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ORIGINAL ARTICLE

Efficacy of lower doses of pioglitazone after stroke or transient ischaemic attack in patients with insulin resistance

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Abstract

Aims: Pioglitazone is a potent insulin-sensitizing drug with anti-atherosclerotic properties, but adverse effects have limited its use. We assessed the benefits and risks of lower versus higher doses of pioglitazone taken by participants in the Insulin Resistance Intervention in Stroke Trial.

Materials and Methods: Efficacy [myocardial infarction (MI) or recurrent stroke] new-onset diabetes) and adverse outcomes (oedema, weight gain, heart failure and bone fracture) were examined for subjects assigned to pioglitazone or placebo within strata defined by mode dose of study drug taken (i.e. the dose taken on most days in the study).

Results: Among the 1938 patients randomized to pioglitazone, the mode dose was <15 mg/day in 546 participants, 15 mg/day in 128, 30 mg/day in 89, and 45 mg/day in 1175. There was no significant effect on stroke/MI or new-onset diabetes with <15 mg/day. For 15 mg/30 mg/day pooled, the adjusted hazard ratios (95% CI) for stroke/MI were 0.48 (0.30, 0.76; $p = .002$) and 0.74 (0.69, 0.94) for 45 mg/day. For new-onset diabetes, the adjusted hazard ratios were 0.34 (0.15, 0.81; $p = .001$) and 0.31 (0.59, 0.94; $p = .001$) respectively.

For oedema, weight gain and heart failure, the risk estimates for pioglitazone were lower for subjects taking <45 mg daily. For fractures, the increased risk with pioglitazone was similar across all dose strata.

Conclusions: Lower doses of pioglitazone appear to confer much of the benefit with less adverse effects than the full dose. Further study is needed to confirm these findings so that clinicians may optimize dosing of this secondary prevention strategy in patients with stroke.

KEYWORDS
cardiovascular disease, dose, insulin resistance, pioglitazone, randomized trial, thiazolidinediones

1 | INTRODUCTION

Insulin resistance is a common condition that is closely related to older age, increasing weight and genetic predisposition.[1] It affects the large majority of patients with type 2 diabetes, in which it is considered a fundamental aetiological factor.[2] Insulin resistance is also an established independent risk factor for vascular disease, including stroke and myocardial infarction (MI), and partly explains the association between diabetes and increased risk for these diseases. Insulin resistance is widely prevalent among patients with cerebrovascular and coronary artery disease who do not have diabetes.[3] Effective therapies for insulin resistance include weight loss, dietary improvement[4,5] and exercise. One effective pharmacological strategy is the thiazolidinedione, pioglitazone, a potent agonist of the nuclear hormone receptor, peroxisome proliferator-activated receptor-γ, with insulin sensitizing, anti-atherosclerotic and anti-inflammatory properties.[6] Pioglitazone is also a partial agonist of peroxisome proliferator-activated receptor-α,[6] which promotes catabolism of fatty acids, improving atherogenic plasma lipid profiles.[7] Thiazolidinediones also have vasodilatory effects mediated by endothelial release of nitric oxide induced by insulin,[8,9] and significantly reduce blood pressure in diabetics with resistant hypertension.[10]

In 2016, we reported results from the Insulin Resistance Intervention in Stroke (IRIS) trial,[11] in which pioglitazone reduced the risk of MI or recurrent stroke among patients without diabetes who had a recent stroke or transient ischaemic attack (TIA), and insulin resistance defined by a homeostasis model assessment of insulin resistance (HOMA-IR) score >3.0.[11] Not surprisingly, most participants had prediabetes at baseline. Per protocol, the dose of pioglitazone or matching placebo was titrated, if tolerated, from 15 to 45 mg/day over 8 weeks. The dose could be down-titrated in participants with adverse effects at higher doses.

