Effects of an enhanced secondary prevention program for patients with heart disease: A prospective randomized trial

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BACKGROUND: Secondary prevention medications in cardiac patients improve outcomes. However, prescription rates for these drugs and long-term adherence are suboptimal.

OBJECTIVE: To determine whether an enhanced secondary prevention program improves outcomes.

METHODS: Hospitalized patients with indications for secondary prevention medications were randomly assigned to either usual care or an intervention arm, in which an intensive program was used to optimize prescription rates and long-term adherence. Follow-up was 19 months.

RESULTS: A total of 2643 patients were randomly assigned in the study; 1342 patients were assigned to usual care and 1301 patients were assigned to the intervention arm. Prescription rates were near optimal except for lipid-lowering medications. Rehospitalization rates per 100 patients were 136.2 and 132.6 over 19 months in the usual care and intervention groups, respectively ($P=0.59$). Total days in hospital per patient were similar (10.9 days in the usual care group versus 10.2 days in the intervention group; P not significant). Crude mortality was 6.2% and 5.5% in the usual care and intervention groups, respectively, with no significant difference ($P=0.15$) in overall survival. Post hoc analysis suggested that after the study team became experienced, days in hospital per patient were reduced by the program (11.1 ± 0.91 and 8.9 ± 0.61 in the usual care and intervention groups, respectively; $P<0.05$).

CONCLUSIONS: The intervention program failed to improve outcomes in the present study. One explanation for these results is the near optimal physician compliance with guidelines in both groups. It is also possible that a substantial learning curve for the staff was involved, as suggested by the reduction in total days in hospital in the intervention patients during the second part of the study.

Key Words: *Guideline adherence; Secondary prevention*

Secondary prevention with lipid-lowering agents, antiplatelet drugs, angiotensin-converting enzyme inhibitors, beta-blockers and anticoagulants is effective in reducing morbidity and mortality in cardiac patients (1-11). However, the benefits have not been fully realized because of suboptimal prescription rates for these medications and, frequently, poor long-term adherence to these therapies by patients (5,11-30). Various strategies have evolved to optimize the use of proven effective therapies (31-45). Data

Les effets d'un programme de prévention secondaire amélioré pour des personnes atteintes de cardiopathie : Un essai aléatoire prospectif

HISTORIQUE : Les médicaments de prévention secondaire améliorent les issues chez les patients cardiaques. Cependant, les taux de prescription de ces médicaments et l'observance à long terme sont sous-optimaux.

OBJECTIF : Déterminer si un programme de prévention secondaire amélioré assure de meilleures issues.

MÉTHODOLOGIE : Des patients hospitalisés ayant des indications de prendre de médicaments de prévention secondaire ont été divisés au hasard entre les soins habituels ou une intervention sous forme de programme intensif pour optimiser les taux de prescription et l'observance à long terme. Le suivi a duré 19 mois.

RÉSULTATS : Au total, 2 643 patients ont été sélectionnés au hasard dans l'étude : 1 342 patients ont été attribués au groupe de soins habituels, et 1 301 patients, au groupe d'intervention. Les taux de prescription étaient presque optimaux, sauf pour les médicaments visant à réduire les taux de lipide. Les taux de réhospitalisation par tranche de 100 patients étaient de 136,2 et 132,6 sur 19 mois au sein des groupes de soins habituels et d'intervention, respectivement ($p = 0,59$). Les jours totaux d'hospitalisation par patient étaient similaires (10,9 jours au sein du groupe de soins habituels et 10,2 au sein du groupe d'intervention; p non significatif). Le taux brut de mortalité était de 6,2 % et 5,5 % au sein des groupes de soins habituels et d'intervention, respectivement, sans différence significative ($p = 0,15$) de survie globale. L'analyse ultérieure laisse supposer que lorsque l'équipe de l'étude a pris de l'expérience, les jours d'hospitalisation par patient ont diminué ($11,1\pm0,91$ et $8,9\pm0,61$ dans les groupes de soins habituels et d'intervention, respectivement; $p < 0,05$).

