Cluster Randomized Controlled Trial of a Patient and General Practitioner Intervention to Improve the Management of Multiple Risk Factors After Stroke

Stop Stroke

Charles David Alexander Wolfe, FFPH; Judith Redfern, PhD; Anthony George Rudd, FRCP; Andrew Peter Grieve, PhD, DSc; Peter Ulrich Heuschmann, MD, MPH; Christopher McKevitt, PhD

Background and Purpose—Stroke is a major public health concern worldwide and survivors remain at high risk of recurrence. Secondary prevention requires management of multiple risk factors but current management is suboptimal. Evidence of the effectiveness of interventions to improve poststroke risk factor management from well-designed trials is limited. We assessed the effectiveness of a patient and general practitioner systematic follow-up intervention to improve risk factor management after stroke.

Methods—We undertook a pragmatic cluster trial involving 523 consecutive incident stroke survivors identified using the population South London Stroke Register and registered with general practices in inner-city London. Practices were randomized to receive the intervention or usual care. The intervention entailed systematically identifying stroke survivors’ risk factors for recurrence and providing tailored evidence-based management advice to general practitioners, patients, and caregivers at 10 weeks, 5 months, and 8 months poststroke. The primary outcome was management of key modifiable risk factors for stroke at 1 year with 3 end points: treatment with antihypertensive therapy, treatment with antiplatelet therapy, and smoking cessation. Hierarchical testing was used to adjust for multiple endpoints. Analysis was by intention to treat. This study is registered as number ISRCTN10730637.

Results—The absolute risk reduction (and 95% CI) for each outcome was

- 3.7% (−13.0% to 5.6%) for treatment with antihypertensives;
- 2.3% (−12.0% to 7.6%) for treatment with antiplatelets; and
- 0.6% (−14.5% to 13.5%) for smoking cessation. Treatment effects were confirmed in the generalized linear model adjusting for clustering and predefined confounders.

Conclusions—No improvement in risk factor management was demonstrated as a result of this patient, caregiver, and healthcare professional systematic follow-up system. Further evidence of how to effectively alter behavior of patients/caregivers and professionals is required if tailored information on risk and its treatment is to be of any clinical benefit. (Stroke. 2010;41:2470-2476.)

Key Words: smoking cessation stroke risk factors

Stroke is a leading cause of adult death and disability worldwide. Estimates of recurrence of stroke after an initial event range considerably due to differences in definition and sampling frames, but recurrence is 1 potentially useful outcome that may reflect effective secondary prevention. Recent population-based estimates of recurrence risk vary from 18.5% within 3 months for minor strokes in Oxford, UK,2 to 7% at 1 year for all strokes in South London.3 Recurrence has an increased risk of death, additional disability, or dependence on health services.5 There are national and international guidelines for effective secondary prevention strategies to reduce recurrence risk.6–8 Currently there are both discouraging and encouraging reports about aspects of secondary prevention management in the United Kingdom. Studying general practice records between 1995 and 2005, Raine et al9 showed that only 25.6% of men and 20.8% of women received secondary prevention. A study of Quality and Outcomes Framework data in England between 2005 and 2007 showed that 82.3% of adults had an up-to-date blood pressure recording in 2005 and this increased to 88.3% in 2007.10 The proportion of patients achieving target blood pressure levels ranged from 71% to

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85% in 2005 rising to between 78.6% and 89.4% in 2007. Barriers to risk factor control include: inadequate follow-up and monitoring of stroke survivors by healthcare professionals; inadequate prescribing of secondary prevention therapies; poor information provision; and inadequate self-management of risk factors by patients.\textsuperscript{5,11–17} Interventions to reduce recurrence of myocardial infarction have sought to change organizations, individual healthcare professional practice, or individual patient behavior. Interventions with stroke survivors have incorporated similar strategies to address barriers to risk factor management,\textsuperscript{18} but randomized controlled trial (RCT) evidence is limited to 4 studies evaluating multiple-component interventions.\textsuperscript{19–22} The components of these interventions included: assessment and review by an interdisciplinary stroke team plus personalized self-management plans\textsuperscript{19}; shared medical records; inpatient teaching about stroke plus provision of information leaflets\textsuperscript{21}; monthly risk factor reviews with a specialist stroke nurse; delivery of individualized secondary prevention advice plus use of patient-held records\textsuperscript{22}; and an integrated system of management.\textsuperscript{20} The integrated system had multiple components, including using flowcharts to guide in-hospital and primary care prescribing; delivery of patient education on risk factor management by a nurse coordinator; prearranged follow-up appointments with a general practitioner (GP) at 2 weeks and 3, 6, 9, and 12 months postdischarge; telephone tracking of patients before the appointments to identify risk factor management problems; screening for depressive symptoms and provision of feedback to GPs; nurse coordinator monitoring; and intervention for suboptimal GP prescribing.\textsuperscript{20} Only the integrated management trial demonstrated improved effects on risk factor management outcomes, but analysis was not by intention to treat and clustering was not taken into account.\textsuperscript{20}

