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Taking care of volunteers in a stroke trial: a new assisted-management strategy

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ABSTRACT

Background and purpose: Providing participants with evidence-based care for secondary prevention is an ethical and scientific priority for trials in stroke therapy. The optimal strategy, however, is uncertain. We report the performance of a new approach for delivering preventive care to trial participants.

Methods: Participants were enrolled in the Insulin Resistance Intervention after Stroke trial, which examined the insulin sensitiser, pioglitazone versus placebo for prevention of stroke and myocardial infarction after ischaemic stroke or transient ischaemic attack. Preventive care was the responsibility of the participants' personal healthcare providers, but investigators monitored care and provided feedback annually. We studied achievement of 8 prevention goals at baseline and 3 annual visits, with a focus on 3 priority goals: blood pressure <140/90 mm Hg, low-density lipoprotein (LDL) cholesterol <2.59 mmol/L and antithrombotic therapy.

Results: The proportion of participants achieving the priority goals was highest for antithrombotic use (96–99% in each year) and similar for blood pressure (66–72% in each year) and LDL (68–70% in each year). All 3 priority goals were achieved by 47–52% of participants in any given year. However, only 22% of participants achieved all 3 goals in each year.

Conclusions: A strategy of monitoring care and providing feedback was associated with high average yearly achievement of 3 priority secondary prevention goals, but the majority of trial participants did not persist in being at goal over time.

Trial registration number: NCT00091949.

INTRODUCTION

In stroke clinical trials, all participants should be offered standard preventive care. This fulfils an ethical obligation to participants[1–3] and assures that measurement of the effect of an experimental therapy is not biased by differences in cotherapies between groups or modified by substandard care in the trial as a whole. Investigators disagree, however, on the optimal way of delivering preventive care. One approach is for investigators to directly manage participants.[4–6] Another approach is to rely on participants' personal healthcare providers (HCP) without direct involvement of the study team.[7–12] Proponents of the latter approach argue that it reduces costs, capitalises on established therapeutic relationships and shows how an experimental therapy compares with current community standards. Between these approaches is a strategy in which researchers assist HCPs in managing preventive care.[13] This assisted-management strategy is potentially less expensive than direct management but allows the research team to encourage good preventive care while leveraging established therapeutic relationships.

Despite the importance of preventive care for stroke trial participants, there are scant published data on the actual performance of the basic strategies described above. Without these data, investigators and trial monitors have difficulty designing, appraising, and improving current and future trials.

Herein, we describe the performance of the assisted-management strategy used in the Insulin Resistance Intervention after Stroke (IRIS) trial, which showed that pioglitazone was effective in preventing stroke and myocardial infarction (MI) among non-diabetic patients with a recent ischaemic stroke or transient ischaemic attack (TIA) and insulin resistance.[14] We sought to identify characteristics of the research participants who are at risk for not achieving key prevention goals and may benefit from special attention. Finally, we tested the theory that the quality of preventive care may modify treatment effect by examining the interaction between achievement of prevention goals and response to pioglitazone.

METHODS

IRIS trial design and participants

The design of the IRIS trial has been published.[14 15] Briefly, the IRIS trial was a randomised, double-blind, placebo-controlled trial that tested the effectiveness of pioglitazone, compared with placebo, for prevention of stroke and MI among insulin-resistant, non-diabetic patients with a recent ischaemic stroke or TIA. Major inclusion criteria were age 40 years or older, qualifying ischaemic stroke or TIA within 180 days and insulin resistance. Major exclusion criteria were diabetes, bladder cancer, heart failure and severe medical comorbidity. Between February 2005 and January 2013, the study enrolled 3876 participants from sites in the USA, UK, Canada, Israel, Germany, Australia and Italy. Participants were followed for up to 5 years for safety and outcome events. The protocol was approved by local ethics committees and all patients provided written informed consent.

