Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial

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Context **Type 2 diabetes is emerging as a major health problem, which tends to cluster with hypertension in individuals at high risk of cardiovascular disease.**

Objective **To test for the first time the hypothesis that treatment of hypertensive patients at high cardiovascular risk with the angiotensin-receptor blocker (ARB) valsartan prevents new-onset type 2 diabetes compared with the metabolically neutral calcium-channel antagonist (CCA) amlodipine.**

Design **Pre-specified analysis in the VALUE trial. Follow-up averaged 4.2 years. The risk of developing new diabetes was calculated as an odds ratio (OR) with 95% confidence intervals (CI) for different definitions of diabetes.**

Patients **A sample of 9995 high-risk, non-diabetic hypertensive patients.**

Interventions **Valsartan or amlodipine with or without add-on medication [hydrochlorothiazide (HCTZ) and other add-ons, excluding other ARBs, angiotensin-converting enzyme (ACE) inhibitors, CCAs].**

Main outcome measure **New diabetes defined as an adverse event, new blood-glucose-lowering drugs and/or fasting glucose > 7.0 mmol/l.**

Results **New diabetes was reported in 580 (11.5%) patients on valsartan and in 718 (14.5%) patients on amlodipine (OR 0.77, 95% CI 0.69–0.87, $P < 0.0001$). Using stricter criteria (without adverse event reports) new diabetes was detected in 495 (9.8%) patients on valsartan and in 586 (11.8%) on amlodipine (OR 0.82, 95% CI 0.72–0.93, $P = 0.0015$).**

Conclusion **Compared with amlodipine, valsartan reduces the risk of developing diabetes mellitus in high-risk hypertensive patients. *J Hypertens* 24:1405–1412 © 2006 Lippincott Williams & Wilkins.**

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Keywords: amlodipine, angiotensin receptor blocker, calcium-channel antagonist, cardiovascular disease, clinical trial, hypertension, new-onset diabetes, valsartan

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Introduction

Diabetes mellitus, and in particular type 2 diabetes, is emerging as a major health problem, which tends to cluster with hypertension in individuals at high risk of cardiovascular disease [1]. Hypertension is an insulin-resistant state and hypertensive subjects have an exaggerated tendency to develop diabetes with ageing [2]. Since high blood pressure is encountered in 20% of the adult population [3] and its management is a priority in preventing cardiovascular complications [4], antihypertensive strategies that attenuate the trend towards diabetes might have major public health implications.

In large-scale prospective outcomes trials, treatment with angiotensin-converting enzyme (ACE) inhibitors, calcium-channel antagonists (CCAs) and alpha-blockers is associated with the development of type 2 diabetes less

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frequently than following therapy with diuretics and beta-blockers [5–10], drugs known to predispose to diabetes [11,12]. In this respect, CCAs are considered to be metabolically neutral and less prone than diuretics or beta-blockers to provoke diabetes [8–10].

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) [13–15] was designed to compare cardiac outcomes in treatment regimens based on the angiotensin-receptor blocker (ARB) valsartan and the CCA amlodipine in a population of essential hypertensive patients at high risk of cardiac disease, recruited by a specific predefined age-, risk factor- and disease-dependent algorithm. A total of 15 245 eligible patients in 31 countries were randomized. The VALUE trial results showed no difference between the two drug regimens in the primary composite cardiac endpoint rate or mortality [16,17].

In this pre-specified analysis we aimed to investigate the development of diabetes in the 9995 patients who were non-diabetic at the outset of VALUE, and to examine whether a treatment including an ARB reduces the risk of type 2 diabetes compared with CCA-based treatment. Preliminary data were given previously [16] and we now report the detailed analysis and the background information on the observation. One previous study reported a numerical difference in favour of an ACE inhibitor over a CCB, but its design precluded a formal statistical comparison [10]. Thus, VALUE was the first opportunity to compare formally the effects of any inhibitor of the renin–angiotensin system with a CCA on the development of new-onset diabetes. We also aimed to compare incidences of patients progressing from normal glucose to impaired fasting glucose (5.5–6.9 mmol/l) and diabetes ($\geq$ 7.0 mmol/l).