Following the Medical Research Council Framework for the development and evaluation of complex health service interventions,\textsuperscript{23} we conducted multiple studies over 5 years to inform the development of a novel intervention to improve stroke secondary prevention management. This research entailed: analysis of patterns of poststroke care using the South London Stroke Register (SLSR), reviews of the literature,\textsuperscript{11–22} and qualitative studies with stroke survivors.\textsuperscript{18,24–28} Findings were collated, considered by the research team, and an intervention was designed that aimed to overcome barriers to secondary prevention experienced by patients and practitioners. Table 1 shows the main components of the intervention. The intervention was tested in a pilot study with 25 patients and their GPs evaluated using qualitative interview and observational methods. The pilot study found that the intervention was feasible to deliver and acceptable to stroke survivors and GPs. Some changes were made to content and presentation of information provided in the intervention.\textsuperscript{28}

<table>
<thead>
<tr>
<th>Table 1. The Stop Stroke Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of stroke survivors and current risk factor management through the SLSR</td>
</tr>
<tr>
<td>- Hospital and community stroke survivors identified by a trained researcher as part of routine SLSR data collection</td>
</tr>
<tr>
<td>- Data collected on individual patients, including key risk factors for recurrence (diagnoses of stroke subtype, hypertension, atrial fibrillation, diabetes, smoking, alcohol use, and obesity)</td>
</tr>
<tr>
<td>- Data collected on individual patients’ current risk factor management, including medication prescribed on hospital discharge or within 6 weeks of stroke</td>
</tr>
<tr>
<td>Production of individualized secondary prevention package for patients, caregivers, and their GP</td>
</tr>
<tr>
<td>- SLSR data entered onto the computer and analyzed using predefined evidence-based computer algorithms to create a risk factor profile for each patient outlining their risk factors, current risk factor control, and treatment strategies</td>
</tr>
<tr>
<td>- Computer system generates a “keeping well plan” for patient and caregiver with evidence-based information and advice tailored to the individual on strategies to improve current risk factor management; plan printed in hard-copy form</td>
</tr>
<tr>
<td>- Computer system generates evidence-based secondary prevention plan tailored for the patient’s GP outlining individual patient’s risk factors, current risk factor management, and relevant UK intercollegiate guidelines on best practice for management; plan printed in hard-copy form</td>
</tr>
</tbody>
</table>

Distribution, dose, and follow-up
- Patient and caregiver “keeping well plans” sent by mail; GP secondary prevention plans either sent electronically or by post depending on individual preference
- Patients followed up as part of SLSR routine follow-up data collection at 3 and 6 months poststroke; data collected on changes to risk factor diagnoses and current management
- SLSR follow-up data entered onto computer; computer generates modified plans with updated information on individual patient’s risk factors; modified plans sent to patients, caregivers, and GPs
- No. of plans (dose) sent to participants varies depending on when patients are identified by SLSR; participants could receive a maximum of 3 doses of the intervention

Methods

Study Design and Participants
In 2003, all GPs and their practice managers located in practices in 2 boroughs in inner-city London were invited to participate in the trial. The invitation letter was signed by the principal investigator (C.D.A.W.) and a lead stroke clinician (A.G.R.). No GPs declined. Practices in the intervention arm were also visited by C.D.A.W. or A.G.R. to provide information on the trial. GP practices were randomized with stratification by practice size (≥10 000 patients or <10 000) and by number of practitioners (single- or multiple-handed). The computer-generated allocation sequence was produced by an independent statistician and only revealed to the trial coordinator. Practices (n=136) were allocated to receive the intervention or usual care (control group). The intervention is outlined in Table 1. Participants were patients with stroke registered on the SLSR between July 2003 and June 2006 residing in the 2 boroughs. There were no exclusions based on GP practice characteristics, the patient’s age, comorbidity, or disability. Patients were eligible if they were identified by the research team within 6 months of the date of the stroke, were registered with a study GP, and alive 6 weeks poststroke. Patients were recruited by a trained researcher in the hospital or the patient’s own home. All patients gave informed consent and were given up to 6 months from the date of their stroke to do so. Patients were randomized according
to their GP practice allocation. A computerized system informed the trial coordinator of the identity of patients and GPs requiring the intervention. Intervention recipients (patients, caregivers, and GPs) were not blind to the intervention.