CONCLUSIONS : Le programme d'intervention n'améliorait pas les issues dans la présente étude. L'une des explications de ces résultats, c'est l'observance presque optimale des lignes directrices au sein des deux groupes. Il est également possible qu'une courbe d'apprentissage importante du personnel soit entrée en ligne de compte, telle que le laisse supposer la réduction des jours totaux d'hospitalisation chez les patients du groupe d'intervention pendant la deuxième partie de l'étude.

collected before and after implementation of a variety of programs suggest that they are effective, but most randomized studies focused on prescription rates rather than on clinical outcomes. Systematic efforts to optimize prescription rates and long-term adherence to secondary prevention therapies should result in improved outcomes, but there are limited data to verify the effectiveness of programs focused on those goals. Moreover, the environments in which studies were performed varied substantially,

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which may have important implications in terms of what can be achieved in a given constituency. At the extremes, if guidelines are infrequently followed, much should be achievable with improved practices and adherence, whereas there may be little potential for improved outcomes if local practice is already close to optimal.

We performed a prospective randomized controlled study to determine whether a comprehensive program designed to optimize prescription rates for secondary prevention medications in cardiac patients and long-term adherence to therapy improves outcomes. The study was performed in a tertiary care referral hospital, where prestudy-documented prescription rates for acetylsalicylic acid (ASA), angiotensin-converting enzyme inhibitors, anticoagulants and beta-blockers, but not lipid-lowering agents, were close to optimal at the time the protocol was initiated. The primary end points included the number of rehospitalizations and days in hospital. It is important to note that because of the near-optimal prescription rates for secondary prevention medications (except for lipid-lowering agents), with almost no need to cue cardiologists, and because patients were frequently cared for by intervention and usual care cardiologists, the study effectively only assessed whether our relatively intensive effort to improve long-term patient adherence improves outcomes.

METHODS

The present study, which was approved by the local institutional ethics review board, was performed between March 1996 and January 2000. Informed consent, which included permission to obtain data from the provincial health care database, the Blue Cross insurance plan, hospital databases and community pharmacies, was obtained from all patients. Hospitalized cardiac patients on cardiac wards with indications for secondary prevention with ASA (for coronary artery disease), lipid-lowering agents (for coronary artery disease), beta-blockers (for postmyocardial infarction and heart failure), angiotensin-converting enzyme inhibitors (for left ventricular dysfunction) or anticoagulants (for atrial fibrillation) were enrolled (Figure 1). Patients who could not communicate effectively, had a terminal illness, were from out of province or were unwilling to cooperate were excluded. All patients were under the care of cardiologists.

Random assignment

Cardiologists were paired according to similar practice type and randomly assigned by coin flip to either the usual care (15) or the intervention arm (15). Patients were assigned to either arm (within two to three days of admission) according to the attending cardiologist at the time of random assignment; this was to limit exposure to cardiologists in both arms that may impact the assessment of the program's effectiveness in optimizing prescription rates. Because the cardiologists provided care in blocks of time on the hospital service, many patients were ultimately cared for by cardiologists from both arms. After enrolment of 500 patients, it was apparent that the numbers of patients were unevenly distributed. Of note, it was also apparent at that time that there was almost no need to cue physicians; therefore, interventions were effectively patient-related, and not physician-related. To achieve a more even distribution between the groups, two usual care cardiologists were reassigned from the usual care to the intervention arm.

Intervention protocol (Figure 1)

Patients in the intervention group were provided individual and group counselling related to their medications and conditions.