Preventive care was provided by each participant's personal HCP. If a participant did not have a personal physician, the site investigator was instructed to assist the patient in finding one to supervise their risk factor management. IRIS investigators monitored blood pressure, lipid profiles, body weight, aspirin use and prescription medications, cigarette smoking, alcohol use, and exercise habits and provided results—compared to goals—to participants and HCPs in baseline and annual letters (see online supplementary figures S1–S3). Participants and HCPs were encouraged to achieve the goals.

The IRIS goals were based on US guidelines in effect in 2005, including those from the American Heart Association/American Stroke Association (AHA/ASA), the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the National Cholesterol Education Program, although published guidelines for management of lipids, anticoagulation and antiplatelet therapies changed slightly during the course of the trial (see online supplementary data).

Statistical analyses

The study cohort for the present analysis was restricted to IRIS participants from countries with at least 150 randomised participants to allow stable within-country performance estimates. The proportion of participants achieving each of eight secondary prevention goals was reported for the study cohort overall and by country at baseline and at years 1, 2 and 3 during follow-up. The primary focus of our analysis was achievement of the three prevention goals most commonly monitored and thought to be readily achievable with appropriate pharmacotherapy: blood pressure <140/90 mm Hg, low-density lipoprotein (LDL) cholesterol <2.59 mmol/L and the use of anticoagulant or antiplatelet (antithrombotic) therapy. We report the percentage of participants at baseline and during follow-up who met all three of these priority goals. To identify features associated with non-achievement of these priority goals consistently over time, we compared the group of participants who met all three goals at baseline and at years 1, 2 and 3 to participants who met fewer than all three goals at each of these time points. Bivariate associations between baseline features (including demographic, clinical and geographic characteristics) and consistent achievement or consistent non-achievement of the priority goals were quantified by the ORs and 95% CIs, with statistical significance assessed by χ^2 tests for differences in proportions. A p value of <0.05 was used to demarcate statistical significance. A logistic regression model with stepwise selection of predictors (and p value of 0.05 for entry and retention) was used to assess the independent association of the patient-level features found to be significant in bivariate analyses. We also examined the occurrence of the primary outcome in the IRIS trial (fatal and non-fatal stroke or MI) according to randomised treatment assignment in the subgroups of participants defined by meeting or not meeting all three priority goals at baseline. The Cox model was used to estimate the effect of pioglitazone relative to placebo as a HR with 95% CIs and to test for treatment by subgroup interaction.

RESULTS

Baseline characteristics for the study cohort are shown in table 1. Some minor differences were observed between countries. Participants from the USA tended to be younger and more likely to be black compared with those enrolled from the UK, Canada, Israel and Germany (see online supplementary table S1).

Achievement of prevention goals in all countries combined is shown in table 2. The proportion of participants achieving physiological goals in each year was lower for body mass index (BMI) compared with blood pressure or LDL cholesterol. Adherence to antithrombotic therapy was higher compared with adherence to statin therapy and fell slightly for both over time. By year 3, 96% of the surviving patients were on an antithrombotic agent compared with 78% of participants on a statin. Among behavioural goals, achievement was highest for safe alcohol use (93–95% in each year), followed by abstinence from cigarette smoking (84% in each year) and aerobic exercise (46–48% in each year). Adjustments were not made for missing data (see online supplementary table S2).

The proportion of participants achieving all three priority goals in all countries combined increased slightly from 47% at baseline to 52% at year 3 (table 2). From year to year, however, many participants transitioned back and forth from achieving to not achieving the priority goals (table 3). Only 22% (522/2345) of participants with complete data achieved all priority goals at each of the four assessments from baseline through year 3.

Geographic variation in achievement of the three priority goals is summarised in table 4 for measurements at