The study design was approved by 2 local research ethics committees.

### Outcome Measures

The primary outcome was management of key modifiable risk factors for stroke at follow-up between 1 year and 18 months poststroke. The trial steering committee proposed the 18 month cutoff for completion of follow-up to accommodate the difficulties of locating and contacting participants in this inner-city population with high levels of socioeconomic deprivation and residential mobility. At the time the trial protocol was developed, the guidelines for poststroke risk factor management differed from current recommendations, particularly in relation to treatment with antihypertensive and cholesterol-lowering therapies. The primary and secondary outcomes for the study reflect recommendations for risk factor management outlined in the first edition of National Clinical Guidelines for Stroke published in 2000.29 There were 3 primary end points: (1) treatment with antihypertensive therapy for participants with hypertension diagnosed at baseline; (2) treatment with antiplatelet therapy for participants diagnosed with ischemic stroke at baseline and not treated with anticoagulant therapy at follow-up; and (3) smoking cessation for smokers at baseline. Secondary outcomes included management of other risk factors at follow-up: treatment with statins for patients with high cholesterol diagnosed at baseline; treatment with anticoagulant therapy for participants with diagnoses of ischemic stroke and atrial fibrillation at baseline; treatment with insulin or oral hypoglycemics for those diagnosed with diabetes at baseline, alcohol use (where hazardous alcohol use is defined as >14 U/week women, >21 U/week men); and receipt of written information about stroke.

### Procedures

Outcome data were collected through the SLSR at baseline and at follow-up. At baseline, participants were visited in the hospital or their place of residence and a face-to-face interview conducted by a trained researcher blind to the treatment allocation. Data were collected on participants’ socioeconomic characteristics, including date of birth, sex, socioeconomic status, measured using occupational classification,30 ethnic group, and prestroke self-reported smoking status. Data on other prestroke risk factors were collected on participants’ socioeconomic characteristics, including occupation, workers and less likely to be independent in activities of daily living (Barthel Index) both prestroke and at 5 to 10 days poststroke.

Comparison of self-reported smoking data and concentrations of blood cotinine shows that 5 of 83 (9.8%) smokers who completed both self-report and a blood cotinine test and reported not smoking at follow-up had a salivary cotinine concentration >15 ng/mL. Two hundred fifty-five of 395 (64.6%) participants with hypertension at baseline were treated with antihypertensive therapy at follow-up, 228 of 379 (60.2%) participants with ischemic stroke at baseline, not on anticoagulant therapy, were treated with antiplatelet therapy at follow-up, and 43 of 154 (27.9%) smokers at baseline had quit smoking at follow-up. Table 3 shows the ARR due to the intervention and 95% CIs for all primary and secondary outcomes. There was no effect on ARR for any primary outcome; adjusted analyses showed a trend in favor of the control arm for all outcomes (Table 4). There was no effect on ARR for any secondary outcome except for receipt of written information about stroke (ARR, 8.9; 95% CI, 0.05 to 17.24).

### Results

The Figure shows the trial profile. Five hundred twenty-three participants consented and were randomized into the trial. The intervention was not delivered to 36 participants in the intervention arm; no one in the control arm received the intervention. There was a 5% difference in follow-up between trial arms with 88 of 274 lost to follow-up (including deaths) in the intervention arm compared with 66 of 249 control subjects. The mean number of patients per practice over the 3-year recruitment period was 5.57 in the intervention arm and 4.41 in the control arm.

Table 2 shows baseline characteristics of participants in each trial arm. There were no differences between participants on any sociodemographic, clinical, or risk factor characteristics at baseline. However, there was a trend toward those in the intervention arm being more likely to be manual workers and less likely to be independent in activities of daily living (Barthel Index) both prestroke and at 5 to 10 days poststroke.

