AVAPROMISE: A randomized clinical trial for increasing adherence through behavioural modification in essential hypertension

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BACKGROUND: Patients with hypertension often do not adhere to their medications.
OBJECTIVE: To improve medication adherence in patients with essential hypertension by modifying their behaviours.
PATIENTS AND METHODS: From general practice settings, 4864 patients with essential hypertension were recruited and randomly assigned to receive the angiotensin receptor blocker irbesartan (Avapro) with (intervention group) or without (nonintervention group) a behavioural modification program (Avapromise) based on a model of change. Patients were followed up for 12 months. Patients were subgrouped based on their stage of change in the behavioural change continuum, and the intervention was tailored to address the needs of the particular subgroup. The primary efficacy measure was rate and time to discontinuation with irbesartan.
RESULTS: At the end of the study, there was no significant difference in the discontinuation rates between the intervention (25.4%, 95% CI 23.7 to 27.2) and nonintervention (25.5%, 95% CI 23.8 to 27.3) groups (P=0.94). The time to discontinuation (P=0.87) and the extrapolated rate of discontinuation estimated from the Kaplan-Meir curve (intervention 23.1%, 95% CI 21.3 to 24.8; nonintervention 23.5%, 95% CI 21.8 to 25.3) were not different between the groups.
CONCLUSIONS: This behavioural modification intervention based on a model of change was not efficacious at increasing rates of adherence in patients with essential hypertension in this setting. More individualized interventions may be required to increase adherence in this population.

Key Words: *Angiotensin; Behaviour modification; Hypertension*

Hypertension is an established cardiovascular risk factor and can lead to stroke, myocardial infarction and premature death (1,2). However, despite widespread availability of therapy, hypertension is inadequately controlled and poses a significant risk (3). A Canadian Heart Health survey showed that hypertension was controlled (blood pressure less than 140/90 mmHg) in only 16% of those treated for hypertension and uncontrolled in 23%, despite receiving therapy (4). Suboptimal adherence to therapy is a common cause of uncontrolled hypertension (5). An estimated 16% to 50% of patients with hypertension discontinue their therapy within the first year (6,7).

In a recent overview of randomized, controlled trials (RCTs) of interventions used to improve patient adherence to medication in hypertensive populations, the interventions with positive effects were complex and intensive (8). Also, measurement of adherence in an RCT setting could preclude generalizability of the 'treatment' effect because of the nature of the study design (9). It would, therefore, be desirable to examine the effects of an intervention that would be relatively simple and conducted in a usual care setting. Moreover, it would be useful to use an intervention that combined both lifestyle modification and reinforcement, and could potentially affect adherence to therapy by modifying behaviour.

Irbesartan (Avapro, Bristol Myers Squibb/Sanofi-Synthelabo, Canada) is a long acting angiotensin II receptor blocker (ARB). In controlled clinical trials comprising patients with mild to moderate hypertension, seated systolic and diastolic blood pressure reductions achieved with irbesartan were either equal or superior to those achieved with concomitantly used agents. Irbesartan has demonstrated efficacy relative to hydrochlorothiazide, losartan and enalapril (10-12). It has also demonstrated an excellent safety and tolerability profile. Irbesartan can be used alone or in combination with other agents such as thiazides in patients whose hypertension is inadequately controlled by single-drug therapy.

A randomized, open-label, 12-month, phase IV trial comprising patients with essential hypertension was conducted to study the effectiveness of Avapromise, a behavioural modification intervention to increase the adherence of patients receiving treatment with irbesartan in the usual care setting. It is our understanding that this is the largest study conducted with the primary aim of influencing adherence to therapy.

PATIENTS AND METHODS

Patient recruitment and follow-up were conducted by Innovus Inc (Canada), and the data were analyzed by BTB Associates (Canada).

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Patients

The trial was designed as a randomized, multicentre, open-label, two-arm study comprising patients with essential hypertension. General practitioners who were willing to participate in the study recruited patients from within their practices based on who, in their opinion, would benefit from therapy with irbesartan. Patients who satisfied the inclusion and exclusion criteria (Table 1), and gave their informed consent were entered into the study.

Patients were randomly assigned to receive a once daily dose of irbesartan 150 mg that could be increased to 300 mg, with or without the intervention Avapromise. The Avapromise intervention was designed to modify behaviour by medication adherence through reinforcement and lifestyle modification. It is made up of two elements that are delivered in unison. The first element attempts to reinforce medication adherence behaviours by using medication reminder letters, blood pressure diaries and telephone nurse counselling sessions. The second element addresses issues of lifestyle management through educational brochures dealing with topics such as healthy living, nutrition, physical fitness and stress management. Patients randomly assigned to receive Avapromise were mailed the material at one, two, three, four, six and 12 months. The receipt schedule of the different components of this intervention is highlighted in Table 2. Patients in the control arm received usual care educational materials in their physicians' offices.