Methods

Study design, patients and treatment

The design of VALUE has been described in detail elsewhere [1]. A total of 15 245 patients with treated or untreated hypertension [systolic/diastolic blood pressure (SBP/DBP) $\geq$ 140/90 mmHg] were randomized to valsartan- or amlodipine-based regimens. As 5250 patients had diabetes at baseline, 9995 patients were included in this study of development of new-onset diabetes. Patients were followed for 4–6 years with regular visits. Upward-titration of medication was implemented in five steps to reach a goal blood pressure (BP) of $<$ 140/90 mmHg. First, the doses of double-blind medication were doubled, to 160 and 10 mg, respectively, then hydrochlorothiazide (HCTZ) was given as first add-on treatment (12.5–25 mg daily) in both arms. Further antihypertensive drugs, excluding other ARBs, could be given to achieve BP control. ACE inhibitors or CCAs were allowed only if these drugs were clinically indicated for reasons other than hypertension.

Definition of study end points

At baseline, diabetes was defined by 1985 WHO criteria (fasting glucose $>$ 7.8 mmol/l). In 1999, during the course of the study, a WHO working group changed the definition to a fasting glucose of $\geq$ 7.0 mmol/l [18]. Consequently the new-onset diabetes in this report is defined as fasting glucose of $\geq$ 7.0 mmol/l during the study in patients with glucose $<$ 7.0 mmol/l at entry.

During the blinded phase of the study, it became apparent that antihypertensive agents had differing potentials to induce new-onset diabetes [5–10,19], and fasting blood glucose estimation was therefore included as mandatory at study end. Otherwise, information on new diabetes was collected prospectively throughout the study by scrutinizing the adverse event reports and by detecting usage of blood-glucose-lowering drugs in the concomitant medication database. Investigators were encouraged to use the new (1999) WHO criteria in diagnosing new-onset diabetes reported as adverse events and this protocol was pre-specified in a study newsletter. In order to detect new-onset diabetes we first excluded all patients who at entry were diagnosed as diabetics, received antidiabetic agents, or had abnormal glucose levels. To detect new-onset diabetes mellitus, the criteria described below were applied to the VALUE patients at risk of new-onset diabetes. In the primary analysis at least one of the following three criteria was used, but patients were counted only once for the diagnosis of new diabetes.

(1) We accepted a diagnosis of diabetes reported as an adverse event during the trial by investigators, who were strongly encouraged to use WHO 1999 criteria [18]: fasting glucose $\geq$ 7.0 mmol/l and/or $\geq$ 11.1 mmol/l at 2 h after oral intake of 75 g glucose if venous plasma or serum, and/or $\geq$12.2 mmol/l if capillary full blood, on two separate occasions.
(2) We scrutinized study reports of concomitant medication for patients who were started on an oral blood-glucose-lowering drug or insulin during the course of the trial. This database contained a detailed directory of drugs by both generic and trade names in all participating countries.
(3) At the study end, a single venous blood sample was drawn for plasma or serum glucose determination in the central laboratory. A diagnosis of new-onset diabetes was made if the patient was reported to be fasting and the glucose concentration was $\geq$ 7.0 mmol/l.

In order to strengthen the definition of diabetes, a secondary analysis excluding cases reported in adverse event forms was carried out, and the number of new diabetics by each of the three criteria was counted separately.

Statistical analysis

In the treatment comparison, odds ratios (OR) and 95% confidence intervals (CI) were calculated for patients who were not diabetic at baseline. A two-tailed *P*-value of less than 0.05 was considered to be significant. Comparison of incidence of participants progressing from normal glucose to impaired fasting glucose (5.5–6.9 mmol/l) and diabetes ($\geq$ 7.0 mmol/l) was done with Cochran–Mantel–Haenszel statistics. Statistical Analysis System (SAS Inc., Cary, North Carolina, USA) was used for all analyses.

