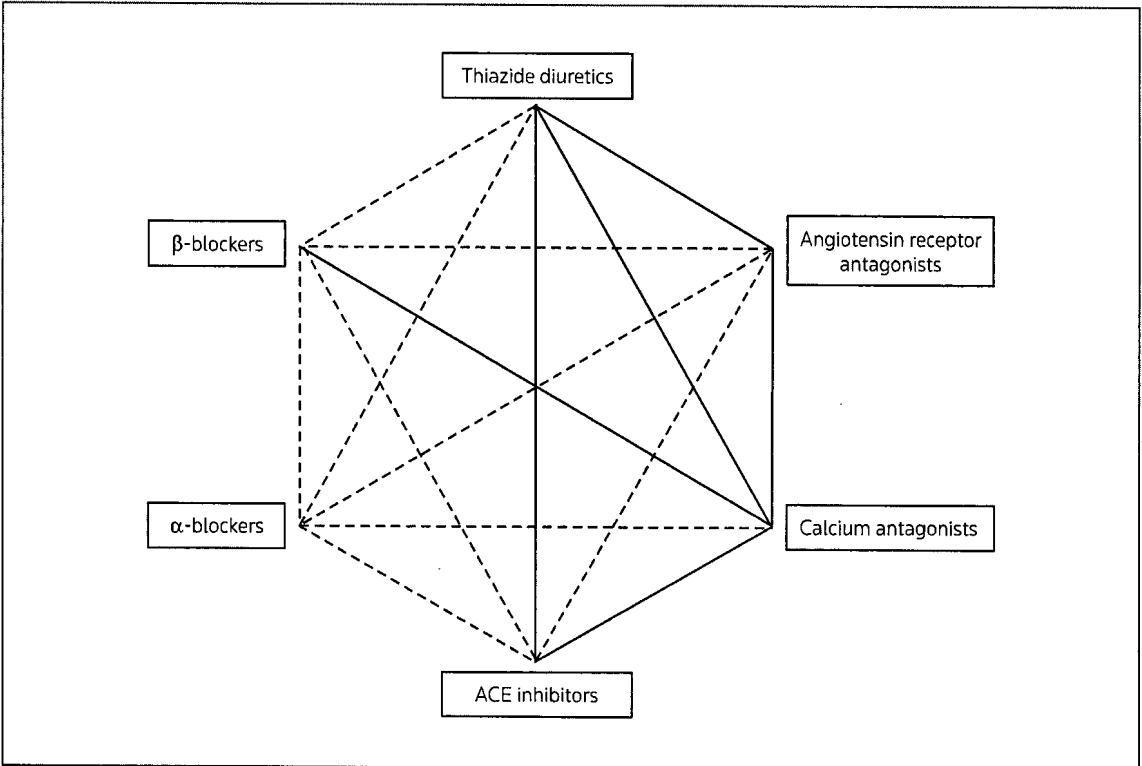


Figure 1. Hypertension treatment scheme. Possible combinations of classes of antihypertensive drugs. The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials. ACE, angiotensin-converting enzyme. From Mancia, G., De, B.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(6): 1105-87 with permission from Wolters Kluwer Health.

140/90 mmHg for patients with uncomplicated hypertension, and furthermore, for the majority of the hypertensive population who have concomitant disease, including diabetes, chronic kidney disease or coronary heart disease (4). In addition, combinations of drugs from different classes provide different and complementary mechanisms of action, which may help to minimize side effects associated with the respective monotherapy (3). Secondly, the combination of two drugs in one tablet improves patient compliance and, in the U.S., where a copayment is usually required for each prescription, a combination will be less expensive than separate prescriptions. Lastly, the most widely prescribed CCB in the U.S., amlodipine, is now a generic drug and therefore available as an inexpensive and highly effective partner to both ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) (5). The initiation of drug therapy with more than one agent may increase the likelihood of achieving the BP target in a more timely fashion, but particular caution is advised in choosing patient group-compatible antihypertensives.

ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) was the first trial to test two fixed-dose combinations (the ACEi benazepril in combination with either the diuretic HCTZ or the CCB amlodipine) (6). It was shown that a combination including amlodipine was superior to that including HCTZ in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. The trial was stopped early because of the significantly higher morbidity and mortality in the patient group receiving HCTZ. This led to a shift of thinking about how to combine antihypertensive drugs, and resulted in modification of diuretic- towards CCB-based combinations.