Prescription of additional antihypertensive medications was permitted. Randomization to Avapromise was done by site (recruiting physicians' offices), such that all the patients within one site were randomly assigned to the same treatment regimen to avoid contamination and minimize investigator bias. Due to the nature of the intervention, blinding was not possible. Randomization was done using a computer-generated algorithm.

Patients were telephoned at two, five, eight and 12 months to estimate their adherence to irbesartan as well as to note the incidence of adverse events and the use of related health services. After the enrolment visit, subsequent visits were decided between patient and physician. The duration of the study was 12 months.

The primary effectiveness measure was patient discontinuation with their irbesartan treatment regimens following up to 12 months of treatment for essential hypertension. The impact of the Avapromise intervention on patient compliance with irbesartan was assessed by comparing the rate and time to discontinuation between these two groups of patients. The 'time to discontinuation' was defined as a negative response to a telephone follow-up question "Are you taking your Avapro (irbesartan) every day?", asked as part of a normal patient follow-up at two, five, eight and 12 months.

Enrolment began on December 19, 1998, and the sponsor decided to terminate the study on November 30, 2000, after the required number of discontinuations had been observed. At that time, the patients still enrolled in the study were contacted a final time by telephone.

TABLE 1
Inclusion and exclusion criteria for a randomized, clinical trial designed to increase adherence to hypertension medications through behavioural modification

Inclusion criteria
History of diastolic blood pressure higher than 90 mmHg and/or systolic blood pressure higher than 140 mmHg, and untreated; or current hypertension treatment requiring alteration in the opinion of the physician
Aged 18 to 79 years and, if female, unable to become pregnant
Willingness to give informed consent
Exclusion criteria
If female, pregnant or breast-feeding, or of childbearing potential
Taking any investigational drug given within 30 days of initiation of therapy, and participation in other clinical studies while enrolled in this protocol
Undergoing peritoneal dialysis
Presence of any of the following conditions:
Cardiovascular disorders
– Renovascular hypertension
– Cerebrovascular accident or current transient ischemic attacks within the past six months
– Myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within the past six months
– Clinically significant atrioventricular conduction disturbances, arrhythmias and/or tachyarrhythmias
– Significant signs of heart failure
Allergies/hypersensitivity
– Known hypersensitivity or contraindication to irbesartan, or any other angiotensin receptor blocker
Other
– Requiring active treatment for substance abuse within the past two years
– Mentally or legally incapacitated
– Any other condition or therapy that, in the investigator's opinion, or as indicated in the prescribing information for irbesartan, might pose a risk to the patient or interfere with the study objectives

TABLE 2
AVAPROMISE receipt schedule

Month	Stage of change
1	Enrolment package
2	Blood pressure: Know the numbers by heart (diary)
	Hypertension – A Self-Management Approach (book)
3	Medication reminder letter
	Where Fitness Fits in Your Life (brochure/poster)
	Telephone nurse counselling session #1
4	Medication reminder letter
	How to Enjoy Eating Well (brochure/poster)
	Telephone nurse counselling session #2
6	Medication reminder letter
	Taking Charge of Managing Stress (brochure/poster)
	Telephone nurse counselling session #3
8	Medication reminder letter
	The Good News on…Communication (Doctor/Patient Communication)
10	Medication reminder letter
	The Good News on…Fitness (Walking)
	Telephone nurse counselling session #4
12	Letter
	Patient satisfaction survey

Statistical considerations

Sample size: In the absence of pre-existing data on 12 month discontinuation rates with irbesartan, it was assumed that at least 50% of the required number of patient discontinuations would occur within that period. A difference in the number of discontinuations between treatment groups of 4% was considered clinically relevant. If it is assumed that 20% of patients assigned to receive the medication without the intervention, compared with 16% assigned to receive the medication with Avapromise, would discontinue their medication within one year (an absolute difference of 4%), 2561 discontinuations would have to be observed. A sample size of 5000 patients was considered adequate (90% power) to detect the difference using a two-sided test of statistical significance (logrank test) at the 5% level. The total number of patient discontinuations was monitored throughout the study to determine when the required number of discontinuations had occurred. The study was terminated when 50% of the required discontinuations (1281) were observed by 12 months, and there was adequate power to note statistical differences.