Results

VALUE randomized a total of 15 245 patients. The new WHO diabetes definition increased the number of diabetics at entry; 222 and 205 additional patients in the valsartan and amlodipine groups, respectively, were considered to have diabetes and were not included in the analysis. In total, 5250 patients had diabetes based on WHO 1999 criteria at baseline and 9995 patients were eligible for new-onset diabetes analysis. Of these 5032 were in the valsartan arm and 4963 were in the amlodipine arm. There were no differences between the two groups in baseline demographics and blood pressures, qualifying risk factors and diseases (Table 1) and baseline medication (Table 2). All previous antihypertensive drugs, but not aspirin or statins, were discontinued at randomization. Medication at primary end point or stroke, or at study end, is shown in Table 2; somewhat more antihypertensive medication, including open-label diuretics, were given in the valsartan arm compared to the amlodipine arm, while there was no difference for aspirin or statins. As in the main study groups [16], there were no differences in primary cardiac end points in the study groups that did not have diabetes at the outset, 8.22% (408 of 4963) on amlodipine and 8.66% (436 of 5032) on valsartan (hazard ratio = 1.06, 95% CI 0.93–1.22, $P = 0.39$), and the overall systolic and diastolic blood pressures were higher (2.1/1.5 mmHg) on valsartan than on amlodipine ($P < 0.0001$).

New-onset diabetes, as defined by all three criteria described in the Methods section, was detected in 1298 patients. Of these 580 (11.5%) patients were in the valsartan arm and 718 (14.5%) patients were in the amlodipine arm (OR 0.77, 95% CI 0.69–0.87, $P < 0.0001$) (Fig. 1, Table 3). When using the more strict criteria, excluding adverse event reports, rates were 495 (9.8%) on valsartan and 586 (11.8%) on amlodipine (OR 0.82, 95% CI 0.72–0.93, $P = 0.0015$) (Table 3). Cumulative rates for the three criteria that identified new diabetes are shown in Fig. 1. A significant difference in favour of less diabetes on valsartan was seen regardless of criterion. The incidences of diabetes reported as *adverse events* were 328 (6.5%) on valsartan and 436 (8.8%) on amlodipine (OR 0.72, 95% CI 0.62–0.84, $P < 0.0001$); as *new use of blood-glucose-lowering drugs* 254 (5.0%) on valsartan and

Table 1 Demographic variables, qualifying risk factors and diseases in patients without diabetes at baseline[a]

Demographic characteristics	Valsartan ($n = 5032$)	Amlodipine ($n = 4963$)
Age (years)	67.3 ± 8.2	67.2 ± 8.3
Male	2953 (58.68%)	2889 (58.21%)
Female	2079 (41.32%)	2074 (41.79%)
Race [number (%)]		
Caucasian	4584 (91.10%)	4524 (91.15%)
Black	164 (3.26%)	156 (3.14%)
Oriental	168 (3.34%)	170 (3.43%)
Other	116 (2.31%)	113 (2.28%)
Region [number (%)]		
Asia	140 (2.78%)	149 (3.00%)
Europe	3154 (62.68%)	3124 (62.95%)
Latin America	199 (3.95%)	194 (3.91%)
North America	1402 (27.86%)	1373 (27.66%)
Rest of world	137 (2.72%)	123 (2.48%)
Height (cm)	167.3 ± 9.8	167.2 ± 9.8
Weight (kg)	78.3 ± 15.2	78.3 ± 15.4
Body mass index (kg/m^2)	27.9 ± 4.6	28.0 ± 4.8
Systolic blood pressure (mmHg)	153.8 ± 19.0	154.1 ± 19.0
Diastolic blood pressure (mmHg)	87.7 ± 10.9	88.0 ± 10.7
Heart rate (beats/min)	71.2 ± 10.6	71.5 ± 10.6
Risk factors [number (%)]		
Current smoking	1291 (25.66%)	1306 (26.31%)
Total cholesterol (> 240 mg/dl or > 6.2 mmol/l)	1778 (35.33%)	1779 (35.85%)
Left ventricular hypertrophy (without strain pattern)	653 (12.98%)	623 (12.55%)
Proteinuria (> 1+ on dipstick)	990 (19.67%)	969 (19.52%)
Serum creatinine (> 1.7 mg/dl or > 150 μmol/l)	189 (3.76%)	165 (3.32%)
Diseases [number (%)]		
History of coronary heart disease	2462 (48.93%)	2421 (48.78%)
History of peripheral arterial occlusive disease	737 (14.65%)	736 (14.83%)
History of stroke or transient ischemic attacks	1106 (21.98%)	1062 (21.40%)
Left ventricular hypertrophy (with strain pattern)	316 (6.28%)	327 (6.59%)
Left ventricular hypertrophy (with or without strain pattern)	969 (19.26%)	950 (19.14%)

[a]Plus–minus values are mean ± SD. No significant differences between groups.