Figure 1) Flow diagram outlining the study design

Videos and printed materials were used to promote long-term adherence to the therapies. In addition, postdischarge measurement of serum lipid levels (the standard in the region at the time) was arranged when appropriate. The intent was to cue cardiologists to consider assessment for indications for secondary prevention, eg, to measure serum lipid levels, to assess left ventricular function or to prescribe (according to agreed on guidelines) therapy for secondary prevention, if it appeared that this may not be done in a timely manner. Pharmacy care maps, including long-term plans, were sent to patients' family physicians and pharmacists. One week following discharge, a study pharmacist contacted patients to review their medications and assist with medication-related problems. Subsequently, a study nurse performed scheduled contacts at one month, quarterly for 12 months and then six months later. There was no time restriction for telephone interactions. Nurses and pharmacists ensured that prescriptions were properly followed and determined whether there were medication-related problems. It is important to note that the staff also facilitated resolution of any other medical problems encountered. Community pharmacists assisted by actively counselling patients in the intervention group only. In the usual care group, no interventions were performed by study personnel; patients only received support generally available in the hospital and community.

Data collection

Data related to medication use, medical encounters and outcomes were collected by nurses in the intervention group and by non-medical staff in the usual care group. Supplemental and corroborative data, particularly the predefined end points, were obtained from the provincial department of health, Blue Cross and individual hospitals. The sponsor of the study was not involved in data collection or analysis.

Statistical analysis

Baseline characteristics were compared for uniformity using the *t* test for comparison of means and χ^2 for comparison of categorical variables. The total number of rehospitalizations, each defined as a period of continuous care in any acute care hospital, regardless

TABLE 1
Patient characteristics

	Control group (n=1342)	Intervention group (n=1301)
Age, years (mean $\pm$ SD)	64.1 $\pm$ 10.7	63.8 $\pm$ 11.3
Male sex, n (%)	994 (74.1)	913 (70.2)
Smoker, n (%)	948 (70.6)	958 (73.6)
Diabetes, n (%)	258 (19.2)	254 (19.5)
Hyperlipidemia, n (%)	230 (17.4)	191 (14.9)
Hypertension, n (%)	651 (48.5)	645 (49.6)
History of coronary artery disease, n (%)	756 (56.3)	685 (52.7)
Current coronary artery disease, n (%)	1169 (88.2)	1153 (88.6)
History of myocardial infarction, n (%)	550 (41.0)	487 (37.4)
Current myocardial infarction, n (%)	342 (25.8)	397 (30.9)
History of congestive heart failure, n (%)	100 (7.5)	84 (6.5)
Current LV dysfunction, n (%)	242 (18.3)	240 (18.7)
Angiography, n (%)	1068 (79.6)	1061 (81.6)
CABG, n (%)	105 (7.8)	128 (9.8)
PCI, n (%)	322 (24)	368 (28.3)
Valve disease, n (%)	146 (10.9)	121 (9.3)
Atrial fibrillation, n (%)	150 (11.3)	134 (10.4)
Other arrhythmias, n (%)	69 (5.2)	81 (6.3)

P not significant for all comparisons between groups. CABG Coronary artery bypass graft surgery; LV Left ventricular; PCI Percutaneous coronary intervention

of transfers between hospitals, was summed over 19 months post-discharge. Rates were calculated from total rehospitalizations divided by the period of follow-up, using right-censoring for individuals who died. Accumulated monthly rates were based on the total number of rehospitalizations, divided by the number of patients being followed during that month. Total days in hospital were also documented. Similarly, separate *t* tests were also performed that compared rehospitalizations and days in hospital for the secondary analysis in the two groups during the two intervals, testing for a time and treatment interaction. A survival analysis approach, with time to first event, was used. Mortality during the 19 months of follow-up was compared using the log rank test. Also assessed was the contribution of the variation in cardiologists to the results according to the CONSolidated Standards Of Reporting Trials (CONSORT) guidelines for cluster randomized trials (46).

Patient-reported adherence to medications was compared between the two groups for each class of drugs by χ^2 analysis.