These findings launched the development of new, fixed, drug-drug combinations containing RAS blocking agents, especially ARBs in combination with amlodipine. Combinations of valsartan, olmesartan and telmisartan with amlodipine have also been introduced. Herein we review one of these combinations, telmisartan and amlodipine, and its use in the treatment of hypertensive high-risk patients.

EVIDENCE FOR TELMISARTAN AND AMLODIPINE

Telmisartan

Telmisartan is an ARB used in the treatment of hypertension. ARBs are primarily used for the treatment of hypertension when the patient is intolerant to ACEi ther-

apy. They do not inhibit the breakdown of bradykinin or other kinins, and are thus only rarely associated with the persistent dry cough and/or angioedema that limit ACEi therapy (Fig. 2). Telmisartan has binding affinity 3,000 times greater for angiotensin II type 1 (AT_1) than type 2 (AT_2) receptors and has the longest half-life ($t_{1/2} = 24$ h) compared to other ARBs (7), and hence possesses a long duration of action. In addition to blocking the RAS, telmisartan acts as a selective modulator of peroxisome proliferator-activated receptor PPAR γ , a central regulator of insulin and glucose metabolism. It is believed that this dual mode of action of telmisartan may provide protective benefits against the vascular and renal damage caused by diabetes and CVD.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) (8) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) (9) trial, examined the role of telmisartan when used alone or in combination with an ACEi in high-risk individuals with controlled hypertension.

Results of the ONTARGET study showed that in patients who have vascular disease or high-risk diabetes, but do not have HF, telmisartan was an equally effective alternative to ramipril and was less likely to cause angioedema (8). It is therefore the only ARB with proven cardiovascular protective benefits beyond BP reduction in a high-risk population. In this study, telmisartan was shown to conserve 95% (95% confidence interval [CI]: 83.2-106.3) of the benefits of ramipril assessed by the primary composite outcome, and 105% (95% CI 91.6-119.0) of the benefits assessed by the secondary outcome of cardiovascular death, myocardial infarction (MI) and stroke. This leaves most clinicians with two distinct choices: ACEi or ARBs in high-risk persons, including those with stable coronary disease, hypertension and diabetes. The ONTARGET study therefore does not rule out the use of an ACEi/ARB combination in severe HF, where angiotensin escape mechanisms are expressed and a dual blockade may be necessary (10, 11). However, lower BP seen with the combination therapy did not lead to fewer endpoints, as would be expected in the high-risk population without overt HF, making interpretation of the ONTARGET data challenging (12). The TRANSCEND study compared temisartan and placebo in high-risk patients intolerant to ACEi. Telmisartan was well tolerated in patients unable to tolerate ACEi, and rates of cardiovascular death, MI or stroke were modestly reduced when patients took telmisartan. Fewer patients were hospitalized for any cardiovascular reason compared to

