

# Effectiveness of telephone counselling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomised controlled trial

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## Abstract

**Objective** To investigate the effects of compliance and periodic telephone counselling by a pharmacist on mortality in patients receiving polypharmacy.

**Design** Two year randomised controlled trial.

**Setting** Hospital medical clinic.

**Participants** 502 of 1011 patients receiving five or more drugs for chronic disease found to be non-compliant at the screening visit were invited for randomisation to either the telephone counselling group (n = 219) or control group (n = 223) at enrolment 12-16 weeks later.

**Main outcome measures** Primary outcome was all cause mortality in randomised patients. Associations between compliance and mortality in the entire cohort of 1011 patients were also examined. Patients were defined as compliant with a drug if they took 80-120% of the prescribed daily dose. To calculate a compliance score for the whole treatment regimen, the number of drugs that the patient was fully compliant with was divided by the total number of prescribed drugs and expressed as a percentage. Only patients who complied with all recommended drugs were considered compliant (100% score).

**Results** 60 of the 502 eligible patients defaulted and only 442 patients were randomised. After two years, 31 (52%) of the defaulters had died, 38 (17%) of the control group had died, and 25 (11%) of the intervention group had died. After adjustment for confounders, telephone counselling was associated with a 41% reduction in the risk of death (relative risk 0.59, 95% confidence interval 0.35 to 0.97; P = 0.039). The number needed to treat to prevent one death at two years was 16. Other predictors included old age, living alone, rate of admission to hospital, compliance score, number of drugs for chronic disease, and non-treatment with lipid lowering drugs at screening visit. In the cohort of 1011 patients, the adjusted relative risk for death was 1.61 (1.05 to 2.48; P = 0.029) and 2.87 (1.80 to 2.57; P < 0.001) in patients with compliance scores of 34-66% and 0-33% compared with those who had a compliance score of 67% or more.

**Conclusion** In patients receiving polypharmacy, poor compliance was associated with increased mortality. Periodic telephone counselling by the pharmacist improved compliance and reduced mortality.

**Trial registration** International Standard Randomised Controlled Trial Number Register: SRCTN48076318.

## Introduction

Many drugs for chronic conditions—notably cardiovascular disease—reduce morbidity and mortality in

controlled clinical trial settings.<sup>1 2</sup> They may be less effective in clinical practice, however, because of poor compliance—only half of patients who receive polypharmacy are fully compliant.<sup>3 4</sup> Although interventions such as telephone or postal reminders from pharmacists improve compliance, their effect on clinical outcome is not known.<sup>5-8</sup> We investigated whether periodic telephone counselling by a pharmacist to reinforce compliance and ensure continuity of care reduced mortality in patients receiving polypharmacy and whether compliance was associated with mortality.

## Methods

### Participants

Our study was a two year, prospective, randomised, controlled study conducted at a specialist medical clinic in Hong Kong (see [bmj.com](http://bmj.com) for details of health care in Hong Kong). We recruited patients between October 1998 and June 1999. We screened records the day before patients attended the clinic. The inclusion criterion was prescription of five or more drugs on at least two consecutive visits to the clinic. We assessed compliance only for drugs prescribed on a chronic basis. We invited non-compliant patients for randomisation at the next follow-up visit, usually 12-16 weeks later.

### Screening and definition of compliance

Using a structured questionnaire (see appendix on [bmj.com](http://bmj.com)), the pharmacist asked the patient to describe their regimen. They were asked whether they had missed any doses, changed their regimens, or had drugs left over. This information was checked against dispensing information. We defined patients as compliant with a drug if they had taken 80-120% of the prescribed daily dose. To calculate a compliance score for the whole treatment regimen, we divided the number of drugs that the patient was fully compliant with by the total number of prescribed drugs and expressed it as a percentage. Only patients who complied with all prescribed drugs were considered fully compliant (compliance score of 100%). We assessed compliance at screening, randomisation, and two year follow-up. Patients received a brief education about compliance at the screening visit.

### Randomisation and intervention

The pharmacist was blinded to the randomisation. Patients allocated to the intervention group received a



The structured questionnaire is on [bmj.com](http://bmj.com)



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10-15 minute telephone call from our pharmacist at the midpoint between clinic visits throughout the study period. The pharmacist asked about the patient's treatment regimens, clarified any misconceptions, explained side effects, and reinforced the importance of compliance and self care. Patients in the control group received no telephone interventions.