Table 2 Cardiovascular drugs in patients without diabetes at baseline[a]

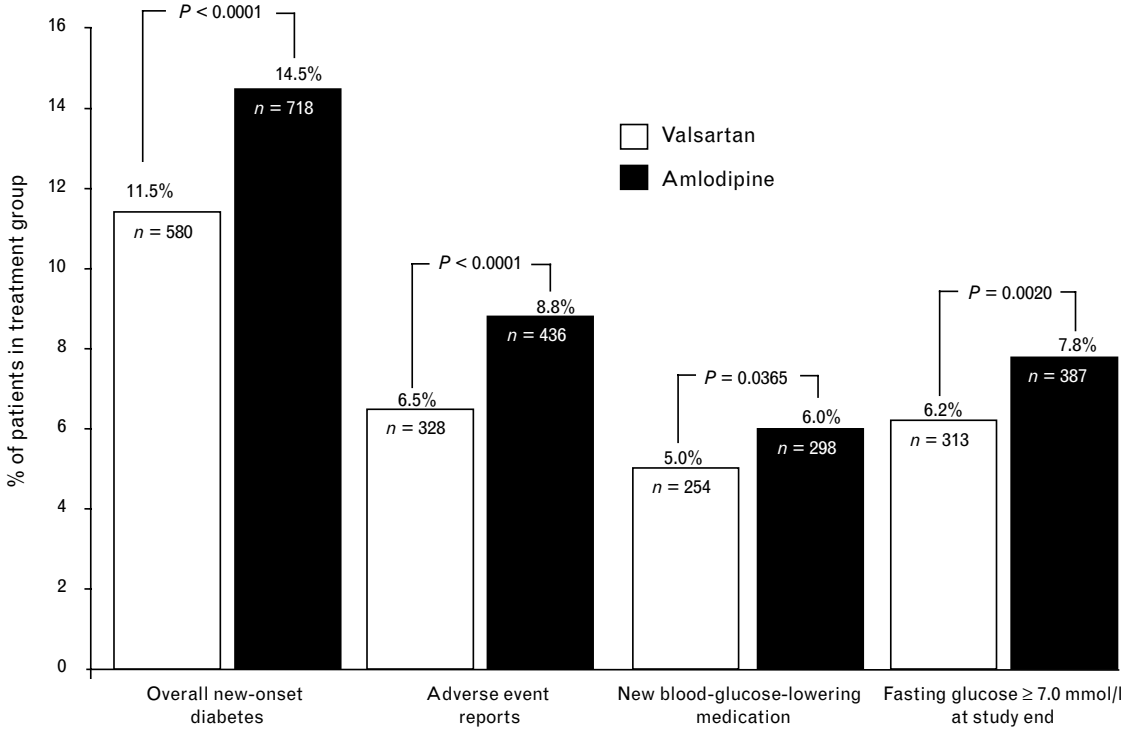
	Valsartan ($n = 5032$)	Amlodipine ($n = 4963$)
Drugs at randomization		
ACE inhibitors	1889 (37.5%)	1856 (37.4%)
Angiotensin-receptor blockers	533 (10.6%)	522 (10.5%)
Alpha-blockers	345 (6.9%)	312 (6.3%)
Aspirin	3006 (59.7%)	2911 (58.7%)
Beta-blockers	1788 (35.5%)	1778 (35.8%)
Calcium-channel antagonists	2069 (41.1%)	2014 (40.6%)
Diuretics only	1309 (26.0%)	1304 (26.3%)
Combination with diuretics	432 (8.6%)	380 (7.7%)
Other antihypertensives	411 (8.2%)	374 (7.5%)
Statins	1630 (32.4%)	1615 (32.5%)
Drugs at primary end point or stroke, or at the final visit for patients without an event		
Valsartan 80 mg or amlodipine 5 mg	830 (16.5%)	1095 (22.1%)
Valsartan 160 mg or amlodipine 10 mg	567 (11.3%)	759 (15.3%)
Valsartan or amlodipine + HCTZ	1317 (26.2%)	1219 (24.6%)
Valsartan or amlodipine + other add-on	1104 (21.9%)	784 (15.8%)
Treatment without valsartan or amlodipine	1214 (24.1%)	1106 (22.3%)
Treatment with diuretic[b] + beta-blocker	924 (18.4%)	892 (18.0%)
Aspirin	3749 (74.5%)	3656 (73.7%)
Statins	2360 (46.9%)	2344 (47.2%)

ACE, angiotensin-converting enzyme; HCTZ, hydrochlorothiazide [a]Number, with % of total number of patients in parentheses. [b]Diuretic includes HCTZ.

