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Risk factor assessment for new onset diabetes: literature review

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Metabolic syndrome (MS), typified by hypertension, abdominal obesity, dyslipidaemia and impaired glucose metabolism, is a precursor of type 2 diabetes. Thiazide diuretics (TD) and beta-blockers are associated with increased risk of diabetes in patients with hypertension; however, the role of these agents in development of diabetes in MS patients is unknown. We reviewed the literature regarding risk factors for diabetes development and compared this with data from the Study of Trandolapril/Verapamil SR And Insulin Resistance (STAR), which investigated the effects of two fixed-dose combinations (FDCs) [trandolapril/verapamil SR and losartan/hydrochlorothiazide (L/H)] on glucose control and new diabetes in MS patients. In STAR, logistic regression modelling identified haemoglobin A1c [odds ratio (OR) 4.21 per 1% increment; $p = 0.003$), L/H treatment (OR 4.04; $p = 0.002$) and 2-h oral glucose tolerance test glucose levels (OR 1.39 per 10 mg/dl increments; $p < 0.001$) as baseline predictors of diabetes. These data support prior analyses and suggest that choice of antihypertensive agent is important. Patients with MS may be at lower risk of diabetes when using a FDC calcium channel blocker + angiotensin-converting enzyme inhibitor compared with an angiotensin receptor blocker + TD.

Keywords: angiotensin receptor blocker, calcium channel blocker, metabolic syndrome, thiazide diuretic, type 2 diabetes
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Introduction

Risk factors for type 2 diabetes have been identified and include obesity, impaired glucose metabolism, older age, family history of diabetes, physical inactivity and, more recently, hypertension [1,2]. Recent interest in preventing incident diabetes has focused on those patients with impaired glucose metabolism. The American Diabetes Association (ADA) defines impaired fasting glucose as having a fasting glucose of 100–125 mg/dl (5.6–6.9 mmol/l) or impaired glucose tolerance [2-h plasma glucose 140–199 mg/dl (7.8–11.0 mmol/l)]. The ADA recommends that such patients be monitored for incident diabetes every 1–2 years and that appropriate treatment for cardiovascular disease risk factors (hypertension, dyslipidaemia and tobacco use) be initiated [3].

Metabolic syndrome (MS) is the clustering of multiple disorders that include insulin resistance, dyslipidaemia, hypertension and abdominal obesity [4–6] and is generally accepted as a precursor to type 2 diabetes [7–11] as well as increased risk of cardiovascular disease [4,12]. Moreover, there is a twofold greater risk of developing

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diabetes in hypertensive patients compared with normotensive patients [13]. All such patients will require management of hypertension; thus, physicians can benefit from knowing the metabolic impact of antihypertensive agents, especially in patients with impaired glucose metabolism. The growing incidence of MS, estimated to be as many as 72 million persons in the US alone, reinforces the importance of appropriate antihypertensive prescribing, especially because more than one third of these persons have hypertension [14–16].

Retrospective analyses of many clinical trials demonstrated that diuretics and beta-blockers (BBs) increased the risk of new diabetes in those with impaired glucose tolerance; however, it was thought that concomitant use of a renin–angiotensin–aldosterone system (RAAS) blocker would ameliorate this risk [17,18]. The results of the Study of Trandolapril/Verapamil SR And Insulin Resistance (STAR) called this conclusion into question. STAR was a multicenter, prospective, randomized, open-label, blinded end-point (PROBE) study [19]. It included 240 patients with MS, defined as impaired glucose tolerance and hypertension plus one additional risk factor, randomized to a fixed-dose combination (FDC) of trandolapril/verapamil (T/V) 2/180 mg or losartan/hydrochlorothiazide (L/H) 50/12.5 mg. Patients were treated to a systolic blood pressure (SBP) goal of $<$130 mmHg for 52 weeks, with dose titration and other antihypertensive drugs added if needed. A significant difference in the primary outcome, difference in glucose tolerance as assessed by change from baseline to study end in 2-h blood glucose [determined by a 75-g oral glucose tolerance test (OGTT)], was noted, with increased impairment of glucose metabolism in the L/H group. The changes in metabolic control were paralleled with increased incident diabetes (T/V 11.0 vs. L/H 26.6%; $p = 0.002$ at study end) [19].

The purpose of this paper is to review current knowledge regarding the risk factors associated with the development of incident diabetes in patients receiving antihypertensive agents. In addition, this paper also addresses the relevance of these prior observations in hypertensive patients with those of the STAR study, which focused on patients with MS and hypertension.