## Outcome measures and data collection

The primary endpoint was the time from randomisation to death from any cause. Other endpoints included changes in the rate of admission to hospital, number of emergency room visits, and hospital stay in the two years before and after the screening visit, as well as changes in compliance.

## Statistical analysis

For the primary analysis of the randomised group, we used an intention to treat analysis. We compared death rates and expressed the results as relative risks and 95% confidence intervals. We built a model to select predictors of mortality, including non-intervention by the pharmacist, age, sex, severity of disease, compliance scores, number of concomitant drugs, and use of life saving drugs at screening visit.

In the secondary analysis of the entire cohort of patients, we used regression and obtained hazard ratios for mortality in patients, according to their baseline compliance scores; those with a compliance score of 67% or more were used as the referent group. See [bmj.com](http://bmj.com) for estimation of sample size.

## Results

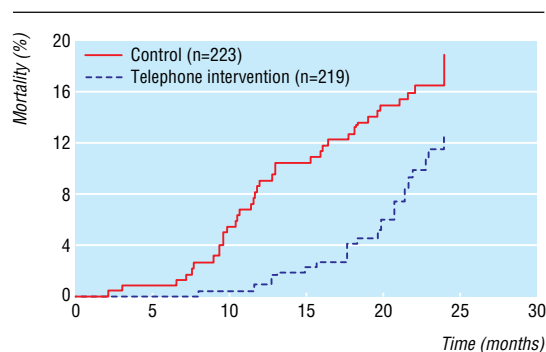
### Primary analysis of randomised cohort

#### Characteristics of the patients

We interviewed 1011 patients taking multiple drugs for chronic conditions (49% male; mean age 71 years, SD 10, range 34-96; mean number of drugs taken 5.9, 1.2, 5-14). Of these, 502 were non-compliant and were invited for enrolment at the next follow-up visit. Sixty patients defaulted at the subsequent visit, so only 442 patients were randomised at enrolment. Of these, 236 patients turned compliant; we randomised 117 to the intervention group and 119 to the control group. Of the 206 patients who remained non-compliant at enrolment, we randomised 102 to the intervention group and 104 to the control group. Baseline characteristics were similar except that the control group had a lower compliance score and lower use of lipid lowering and antiplatelet drugs. Most of the patients were elderly, lived with family members, and had been admitted to hospital many times.

#### Effects of telephone counselling

We observed all patients for at least two years or until death; mean follow-up was 23.2 months (SD 4.5). Each patient in the intervention group had six to eight telephone calls from the same pharmacist between clinic visits. At two years, 38 patients (17%) had died in the control group compared with 25 (11%) in the intervention group (fig 1). After we adjusted for confounding variables, the intervention was associated



**Fig 1** Kaplan-Meier estimates of effect of telephone intervention by a pharmacist on all cause mortality in patients receiving polypharmacy (relative risk for intervention 0.59, 95% confidence interval 0.35 to 0.97,  $P=0.039$  after adjusting for confounding factors)

with a 41% reduction in the relative risk of all cause mortality and the number needed to treat to prevent one death was 16.

At enrolment, half of the participants had become compliant after a brief talk by a pharmacist at the screening visit. Of the 236 patients who changed to being compliant, 14 of 117 (12%) died in the intervention group and 18 of 119 (15%) in the control group. Of the 206 who stayed non-compliant at enrolment, 11 of 102 (11%) died in the intervention group and 20 of 104 (19%) in the control group. Compliance was reassessed at the end of the two year study in patients who survived. Fewer patients who were non-compliant at enrolment remained non-compliant at the study end in the intervention group than in the control group (7% (7 of 102) *v* 18% (19 of 104),  $P<0.001$ ). More patients who turned compliant at enrolment remained compliant in the intervention group than in the control group (81% (95 of 117) *v* 58% (69 of 119),  $P=0.038$ ).

#### Effect of drug use and other factors on mortality

After we adjusted for all confounding variables including use of drugs at baseline, only old age, living alone, lack of pharmacist's intervention, number of drugs for chronic conditions, length of hospital stay during the study period, compliance scores, and not taking lipid

Regression analysis of all cause mortality at two years in patients receiving polypharmacy randomised to either intervention (telephone counselling) or control groups after adjusting for sociodemographic characteristics, comorbidities, use of drugs, and compliance at screening visit

Independent variables	Relative risk (95% CI)	P value
Age	1.05 (1.02 to 1.08)	0.001
Living alone	3.56 (1.28 to 9.88)	0.015
Telephone counselling by pharmacist	0.59 (0.35 to 0.97)	0.039
No of concomitant drugs	1.27 (1.05 to 1.54)	0.015
Length of hospital stay (past 24 months)	1.02 (1.01 to 1.03)	<0.001
Baseline drug compliance score	0.98 (0.97 to 0.99)	<0.001
Taking lipid lowering drugs at baseline	0.28 (0.10 to 0.82)	0.020

Dependent variable: death=1.