RESULTS

Patient characteristics

A total of 2643 patients were enrolled in the study and followed for the full 19 months; 1342 patients were randomly assigned to usual care and 1301 to the intervention group (Figure 1). Table 1 lists the patient characteristics and discharge diagnoses related to the initial hospitalization. There were no significant differences in age, sex or discharge diagnoses between groups. A large majority of patients had various manifestations of coronary artery disease.

Rehospitalizations

Figure 2 shows the cumulative rehospitalization rates for both groups. During the 19 months' follow-up, there were 136.2 rehospitalizations per 100 patients in the usual care group compared with 132.6 admissions per 100 patients in the intervention group (*P* not significant). Time to first rehospitalization (Figure 3) was

Figure 2) Cumulative rehospitalization rates during a 19-month follow-up

Figure 3) Kaplan-Meier plot depicting freedom from rehospitalization

Figure 4) Plot depicting rehospitalization frequencies

also similar in both groups. Of the total, 52% of the readmissions occurred within six months. One-half of patients were readmitted at least once by the sixth month, but 36% of patients were not rehospitalized during the full study period. Readmission rates were not normally distributed (Figure 4); the modal value among those readmitted was 1, while the average was 2.1, and the range extended to 10 or more readmissions for five patients in the control group and eight in the intervention group. The average number

Figure 5) Total days in hospital per enrolled patient during the whole study, and during the first and second parts of the study

of days in hospital (Figure 5) was 10.9 in the usual care group compared with 10.2 in the intervention group (P not significant).

Mortality

Death occurred in 83 of 1342 usual care patients (6.2%) and in 71 of 1301 patients (5.5%) in the intervention group, with no significant difference (P=0.15) in overall survival.

Post hoc analysis

It took approximately 12 months to achieve an experienced, stable team of nurses and pharmacists. Growth and staff turnover had a considerable effect on the efficiency and cohesion of the interventional approach, which was not initially anticipated. In addition, the cardiology service underwent major organizational changes approximately nine months into the study. To evaluate the possibility that the program became more effective with time, patients were divided into two cohorts by dates of enrolment (up to and after June 30, 1997) without prior consideration of the data. Rehospitalization rates and total days in hospital were also determined for these two time frames. There were no significant differences in the first time frame. However, in the second time frame, the average number of days in hospital per patient (Figure 5) was greater in the usual care group than in the intervention group (11.1 ± 0.91 days versus 8.9 ± 0.61 days, respectively; $P < 0.05$). The number of days in hospital related to rehospitalizations was 6637 in the intervention group ($n=748$) compared with 7902 in the usual care group ($n=713$) over the 19 months of follow-up ($P < 0.05$). This represents an excess in the usual care group of 2210 days per 1000 patients over 19 months. As in the primary analysis, rehospitalization rates were high but similar in the two groups (134.5 and 130.6 per 100 patients in the usual care and intervention groups, respectively) (P not significant).

Cost implications

Extrapolation of data from the second time frame suggests that an intervention program in an environment similar to the one in the present study may achieve important cost reductions. If one assumes a daily cost of \$1,000 (which is close to that incurred during the period of the study), the potential cost savings would approximate \$2.2 million for the 2210 hospital days avoided per 1000 patients over 19 months in the intervention group. Our estimate of the program costs, assigning standard rates of pay for nursing and pharmacy staff, and including the costs associated with six

TABLE 2
Patient adherence to prescribed therapy

	Control group		Intervention group	
	Total patients, n	Adherent patients, n (%)	Total patients, n	Adherent patients, n (%)
ACEIs	693	632 (91)	701	648 (92)
Beta-blockers	971	778 (80)	969	863 (89)*
ASA	1172	1039 (89)	1180	1091 (92)
LL agents	853	663 (78)	937	775 (83)*
Warfarin	285	277 (97)	272	265 (97)

* $P < 0.01$. ACEI Angiotensin-converting enzyme inhibitor; ASA Acetylsalicylic acid; LL Lipid-lowering

Figure 6) Prescription rates for lipid-lowering drugs in a sample of patients over the first 13 months of a 19-month follow-up

to 12 months of team-building, as well as the fixed costs of space and equipment, ranged from \$440,000 to \$726,000, indicating the potential for substantial cost avoidance. Indirect value to patients with fewer days in hospital was not considered.