Methods

Literature Search

A search for randomized clinical trials with cardiovascular or surrogate outcomes that reported on development of new onset diabetes in patients receiving commonly used antihypertensive agents (angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), BBs, calcium channel blockers or diuretics) was performed using PubMed. A secondary search of the references cited in the articles was also performed.

STAR Predictors of New Diabetes

The STAR study design and results have been previously described [19]. Briefly, patients with a diagnosis of MS, including mandatory hypertension and impaired glucose tolerance, were randomized to fixed-dose T/V or L/H and treated to a SBP goal of $<$130 mmHg for 52 weeks. At the end of STAR, patients in the L/H group experienced worsening of glucose metabolism and insulin resistance and an increase in new diabetes compared with the T/V group, while glucose metabolism was unchanged in the T/V group [19]. Two logistic regression models were used to identify baseline characteristics associated with increased risk for new diabetes [defined as a fasting plasma glucose $\geq$6.99 mmol/l (126 mg/dl) and/or 2-h OGTT glucose $\geq$11.10 mmol/l (200 mg/dl) at any time during the study]. Subjects with baseline fasting glucose or 2-h OGTT glucose values and all baseline variables were included. Full model covariates were age (10-year increments), gender (female vs. male), race (white vs. non-white), body mass index (5 kg/m^2 increments), glycosylated haemoglobin A1c [HbA1c (%)], baseline SBP and diastolic blood pressure (DBP) (10 mmHg increments), waistline circumference (10-cm increments), baseline fasting glucose levels (4 categories), baseline 2-h OGTT glucose levels [0.5551 mmol/l (10 mg/dl) increments], baseline high-density lipoprotein [HDL; 0.2586 mmol/l (10 mg/dl) increments], baseline triglycerides [0.1129 mmol/l (10 mg/dl) increments] and treatment with either T/V or L/H. A stepwise logistic regression was performed to select covariates from the full model with a p value of $\leq$0.1 (baseline fasting glucose levels were entered as a continuous variable in this analysis).

RESULTS

Impact of Antihypertensive Drug Treatment on Risk of New Diabetes

New diabetes was a secondary or *post hoc* end-point reported in a total of 16 studies (table 1). Six studies included patients with essential hypertension, six trials included patients with hypertension and additional cardiovascular risk factors, one study included patients at high risk of a cardiovascular event, one study

Table 1 Incidence of new diabetes according to study and drug treatment

Study	Year enrolment started	Patient population	Antihypertensive agents	BP goal (mmHg)	Number without diabetes	Incidence of new diabetes n (%)	Per 1000 patient years	Risk
CAPPP [20]	NA	Hypertensive	ACEi	DBP ≤ 90	5183	337 (6.5)	10.7*	RR 0.79 (0.67–0.94)
			TD/BB		5230	380 (7.3)	11.9*	
STOP-2 [21]	1992	Hypertensive	ACEi	<160/95	1969	93 (4.7)	9.6	RR 0.96 (0.72–1.27)†
			CCB		1965	95 (4.8)	9.9	RR 0.97 (0.73–1.29)†
			Diuretic/BB		1961	97 (4.9)	10.0	
NORDIL [22]	1992	Hypertensive	CCB	DBP < 90	5059	216	9.4	RR 0.87 (0.73–1.04)
			Diuretic/BB		5095	251	10.8	
HOPE [23]	1994	Previous CV event or at least another CV risk factor	ACEi	None	2837	102 (3.6)‡	8.0*	RR 0.66 (0.51–0.85)
			Placebo		2883	155 (5.4)‡	11.9*	
ALLHAT [24]	1994	Hypertensive + CVD risk	Diuretic	<140/90	9727	1128 (11.6)	23.7*	
			CCB		5725	561 (9.8)	20.0*	RR 0.84*
			ACEi		5842	473 (8.1)	16.5*	RR 0.70*
LIFE [25,35]	1995	Hypertensive + LV hypertrophy	ARB ± TD	<140/90	4019	242 (6.0)	13.0	HR 0.75 (0.63–0.88)
			BB ± TD		3979	320 (8.0)	17.5	
ANBP-2 [26,66]	1995	Hypertensive	ACEi	<160/90 (<140/80 if tolerated)	2800	138 (4.9)	12.0*	RR = 0.69*
			Diuretic		2826	200 (7.1)	17.3*	
SCOPE [27]	1997	Hypertensive	ARB	<160/90	2167	93 (4.3)	11.6*	RR = 0.81*
			Placebo		2175	115 (5.3)	14.3*	
CHARM [28]	1999	Heart failure	ARB	None	2715	163 (6.0)	19.1*	HR 0.78 (0.64–0.96)
			Placebo		2721	202 (7.0)	23.6*	
INVEST [29]	1997	Hypertensive + CAD	CCB ± ACEi ± TD	JNC VI	8098	569 (7.0)	25.0	Adjusted HR 0.85 (0.76–0.95)
			BB ± TD ± ACEi		8078	665 (8.2)	30.0	
INSIGHT [30]	1994	Hypertensive + CVD risk	CCB	≤140/90	2508	136 (4.3)	15.6*	RR = 0.77*
			TD + diuretic		2511	176 (5.6)	176 (5.6)	
ALPINE [31]	NA	Hypertensive	ARB ± CCB	<130/85 (<65 years)	196	1 (0.5)	5.1*	NA
			TD ± BB	<140/90 (≥65 years)	196	8 (4.1)	40.8*	
VALUE [32,38]	1997	Hypertensive + CVD risk	ARB ± TD	<140/90	5032	580 (11.5)	27.4*	OR 0.77 (0.69–0.87)
			CCB ± TD		4963	718 (14.5)	34.4*	
ASCOT [33]	1998	Hypertensive + CVD risk	CCB ± ACEi	<140/90 (with diabetes <130/80)	7072	567 (6.0)	11.0	HR 0.70 (0.63–0.78)
			BB ± TD		7040	799 (8.0)	15.9	
DREAM [34]	2001	Impaired FG or GT	ACEi	None	2623	449 (17.1)	57.1*	HR 0.91 (0.80–1.03)
			Placebo		2646	489 (18.5)	61.6*	
STAR [19]	2004	Hypertensive + metabolic syndrome	CCB + ACEi	SBP < 130	91	14 (15.4)§	175.2	Adjusted OR
			ARB + TD		94	33 (35.1)§	375.9	0.23 (0.10–0.53)§