Table 1 Baseline characteristics of study cohort (n=3720)*

Demographic features (%)	
Age (years)	63±11
Male	65
Black race	12
Hispanic ethnicity	4
College education (>12 years)	48
Married/living with partner	71
Clinical history (%)†	
Stroke at entry (vs TIA)	87
Hypertension	72
Hyperlipidaemia	68
Coronary artery disease	12
Atrial fibrillation	7
Carotid artery disease	19
Peripheral vascular disease	6
Current smoker	16
Physical examination	
BMI (kg/m^2)	30±6
Waist (cm)	103±14
Systolic blood pressure (mm Hg)	133±17
Diastolic blood pressure (mm Hg)	79±11
NIH Stroke Scale	0 (0,1)
Modified Rankin	1 (0,2)
Modified mini-mental examination	96 (92, 99)
Laboratory data	
Haemoglobin A_{1c} (%)	5.8±0.4
Homeostasis model assessment‡	4.6 (3.7, 6.2)
Low-density lipoprotein cholesterol (mmol/L)	2.3±0.8
High-density lipoprotein cholesterol (mmol/L)	1.2±0.3
Triglycerides (mmol/L)	1.6±0.8
Concomitant medications (%)	
Statin therapy	82
Aspirin	74
Non-ASA antiplatelet	43
Oral anticoagulants	11
Antithrombotics	99
Geography (%)	
USA	67
Canada	14
UK	7
Israel	5
Germany	4

*Plus–minus values are means±SD. Features are presented as median values (25th centile, 75th centile) when distributions are highly skewed.
†Clinical history variables were defined as follows: stroke versus TIA, see entry criteria; hypertension, self-report; hyperlipidaemia, self-report; coronary artery disease, self-report history of hospitalisation for myocardial infarction, coronary artery bypass graft or coronary stent insertion; atrial fibrillation, history as determined by site investigator; carotid artery disease, baseline carotid stenosis ≥50%; peripheral vascular disease, self-report; current smoking, self-report (uncertain self-report='no').
‡HOMA is an index of insulin resistance based on fasting insulin and glucose values. HOMA >3.0 was used to identify patients with insulin resistance in IRIS.[15]
ASA, American Stroke Association; BMI, body mass index; HOMA, homeostasis model assessment; IRIS, Insulin Resistance Intervention after Stroke; TIA, transient ischemic attack.

Table 2 Achievement of secondary stroke prevention goals by year in all countries combined

				% Meeting physiological goals			% Meeting drug use goals		% Meeting behavioural goals		
Time point	Pts alive	% Meeting all goals	% Meeting priority prevention goals*	BP <140/90 mm Hg	LDL-c <2.59 mmol/L	BMI 18–25 kg/m^2	Statin therapy	Antithrombotic therapy†	Cigarette smoking abstinence	Safe alcohol use‡	Aerobic exercise§
Baseline	3720	3	47	66	70	18	83	99	84	93	48
Year 1	3639	4	49	70	68	17	79	97	84	94	48
Year 2	3543	4	51	71	70	18	80	97	84	95	46
Year 3	3255	4	52	72	70	18	78	96	84	95	47

*Priority prevention goals: BP <140/90 mm Hg, LDL-c <2.59 mmol/L and the use of antithrombotic therapy.
†Antithrombotic therapy includes antiplatelet or anticoagulation therapies.
‡Safe alcohol use defined as ≤2 drinks/day for males and ≤1 drink/day for females.[24]
§Aerobic exercise defined as large-muscle activities at least 3 days/week for a total of 20 min/day.[34]
BMI, body mass index; BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; Pts, participants.

Table 3 Achievement of priority prevention goals over time in all countries combined

	Time period							
	Baseline to year 1		Year 1 to year 2		Year 2 to year 3		Baseline to year 3	
Preventive goal status*	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Stayed at goal	1008	32	1056	37	930	38	522	22
Stayed not at goal	1108	35	1011	36	812	34	463	19
Improved	552	17	410	14	342	14	754	32
Declined	522	16	366	13	338	14	636	27
Pts with data for time period	3190		2843		2422		2345	
Stayed at goal or improved†	1560	49	1466	52	1272	53	1276	54
Goal status unknown‡	438		686		818		895	
Out of trial during period§	92		99		289		480	

*Preventive goal status defined as follows: stayed at goal, at goal in each year in period; stayed not at goal, not at goal in each year in period; improved, started period not at goal but at goal at end of year or in any year in period; declined, started period at goal but not at goal at end of year or in any year in period.
†Proportion of participants in trial and with data who stayed at goal or improved during period.
‡Data missing for at least one priority goal in any year in period.
§Dropped-out, died or exited during time period.
Pts, participants.