298 (6.0%) on amlodipine (OR 0.83 , 95% CI 0.70–0.99, $P = 0.0365$); and as *increased fasting glucose at study end* they were 313 (6.2%) on valsartan and 387 (7.8%) on amlodipine (OR 0.78, 95% CI 0.67–0.92, $P = 0.0020$). Table 3 shows individual or combined criteria for the overall diagnosis of new-onset diabetes.

Treatment with diuretic plus beta-blocker was given in 18.4 versus 18.0% of patients in the two treatment arms, respectively (Table 2). Diabetes developed in 15.8 versus 21.0% of patients receiving diuretics/beta-blockers during the trial in the valsartan and amlodipine group, respectively (OR 0.71, 95% CI 0.56–0.90, $P = 0.005$). In patients

Fig. 1



New-onset diabetes during the study, based on different criteria, among patients in the two treatment arms, classified as non-diabetic at baseline.

Table 3 New-onset diabetes during the study based on fasting glucose ≥ 7.0 mmol/l at baseline and follow-up among patients without diabetes at baseline[a]

End points	Valsartan ($n = 5032$)	Amlodipine ($n = 4963$)	OR (95% CIs)	P value
New-onset diabetes (primary analysis):	580 (11.5%)	718 (14.5%)	0.77 (0.69–0.87)	<0.0001
Patients receiving beta-blockers/diuretics during trial ($n = 1816$)	146 (15.8%)	187 (21.0%)	0.71 (0.557–0.899)	0.0046
Patients not on beta-blockers/diuretics ($n = 8179$)	434 (10.6%)	531 (13.0%)	0.79 (0.688–0.901)	0.0005
Criteria for diabetes:				
Adverse events	85	132		
New blood-glucose-lowering medication	63	60		
Final glucose value[b]	169	194		
Adverse events and new blood-glucose-lowering medication	119	139		
Adverse events and final glucose value	72	94		
New blood-glucose-lowering medication and final glucose value	20	28		
Adverse events, new blood-glucose-lowering medication and final glucose	52	71		
New-onset diabetes excluding adverse events (secondary analysis)	495 (9.8%)	586 (11.8%)	0.82 (0.72–0.93)	0.0015
Criteria for diabetes				
New blood-glucose-lowering medication	182	199		
Final glucose value	241	288		
New blood-glucose-lowering medication and final glucose value	72	99		

[a]Number, with % of total number of patients in parentheses. Diabetes at baseline was defined as patients on drug treatment for diabetes or having fasting glucose ≥ 7.0 mmol/l. [b]Fasting glucose ≥ 7.0 mmol/l. OR, odds ratio; CI, confidence interval.

not given diuretic/beta-blockers, 10.6 versus 13.0% developed diabetes in the valsartan and amlodipine groups, respectively (odds ratio 0.79, 95% CI 0.69–0.90, $P = 0.0005$) (Table 3).

Mean glucose levels fell in the valsartan group from baseline to final visit (from 6.9 ± 0.03 to 6.7 ± 0.04 mmol/l, $P < 0.0001$) but remained unchanged (6.9 ± 0.03 versus 6.9 ± 0.04 mmol/l) in the amlodipine group. There was a significant difference between the treatment groups at the final visit ($P < 0.0001$).

The number of participants progressing from normal glucose to impaired fasting glucose (5.5–6.9 mmol/l) and diabetes (≥ 7.0 mmol/l) was highly significantly smaller on valsartan compared with amlodipine ($P = 0.0006$).