Among patients with prediabetes in the IRIS trial[11] who took 80% of the protocol dose of pioglitazone (including permitted down-titrated doses) over 5 years, there was a significant reduction of systolic and diastolic pressure, significant reduction of serum triglycerides and a significant increase in serum high-density lipoprotein cholesterol. More importantly, there was an 82% reduction of new-onset diabetes, a 43% reduction of stroke or MI over 5 years.[12] These large effects suggest that pioglitazone should be more widely used for secondary stroke prevention.[13]

Pioglitazone is currently indicated for use in patients with type 2 diabetes. The most recent American Heart Association/American Stroke Association guidelines on secondary stroke prevention[14] list pioglitazone as a Class 2B recommendation in patients with stroke who have insulin resistance and glycated haemoglobin (HbA1c) <7%. This recommendation stems directly from the findings of the IRIS trial. Unfortunately, many clinicians are reluctant to use pioglitazone because of adverse effects, particularly weight gain and oedema,[13] and the drug is seldom prescribed by neurologists in their patients with stroke. There is some evidence, however, that lower doses of pioglitazone may offer substantial metabolic benefits with less adverse effects than higher doses. In this study, we therefore assessed the effects of pioglitazone dose with regard to efficacy and tolerability in the IRIS trial.[11]

2 | METHODS

The IRIS trial was a randomized, double-blind trial to test the effectiveness of pioglitazone, compared with placebo, for the prevention of MI or recurrent stroke among patients age ≥40 years with a stroke or TIA within 6 months, no history of type 2 diabetes, HbA1c <7% and insulin resistance by HOMA-IR >3.0.[11,12,15] Patients were excluded for congestive heart failure, severe oedema, or history of or high risk for bladder cancer.

Randomized participants were initiated on one 15 mg tablet daily of pioglitazone or matching placebo. The dose was increased to two tablets (30 mg) after 4 weeks and then three tablets (45 mg) after an additional 4 weeks. At week 8, study participants who were tolerating the full dose were started on one 45 mg tablet of pioglitazone or matching placebo daily for the remainder of the trial. At any point during participation, subjects who developed adverse effects (e.g. excessive weight gain, oedema) were evaluated and could be down-titrated to a dose that was better tolerated. Participants who developed heart failure, bladder cancer, macular oedema or certain fractures were permanently discontinued from study medication but continued to be followed in the trial. Participant interviews were scheduled every 2 weeks for the first 3 months as study medication was titrated. Starting at month 4, telephone interviews were conducted every 4 months, and in-person visits annually. At each follow-up contact, participants were queried about specific adverse effects, new diagnoses, hospitalizations and any problems taking the study drug. Dates of all study drug dose reductions, cessations and restarts were recorded in a protocol tracking database.

The analyses for this post hoc exploratory study were conducted on the as-treated principle.[16] Using the protocol tracking database, we classified the drug status of each participant for each day in the study (<15, 15, 30 or 45 mg). To assess the effect of dose on outcome risk, the mode dose of study drug (i.e., most frequent dose taken) for each subject was calculated over the period from study drug initiation to end of follow-up or date of event (for subjects with a specified outcome event). Mode dose was used as the exposure of interest because patients take a specific dose on each day, not a mean dose. (Exposure defined by mean dose taken is examined in a secondary analysis and presented in Supplementary material.) Hazard ratios (HRs) and 95% confidence intervals (CI) from Cox proportional hazards models were used to quantify the relative risk for subjects taking pioglitazone compared with placebo for strata of mode dose taken (<15, 15, 30, 45 mg/day). Values for $p < .05$ were regarded significant.

The <15 mg stratum was composed of subjects who were off drug (and some who took half of a 15 mg tablet) for most days in the study until the date of event/end of follow-up. Differences in the effect of drug across strata were assessed by inclusion of a treatment by strata interaction term. All models were adjusted for baseline features identified originally by the trial investigators as potentially

important risk features: age, sex, previous stroke before the index event, stroke (vs. TIA) at entry, systolic blood pressure, diastolic blood pressure, cigarette smoking, coronary heart disease and history of hypertension.

The effect of study drug by dose strata was examined for efficacy outcomes (stroke or MI, or new-onset diabetes) and adverse outcomes associated with pioglitazone. The latter were predefined in the study protocol and included: (a) oedema, which was bothersome to the patient (swelling of feet or lower legs that persisted after leg elevation or was associated with discomfort, redness, skin breakdown or difficulty getting shoes on the feet); (b) weight gain of >10 lb (4.5 kg); and (c) severe heart failure (i.e. requiring hospitalization), and serious bone fracture (i.e. requiring surgery or hospitalization). During the IRIS trial, professional bodies published updated definitions for MI and stroke, the two components of the IRIS composite primary outcome.[17,18] Accordingly, the IRIS Data and Safety Monitoring Board agreed to amend the study protocol to allow a pre-planned secondary analysis using these definitions. In this report, we used these updated definitions for stroke and MI.