JNC VI guidelines specified a BP of <130/85 mmHg in patients with diabetes or renal impairment and <140/90 mmHg for all others. ACEi, angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive Therapy and Lipid Lowering Heart Attack Trial; ALPINE, Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation; ANBP-2, Australian National Blood Pressure Study; ARB, angiotensin II receptor blocker; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, beta-blocker; BP, blood pressure; CAD, coronary artery disease; CAPP, Captopril Prevention Project; CCB, calcium channel blocker; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitizone Medication; FG, fasting glucose; GT, glucose tolerance; HOPE, Heart Outcomes Prevention Evaluation; HR, hazard ratio; INSIGHT, Intervention as a Goal in Hypertension Treatment; INVEST, International VErapamil SR-trandolaril Study; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; LV, left ventricular; NA, not available; NORDIL, Nordic diltiazem; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure; SCOPE, Study on Cognition and Prognosis in the Elderly; STAR, Study of Trandolapril/Verapamil SR And Insulin Resistance; STOP-2, Swedish Trial in Old Patients with Hypertension; TD, thiazide diuretic.

*Estimated from the data in the publication.

†Compared against BBs and/or diuretics.

‡Primary, self-reported, diabetes outcome.

§New diabetes at any time during the study. New diabetes at study end-point is 10 (11.0%) and 25 (26.6%) for CCB + ACEi and ARB + TD, respectively. Adjusted OR from stepwise logistic regression model.

randomized patients with heart failure and two studies enrolled patients with MS (STAR) or prediabetes [Diabetes Reduction Assessment with Ramipril and Rosiglitizone Medication (DREAM)]. Incidence of new diabetes per 1000 patient years was highest in STAR (T/V 175.2; L/H 375.9) and DREAM (ACEi 57.1; placebo 61.6). A consistent finding across these studies was the increased risk of diabetes associated with the use of BBs and/or thiazide diuretics (TDs) and the reduced risk of diabetes associated with RAAS inhibition [19–34]. When RAAS inhibition, in particular an ARB, was used in combination with a TD in Losartan Intervention For Endpoint (LIFE) and Valsarton Antihyper Long-term use Evaluation (VALUE), the incidence of new diabetes was reduced. However, in STAR, which was designed to measure changes in glucose metabolism and enrolled only patients with MS, the ARB/TD combination had a significantly higher incidence of new diabetes than the ACEi/calcium channel blocker (CCB) combination.