Table 4 Achievement of priority prevention goals at baseline and year 3—overall and by country*

	All Pts†			Year 3 cohort‡			
	No.	w/Data	Baseline %	No.	w/Data	Baseline %	Year 3%
All participants	3720	3667	47	3240	2529	48	52
USA	2592	2549	46	2246	1683	47	50
Canada	543	538	63	494	420	64	65
UK	256	253	42	211	175	43	53
Israel	178	178	37	166	147	37	45
Germany	151	149	39	123	104	38	38
χ^2 p value			<0.0001			<0.0001	<0.0001

*Priority prevention goals: BP <140/90 mm Hg, LDL-C <2.59 mmol/L and the use of antithrombotic therapy.
†Pts enrolled by country; w/Data=Pts not missing BP, LDL or medication use at baseline.
‡Pts in cohort at year 3 (excludes Pts who died or withdrew prior to year 3); w/Data=Pts with completed year 3 contact and not missing BP, LDL or medication use at baseline and year 3.
BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; Pts, participants.

baseline and year 3. Differences between countries were statistically significant at both time points. Achievement of all priority goals at baseline was highest in Canada (63%) compared with participants in the USA (46%), UK (42%), Germany (39%) or Israel (37%). When we restricted the analysis to participants who had data at baseline and year 3, the rate of achievement within each country was maintained or improved over time. Data for all goals by country are displayed in online supplementary table S3.

In bivariate analysis, several baseline features were significantly associated with consistent achievement of all three priority goals (see online supplementary table S4). In an adjusted multivariable model, five remained significant: male sex, white race, being married or living with a partner, non-smoking status and higher mental status examination score (table 5).

To test the theory that preventive therapy modifies treatment effect, we examined the risk for stroke or MI according to subgroups defined by achievement of the priority goals at baseline (see online supplementary table S5). Estimated HRs were similar in those meeting versus not meeting these goals, suggesting that the benefit of pioglitazone was maintained irrespective of underlying preventive care (p for interaction of treatment with subgroup status, 0.49).

DISCUSSION

At baseline and each annual assessment over 3 years, about half of all participants in the IRIS trial achieved three priority stroke prevention goals under a system of assisted management. Other patients failed most often because of elevated blood pressure and LDL cholesterol. Female sex, non-white race, not living with a spouse or partner, cigarette use and lower cognitive test performance at baseline identified patients who were at increased risk for not achieving prevention goals at any time during follow-up. This information may be used to identify future trial participants for additional support.

Table 5 Baseline features associated with achievement of priority prevention goals from baseline to year 3*

	Bivariate analysis						Adjusted analysis†	
	Feature present		Feature not present					
Baseline feature	Pts	At goal	Pts	At goal	OR‡	p Value	OR	p Value
Male sex	678	56%	307	46%	1.54	0.002	1.40	0.02
White race	846	56%	131	36%	2.26	<0.0001	1.71	0.01
Married/with partner	738	57%	244	42%	1.79	<0.0001	1.47	0.02
Non-smoker	844	55%	141	42%	1.69	0.004	1.62	0.01
3MS score, mean (SD)	95.6 (5.0)§		94.0 (6.7)↵		1.61	<0.0001	1.55	0.0003

*Priority prevention goals: BP <140/90 mm Hg, LDL-c <2.59 mmol/L and the use of antithrombotic therapy. Comparison group is participants not at goal at any time from baseline to year 3.
†Logistic model selected in stepwise procedure considering only significant features in bivariate analysis.
‡OR for being at goal if feature present versus absent for categorical features; OR for 10 unit change in 3MS score.
§Mean + SD for patients at goal.
↵Mean + SD for patients not at goal.
3MS, modified mini-mental state; BP, blood pressure; LDL-c, low-density lipoprotein cholesterol; Pts, participants.