Analysis: Descriptive statistics were used for the analysis of continuous (mean and standard deviation) and categorical (frequency) variables. The primary effectiveness variable was compared between treatment regimens using a combination of categorical and survival analysis techniques. Time to discontinuation was analyzed using survival analysis techniques. Kaplan-Meir survival curves were estimated for each treatment regimen and compared using a logrank test.

RESULTS

The overall trial profile is displayed in Figure 1. A total of 4864 patients were randomly assigned – 2402 to the intervention group and 2462 to the nonintervention group – and were included in the intent-to-treat population. The two groups were similar in terms of their baseline characteristics, including medical history and baseline antihypertensive medication (Tables 3,4,5). The mean age of the patients was 58 years (range 16 to 89 years) in both the arms; 51% of those enrolled were female. Patients were enrolled at a total of 397 centres across Canada.

The treatment groups were similar with respect to history of hypertension, and 84% of patients had chronic hypertension. The mean duration of hypertension was approximately six years (SD=8.1), and 51% of patients had been hypertensive for five years or less. The mean baseline systolic blood pressure was 160 mmHg (SD=16) and the mean diastolic blood pressure was 95 mmHg (SD=9). Approximately 92% of patients were prescribed a starting dose of irbesartan 150 mg once daily, and 7% were prescribed a starting dose of 300 mg once daily.

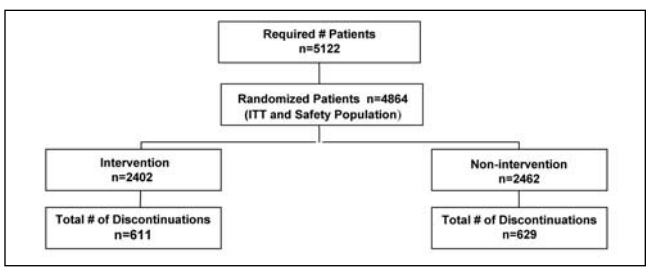

Figure 1) *Profile of a trial designed to improve adherence to medication by patients with essential hypertension. ITT Intent to treat*

TABLE 3
Baseline characteristics of patients assigned to receive irbesartan with (Intervention) or without (Nonintervention) the behavioural modification program AVAPROMISE

Variable	Intervention (n=2402)	Nonintervention (n=2462)	Total (n=4864)
Age, years (range)	57.6 (22-86)	57.8 (16-89)	57.7
Age group, n (%)			
Missing data	59 (2)	41 (2)	100 (2)
10-17 years	2 (<1)	0	2 (<1)
18-29 years	13 (1)	16 (1)	29 (1)
30-39 years	125 (5)	113 (5)	238 (5)
40-49 years	421 (18)	443 (18)	864 (18)
50-59 years	755 (31)	751 (31)	1506 (31)
60-69 years	625 (26)	709 (29)	1334 (27)
70-79 years	381 (16)	375 (15)	756 (16)
>80 years	21 (1)	14 (1)	35 (1)
Sex, n (%)			
Missing data	101 (4)	81 (3)	182 (4)
Female	1257 (52)	1231 (50)	2488 (51)
Hypertension duration, years	5.8	5.4	5.6
Systolic blood pressure, mmHg (SD)	160 (16)	160 (17)	160 (16.7)
Diastolic blood pressure, mmHg (SD)	95 (9)	95 (9.6)	95 (9.3)
Missing data, n (%)	163 (7)	118 (5)	281 (6)
Newly diagnosed, n (%)	218 (9)	265 (11)	483 (10)
Previously diagnosed, n (%)	2021 (84)	2079 (84)	4100 (84)
0-5 years	1210 (50)	1283 (52)	2493 (51)
6-10 years	327 (14)	358 (15)	685 (14)
11-15 years	207 (9)	186 (8)	393 (8)
16-20 years	145 (6)	119 (5)	264 (5)
>20 years	132 (6)	133 (5)	265 (5)

A total of 1240 (25% of 4864) patients discontinued their medications – 611 (25.4%, 95% CI 23.7 to 27.2) from the intervention group and 629 (25.5%, 95% CI 23.8 to 27.3) from the nonintervention group, resulting in a difference of –0.1% (–2.6 to 2.3) between the two groups (P=0.94, Table 6).