Independent variables: age, sex, ability to read labels, living arrangement, rate of admission to hospital, emergency room attendance, hospital stay two years before and during the two year follow-up period, smoking status, pharmacist's telephone counselling, number of concomitant drugs, compliance score, and use of lipid lowering drugs, antiplatelet agents, angiotensin converting enzyme inhibitors, and angiotensin II antagonists at screening visit.

lowering drugs at screening visit were independent predictors for death (table).

**Secondary analysis of the entire cohort: effects of compliance on mortality**

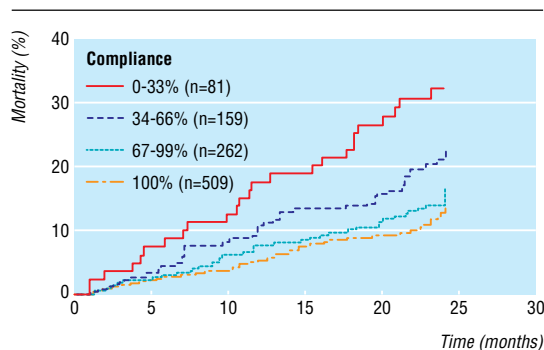
Most of the cohort of 1011 patients were taking drugs for cardiovascular disease, followed by drugs for diabetes. Figure 2 shows the risk of death in patients with 0-33% and 34-66% compliance scores compared with those who had a score of 67% or more. After we adjusted for number of visits to the emergency room and number of hospital admissions in the past 24 months, age, and number of concomitant drugs, hazard ratios were 2.87 (confidence interval 1.80 to 4.57,  $P < 0.001$ ) and 1.61 (1.05 to 2.48,  $P = 0.029$ ) for patients with compliance score of 0-33% and 34-66%. The other independent risk factors were age (1.05, 1.03 to 1.07,  $P < 0.001$ ) and rate of admission to hospital (1.19, 1.14 to 1.25,  $P < 0.001$ ).

**Discussion**

In this single centre, randomised, controlled study, telephone counselling by a pharmacist improved compliance, reduced mortality, and reduced use of healthcare resources in patients receiving polypharmacy. The beneficial effects on mortality remained significant after we controlled for confounding factors, including minor differences in use of drugs at baseline. In most public healthcare settings, patients are managed by different healthcare teams. Regular counselling by our pharmacist might have improved the continuity of care, helped alleviate patients' concerns, and reinforced behavioural changes.

**Assessment of compliance and its associations with mortality**

Given the complexity of these regimens, we relied on direct interviews together with patients' accounts, computerised information, and pill samples to obtain a reasonable estimate of compliance. These interviews provided invaluable insights into the reasons why patients did not follow treatment regimens, which helped our pharmacist target counselling at specific problems.<sup>9</sup> On the basis of this assessment method, half of our participants were non-compliant, and non-



**Fig 2** Kaplan-Meier estimates for 1011 patients receiving polypharmacy according to the compliance score at the screening visit. Relative risks (95% confidence intervals) for death in patients with compliance score of 0-33% and 34-66% were 2.9 (1.8 to 4.6,  $P < 0.001$ ) and 1.8 (1.1 to 2.7,  $P = 0.0098$ ) compared with those who had a score of 67% or more

**What is already known on this topic**

Patients who receive polypharmacy have low levels of compliance

The complexity of the treatment regimen is associated with non-compliance, and non-compliance is associated with increasing risk of death in a stepwise manner

**What this study adds**

Periodic telephone counselling by a pharmacist of non-compliant patients receiving polypharmacy improves compliance with treatment and reduces mortality and use of healthcare resources

compliance increased with complexity of the treatment regimens.<sup>10</sup>

**Importance of reinforcement to changing behaviour**

After brief counselling by our pharmacist at the screening visit, half of the non-compliant patients eligible for randomisation had become compliant at enrolment. Because periodic reinforcements are needed to prevent relapse and maintain behavioural changes, these patients were randomised despite the improvement in compliance.<sup>11 12</sup> At two years, patients who remained non-compliant at enrolment and received no further intervention had the highest death rate. Non-compliant patients in the intervention group had similar death rates to patients who turned compliant at enrolment but did not receive further reinforcement. Thus, continuous support is needed to change behaviour and reinforce positive health behaviours, which over time could be translated into major clinical benefits.