3 | RESULTS

Among the 1938 patients randomized to pioglitazone, the mode dose taken was <15 mg/day in 546 (28.2%) participants, 15 mg/day in 128 (6.6%), 30 mg/day in 89 (4.6%) and 45 mg/day in 1175 (60.6%). The median percentage follow-up time in which participants took their mode dose exceeded 70% in all dose strata. Male participants comprised a larger proportion of subjects taking full mode dose compared with subjects who were on reduced doses (Table 1, Table S1). Median follow-up was 4.8 years (interquartile range 3.4-5.0, range 0-5.0 years).

TABLE 1 Baseline features of participants by mode dose taken[a]

Feature	Mode dose taken			
	<15 mg	15 mg	30 mg	45 mg
	(n = 912)	(n = 233)	(n = 124)	(n = 2604)
Age, years	64 ± 11	62 ± 11	64 ± 10	63 ± 10
Male sex	477 (52)	135 (58)	62 (50)	1861 (71)
BMI, kg/m^2	30.5 ± 6.1	30.7 ± 6.1	30.4 ± 6.4	29.7 ± 5.1
HOMA-IR	5.4 ± 2.7	5.8 ± 3.5	5.9 ± 3.3	5.4 ± 2.6
HbA1c, %	5.8 ± 0.4	5.8 ± 0.4	5.8 ± 0.4	5.8 ± 0.4
HbA1c, mmol/mol	40.2 ± 4.2	40.0 ± 4.2	40.5 ± 4.0	39.9 ± 4.3
Systolic pressure, mmHg	133 ± 18	134 ± 18	134 ± 17	133 ± 17
Diastolic pressure, mm Hg	79 ± 10	80 ± 11	79 ± 9	79± 11
Fasting cholesterol, mmol/L	4.3 ± 1.0	4.3 ± 1.0	4.4 ± 1.0	4.2 ± 1.0
LDL-C, mmol/L	2.3 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	2.2 ± 0.8
HDL-C, mmol/L	1.3 ± 0.4	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3
Fasting triglycerides, mmol/L	1.6 ± 0.9	1.6 ± 0.9	1.6 ± 0.8	1.6 ± 0.8
Current smoker	128 (14)	59 (25)	17 (14)	418 (16)
Stroke (vs. TIA) at entry	769 (85)	210 (91)	106 (85)	2287 (88)
Prior stroke history	116 (13)	36 (15)	24 (19)	311 (12)
Hypertension history	657 (72)	189 (81)	86 (69)	1835 (70)
Atrial fibrillation	87 (10)	13 (6)	10 (8)	153 (6)
Coronary heart disease	91 (10)	34 (15)	18 (15)	319 (12)
Baseline medication				
Statin	736 (81)	185 (79)	98 (80)	2164 (83)
Antiplatelet	824 (91)	220 (94)	116 (94)	2404 (92)
Oral anticoagulant	126 (14)	20 (9)	13 (11)	282 (11)
ACE inhibitor or ARB	483 (53)	131 (56)	62 (50)	1466 (56)
Diuretic	251 (28)	59 (25)	42 (34)	761 (29)
Beta-blocker	304 (33)	92 (39)	45 (37)	786 (30)

[a]Mode dose taken calculated until stroke/myocardial infarction or end of follow-up if no event. Data are mean ± SD or n (%).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TIA, transient ischaemic attack.