There was no statistically significant difference in the duration of irbesartan compliance between the treatment groups. Overall, the average duration of irbesartan compliance was 267 days (SD=127) and was similar between treatment groups (265 days for the intervention group and 269 days for the nonintervention group). The estimated rates of discontinuation, based on the Kaplan-Meier estimates at 12 months, were 23.1% in the intervention group and 23.5% in the nonintervention group. The patterns of the times to discontinuation, as illustrated in the Kaplan-Meier plot (Figure 2), were not significantly different between treatment groups (P=0.877,

TABLE 4
Medical history of patients assigned to receive irbesartan with (Intervention) or without (Nonintervention) the behavioural modification program AVAPROMISE

Variable	Intervention (n=2402)	Nonintervention (n=2462)	Total (n=4864)
Diabetes	296 (12)	316 (13)	612 (13)
Asthma	131 (5)	147 (6)	278 (6)
Angina	85 (4)	102 (4)	187 (4)
Congestive heart failure	19 (1)	27 (1)	46 (1)
Myocardial infarction	57 (2)	62 (3)	119 (2)
Peripheral vascular disease	28 (1)	41 (2)	69 (1)
Stroke	32 (1)	54 (2)	86 (2)
Other cardiovascular disease	45 (2)	47 (2)	92 (2)

TABLE 5
Oral antihypertensive medications used by patients assigned to receive irbesartan with (Intervention) or without (Nonintervention) the behavioural modification program AVAPROMISE in the six months preceding the study

Variable	Intervention (n=2402)	Nonintervention (n=2462)	Total (n=4864)
Beta-blockers, n (%)	399 (17)	378 (15)	777 (16)
Diuretics, n (%)	624 (26)	539 (22)	1163 (24)
ACEIs, n (%)	720 (30)	718 (29)	1438 (30)
CCBs, n (%)	396 (17)	536 (22)	932 (19)
ARBs, n (%)	135 (6)	212 (9)	347 (7)
Other, n (%)	87 (4)	100 (4)	187 (4)
Diuretic plus ACEI, n (%)			
Neither	1273 (53)	1420 (58)	2693 (55)
Either	906 (38)	821 (33)	1727 (36)
Both	219 (9)	218 (9)	437 (9)

ACEI Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; CCB Calcium channel blocker

logrank test). A small proportion of patients were followed up for more than 12 months because of their earlier enrolment, and there was a separation between the two survival curves beyond 450 days.

Fourteen per cent (179 of 1240) of patients prematurely terminated the study. In the two study arms combined, personal preference (34%, 61 of 179), investigator decision (22%, 39 of 179), serious adverse drug reactions (19%, 34 of 179) and other reasons (24%, 44 of 179) were cited as primary reasons for the termination. Five deaths were reported during the study. Fifty-four per cent (668 of 1240) of patients who discontinued irbesartan during the study cited side effects (47%, 311 of 688), lack of efficacy (16%, 109 of 688) and physician instruction (14%, 96 of 688) as some of the primary reasons for termination.

DISCUSSION

A randomized, open label, 12-month study was conducted to determine patients' adherence to antihypertensive therapy with irbesartan by using a behavioural modification intervention called Avapromise in a clinical practice setting. The rate of or time to discontinuation was not different between the two groups. The overall adherence rate was 75% (ie, approximately 25% of patients discontinued medication use) in both

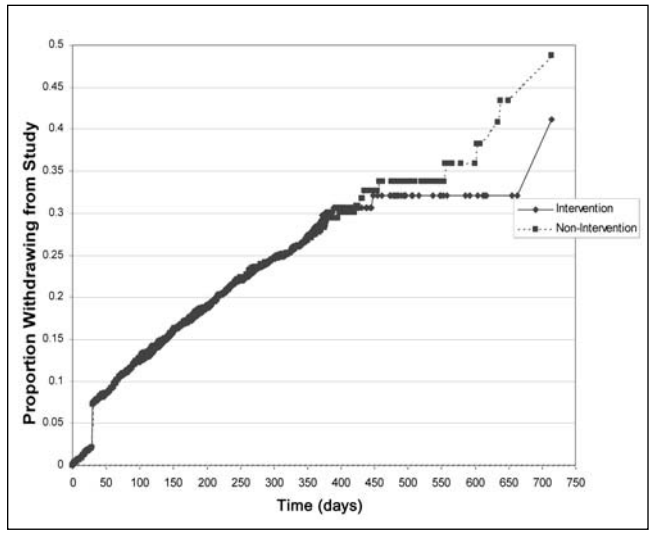

Figure 2) *Kaplan-Meier plot of the time to discontinuation*

arms. On the basis of these observations, it can be stated that the Avapromise intervention did not improve adherence. There are three possible reasons for this lack of improvement.