Discussion

In this study of hypertensive patients with high cardiovascular risk, the ARB valsartan reduced the number of patients who developed new-onset diabetes mellitus compared with the CCA amlodipine. This is the first occasion in which it has been possible to test formally the hypothesis that a drug which blocks the renin–angiotensin system (ARB or ACE inhibitor) differs from a CCA in potential to provoke diabetes mellitus during the treatment of hypertension. The benefit of valsartan in preventing new diabetes was robust and was seen regardless of the criterion for diagnosis of diabetes, whether by adverse events listings, from new usage of drugs for diabetes or by fasting glucose at study end. In absolute terms, valsartan reduced new diabetes by 3% compared with amlodipine over the average length of the study (4.2 years). This translates into a 'number needed to treat' (NNT) of 33 patients to prevent one case of new-onset diabetes.

While the fasting glucose definition of diabetes is dichotomous, the association between fasting glucose and vascular disease is likely continuous and begins at lower levels of fasting glucose. Valsartan also reduced the number of participants progressing from normal fasting glucose to pre-diabetes or impaired fasting glucose, and it may thus favourably affect processes that underlie the development of diabetes.

The change of the WHO criteria during the trial necessitated a change in the definition of the diabetes at baseline. By altering the criterion from fasting glucose > 7.8 to ≥ 7.0 mmol/l, an additional 427 patients were identified as diabetic at baseline, 222 and 205 patients in the valsartan and amlodipine groups, respectively. Thus, the number of patients with diabetes at baseline is at variance with the report of patient's characteristics at baseline in VALUE [14]. This correction was implemented for accuracy and it had no influence on the differential drug effects (data not shown). However, the change in criterion makes between-study comparisons of total rates difficult. Diagnostic criteria have been less well defined in most other studies [5–10], with the exception of the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) [19], where extensive investigations for new-onset diabetes using WHO 1985 criteria were performed.

To date, all prospective, randomized outcome studies in hypertension have shown less new-onset diabetes mellitus in the group receiving an agent that blocks the renin–angiotensin system, either ACE inhibitors or ARBs, than in the comparator group. Hitherto the comparator has been a diuretic [10–15,20] or a beta-blocker [5,19], often in combination. VALUE provides the first formal comparison of new-onset diabetes rates between any inhibitor of the renin–angiotensin system and a CCA,

and the first direct comparison of an ARB and a CCA. This distinction of VALUE from other trials is important since prior trials compared inhibitors of the renin–angiotensin system with diuretics and/or beta-blockers. Both these classes of antihypertensive drugs negatively affect glucose balance [11].

A recent meta-analysis [12] suggests that calcium-channel antagonists are associated with lower rates of new-onset diabetes rates than diuretics/beta-blockers, although potentially these drugs may also negatively impact glucose metabolism. The demonstration in VALUE that the ARB valsartan is associated with lower rates of new-onset diabetes compared to the CCA amlodipine, strongly suggests that positive findings with drugs interfering with the renin–angiotensin system are due to a beneficial effect of these drugs on glucose metabolism. The mechanism responsible for this effect cannot be determined from the VALUE findings. Possible causes are the improvement of microcirculation and a better delivery of glucose and insulin to skeletal muscles [21]. An influence of sympathetic drive as an underlying pathophysiological mechanism has also been suggested [21]. A direct effect on the endocrine pancreas may be involved as saralasin increased pancreatic islet blood flow in an experimental model [22]. It has also been proposed that blockade of the renin–angiotensin system promotes the recruitment and differentiation of adipocytes, which would counteract the ectopic deposition of lipids in other tissues (liver, muscle, pancreas), thereby improving insulin sensitivity and preventing type 2 diabetes [23]. In this context it is interesting to note the slight but significant improvement in glucose levels in the valsartan group compared with amlodipine-based therapy.

Although rates of new diabetes were higher in patients receiving diuretics and beta-blockers, the odds ratio in favour of valsartan was slightly higher in this group than overall. Thus the use of these drugs did not provide an explanation for the difference in outcome [24].

During the course of the study, patients randomized to amlodipine had significantly lower serum potassium than patients who were randomized to valsartan. Glucose intolerance associated with thiazide diuretics has been attributed to potassium depletion [25]. Hypokalaemia may impair glucose tolerance by interfering with insulin release from the pancreas [26,27]. Since hypokalaemia was not associated with add-on treatment with diuretics, diuretic-induced hypokalaemia is unlikely to explain the difference in new-onset diabetes, although a role cannot be excluded entirely. A different effect on body weight of the two drugs can theoretically be involved and cannot be ruled out, as we did not systematically measure body weight at study end.