Baseline Predictors of New Diabetes

Baseline factors associated with risk for new diabetes were reported in Heart Outcomes Prevention Evaluation (HOPE) study, LIFE reduction study, International VErapamil SR-trandolaril Study (INVEST) and Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (table 2). New diabetes was defined by laboratory values (ASCOT, LIFE and STAR) [19,25,33] or by clinically defined parameters such as investigator reported diabetes (INVEST and HOPE) [23,29]. Compared with ASCOT, INVEST, LIFE and HOPE, STAR patients without diabetes at baseline were considerably more overweight/obese, had lower baseline blood pressures (BPs) and were younger. Almost all patients (>90%) in these studies were Caucasian, with the exception of STAR (70%) and INVEST (50%). Baseline plasma glucose, reported in three studies, was higher in ASCOT (fasting 6.2 mmol/l) than in STAR (fasting 5.9 mmol/l) or LIFE (non-fasting 5.4 mmol/l).

Numerous baseline characteristics were reported to be predictors of increased new diabetes in patients with hypertension and/or increased cardiovascular risk (table 3). Different risk factors were analysed by different studies, with some of the largest effects reported for blood glucose (ASCOT, STAR and LIFE) and treatment related factors (STAR and LIFE). Three baseline risk factors were statistically significant among the variables entered in the full STAR model: HbA1c, 2-h OGTT glucose and treatment group (figure 1A). When plasma glucose was analysed in four categories in STAR, increasing baseline fasting glucose levels were associated with increasing incidence of new diabetes as well as a trend to increased risk described as odds ratios (ORs) (figure 1A).

The STAR stepwise logistic model, performed to select covariates from the full model, identified treatment with L/H compared with treatment with T/V and elevated baseline HbA1c (per 1% increment) as risk factors which significantly increased the risk of new diabetes by approximately fourfold ($p \leq 0.001$) (figure 1B). Elevated 2-h OGTT glucose (per 10 mg/dl increments) was also significantly associated with a 33% increased risk of new diabetes ($p < 0.001$). A trend for increased risk of new diabetes was observed for elevated fasting glucose; however, this did not reach statistical significance ($p = 0.064$).

Discussion

Organizations such as WHO, ADA and International Diabetes Federation (IDF) have focused on the prevention of type 2 diabetes in individuals with MS, highlighting the need for clinical studies in these patients. Until recently, the relationship between antihypertensive agent and impaired glucose control or new diabetes was based on secondary outcomes of clinical trials in populations with, or at risk of, cardiovascular disease. STAR is one of the first trials to investigate the effects of a fixed-dose antihypertensive combination on glucose control and development of diabetes in patients with MS. STAR showed that a FDC of an ACEi and a non-dihydropyridine CCB, compared with an ARB and TD combination, achieved BP goals and avoided worsening of 2-h OGTT glucose values. Increased risk for developing diabetes was associated with antihypertensive choice (randomization to L/H), elevated baseline HbA1c and elevated baseline serum glucose levels.

In STAR, new diabetes occurred three to six times more frequently (1000/patient years: T/V 175.2; L/H 375.9) than in DREAM (1000/patient years: ACEi 57.1; placebo 61.6), the other recently completed study in patients at high risk of developing diabetes.

Impaired metabolic control was an important factor for developing diabetes in STAR, which is consistent with LIFE and ASCOT (table 3) [35,36]. While baseline plasma glucose was not a statistically significant predictor of risk for new diabetes in STAR, increasing baseline plasma glucose was associated with a trend to increased risk for new diabetes. Prior studies have reported that factors such as younger age, lipid measures, BP, race and US residency are predictors of diabetes risk in patients treated with antihypertensive medications (table 3) [2,35,36]. In STAR, none of these factors increased the risk for new diabetes.

Table 2 Baseline characteristics of patients from ASCOT, INVEST, LIFE, HOPE and STAR