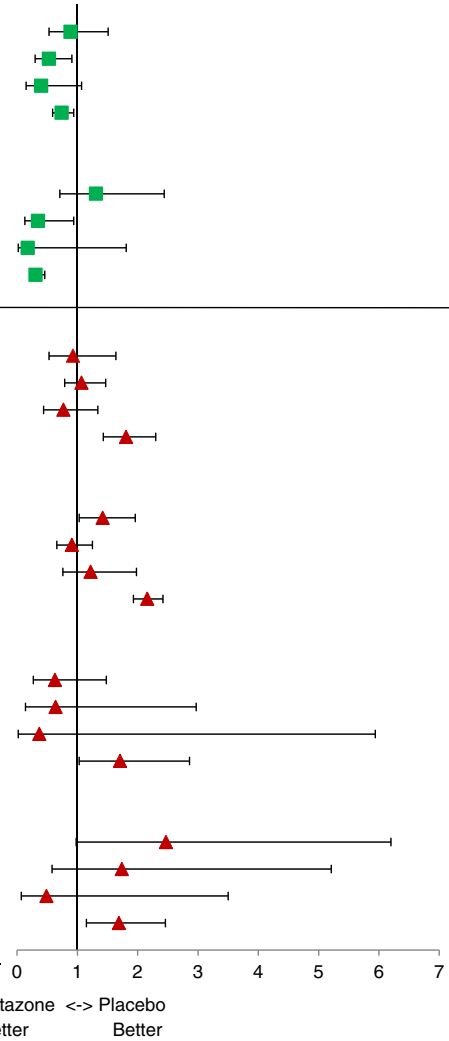
At baseline, the percentages of patients with A1c of <5.6%, 5.7%-6.4% and ≥6.5% were 35.52%, 57.82% and 6.66% for placebo, and 34.62%, 59.39% and 5.99% respectively for pioglitazone (chi-squared test, $p = .37$).

Among participants taking the lowest mode dose (<15 mg/day), there was no significant reduction in risk for the primary outcome of stroke/MI. In contrast, in each mode dose subgroup of ≥15 mg/day, pioglitazone was associated with a significant or nearly significant reduction in risk. However, in a formal test of heterogeneity, adjusted HRs (AHR) did not differ significantly across strata of mode dose taken (interaction $p = .81$) (Table S2; Figure 1).

For participants taking <15 mg daily there was also no reduction in risk for new-onset diabetes. In each dose subgroup of ≥15 mg/day, pioglitazone was associated with strong reductions in risk. Because of this finding and a significant test of heterogeneity across all strata ($p = .0002$), we compared the effect of treatment among participants taking the lowest mode dose with participants taking at least 15 mg/day and found a significant difference in treatment effect with dose [AHR 1.31 (95% CI, 0.71, 2.44) vs. AHR 0.34 (95% CI, 0.24, 0.48); interaction $p = .0001$] (Table S1; Figure1).

For adverse events of oedema, weight gain and heart failure (see above and defined in footnotes of Table 2), risk estimates for pioglitazone were lower for subjects taking <45 mg mode dose than

Event Mode Dose*	Pioglitazone Events / N (%)	Placebo Events / N (%)	Adjusted HR† (95% CI)	Inter-action P value
Stroke/Myocardial Infarction				
<15 mg/day	32 / 546 (5.9)	25 / 366 (6.8)	0.89 (0.53, 1.51)	
15	23 / 128 (18.0)	34 / 105 (32.4)	0.53 (0.30, 0.91)	
30	12 / 89 (13.5)	7 / 35 (20.0)	0.40 (0.15, 1.07)	
45	114 / 1175 (9.7)	179 / 1429 (12.5)	0.74 (0.59, 0.94)	0.81
New Onset Diabetes				
<15 mg/day	29 / 573 (5.1)	16 / 389 (4.1)	1.31 (0.71, 2.44)	
15	7 / 114 (6.1)	11 / 81 (13.6)	0.35 (0.13, 0.94)	
30	3 / 86 (3.5)	2 / 33 (6.1)	0.18 (0.02, 1.81)	
45	34 / 1165 (2.9)	120 / 1432 (8.4)	0.31 (0.21, 0.46)	0.0001
Edema‡				
<15 mg/day	28 / 459 (6.1)	23 / 338 (6.8)	0.93 (0.53, 1.64)	
15	108 / 187 (57.8)	71 / 132 (53.8)	1.07 (0.79, 1.47)	
30	44 / 98 (44.9)	21 / 43 (48.8)	0.77 (0.44, 1.34)	
45	169 / 1194 (14.2)	121 / 1422 (8.5)	1.81 (1.43, 2.30)	0.01
Weight Gain >10lbs§				
<15 mg/day	101 / 429 (23.5)	63 / 340 (18.5)	1.42 (1.03, 1.96)	
15	110 / 165 (66.7)	63 / 102 (61.8)	0.91 (0.66, 1.25)	
30	75 / 108 (69.4)	27 / 47 (57.4)	1.22 (0.76, 1.98)	
45	726 / 1236 (58.7)	500 / 1446 (34.6)	2.16 (1.93, 2.42)	0.001
Heart Failure[Π]				
<15 mg/day	11 / 560 (2.0)	11 / 388 (2.8)	0.63 (0.27, 1.48)	
15	4 / 116 (3.4)	4 / 81 (4.9)	0.64 (0.14, 2.97)	
30	1 / 87 (1.1)	1 / 33 (3.0)	0.37 (0.02, 5.94)	
45	35 / 1175 (3.0)	26 / 1433 (1.8)	1.71 (1.03, 2.86)	0.05
Bone Fracture**				
<15 mg/day	20 / 562 (3.6)	6 / 385 (1.6)	2.47 (0.98, 6.20)	
15	13 / 120 (10.8)	5 / 84 (6.0)	1.74 (0.58, 5.21)	
30	5 / 86 (5.8)	2 / 34 (5.9)	0.49 (0.07, 3.50)	
45	61 / 1170 (5.2)	49 / 1432 (3.4)	1.69 (1.15, 2.46)	0.68