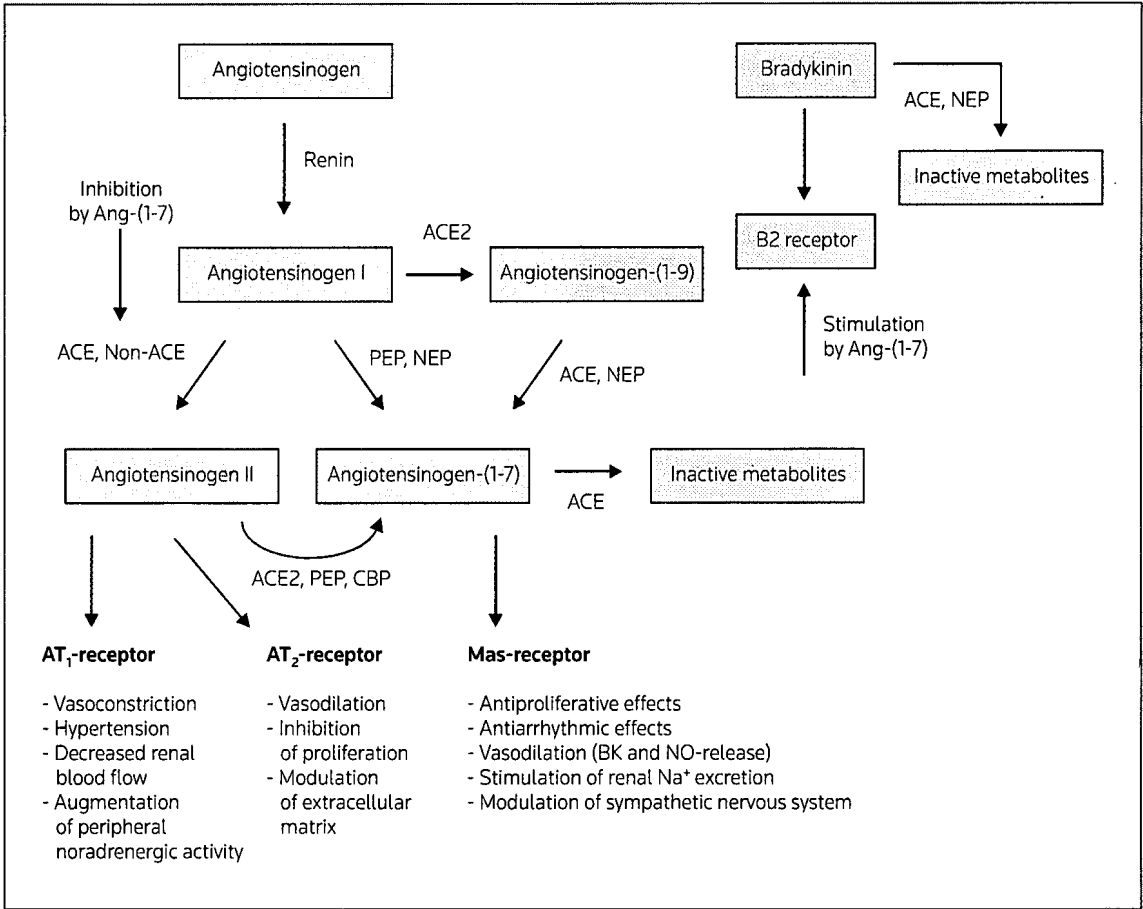


Figure 2. Mode of action of ACE inhibitors and ARBs. Pathways for the formation of biologically active angiotensin peptides. ACE, angiotensin-converting enzyme; ACE2, ACE-related carboxypeptidase; CBP, carboxypeptidase; BK, bradykinine; CBP, carboxypeptidase; EDRF, endothelium-derived relaxing factor; NEP, neutral endopeptidase; NO, nitric oxide; PEP, prolylendopeptidase; PKG, protein kinase G. Reprinted from Vasc Risk Manag, 3(1), Schindler, C., Bramlage, P., Kirch, W., Ferrario, C.M. Role of the vasodilator peptide angiotensin-(1-7) in cardiovascular drug therapy, 125-37, 2007, with permission from Doce Medical Press Ltd.

placebo, and fewer patients on telmisartan compared to placebo discontinued the medication. Given the fact that about 20% of hypertensive patients are unable to tolerate an ACEi, mainly due to cough, but also hypotensive symptoms, renal dysfunction or angioneurotic edema, telmisartan could prove valuable in reducing the occurrence of major cardiovascular events among this specific group of patients (9).

Both diabetes and hypertension confer increased cardiovascular risk, and patients with both conditions have more atherogenic risk factors. The Diabetics Exposed to Telmisartan And enalapril (DETAIL) study was designed to compare the long-term renal outcome

of treatment with telmisartan versus enalapril in patients with type 2 diabetes, mild to moderate hypertension and albuminuria. The study revealed that telmisartan conferred comparable renoprotection to enalapril and was associated with a low incidence of mortality (13). Since all patients were required to be tolerant to ACEi, no major differences in adverse events (AEs) between the enalapril and telmisartan groups were anticipated or seen.

Amlodipine

Amlodipine is a long-acting dihydropyridine-type CCB with a strong BP-lowering potency. Like other CCBs,

amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing BP. Amlodipine has a $t_{1/2}$ of approximately 35-50 h and is usually dosed between 5 and 10 mg as monotherapy.

In the CAMELOT study by Nissen et al. the effects of amlodipine or enalapril were compared versus placebo on cardiovascular events in patients with CHD and normal BP. It was shown that the administration of amlodipine resulted in reduced adverse cardiovascular events (14). This study also showed amlodipine to cause a deceleration of atherosclerosis progression, as visualized by intravascular ultrasound.