Prescription rates

It was rarely necessary to cue cardiologists to implement guidelines because prescription rates were near optimal for all but one of the classes of drugs monitored. Prescription rates were as indicated according to guidelines for angiotensin-converting enzyme inhibitors (89%), ASA (91%), beta-blockers (80%) and anticoagulants (92%). In the case of lipid-lowering agents, it was local practice during the study period to address cholesterol levels after hospital discharge. Prescriptions rates for lipid-lowering medications were 46% and 47% in the usual care and intervention groups, respectively; at discharge and by the end of the first year of the study, these rates were 67% and 80%, respectively (Figure 6).

Long-term adherence (Table 2)

Table 2 lists patient-reported adherence to the prescribed secondary prevention medications; adherence in the intervention group was greater than in the control group only for beta-blockers (89% versus 80%; $P < 0.01$) (Figure 7) and lipid-lowering agents (83% versus 78%; $P < 0.05$).

DISCUSSION

In the present large, prospective randomized controlled study in which all patients were followed for 19 months, a comprehensive, intensive program designed to optimize secondary prevention in

Figure 7) Patient adherence to beta-blocker prescriptions over a 19-month follow-up

cardiac patients failed to reduce the primary end points of rehospitalizations and total days in hospital per patient, as well as the secondary end point of mortality. We anticipated a positive result because of the known effectiveness of secondary prevention, as proven in other randomized placebo-controlled trials (1-11). Given the near-optimal physician compliance with guidelines for secondary prevention in our hospital region, there was limited potential for improving appropriate prescription rates for secondary prevention medications; thus, the study was effectively an attempt to improve outcomes by optimizing patient adherence to therapy. Patient education and monitoring for adherence are widely perceived to be suboptimal in our region. Therefore, we had anticipated that our efforts to improve adherence would have a substantial effect on outcomes. Our results indicate that even our intensive efforts to improve adherence were not sufficient to incrementally improve outcomes when prescription rates were already near optimal.

We considered many factors that might have affected our results. The power of the trial should have been adequate to demonstrate a biologically important effect, given the accumulation of more than 3500 patient-years of observation. It is possible that the total duration of the study (19 months) was too short for benefits to be more apparent; however, given the cumulative proven benefits of secondary prevention, it is not clear that this explains our results. There was little potential for improved prescription rates, as indicated by the near-optimal rates in the usual care arm, except for those for lipid-lowering agents. To illustrate the effectiveness of the program with this well-tolerated class of drugs with clear indications, despite the high prescription rates in the usual care group (approximately twice that in other parts of the country and higher than most other reported rates during the same period [11,47-52]), prescription rates were still somewhat higher in the intervention group. However, the differences between the high rate in the usual care group and the slightly higher rate in the intervention group were not expected to result in a substantial benefit within 19 months compared with what was expected versus placebo (53-56). This is well illustrated by the results from a recent study (57) that focused on lipid-lowering drugs; a very large number of patients needed to be studied for a longer time to demonstrate a significant but relatively small effect. Our patient-reported adherence to therapy data also suggest that there was only a small difference in adherence to beta-blocker and angiotensin-converting enzyme inhibitor prescriptions, which were not expected

to result in detectable differences in outcomes. We also considered that study nurses might have initiated processes, leading to more readmissions than might have occurred if patients had not sought medical attention on their own. However, a detailed analysis of the reasons for rehospitalization did not support that hypothesis.