*Mode dose is calculated until event or end of follow-up if no event.

†Adjusted for age, sex, prior stroke, stroke at entry, SBP, DBP, current smoking, CAD, htn history.

‡Report of new or worse swelling of feet or lower legs that persisted after leg elevation or was associated with discomfort, redness, skin breakdown or difficulty getting shoes on feet.

§Weight change from baseline at any time in trial.

[Π]Heart failure causing or prolonging hospitalization or causing death.
For 30 mg/day dose, adjusted HR not calculable so unadjusted HR is shown.

**Bone fracture resulting in hospitalization or surgery

FIGURE 1 Efficacy and adverse events by treatment and mode dose taken. Forest plot shows the rate and adjusted hazard ratios (HRs) of outcomes by strata of mode dose of pioglitazone compared with placebo, for stroke/myocardial infarction, new-onset diabetes, weight gain, heart failure and bone fracture. Lower doses of pioglitazone appear to confer much of the benefit, with less adverse events, except for fractures. CAD, coronary artery disease; DBP, diastolic blood pressure; htn, hypertension; SBP, systolic blood pressure

TABLE 2 Efficacy outcomes and adverse events by mode dose taken (with pooled 15 mg/30 mg doses vs. 45 mg daily)

	Pioglitazone			Placebo			Unadjusted			Adjusted[b]		
Mode dose taken (mg/day)	Pts	Events	Rate (%)	Pts	Events	Rate (%)	HR	(95% CI)	*p*	HR	(95% CI)	*p*
Stroke or MI												
15 or 30	217	35	16	140	41	29	0.48	(0.3, 0.75)	.001	0.48	(0.3, 0.76)	.002
45	1175	114	10	1429	179	13	0.76	(0.6, 0.96)	.02	0.74	(0.59, 0.94)	.01
	1392	149	11	1569	220	14				Interaction *p*		.06
New onset diabetes												
15 or 30	200	10	5	114	13	11	0.38	(0.16, 0.86)	.02	0.34	(0.15, 0.81)	.01
45	1165	34	3	1432	120	8	0.33	(0.23, 0.49)	<.001	0.31	(0.21, 0.46)	<.0001
	1365	44	3	1546	133	9				Interaction *p*		.59
Oedema[c]												
15 or 30	285	152	53	175	92	53	0.96	(0.74, 1.24)	.74	0.94	(0.72, 1.23)	.68
45	1194	169	14	1422	121	9	1.71	(1.35, 2.16)	<.0001	1.81	(1.43, 2.3)	<.0001
	1479	321	22	1597	213	13				Interaction *p*		.001
Weight gain[d]												
15 or 30	273	185	68	149	90	60	1.02	(0.79, 1.31)	.90	1.02	(0.79, 1.32)	.87
45	1236	726	59	1446	500	35	2.15	(1.92, 2.41)	<.0001	2.16	(1.93, 2.42)	<.0001
	1509	911	60	1595	590	37				Interaction *p*		<.0001
Heart failure[e]												
15 or 30	203	5	2	114	5	4	0.52	(0.15, 1.81)	.30	0.41	(0.11, 1.55)	.19
45	1175	35	3	1433	26	2	1.63	(0.98, 2.71)	.06	1.71	(1.03, 2.86)	.04
	1378	40	3	1547	31	2				Interaction *p*		.09
Bone fracture[f]												
15 or 30	206	18	9	118	7	6	1.36	(0.57, 3.27)	.49	1.16	(0.47, 2.86)	.75
45	1170	61	5	1432	49	3	1.52	(1.04, 2.21)	.03	1.69	(1.15, 2.46)	.007
	1376	79	6	1550	56	4				Interaction *p*		.61