	All patients		Patients without diabetes at entry							
	ASCOT [33]*			LIFE [35] (n = 7998)		HOPE [37]		STAR†		
	CCB (n = 9639)	BB (n = 9618)	INVEST [2] (n = 16176)	Did not develop diabetes (n = 7436)	Developed diabetes (n = 562)	ACEi (n = 2837)	Placebo (n = 2883)	Total (n = 185)	T/V (n = 91)	L/H (n = 94)
Female, n (%)	2258 (23)	2257 (23)	8315 (51)	4015 (54)	287 (51)	583 (21)	575 (20)	94 (51)	48 (53)	46 (49)
Male, n (%)	7381 (77)	7361 (77)	7861 (49)	3421 (46)	275 (49)	2254 (79)	2308 (80)	91 (49)	43 (47)	48 (51)
Age (years) (s.d.)	63.0 (8.5)	63.0 (8.5)	66 (10)	66.9 (7.0)	66.4 (6.8)	66.3 (6.7)	65.9 (6.9)	56.5 (9.7)	57.1 (10.0)	55.9 (9.5)
Caucasian, n (%)	9187 (95)	9170 (95)	8131 (50)	6990 (94)	517 (92)	2604 (92)	2644 (92)	132 (71)	66 (73)	66 (70.2)
Fasting plasma glucose (mmol/l) (s.d.)	6.2 (2.1)	6.2 (2.1)	NA	5.4 (1.0)‡	6.5 (1.6)‡	NA	NA	5.9 (0.4)	5.8 (0.5)	5.9 (0.4)
SBP (mmHg) (s.d.)	164.1 (18.1)	163.9 (18.0)	151 (19.5)	174 (14)	177 (15)	136.4 (19.5)	136.7 (19.4)	146.1 (15.9)	145.2 (15.1)	147.0 (16.6)
DBP (mmHg) (s.d.)	94.8 (10.4)	94.5 (10.4)	88 (12.0)	98 (9)	99 (9)	78.2 (10.5)	78.7 (10.5)	87.5 (9.9)	87.1 (10.0)	87.9 (9.8)
BMI (kg/m^2) (s.d.)	28.7 (4.6)	28.7 (4.5)	29 (7.5)	27.5 (4.5)	30.4 (5.0)	26.9 (3.9)	27.2 (4.0)	34.3 (6.9)	34.0 (6.2)	34.6 (7.5)
HDL (mmol/l) (s.d.)	1.3 (0.4)	1.3 (0.4)	NA	1.5 (0.4)	1.30 (0.37)	16.6%§	18.5%§	1.3 (0.3)	1.3 (0.4)	1.3 (0.3)

ACEi, angiotensin-converting enzyme inhibitor; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, beta-blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; HOPE, Heart Outcomes Prevention Evaluation; INVEST, International VErapamil SR-trandolaril Study; L/H, losartan/hydrochlorothiazide; NA, not available; SBP, systolic blood pressure; STAR, Study of Trandolapril/Verapamil SR And Insulin Resistance; T/V, trandolapril/verapamil.

*Data only available for entire 19 257 patients, of whom 14 120 patients did not have diabetes at the start of the study and were used in analysis.

†No significant differences between the T/V and L/H groups.

‡Non-fasting.

§Patients with HDL > 34.7 mg/dl.

Table 3 Baseline characteristics associated with risk for incident type 2 diabetes for ASCOT, INVEST, LIFE, HOPE and STAR

	ASCOT [36], HR (95% CI)	INVEST [2], HR (95% CI)	LIFE [35]*, HR (95% CI)	HOPE [37]†, RR	STAR‡, OR (95% CI)
Demographic factors					
Race	—	1.64 (1.15–2.34); $p < 0.01$ (multiracial/other vs. white) 1.21 (1.05–1.39); $p < 0.01$ (Hispanic vs. white)	—	—	1.51 (0.52–4.42) $p = 0.448$ (white vs. non-white)
US residency	—	1.62 (1.37–1.91); $p < 0.001$	—	—	—
Age (increments)	0.94 (0.90–0.96); $p < 0.01$ (5 years) (age > 55 years)	0.90 (0.85–0.96); $p < 0.001$ (10 years)	—	—	0.83 (0.47–1.44); $p = 0.502$ (10 years)
Gender	0.98 (0.84–1.14); $p = 0.75$ (male vs. female)	—	—	—	0.83 (0.29–2.36); $p = 0.729$ (female vs. male)
Obesity measures					
BMI (increments)	1.49 (1.38–1.62); $p < 0.001$ (5 kg/m^2)	1.05 (1.04–1.06); $p < 0.001$ (5 kg/m^2)	1.08 (1.07–1.10); $p < 0.001$ (1 kg/m^2)	—	0.84 (0.52–1.35); $p = 0.467$ (5 kg/m^2)
BMI $\leq$27.7 kg/m^2	—	—	—	0.41	—
Waist circumference (10-cm increments)	—	—	—	—	1.26 (0.79–2.00); $p = 0.328$
Waist-to-hip ratio $\leq$ 0.93	—	—	—	0.58	—
Blood glucose level factors					
Non-fasting glucose levels (1 mmol/l increments)	—	—	1.63 (1.56–1.70); $p < 0.001$	—	—
2-h OGTT glucose level (10 mg/dl increments)	—	—	—	—	1.39 (1.19–1.62); $p < 0.001$
Fasting blood glucose >5 mmol/l	5.80 (5.24–6.43); $p < 0.001$	—	—	—	—
HbA1c (1% increments)	—	—	—	—	4.21 (1.63–10.88); $p = 0.003$
Cholesterol-related factors					
HDL cholesterol (increments)	0.72 (0.58–0.89); $p < 0.01$ (1 mmol/l)	—	0.36 (0.28–0.45); $p < 0.001$ (1 mmol/l)	—	0.93 (0.79–1.10); $p = 0.394$ (10 mg/dl)
History of hypercholesterolaemia	—	1.17 (1.04–1.31); $p = 0.01$	—	—	—
Total cholesterol (1 mmol/l increments)	0.89 (0.84–0.94); $p < 0.001$	—	—	—	—
Triglycerides (increments)	1.12 (1.07–1.17); $p < 0.001$ (1 mmol/l)				0.96 (0.91–1.01); $p = 0.092$ (10 mg/dl)
Treatment					
Randomization to	—	0.85 (0.76–0.95) verapamil- vs. atenolol-based strategy; $p < 0.01$	0.71 (0.60–0.84) losartan- vs. atenolol-based treatment; $p < 0.001$	—	—
Not taking BB				1.02	
Not taking diuretic				0.66	
No BB or diuretic use				0.62 (0.43–0.90)	
Prior antihypertensive treatment	—	—	1.48 (1.20–1.82); $p < 0.001$	—	—
ACEi/CCB vs. BB/TD	0.66 (0.59–0.74); $p < 0.001$	—	—	—	—
ARB/TD vs. ACEi/CCB	—	—	—	—	4.04 (1.64–9.92); $p = 0.002$
Blood pressure					
Hypertension vs. no hypertension	—	—	—	1.35	—