Post hoc analysis

Without prior consideration of the data, we reasoned that there might have been an important learning curve related to rapid growth of the study team, as well as a possible effect from the restructuring of cardiac services during the first half of the study. The post hoc analysis provided some intriguing data. The outcomes during the first half of the study were similar to those during the whole study period. However, the analysis also suggested that the program was more effective during the second time period – patients in the intervention arm spent substantially fewer days in hospital during the second half of the study. Statistical analysis of time-dependence of differences in the number of days in hospital also supports this interpretation of our results; there was a trend ($P=0.08$) suggesting increased effectiveness in the intervention group over time. Thus, the post hoc analysis suggested that after the study team had acquired sufficient skills to be most effective and the team was stable, with minimal staff turnover, an important difference in the number of days in hospital might have been achieved by the program with considerable cost savings.

If this interpretation of the results is valid, there are important implications regarding implementation of such programs. Our experience leads us to believe that such a program is complex and requires a stable team with considerable experience to be effective; the learning curve is perhaps as long as six to 12 months. Because this was not our primary, a priori, hypothesis, we cannot conclude a cause and effect relationship. Nevertheless, this finding is consistent with our observation that such programs are more difficult to implement than we had originally considered.

Resource use

In contrast to patients involved in multicentre drug trials, our patients more likely reflected the mix normally encountered in many tertiary care institutions. Only patients with terminal diseases, those in nursing or long-term care facilities and those unable to communicate were excluded from the study; approximately 80% of those approached agreed to be in the study. Thus, the observed readmission rates and hospital days should have more closely reflected outcomes than in more patient-selective treatment trials (1-11). Our data highlight the substantial cost burden related to rehospitalization of cardiac patients. Overall, there were more than 130 readmissions per 100 patients over 19 months, with approximately one-half occurring within six months. The vast majority of these were not elective. It is also noteworthy that data from the provincial database identified admissions to other hospitals that would otherwise have been missed, despite the detailed data collection by the study team from the patients themselves.

Study limitations

The random assignment was designed to study the effects of the intervention program on prescription rates, and to study the effects of the patient-directed interventions. There was a slight trend toward reduced mortality in the intervention arm ($P=0.15$), so a larger study might have shown a significant difference. There were almost no opportunities to cue the cardiologists, so simpler random assignment would have sufficed. Nevertheless, there were no differences among any of the characteristics between groups (in those listed and in many others considered), which supports the

validity of the random assignment. Transfer of care of patients between cardiologists from both groups was frequent because of short clinical service blocks; thus, patients were frequently cared for by both usual care and intervention cardiologists. Furthermore, because there was no demonstrable effect of the attending cardiologists on the results, we suggest that although the reassignment of two cardiologists (after fewer than one-fifth of patients were enrolled) from the usual care to the intervention group might be considered to have been inappropriate, this should not have impacted the results. Although the study can be considered a cluster trial, the lack of interventions related to the prescription rates suggests that the trial can be considered to be a nonclustered study for analysis purposes.

Physician behaviour was not modified, and analysis of potential cardiologist-related effects also showed no effect, which supports the absence of a cluster effect. Secondary prevention in cardiac diseases has evolved since the study was performed and standards have changed. However, there is little reason to expect these kinds of programs to be more or less effective as guidelines evolve. The patient-directed component would still have the same goals when patient education and adherence to therapy are the main issues.

There are significant limitations to using patient-reported adherence to therapy data – some patients are reluctant to admit

to failure to take medications as prescribed. However, the data remain consistent with a small, positive effect in adherence with some prescriptions in the intervention group.

Study implications

Our results suggest that an intensive program designed to optimize secondary prevention in heart disease was ineffective in improving outcomes in our region in which the standard of care, measured by prescription rates and mortality from acute myocardial infarction, is very high (58). However, the post hoc analysis of our results suggests that there may be an important learning curve in implementing such a program and that improved outcomes may be achievable with a well-trained team. Our results suggest that the environment in which a disease management program is being considered should be carefully evaluated and that it may be best to focus on areas that can be improved to maximize cost-effectiveness. Comprehensive programs in health regions where secondary prevention is not practised according to guidelines may be effective, whereas programs that focus only on specific goals, such as patient adherence to therapy, may suffice where the standard of practice is already high.

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