A comparison with prevention data published by other secondary stroke trials suggests that the IRIS strategy was at least as successful as more intensive approaches.[16–23] For example, at 1 year after randomisation, 70% of IRIS participants achieved BP <140/90 mm Hg, which was the same proportion of participants achieving systolic BP <140 mm Hg in a trial of intracranial vascular stenting that directly managed participants[18] and higher than the 50% reported in a trial of warfarin that employed joint management by investigators and personal physicians.[20] Likewise, the 68–70% of IRIS participants who achieved an LDL cholesterol <2.59 mmol/L in the first 2 years of follow-up was similar to the 64–71% reported in a direct-management trial[16] and higher than the 56% in a joint-management trial.[20] Achievement of the prevention goals for statin and antithrombotic therapies and cigarette smoking was similar or superior in IRIS compared to other recent trials.[16 22 23 17–21]

For safe alcohol use and aerobic exercise, it is difficult to compare IRIS to other secondary stroke trials because of limitations of published data and variable treatment goals. In two trials reporting alcohol use after baseline, the criterion for being at goal was abstinence in one[22] and any use in the other.[20] Unlike IRIS, neither trial used a goal based on widely accepted guidelines for safe alcohol use.[24] In two trials reporting aerobic exercise after baseline, the criterion for being at goal was at least 30 min/week in one (49% met goal)[22] and at least 90 min/week in the other (55–62% met goal),[4 18] compared to at least 60 min/week in IRIS (46–48% met goal). The lower proportion in IRIS was relative to data from a direct-management trial that employed an intensive programme for behavioural risk modification.[4]

Achievement of secondary prevention goals in IRIS was superior to achievement described in community-based cohorts of patients with cardiovascular disease or risk equivalents. At least two-thirds (66–72%) of IRIS participants achieved goal blood pressure compared with only 46% of patients with previous stroke or TIA[25] and 53% of Americans with documented hypertension.[26] The majority of IRIS participants (68–70%) achieved goal LDL cholesterol levels compared with 41% of patients with previous stroke or TIA[25] and 64–65% of Americans receiving treatment for high LDL cholesterol.[27] Additional comparisons with observational studies confirm that IRIS participants were as or more likely to achieve standard prevention goals.[25–33]

The proportion of IRIS participants with a normal BMI (17–18%) was below the proportion of Americans aged >40 years (25–28%).[26] However, a comparison of the BMI of IRIS participants to other cohorts is not informative because participants were required to have insulin resistance, a condition closely associated with obesity and the therapy tested, pioglitazone, can lead to weight gain.

The significant variability in achievement of prevention goals between countries was not explained by patient-level factors (see online supplementary table S6). Other possible explanations include employment of different guidelines than those used in IRIS or receipt of care within diverse healthcare systems that differentially cover the cost of provider visits and medications. The finding of variability between countries has potential implications for clinical trial research when uniform application of a protocol is important.

We observed no interaction between achievement of preventive care goals and treatment effect in the IRIS trial. Pioglitazone was associated with a significant reduction in risk for MI and stroke even among participants who met all priority goals for secondary prevention at baseline.

For the purpose of documenting benchmarks for research studies involving secondary prevention, the IRIS trial has several limitations. First, we did not gather information on new indications for anticoagulation therapy after baseline (eg, new onset atrial fibrillation) and, therefore, could not appraise appropriate use of this therapy during all phases of our research. Second, blood pressure status was classified based on values obtained during annual visits; the use of home measurements might have demonstrated improved control. Third,

because IRIS participants had mild stroke severity, we do not know if preventive therapy would be different in a cohort with greater severity. Finally, because IRIS tested a medication used in the treatment of diabetes, we are unable to comment on achievement of glycaemic goals.

CONCLUSIONS

Our findings describe the quality of preventive care that was achieved in an international stroke trial using a new assisted-management strategy. Although the new strategy compared favourably to those employed in prior trials, there is room for improvement. Rates of achievement of the prevention goals for blood pressure and LDL cholesterol were less than rates for statin and antithrombotic therapies, and achievement of prevention goals over time was inconsistent. Further research is needed into ways to ensure sustained, high-quality risk management for volunteers in clinical trials.

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