A quantitative overview of 12 trials in 94,338 patients was conducted by Wang et al. (15), which investigated the efficacy of amlodipine or ARBs for the prevention of stroke and MI in patients with hypertension, coronary artery disease or diabetic nephropathy. The trials involving an amlodipine group showed that it provided more protection against stroke and MI than other antihypertensive drugs. Compared with other drug regimens and evidenced by ALLHAT (16) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (17), amlodipine-based antihypertensive regimens might confer better outcome benefits, possibly by lowering central SBP or ambulatory pressure over 24 h (15).

The ASCOT-BPLA compared the effect of combinations of either amlodipine with perindopril (ACEi) vs. atenolol (β -blocker [BB]) with HCTZ on nonfatal MI and fatal CHD in multicenter, prospective, randomized, controlled trials in 19,257 hypertensive patients aged 40-79 years with at least 3 other cardiovascular risk factors. Patients were assigned to either amlodipine 5-10 mg, adding perindopril 4-8 mg as required (amlodipine-based regimen; $n = 9,639$), or atenolol 50-100 mg, adding bendroflumethiazide 1.25-2.5 mg and potassium as required (atenolol-based regimen; $n = 9,618$). Primary endpoints were nonfatal MI and fatal CHD. Compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 vs. 474; unadjusted hazard ratio [HR] 0.90; 95% CI: 0.79-1.02; $P = 0.1052$), fatal and nonfatal stroke (327 vs. 422; unadjusted HR: 0.77; 95% CI: 0.66-0.89, $P = 0.0003$), total cardiovascular events and procedures (1,362 vs. 1,602; 0.84; HR: 95% CI: 0.78-0.90, $P < 0.0001$), and all-cause mortality (738 vs. 820; HR: 0.89, 95% CI: 0.81-0.99; $P = 0.025$). The incidence of developing diabetes was less on the amlodipine-based regimen (567 vs. 799; HR: 0.70;

95% CI: 0.63-0.78, $P < 0.0001$) (17). These data demonstrated that the amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen.

A recent meta-analysis by Law et al. (18), in which a BP difference was examined between an antihypertensive agent and control, showed the efficacy of CCBs in preventing HF to be only slightly lower than that of other antihypertensive agents (19% vs. 24%). The question thus revolves around how much of this apparent inferiority of CCBs is a real limitation in their cardiovascular protection, the result of a difficulty in diagnosing a clinically relevant but soft outcome such as an incipient HF, or a consequence of trial designs preventing the use of diuretics and ACEi (agents essential in HF therapy) in patients randomized to CCBs (2).

COMBINATION TREATMENT WITH TELMISARTAN/ AMLODIPINE

Blood pressure-lowering efficacy

Several studies confirm that the telmisartan and amlodipine combination is effective and well tolerated in difficult-to-treat patients at cardiovascular risk, and in patients who have diabetes, are obese, elderly or not controlled by amlodipine alone (19-23). In a double-blind trial involving 1,461 patients with hypertension, the effects of various doses of either telmisartan (0, 20, 40 or 80 mg) plus amlodipine (0, 2.5, 5 or 10 mg) were examined during an 8-week period (20). Both telmisartan (irrespective of amlodipine dose; $P < 0.0001$) and amlodipine (irrespective of telmisartan dose; $P < 0.0001$) were shown to significantly lower BP, without evidence of counterproductive telmisartan-by-amlodipine interactions at any dose (not involving patients treated with placebo; $P = 0.1777$). As expected, the greatest reduction in DBP and SBP was observed when employing the combination therapy telmisartan/amlodipine as compared with respective monotherapies (Fig. 3). The greatest overall reduction in BP was observed with telmisartan 80 mg plus amlodipine 10 mg (mean reduction in SBP/DBP: $-26.4/-20.1$ mmHg; $P < 0.05$ vs. both monotherapies) (20). When the mean reductions in DBP or SBP were analyzed according to baseline categories, the four key combinations (telmisartan 40 or 80 mg plus amlodipine 5 or 10 mg) were all shown to consistently reduce BP even in patients with high baseline DBP (≥ 110 mmHg) and in patients with high baseline SBP (> 160 mmHg). BP drops of more than 20