[a]Mode dose is calculated until event or end of follow-up if no event.
[b]Adjusted for age, sex, previous stroke, stroke at entry, systolic blood pressure, diastolic blood pressure, current smoking, coronary artery disease, hypertension history.
[c]Report of new or worse swelling of feet or lower legs that persisted after leg elevation or was associated with discomfort, redness, skin breakdown or difficulty getting shoes on feet.
[d]Weight gain >10 lb (4.5 kg) from baseline at any time in trial.
[e]Heart failure causing or prolonging hospitalization or causing death.
[f]Bone fracture resulting in hospitalization or surgery.
Abbreviations: HR, hazard ratio; MI, myocardial infarction.

for subjects taking the full 45 mg mode dose (Tables S3 and S4). For fractures, however, the increased risk in the pioglitazone subgroups was similar across all dose strata, overall and by sex (Table S4).

When mean dose taken was examined, 476 (24.6%) of participants assigned to pioglitazone took <15 mg/day, 311 (16.0%) took 15-29 mg/day, 215 (11.1%) took 30-39 mg/day and 936 (48.3%) took ≥40 mg/day. Findings by mean dose taken were broadly similar to the analyses by mode dose, except that the risk for oedema and weight gain with pioglitazone was elevated across all dose strata above the lowest dose (Tables S2; Figure 1).

Figure 1 presents the results for efficacy and adverse effects for all groups of doses, and they are presented in the Supporting Information (Tables S2 and S3). Table 2 presents the efficacy and adverse outcomes comparing a pooled mode dose of 15/30 mg daily versus 45 mg daily. The lower doses conferred much of the benefit of the 45 mg dose, with less adverse effects; for serious fractures, the difference was not significant.

When mean dose taken was examined, 476 (24.6%) of participants assigned to pioglitazone took <15 mg/day, 311 (16.0%) took 15-29 mg, 215 (11.1%) took 30-39 mg and 936 (48.3%) took ≥40 mg/day. (Table S5). Findings by mean dose taken were broadly similar to the analyses by mode dose, except that the risk for oedema and weight gain with pioglitazone was elevated across all dose strata above the lowest dose (Tables S6 and S7).

4 | DISCUSSION

In this post hoc exploratory analysis of data from the IRIS trial, we found that 15 and 30 mg daily doses of pioglitazone had similar efficacy for the prevention of stroke and MI compared with the higher dose of 45 mg. Moreover, these lower doses also appeared to be better tolerated, except for fracture. The reduction of new-onset diabetes observed with the 15 or 30 mg daily dose compared with 45 mg daily was similar to the reduction in the main study endpoint of stroke or MI. Together, these findings suggest that much of the benefit of pioglitazone may be achieved at lower doses than the maximum approved dose.

Participants randomized to pioglitazone had lower blood pressure, fasting glucose and serum triglycerides, and higher high-density lipoprotein cholesterol at the end of the study. As the ratio of triglycerides to high-density lipoprotein cholesterol is a marker of insulin resistance,[19] it is probable that these changes were because of effects of pioglitazone on insulin resistance. In the parent IRIS trial, HOMA scores were measured at baseline and after 1 year. As reported in the supplement to that paper, HOMA-IR increased in the placebo group by +0.4 units, whereas it declined in the pioglitazone group by −1.3 units ($p < .0001$).[11] Cardiovascular benefits from pioglitazone are probably mediated through its multiple metabolic and vascular effects, including improvements in glycaemia, insulin sensitivity, dyslipidaemia, blood pressure, inflammatory markers, endothelial function and possibly direct anti-atherosclerotic effects.[20,21]