(*Continued*)

SBP, continuous mmHg (10 mmHg increments)	1.07 (1.04–1.10); $p < 0.001$	—	1.18 (1.12–1.25); $p < 0.001$	—	1.05 (0.74–1.49); $p = 0.795$
DBP, continuous mmHg (10 mmHg increments)	—	—	—	—	1.00 (0.55–1.82); $p = 0.998$
Others					
Alcohol intake (units/week)	0.99 (0.99–1.00); $p = 0.02$				
Use of non-CAD medication	1.25 (1.11–1.40); $p < 0.001$				
Left ventricular hypertrophy		1.27 (1.10–1.46); $p < 0.01$			
Prior stroke/TIA		1.26 (1.03–1.56); $p = 0.03$			
Coronary revascularization		1.18 (1.03–1.35); $p = 0.02$			
Without microalbuminuria			0.66		

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BB, beta-blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; HOPE, Heart Outcomes Prevention Evaluation; HR, hazard ratio; INVEST, International VErapamil SR-trandolapril Study; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure; STAR, Study of Trandolapril/Verapamil SR And Insulin Resistance; TD, thiazide diuretic; TIA, transient ischaemic attack.
*Results from multivariate model for all patients without diabetes at baseline (model 1).
†Data were calculated from data from prespecified subgroups included in the publication, except for study drug use.
‡For purposes of comparison included baseline factors that were not significant in the full model.

Antihypertensive agent was strongly associated with developing diabetes in STAR. Patients without diabetes at baseline who were randomized to L/H were at four times greater risk of developing diabetes than their counterparts who received T/V. The magnitude of the treatment effect (L/H OR 4.04; $p = 0.002$) is similar to that of HbA1c (OR 4.21 per 1% increment; $p = 0.003$), and three times greater than that of 2-h OGTT glucose (OR 1.39 per 10 mg/dl increments; $p < 0.001$). Prior studies identified antihypertensive choice to be predictive of new diabetes (table 3) [2,33,35–37]. In ASCOT, diabetes risk was lower in patients receiving an ACEi/CCB regimen compared with patients receiving a BB/diuretic combination [36]. In HOPE, patients who never took a diuretic or a BB had a significantly lower risk of new diabetes. However, a small increase in diabetes risk was noted for the subgroup of patients not receiving a BB [37]. In VALUE, increased risk of diabetes was noted for treatment with amlodipine compared with valsartan [38]. Results from STAR support the overall hypothesis that certain antihypertensive agents may be pro-diabetic and suggest that choice of therapy – particularly in patients with MS who are at higher risk of diabetes – is extremely important.