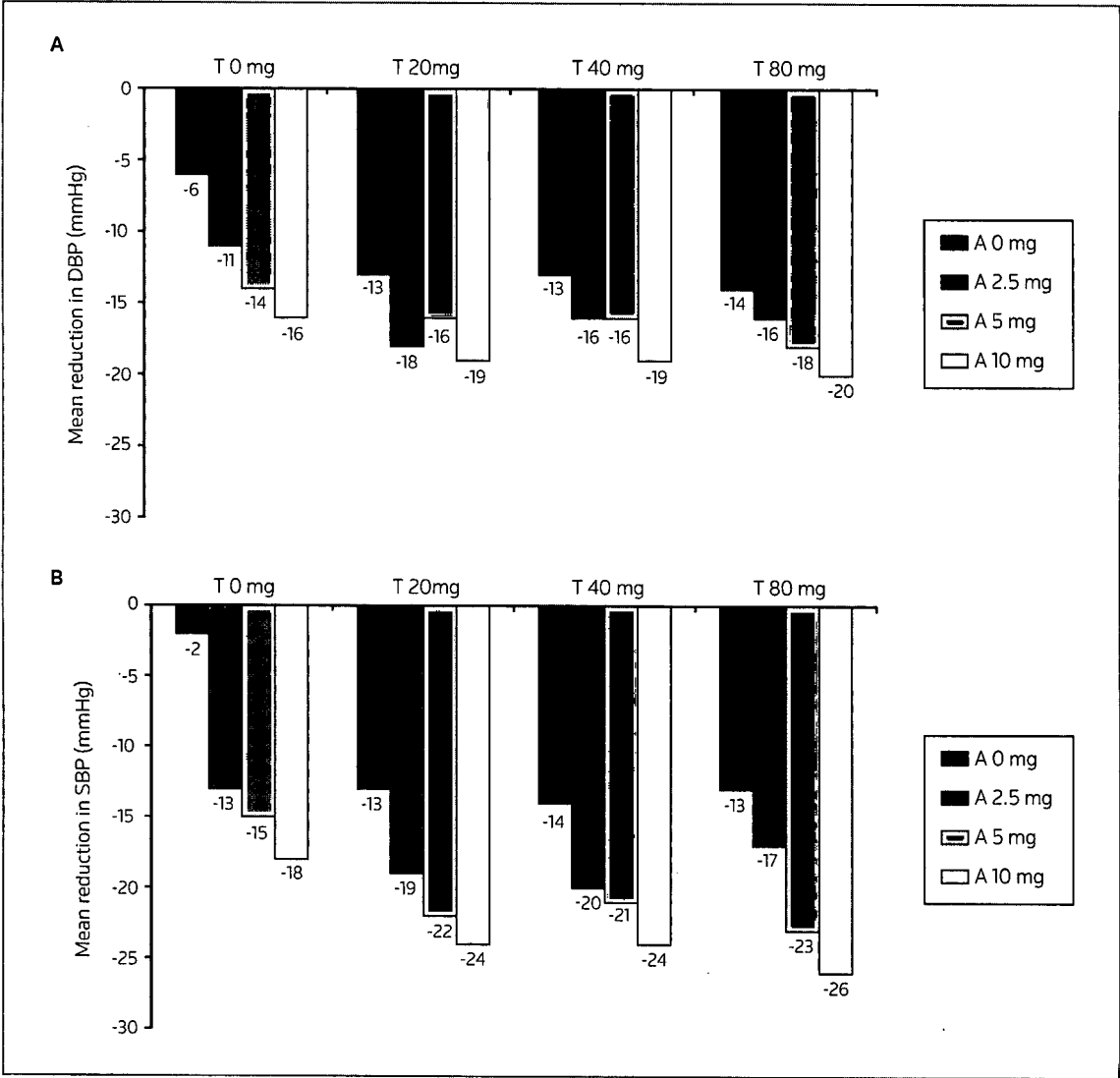


Figure 3. Antihypertensive effects of telmisartan-amlodipine at different doses. Effect of 8 weeks of treatment with telmisartan (T) 0, 20, 40, 80 mg plus amlodipine (A) 0, 2.5, 5, 10 mg on the change from baseline in the in-clinic seated trough (A) diastolic blood pressure (DBP; mmHg) or (B) systolic blood pressure (SBP; mmHg). $P < 0.05$ vs. T monotherapy. $P < 0.05$ vs. A monotherapy. Adapted with permission from Littlejohn, T.W. 3rd., Majul, C.R., Olvera, R. et al. Results of treatment with telmisartan-amlodipine in hypertensive patients. J Clin Hypertens (Greenwich) 2009, 11(4): 207-13.

mmHg DBP and more than 30 mmHg SBP were achieved with the combinations of telmisartan 40 or 80 mg and amlodipine 10 mg. Also, there was no relevant telmisartan-by-amlodipine interaction ($P = 0.2299$), thereby demonstrating that both substances have additive effects when combined in the investigated dose range (21).