These data must be interpreted cautiously. Limitations were that patients were not randomized to the dose strata, and unavoidably, the number of patients in some strata was small. All patients assigned to active therapy were intended to be titrated to the maximum dose of 45 mg. Those individuals who ended up on lower doses had elected or were recommended by the site investigators to take a reduced dose. As this recommendation was made generally in response to adverse events, individuals on lower doses were those who were unable to tolerate the protocol dose of 45 mg. Because adverse events (such as oedema and weight gain) probably steered these participants towards the lower doses, comparisons for both trial outcomes and adverse events is challenging, with a probably inherent bias towards more adverse events in those at the lower doses.

Another limitation is that we assessed insulin resistance by the HOMA-IR, which incorporates only fasting insulin and glucose levels, and is therefore mainly a measure of hepatic insulin sensitivity. Postprandial testing (e.g. the Matsuda Index) or the classic insulin-glucose clamp technique would better assess muscle insulin sensitivity, which is viewed as the more important and predictive metabolic feature in insulin-resistant individuals. In a large clinical trial such as IRIS, testing beyond fasting labs would introduce significant cost and complexity. HOMA-IR does correlate with these tests, and remains a commonly used, pragmatic surrogate in clinical trials.[22]

In the initial investigations of pioglitazone as diabetes medication, the lower doses of 15 and 30 mg were shown to be less efficacious in reducing fasting plasma glucose and HbA1c than the eventually maximum approved dose of 45 mg.[23] This led to the recommendation in the package label to advance the dose to 45 mg in those not responding adequately to lower doses from the standpoint of glycaemia. Weight gain was also dose-related in these studies.[23]

In 2016, the IRIS trial[11] was the first to show protection against atherosclerosis-associated events by the thiazolidinedione pioglitazone in a non-diabetic stroke population with insulin resistance. Decades of epidemiological data had previously strongly suggested a positive relationship between insulin resistance and cardiovascular disease,[24-28] including stroke.[29] Insulin resistance has been implicated as a potentially direct causative factor in atherogenesis.[29,30] The first evidence of secondary stroke prevention with a drug designed to reduce insulin resistance was the PROactive trial, which randomized patients with type 2 diabetes and overt macrovascular disease to either pioglitazone or placebo on top of their background diabetes therapy.[31] A follow-up subgroup analysis reported a striking 47% relative risk reduction (RRR) in stroke in the 984 PROactive participants with previous stroke.[32] Notably, the effect size of pioglitazone in PROactive and that in the original, intention-to-treat (ITT) analysis of IRIS (RRR 24%), compare favourably with those of routine and guideline-directed secondary stroke prevention strategies, such as antiplatelet therapy, renin-angiotensin system blockade and statin drugs to lower low-density lipoprotein cholesterol. However, as many patients stop pioglitazone because of adverse effects, particularly weight gain and oedema, ITT analyses may underestimate the true benefit of pioglitazone among patients who actually adhere to it. The point estimates for the HRs in the aforementioned IRIS analysis of participants with prediabetes who took at least 80% of the protocol dose were even stronger, with an RRR of 43% in the risk of stroke/MI and an RRR of 82% (vs. 52% RRR in the ITT analysis) in the risk of incident type 2 diabetes.[12]

Weight gain and oedema remain major obstacles to the use of pioglitazone. It should be noted, however, that weight gain on pioglitazone is associated with a greater decrease in HbA1c and greater improvements in insulin sensitivity and beta cell function in patients with type 2 diabetes.[28,33,34] Interestingly, in the PROactive trial, weight gain actually predicted lower mortality.[35] Several mechanisms contribute to oedema from this medication: salt and water retention because of effects on the renal tubular epithelial sodium channel[36] and other effects in the collecting duct and perhaps increased vascular permeability.[37] However, oedema also reflects the effects of pioglitazone to promote vasodilation,[9,38] which has a blood pressure-lowering effect that may be beneficial in secondary prevention.[39,40]