First, Avapromise was a relatively low resource-intensive intervention, which probably contributed to its lack of efficacy. As noted in the overview by Haynes et al (8), RCTs of interventions that were very intensive and complex tended to yield positive results. Furthermore, in studies designed to improve the adherence of hypertensive patients to medications, these measures included medical care provided at the work site, special pill containers, support groups, feedback, reinforcement, etc (13,14). For the Avapromise study, protocol-defined physician office visits could have added an element of reinforcement during the duration of the study but would have precluded its generalizability to usual care settings.

Second, the literature demonstrates that the success rate for demonstrating statistically significant results in adherence studies is not very high. Once again, the overview by Haynes et al (8) noted that, among the studies that met their eligibility criteria, a little more than one-half (10 of 19) demonstrated a significant result, possibly because adherence itself, as a behavioural phenomenon, requires more detailed study. By extension, studies designed to demonstrate enhanced adherence would require a rethink of the paradigms and methods that have been used so far to measure or improve it.

Third, because adherence in the control group was quite high, interventions to increase it further would perhaps have a lower likelihood of success.

Finally, AVAPROMISE was designed to influence behaviour as a whole rather than to influence medication adherence per se. Providing patients with a broader perspective on the tools required to manage their lifestyles was deemed important enough to influence medication adherence indirectly through behavioural modification. Although these are important issues, interventions to improve adherence in hypertension management by lifestyle modification may not affect medication adherence – a different behaviour that may require specific interventions.

A limitation of this study is that the effect of adherence on blood pressure control was not a predefined end point. However, it is being investigated in a substudy. In this study,

TABLE 6
Rate of and time to discontinuation in the intent-to-treat patient population*

	Time point	Intervention, % (95% CI)	Nonintervention, % (95% CI)	Difference†
Patient withdrawal rate	End of study	25.4 (23.7-27.2)	25.5 (23.8-27.3)	–0.1% (–2.6-2.3)
				P=0.948
Cumulative withdrawal rate§	6 months	11.9 (10.6-13.2)	12.0 (10.7-13.3)	P=0.8770‡
	9 months	17.6 (16.0-19.1)	17.9 (16.4-19.5)	
	12 months	23.1 (21.3-24.8)	23.5 (21.8-25.3)	
	>12 months	28.5 (26.4-30.5)	27.8 (25.8-29.7)	

**Based on the intent-to-treat patient population after imputing of missing or extreme patient outcomes (ie, duration of irbesartan compliance); †Difference between the intervention and the nonintervention groups; ‡Logrank P value for comparison survival curves between treatment groups: χ^2 test with one degree of freedom; §Based on Kaplan-Meier estimates taken at time points immediately after day 180 (six months), day 270 (nine months), 365 (12 months) and last day (more than 12 months) from the Kaplan-Meier curve*

two estimates of blood pressure control using a 24 h ambulatory blood pressure monitoring technique (at enrolment and at study termination or discontinuation) are being used. Also, because physicians determined patient eligibility for the study, it is not possible to determine whether there was a selection bias in the nature of enrolment. Involving sequential enrolment may perhaps better benefit future studies of similar design but not affect usual clinical practice.

This study also had some unique strengths. First, to our knowledge, this was the largest prospective study on adherence that has ever been conducted. Second, because it was conducted in a usual care setting, the inclusion and exclusion criteria were fairly nonrestrictive and physicians had wide discretionary powers. As a result, physicians could titrate, or add or switch medication class (except converting enzyme inhibitors) or dose, which enhances the external validity or generalizability of the study.

The literature shows that ARBs are associated with relatively higher rates of adherence than other antihypertensive classes. A recent analysis of the Saskatchewan database revealed higher adherence to ARBs at the end of two years (70%, P<0.01) than to all other classes of antihypertensive medications (15). Also, when patients were prescribed ARBs as initial therapy, adherence rates were higher. In a retrospective cohort analysis using a large pharmaceutical benefits management organization database, patients who received ARBs as initial therapy were significantly more adherent (64%, P<0.05) than other therapies (16). The adherence rates found in this study are significant given that irbesartan was not initial therapy for a majority of patients. The reasons for higher adherence may be attributed to increased tolerability and efficacy, requiring fewer discontinuations.

CONCLUSIONS

Adherence to ARBs seems to be well documented. The Avapromise study is thus far the biggest clinical trial designed and conducted for increasing adherence to medication in a hypertensive population. For increasing adherence, the transtheoretical model of change offers interesting insights, and therapies with better adaptability and intensity may offer further validation in this setting. The effect of interventions on adherence may be better evaluated using methods specifically designed to change adherence-related behaviour through a better understanding of its causal mechanisms and may thus provide a better validation of the hypothesis tested in this study. However, a more 'patient-specific' intervention based on individual needs may prove to be more effective and mandates further research.

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