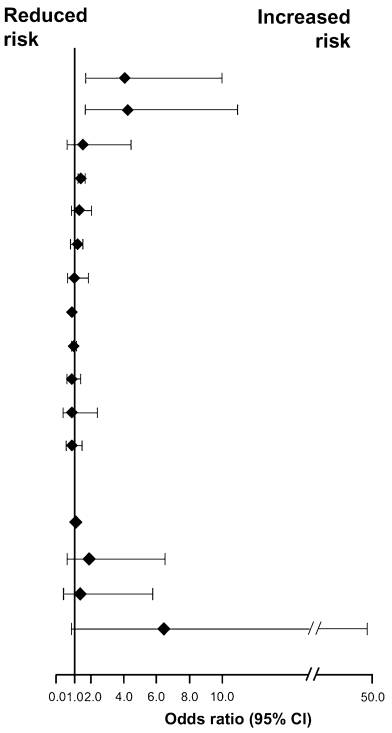
Multidrug antihypertensive therapy is often needed in patients with MS because of lack of efficacy of monotherapy [7,39,40]. FDC agents have been developed to improve patient compliance and BP control, many with a RAAS-blocking agent with a TD. It has been recognized for over four decades that TDs impair glucose tolerance [41,44,45].[42,43]

Various mechanisms for diuretic-induced glucose intolerance have been suggested. TDs may impair glucose tolerance through lowering serum potassium and/or magnesium levels [45–52]. Consistent with this notion are observations that TDs dose dependently elicit hypokalaemia, hypomagnesaemia, hyperuricaemia, hyperlipidaemia and glucose intolerance [51,52]. The mechanism causing drug-induced hypokalaemia and hypomagnesaemia is increased delivery of sodium to the distal convoluted tubule [45].

Several putative mechanisms, some impugning the development of hypokalaemia and/or hypomagnesaemia, have also been investigated. For example, in an isolated perfused pancreas study, insulin secretion was decreased in a low-potassium state and increased in a high-potassium state [44]. In non-experimentally generated hypokalaemic state, impaired glucose tolerance was produced through impaired insulin secretion [53]. In a study of patients with chronic disease characterized by hypokalaemia, there was an elevated pro-insulin (less active than insulin) to insulin secretion/serum levels, which

A

Baseline variable	New diabetes no. (%)	Adjusted OR (95% CI)	*p* Value
L/H treatment group (vs.T/V)		4.04 (1.64–9.92)	0.002**
HbA1c (%)		4.21 (1.63–10.88)	0.003**
Race (white vs.non-white)		1.51 (0.52–4.42)	0.448
2-hr OGTT glucose (10 mg/dl increments)		1.39 (1.19–1.62)	<0.001***
Waist (10 cm increments)		1.26 (0.79–2.00)	0.328
SBP (10mmHg increments)		1.05 (0.74–1.49)	0.795
DBP (10mmHg increments)		1.00 (0.55–1.82)	0.998
Triglycerides (10mg/dL increments)		0.96 (0.91–1.01)	0.092
Total HDL (10 mg/dl increments)		0.93 (0.79–1.10)	0.394
BMI (5kg/m^2 increments)		0.84 (0.52–1.35)	0.467
Female vs.male		0.83 (0.29–2.36)	0.729
Age (10-year increments)		0.83 (0.47–1.44)	0.502
Baseline fasting glucose (mg/dl)			
<100	5 (12.8)	1.00	–
≥100 to <110	23 (25.3)	1.93 (0.57–6.47)	0.289
≥110 to <120	13 (29.5)	1.42 (0.35–5.73)	0.625
≥120	6 (66.7)	6.46 (0.84–49.64)	0.073



B

Baseline variable	OR (95% CI)	*p* Value
L/H treatment group (vs.T/V)	4.39 (1.88–10.27)	<0.001***
HbA1c (%)	3.88 (1.71–8.80)	0.001***
Fasting glucose (10mg/dl increments)†	1.55 (0.98–2.46)	0.064
2-hr OGTT glucose (10mg/dl increments)	1.33 (1.17–1.52)	<0.001***

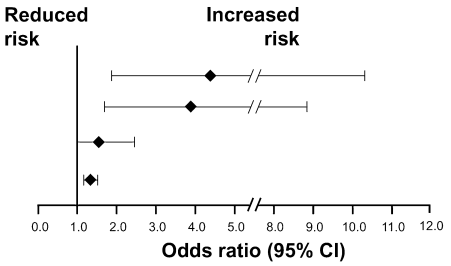


Fig. 1 Predictors of increased risk for new diabetes from the Study of Trandolapril/Verapamil SR And Insulin Resistance (STAR) study. Baseline characteristics were assessed by logistic regression (A) and step-wise Cox proportional hazards modelling (B) to determine the role in predicting new diabetes. New onset diabetes was defined as fasting blood glucose ≥126 mg/dl and/or 2-h glucose (oral glucose tolerance test (OGTT)] K200 mg/dl. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001. Patients with baseline fasting blood glucose ≥126 mg/dl and/or 2-h OGTT ≥200 mg/dl were excluded from the analyses. HbA1c, haemoglobin A1c; L/H, losartan/hydrochlorothiazide; OR, odds ratio; T/V, trandolapril/verapamil.