Prevention of new diabetes is a priority in patients at high risk, whether or not they have established hypertension [28,29]. Although it is an end point in outcome trials in hypertension, new-onset diabetes requires long-term follow-up to clarify its prognostic importance and, so far, no study had documented that limiting long-term onset of diabetes translates into a reduced incidence of cardiovascular events. In recent observational studies, people who developed new-onset diabetes had the same high cardiovascular risk as patients who had diabetes at the outset, but several years of observation were needed before the prognostic curves separated them from people without diabetes [30–34]. Since in a typical outcome trial in hypertension, the average follow-up is about 5 years, the average duration of new-onset diabetes will only be about 2.5 years and, in consequence, the impact of this complication on cardiovascular risk will be underestimated. However, patients who develop diabetes may need drug treatment to control glucose level from the time of diagnosis, increasing the burden of disease. In VALUE the need for initiation of blood-glucose-lowering drugs was significantly lesser in the valsartan group compared with the amlodipine-treated patients.

In summary, we tested for the first time the hypothesis that an inhibitor of the renin–angiotensin system would be more effective than a calcium-channel antagonist for prevention of new-onset diabetes in hypertension, and we found that valsartan prevented new-onset type 2 diabetes mellitus compared with the calcium-channel antagonist amlodipine in the treatment of hypertensive patients at high cardiovascular risk.

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Appendix: VALUE committees

Executive Committee

Stevo Julius (Chair/USA), Sverre E. Kjeldsen (Associate Chair/Norway), Hans R. Brunner (Switzerland), John H. Laragh (USA), Gordon McInnes (UK), M. Anthony Schork (USA), Michael A. Weber (USA), Alberto Zanchetti (Italy), Lennart Hansson (Sweden).

Steering Committee

Felipe Martinez (Argentina), John Amerena (Australia), Dieter Magometschnigg (Austria), Jean-Paul Degaute (Belgium), Wille Oigman (Brazil), Pierre Larochelle (Canada), Jun Ren Zhu (China), Jiri Widimský (Czech Republic), Ole Lederballe Pedersen (Denmark and Iceland), Silja Majahalme (Finland), Xavier Girerd (France), Roland Schmieder (Germany), Kostantinos Siamopoulos (Greece), Bela Herczeg (Hungary), Faustinus P. Rudyatmoko (Indonesia), Ian Graham (Ireland), Reuven Viskoper (Israel), Giuseppe Mancia (Italy), Cesar Calvo-Vargas (Mexico), Nicolaas J. Holwerda (Netherlands), Morten Rostrup (Norway), Øyvind Størset (Norway), Andrezej Cieslinski (Poland), Ricardo Seabra Gomes (Portugal), Janna Kobalava (Russia), Ivan Balazovjech (Slovak Republic), Graham Cassel (South Africa), Antonio Coca (Spain), Edouard Battegay (Switzerland), Nevres Koylan (Turkey), Thomas MacDonald (UK), Kenneth Jamerson (USA).

Endpoint Committee

Luis M. Ruilope (Chair/Spain), Gregory Alberts (USA), Vivencio Barrios (Spain), Arie J. Man in't Veld (Belgium), Per Omvik (Norway), William Parmley (USA), Enrico Agabiti Rosei (Italy), Svend Strandgaard (Denmark), Myron H. Weinberger (USA).

Endpoint Co-ordinating Centre (Madrid, Spain)

Ana Garçia de Castro (medical back-up), Josefa Navarro, Alexandra Rissmann, Pilar Martinez Gutierrez, Isabel Martinez Gutierrez.

Data and Safety Monitoring Board

Stephen MacMahon (Chair/Australia), Henry R. Black (USA), Thomas Fleming (USA), Peter Sleight (UK).

Operations Committee

Stevo Julius (USA), Sverre E. Kjeldsen (Norway), Tsushung Hua (Novartis, East Hanover, New Jersey, USA), Beverly Smith (Novartis, East Hanover, New Jersey, USA), Deborah James (Novartis, East Hanover, New Jersey, USA), Francis Plat (Novartis, Basel, Switzerland), Steffan Ekman (Novartis, Basel, Switzerland), Patrizia Kobi (Novartis, Basel, Switzerland).