Blood pressure reduction of telmisartan/amlodipine versus other combinations of antihypertensives

In the past, results from BP-lowering trials did not show a clear difference between the effects of the various classes of antihypertensive drugs on major cardiovascular events, i.e., the choice of drugs was generally interpreted to be less important than their respective ability

to lower BP (5). Newer findings from the ASCOT showed that an ACEi plus a CCB provide additional cardiovascular benefits over the combination of either BB plus a diuretic, indicating that inclusion of a diuretic might not be the best choice for combination therapy. Results from the ACCOMPLISH trial suggested that patients receiving an ACEi plus CCB respond better than patients receiving an ACEi and a diuretic (24). Furthermore, the use of a CCB in both ASCOT and ACCOMPLISH could have reflected additional benefits of CCBs, particularly in the high-risk patients enrolled in these two trials. CCBs have a potent vasodilating effect, but sympathetic nervous activity is also enhanced, which is being suppressed by the combination with ARBs. Combining ARBs and CCBs is a useful approach not only in additive BP-lowering, but also in decreasing lower extremity edema induced by CCB. These agents demonstrate benefits associated with their respective drug classes. The ARBs confer stroke protection, renal protection and tolerability similar to placebo, without dose-related symptomatic and metabolic AEs. On the other hand, CCBs are beneficial in reducing stroke, and treating angina and cardiac ischemia (25). Data from Littlejohn et al. suggest that despite significant BP-lowering effect, there are very few adverse orthostatic changes, including hypotension, with high-dose telmisartan/amlodipine combinations. This is consistent with the safety profile of telmisartan and amlodipine, both of which have a low propensity to cause orthostatic effects (21).

End organ protection

There is evidence that the cardiovascular benefits of specific classes of antihypertensive drugs extend beyond lowering BP (26). Experimental work has shown that amlodipine effectively increases the availability of vascular endothelial nitric oxide (NO) (27), whereas other studies have shown that the combined effects of amlodipine and an ACEi on NO are greater than the effect with either drug alone (6 and references therein). RAS blockade with ACEi or ARBs has turned out to be beneficial for all stages of hypertension. Both ACEi and ARBs can prevent or reverse endothelial dysfunction and atherosclerosis, thereby reducing the risk of cardiovascular events. Both ACEi and ARBs have been shown to reduce target organ damage in organs such as the kidney, brain and heart, and decrease cardiovascular mortality and morbidity in patients with congestive HF. Experimental data suggest an effect of ACEi and ARBs on the number and function of endothelial progenitor cells, revealing additional mechanisms of action of these drugs (28). Telmisartan showed renal protective benefits

in hypertensive type 2 diabetic patients with microalbuminuria or proteinuria (29), and the telmisartan-amlodipine combination was also found to decrease the urinary albumin excretion rate in hypertensive diabetic patients with microalbuminuria (30). Clinical studies have shown that ARBs such as telmisartan can be superior to other antihypertensive drugs in the prevention of stroke, even if there are no differences in BPs (31). Findings from animal experiments suggest that the underlying mechanisms include not just inhibition of the detrimental peripheral and central actions of angiotensin II mediated by AT₁ receptors, but also stimulation of the unopposed AT₂ receptor that is upregulated in the area of ischemia.

Amlodipine was found to prevent intima-media thickening (32, 33). In a meta-analysis of the effects of antihypertensive treatment on left-ventricular mass (LVM), CCBs and ARBs were reported to reduce LVM index by 11% and 13%, respectively, which are numerically greater reductions than those observed with other antihypertensive agents (34).

Tolerability and safety

The combination of telmisartan/amlodipine was demonstrated to be effective and well tolerated, with less peripheral edema (telmisartan 40-80 mg and amlodipine 5-10 mg 5.2% vs. amlodipine 10 mg 17.8%) compared with amlodipine 10 mg alone. It also provided effective BP reduction and control (< 140/90 mmHg) in patients whose BP was not controlled with amlodipine 5-10 mg alone, and in hypertensive patients at risk of cardiovascular events, including patients with type 2 diabetes, the elderly and obese patients (20, 21, 35, 36).