Our results suggest that doses of pioglitazone lower than the maximal 45 mg dose may be better tolerated but still prevent cardiovascular events. Lower doses may be more acceptable to patients and clinicians, leading to increased implementation of this novel approach to risk reduction. Moreover, oedema can be controlled by the addition of a diuretic, and, in this regard, amiloride may be particularly effective.[41] Furthermore, in patients with diabetes, weight gain and perhaps even fluid retention, can conceivably be mitigated by combining pioglitazone with other glucose-lowering medications and recently was shown to have cardiovascular benefits, such as a glucagon-like peptide-1 receptor agonist or a sodium-glucose cotransporter 2 inhibitor.[42-45]

Several investigators have explored lower doses of pioglitazone in non-randomized studies. In a non-randomized open-label 12-week study from India, 90 patients with HbA1c >7.0% despite 3 months of treatment with metformin or sulphonylurea were assigned to pioglitazone 7.5, 15 or 30 mg daily.[46] The 7.5 mg dose was equally efficacious in lowering HbA1c levels but was not as efficacious for lowering the HOMA-IR score. A smaller study from Japan focusing on heart failure involved 40 patients on daily doses of 7.5, 15 and 30 mg. The authors reported that the 7.5 mg dose had similar effects on HbA1c and HOMA-IR, with a lesser increase in B-type natriuretic peptide, a marker of volume overload.[47] As these studies were conducted in Asian populations, and race and lower baseline body weight may have contributed to these effects. A randomized trial, the Thiazolidinediones Or Sulphonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT),[48] in which the mean dose of pioglitazone taken was 23 mg daily, failed to show reduction in the composite primary outcome of major adverse cardiovascular events with pioglitazone versus sulphonylureas added to baseline metformin therapy. However, this was a primary prevention trial with 89% of participants having no cardiovascular disease at baseline. In addition, 28% discontinued study medication during the trial. In this light, an on-treatment analysis showed a significant reduction in a composite secondary composite major adverse cardiovascular event outcome (which included all revascularizations and major leg amputations) in the pioglitazone group compared with the sulphonylurea group (HR 0.67, 95% CI 0.47-0.96, $p = .03$).

The finding of similar fracture rates across dose categories deserves further discussion. The effect of pioglitazone in bone has been the subject of multiple reviews.[49-51] To date, there is no agreement on precisely how the drug affects the skeleton, although a deleterious impact on bone density and/or bone quality is suspected. Increased fracture rates have been detected predominantly in postmenopausal women. A dedicated lower-dose trial would be needed to determine the absolute effect of lower dose pioglitazone on the risk of fracture.

The IRIS trial did not include intensive mitigation strategies for prevention of fragility fractures, such as bone density screening and medications to treat osteoporosis. It is at least plausible that patient selection and intensive fracture risk reduction efforts could improve the risk to benefit ratio for pioglitazone with respect to bone health. Viscoli et al. calculated that there was a 1.6% increase in fractures that were probably because of pioglitazone (low-energy, non-pathological) and they suggested that therapy for osteoporosis might help reduce this risk.[52] They also proposed a point score system to identify patients at low risk for fracture, resulting in a more favourable benefit-risk profile for pioglitazone therapy after ischaemic stroke or TIA.[53]

5 | CONCLUSION

To our knowledge, our exploratory findings are the first from a randomized trial to suggest that daily doses less than the maximal 45 mg of pioglitazone are better tolerated while maintaining substantial efficacy in reducing cardiovascular events and new-onset diabetes in patients with stroke or TIA. Despite the stated limitations, these findings contribute significantly to our understanding of the treatment of insulin resistance. Given the potent cardiovascular benefits of this insulin-sensitizing drug in patients with stroke, lower-dose trials in patients with cerebrovascular disease are warranted. Results of such trials might delineate a treatment strategy that could overcome the current reluctance of both prescribers and patients to use this medication in secondary stroke prevention.

CONFLICT OF INTEREST

WK, CV, SEI, JDS, KF and LY were investigators in the IRIS trial, which received study medication and placebo from the manufacturer, Takeda Pharmaceuticals International. Takeda Pharmaceuticals International had no role in the design, analysis or reporting of the study, which was funded by NINDS (grant number U01NS044876). The other authors declare that they have no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are available through the NINDS

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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