**Limitations of our study**

As with most health service research, blinding was not possible because the intervention was complex and caregivers were involved.<sup>13</sup> To minimise these potential biases, we used predefined inclusion and exclusion criteria, randomisation, and a structured questionnaire to document compliance. We also used hard endpoints such as all cause mortality and rates of admission to hospital to reduce detection bias with adjustment for potential confounders. Despite the encouraging results, we need to examine other sociological, cognitive, psychological, and behavioural determinants that may influence compliance and clinical outcomes. These results need to be replicated using a multicentre, randomised strategy, and such a study is being carried out in patients with chronic heart failure.<sup>14</sup>

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Ethical approval: Chinese University of Hong Kong clinical research ethics committee.

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## Underinvestigation and undertreatment of carotid disease in elderly patients with transient ischaemic attack and stroke: comparative population based study

Jack F Fairhead, Peter M Rothwell

### Abstract

**Objective** To identify any underinvestigation of older patients with transient ischaemic attack (TIA) and stroke.

**Design** Comparative population based studies.

**Setting** Routine clinical practice in all secondary care services in Oxfordshire and a nested population based study of incidence of transient ischaemic attack and stroke (the Oxford vascular study—OXVASC).

**Participants/population** All patients undergoing carotid imaging for ischaemic retinal or cerebral transient ischaemic attack or stroke from 1 April 2002 to 31 March 2005 in the Oxford vascular study (n = 91 105) and from 1 April 2002 to 31 March 2003 in routine clinical practice (n = 589 899).

**Main outcome measures** Age specific rates of carotid imaging, diagnosed  $\geq 50\%$  symptomatic carotid stenosis, and subsequent endarterectomy, in patients with recent transient ischaemic attack or stroke.

**Results** Of patients with recent carotid territory transient ischaemic attack or ischaemic stroke, 575 in routine clinical practice and 402 in the Oxford vascular study had carotid imaging, with similar rates up to the age of 80. The incidence of  $\geq 50\%$  symptomatic stenosis increased steeply with age, particularly in those aged  $\geq 80$ . Compared with investigations in patients in the Oxford vascular study, the rates of carotid imaging (relative rate 0.36, 95% confidence interval 0.28 to 0.46,  $P < 0.0001$ ), diagnosis of  $\geq 50\%$  symptomatic stenosis (0.33, 0.16 to 0.69,  $P = 0.004$ ), and carotid endarterectomy (0.19, 0.06 to 0.63,  $P = 0.007$ ) in this age group in routine clinical practice were all substantially lower.

**Conclusions** Incidence of symptomatic carotid stenosis increases steeply with age, but, despite

good evidence of major benefit from endarterectomy in elderly patients and a willingness to have surgery, there is substantial underinvestigation in routine clinical practice in patients aged  $\geq 80$  with transient ischaemic attack or ischaemic stroke.

### Introduction

Several audits have shown lower rates of treatment to prevent stroke in older people.<sup>1-4</sup> Similar observations in several other specialties have led to accusations of ageism.<sup>5-9</sup> Lower rates of treatment in older people, however, might legitimately reflect a lack of applicable randomised evidence of effectiveness,<sup>10 11</sup> increased frequency of contraindications to treatment, or patients' choice. To distinguish between ageism and legitimately reduced use of stroke prevention in older people we studied rates of imaging and endarterectomy for recently symptomatic carotid stenosis. This intervention is unusual in that there is strong evidence of benefit in elderly patients,<sup>12</sup> and good evidence that data from trials are probably generalisable to routine clinical practice.<sup>13</sup> Nevertheless, lower rates of treatment in elderly patients could be due to a reduction in incidence of symptomatic carotid stenosis with age, contraindications to surgery, or reluctance by patients to consider surgery. To identify any evidence of inappropriate underinvestigation or undertreatment, or both, we compared age specific rates of carotid imaging,  $\geq 50\%$  symptomatic carotid stenosis, and subsequent endarterectomy in patients with recent transient ischaemic attack or stroke in a population

Editorial by Young

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