The safety analysis showed that the number of patients experiencing an AE was comparable among combination therapy (37.9%) and telmisartan (36.8%) and amlodipine (36.1%) monotherapies. Retention and drug adherence were high (92% and 98.4%, respectively). Although CCB-induced edema is not a new finding, the underlying mechanism is still not fully understood. It may involve pronounced vasodilatation in precapillary vessels, which could result in abnormal intracapillary pressure or it could be linked to interference in local vasodilator control. Renin-angiotensin-aldosterone system (RAAS) blockade is known to attenuate this effect, possibly via normalization of intracapillary pressure. However, the attenuation of edema has not been observed with some other combinations, such as amlodipine plus HCTZ (20, 37, 38).

Compliance

Poor compliance to antihypertensive therapy remains the greatest therapeutic challenge contributing to the lack of adequate BP control among patients with hypertension (39). Noncompliance can be attributed to patients' concerns over drug-related side effects, inconvenient or complicated dosing regimens, lack of patient education and health-related quality of life aspects (40). A study by Bramlage and Hasford (41) examined the cost consequences of poor persistence with pharmaceutical interventions in arterial hypertension. Their study aimed to evaluate not only the antihypertensive effects of drugs, but also to review patients' persistence with different pharmacotherapies, in order to explore the related expenditure, such as drug costs, overall healthcare expenditure and productivity costs. The study found that ARBs were favored in antihypertensive efficacy over other drug classes (ARBs > BBs > CCBs = thiazides > ACEi for SBP), as well as with regards to the treatment was highest with ARBs (ARBs > ACEi > CCBs > BBs > diuretics). Although drug costs for ARBs were found to be higher than with any other drug class, better compliance leads to substantial decreases in direct and indirect drug costs.

The fixed-dose combination of telmisartan/amlodipine can reduce the number of tablets taken by the patient and help to increase patient compliance and persistence, thus increasing effectiveness and lowering non-drug medical costs.

COMPELLING INDICATIONS

Certain patient populations appear to derive particular therapeutic benefit from specific combinations of antihypertensive agents. Diuretics such as HCTZ are particularly effective at reducing SBP and are therefore recommended for the treatment of elderly patients with isolated systolic hypertension (42). When comparing the results of various antihypertensive medication studies, special attention should be given to the individual study design and whether it is really representative for the entire hypertensive patient population. One such example is ACCOMPLISH, where the cardiovascular risk reduction of benazepril 40 mg combined with amlodipine 10 mg was compared with that of benazepril 40 mg/HCTZ 25 mg in hypertensive patients. The study was designed for a limited, high-risk population with hypertension with compelling indications: 60% in the ACCOMPLISH trial had diabetes, 36% previous coronary revascularization, 23.5% previous MI and 11.5% pre-

vious hospitalization for unstable angina. Patients with a history of symptomatic HF or evidence of left ventricular ejection fraction < 40% were excluded from the trial (24). Therefore, patients included in the ACCOMPLISH trial could be regarded as having compelling indications for the use of CCBs over thiazide diuretics (43). Clinical trials have shown that some classes of antihypertensives can reduce the cardiovascular morbidity in patients with specific indications. The Joint National Committee (JNC) 7 guidelines recommend the use of specific antihypertensive classes in such patient groups based on such evidence (Table I). ARBs are recommended for patients with HF, diabetes and chronic kidney disease (26). According to the ESH guidelines, conditions that favor the use of ARBs are diabetic nephropathy (type 2), diabetic microalbuminuria, proteinuria, left ventricular hypertrophy and inability to tolerate ACEi (3).

Obesity, hypertension, dyslipidemia and glucose intolerance cluster in the insulin resistance syndrome. About 40% of essential hypertensive patients are insulin-resistant and the risk of any cardiovascular event or stroke is almost doubled when the hypertensive patient is diabetic (22, 44). The tight control of BP induces a marked decrease in rates of cardiovascular events. Several studies have demonstrated that CCBs improve glucose tolerance in hypertensive patients (22, 45, 46). According to the JNC 7, thiazide diuretics, BBs, ACEi, ARBs and CCBs are beneficial in reducing CVD and stroke incidence in patients with diabetes. ACEi- or ARB-based treatments favorably affect the progression of diabetic nephropathy and reduce albuminuria. ARBs have also been shown to reduce progression to macroalbuminuria (26). In a study comparing the effects of amlodipine and telmisartan on glycemic control and insulin sensitivity in hypertensive type 2 diabetic patients, Negro et al. found telmisartan to have a relative advantage with respect to amlodipine in obtaining a better metabolic profile (22).