may have contributed to impaired glucose tolerance [48]. In a quantitative analysis of prior trials, a relationship was observed between decreased serum potassium and glucose tolerance; however, it appeared that glucose intolerance with diuretic therapy could not be fully explained by hypokalemia [45]. Indeed, TD therapy is associated with reduced peripheral insulin sensitivity that may be independent of changes in serum potassium [46,47,54].

Another mechanism for TD-induced glucose intolerance could be modest increases in serum aldosterone in response to modest TD-induced volume contraction [45,46,55–60]. Increased circulating levels of aldosterone are present in the cardiometabolic syndrome and have been shown to decrease in obese postmenopausal women with modest (5%) weight loss [56]. A recent study showed that the prevalence of the cardiometabolic syndrome was higher in hypertensive persons with primary hyperaldosteronism (41%) than in those with essential hypertension (30%) and that fasting hyperglycaemia (≥110 mg/dl) was more prevalent with primary aldosteronism than with essential hypertension [57]. These observations may be related to known effects of aldosterone to increase inflammatory cytokines and

oxidative stress in skeletal muscle, adipose tissue and the liver [58–60]. Consistent with this notion, in a rodent model with increased mineralocorticoid levels, low, non-BP-lowering doses of spironolactone, delivered by osmotic minipumps over 3 weeks, improved skeletal muscle insulin–induced glucose uptake in conjunction with lowering skeletal muscle levels of reactive oxygen species and other markers of inflammation [60]. Thus, elevated aldosterone in response to slight volume reduction may play a role in diuretic-induced glucose intolerance.

It has been suggested that when combined with a diuretic, a RAAS blocker effectively reduces the risk of new diabetes resulting from the use of a diuretic. The results from this STAR analysis do not support this assertion. Compared with the fixed-dose ACEi/CCB combination, the ARB/diuretic combination was associated with increased diabetes risk. ACEi and ARBs have been reported to improve insulin sensitivity and glucose metabolism [61]. CCBs, in particular the non-dihydropiridine CCB verapamil SR that was studied in STAR, have been considered to be metabolically neutral with respect to glycaemic control [62–64]. The question of whether RAAS-blocking agents are protective against the development of diabetes has been the subject of much scrutiny, and data from multiple studies (table 1) and meta-analyses would suggest that they do [65]. However, the recently completed DREAM study would suggest otherwise [34]. After a median 3 years of follow-up, no difference between ramipril and placebo was noted for the primary outcome of diabetes or death in patients with prediabetes (defined as an impaired fasting glucose or impaired glucose tolerance). The results from DREAM support those of STAR, which suggest that the difference in risk arose from the detrimental effects of the TD, which were not overcome by the ARB.

A limiting factor to the STAR analyses was the 1-year follow-up. It is possible that with longer follow-up, other traditional risk factors would also be significant predictors for new diabetes in patients with MS. Another limitation may be the sample size. It should be noted that the sample size was sufficient to test the hypothesis of a treatment difference in change from baseline to study end in 2-h OGTT glucose; however, it may not be large enough to identify other risk factors. Furthermore, with the smaller sample size it was feasible to administer the 2-h OGTT at multiple time points and therefore obtain accurate and specific data regarding the metabolic consequences of the fixed-dose antihypertensive combinations.

This analysis reinforces the concept that therapy in complex disease states requires focus on not just a single goal, such as BP control, but also on other factors that may be affected by treatment choice. Ideally, lifestyle changes and treatment of risk factors, like hypertension, can help prevent diabetes [3]. Results from STAR, supported by historical data, suggest a need for amending current guidelines that recommend a diuretic as first-line therapy for hypertension, especially in patients with MS who are at high risk for developing type 2 diabetes. As the number of patients meeting the criteria of MS increases and in particular those with hypertension, clinicians can no longer ignore the effects of treatment choice in patients with MS.

These data from STAR show that use of an ARB/TD FDC contributes to worsening glycaemic control and expose patients to a fourfold increased risk of developing diabetes. These results indicate that the choice of BP therapy can impact patient health and that patients with MS may benefit from antihypertensive therapy with T/V to avoid the greater risk of new diabetes that may be associated with using an ARB/TD.

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