DISCUSSION

Cardiovascular disease can be seen as a path starting from risk factors such as hypertension, progressing to atherosclerosis, target organ damage, and ultimately to MI, HF, stroke or death. Several guidelines advocate the use of two-drug combinations in patients with stage 2 hypertension (3, 26). The essential goal of treatment should be the prevention of the important endpoints of hypertension, such as MI, stroke and HF. Specific patient populations derive particular therapeutic benefit from specific combinations of antihypertensive agents (17, 47).

Table I. Clinical trial and guideline basis for compelling indications for individual drug classes (from JNC 7 ref. 26).

Compelling indication	Recommended drugs					
	Diuretic	β-Blocker	ACEi	ARB	CCB	Aldo ANT
Heart failure	*	*	*	*		*
Post-myocardial infarction		*	*			*
High coronary disease risk	*	*	*		*	
Diabetes	*	*	*	*	*	
Chronic kidney disease			*	*		
Recurrent stroke prevention	*		*			

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Aldo ANT, aldosterone antagonist.

The choice of antihypertensive drug thus depends on its particular properties, advantages and limitations as viewed with respect to the compelling indications it is to be used for, thus enabling physicians to make the most appropriate choice in individual patients. The most widely used drug classes are thiazide diuretics, ACEi, CCBs, BBs and ARBs. Although as of 2009 the best available evidence favors thiazide diuretics as the first-line treatment of choice for high BP (48), there are at least two possible reasons why diuretics do not protect against cardiovascular events in high-risk patients to the same extent as other classes of drugs. Firstly, diuretics have long been known to reduce insulin sensitivity, which has now been shown to be accompanied by an increase in the amount of visceral fat (5, 49). Secondly, the rise in serum uric acid associated with the use of diuretic possibly has a much more serious effect on cardiovascular risk than was previously thought. Therefore, diuretics could be a suitable choice for relatively low-risk patients in whom the adverse effects are outweighed by the antihypertensive benefit. The choice of antihypertensive should therefore depend on the compelling indications individually assessed for each patient.

In that context, the combination of telmisartan/amlodipine is especially suitable for the treatment of severely hypertensive, high-risk patients, because it offers substantial and sustained 24-h BP-lowering and is well tolerated in a range of patients with hypertension at risk for cardiovascular events. This includes patients with type 2 diabetes, obese patients, the elderly, black patients and those not controlled by monotherapy alone. Littlejohn et al. (21) showed that the high-dose combination of telmisartan 80 mg plus amlodipine 10 mg led to a BP

(< 140/90 mmHg in 77%) and DBP control rate (< 90 mmHg in 85%), suggesting that almost all severe patients can achieve therapeutic targets with this dose. Given that even relatively small reductions in DBP (–5 to –6 mmHg) or SBP (–10 to –12 mmHg) can translate into fewer cardiovascular events (as shown in the ACCOMPLISH trial), the high-dose combinations of telmisartan–amlodipine may substantially reduce the cardiovascular risks associated with moderate or severe hypertension.

CONCLUSIONS

Multiple regulatory pathways are involved in the regulation of BP, and therefore combinations of agents that act by different mechanisms can have complementary actions and be more effective than monotherapy. Treatment with ARBs plus CCBs can be considered an effective strategy to bring hypertensive patients to the BP target, including those with moderate or severe hypertension. Littlejohn et al. demonstrated that the greatest reduction in BP (SBP/DBP –26.5 ± 1.2/–21 ± 0.8 mmHg) was achieved with the highest dose combination of telmisartan 80 mg plus amlodipine 10 mg and the SBP/DBP response rates were > 90%. The BP control (< 140/90 mmHg) and DBP control (< 90 mmHg) obtained with this combination was 77% and 85%, respectively. Furthermore, the findings show that telmisartan 40–80 mg plus amlodipine 5–10 mg provides highly effective BP lowering (up to –26.5 mmHg for SBP), and peripheral edema is up to 59% less when telmisartan 40 mg is used in combination with amlodipine 10 mg compared with amlodipine 10 mg monotherapy alone. These findings clearly indicate that telmisartan 40–80 mg plus amlodipine

ine 5-10 mg is an effective treatment option in patients with moderate to severe hypertension (21).

DISCLOSURES

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