Comparison of self-reported smoking data and concentrations of blood cotinine shows that 5 of 83 (9.8%) smokers who completed both self-report and a blood cotinine test and reported not smoking at follow-up had a salivary cotinine concentration >15 ng/mL. Two hundred fifty-five of 395 (64.6%) participants with hypertension at baseline were treated with antihypertensive therapy at follow-up, 228 of 379 (60.2%) participants with ischemic stroke at baseline, not on anticoagulant therapy, were treated with antiplatelet therapy at follow-up, and 43 of 154 (27.9%) smokers at baseline had quit smoking at follow-up. Table 3 shows the ARR due to the intervention and 95% CIs for all primary and secondary outcomes. There was no effect on ARR for any primary outcome; adjusted analyses showed a trend in favor of the control arm for all outcomes (Table 4). There was no effect on ARR for any secondary outcome except for receipt of written information about stroke (ARR, 8.9; 95% CI, 0.05 to 17.24).
Results of exploratory analysis showed that by excluding those lost to follow-up, the proportion treated on each primary outcome rose to: 127 of 140 (90.7%) for control arm participants treated for hypertension and 128 of 142 (90.7%) for intervention arm participants (ARR, -0.01, 95% CI, -0.08 to 0.67); 108 of 121 (89.3%) for control arm participants treated with antiplatelet therapy and 120 of 132 (90.9%) for intervention arm participants (ARR, 0.02; 95% CI, -0.06 to 0.09); and 22 of 60 (36.7%) smokers in the control arm had quit and 21 of 48 (43.8%) smokers in the intervention arm (ARR, 0.07; 95% CI, -0.11 to 0.25). In this analysis, the trend in favor of the control arm disappeared but there remained no treatment effect.

Discussion
This trial evaluated a patient and GP stroke secondary prevention intervention targeting a population sample of all stroke survivors and developed following UK Medical Research Council-recommended guidance for complex intervention development. Despite considerable early phase work (16; 24 to 28), no effect of the intervention on any primary or secondary risk factor management outcomes was demonstrated. One explanation may be that usual care was better than anticipated at managing risk factors. During the course of the trial, the UK Department of Health introduced the quality and outcomes framework to improve outcomes in primary care, including a pay-per-performance strategy for management of key chronic disease risk factors. Results from an analysis of quality and outcomes framework data in England, 2005 to 2007, suggest that this may have led to improvements in base levels of risk factor control for stroke survivors that could have reduced the power of the intervention to influence trial outcomes.10 Achievement of blood
pressure targets for stroke survivors registered at GP practices in the study area was shown to improve from 79% to 86% during the course of the trial. A recently reported trial of a similar intervention to improve secondary prevention in patients with heart disease suggested that a ceiling effect in influence routine access to health services or to encourage those with suboptimal risk factor management may be insufficient to ensure that those with suboptimal risk factor management are recalled for further investigation and may be less effective than payment in influencing GP prescribing practices.

Table 2. Baseline Characteristics of Participants Including Key Stroke Risk Factors

<table>
<thead>
<tr>
<th>Key risk factors*</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>61 (22.34)</td>
<td>50 (20.24)</td>
</tr>
<tr>
<td>Female</td>
<td>126 (46.15)</td>
<td>118 (47.77)</td>
</tr>
<tr>
<td>Ethnic group, white</td>
<td>177 (64.84)</td>
<td>162 (65.59)</td>
</tr>
<tr>
<td>Social class, manual</td>
<td>176 (64.47)</td>
<td>142 (57.49)</td>
</tr>
<tr>
<td>Prestroke independence in ADL (Barthel Index = 20)</td>
<td>225 (82.72)</td>
<td>214 (86.64)</td>
</tr>
<tr>
<td>Independence in ADL 5–10 days poststroke (Barthel Index = 20)</td>
<td>87 (30.08)</td>
<td>80 (36.10)</td>
</tr>
<tr>
<td>Single-handed GP</td>
<td>30 (10.99)</td>
<td>32 (12.96)</td>
</tr>
<tr>
<td>Subtype ischemic stroke</td>
<td>235 (86.08)</td>
<td>213 (86.23)</td>
</tr>
</tbody>
</table>

**Key risk factors defined using diagnoses made prestroke and pre-discharge (hospitalized patients only): (1) hypertension diagnosed based on: a hospital or GP record of hypertension, treatment with antihypertensive therapy prestroke, a hospital or GP record of blood pressure >140/90 mm Hg prestroke; (2) hypercholesterolemia diagnosed based on: a hospital or GP record of hypercholesterolemia, treatment with statins prestroke; (3) hazardous alcohol use defined as >14 units alcohol/week for women, >21 units alcohol/week for men. ADL indicates activities of daily living.

At the start of the trial, we had estimated that the prevalence of untreated hypertension at 3 months poststroke was 30%, but exploratory analysis of the trial results showed that only 10% of trial participants with hypertension who completed follow-up were untreated. Over and above the improved quality and outcomes framework management, the intervention may not have had the power to influence GP consulting or patient self-management as intended. Although the trial demonstrated an impact on the process of secondary prevention management (receipt of written information about stroke), process change did not affect outcomes (improved risk factor management). Based on existing evidence and our theoretical work, we had hypothesized that a multiple component approach targeting patient, caregiver, and GP, 3 over time points, would have a stronger influence on risk factor management than a single component intervention. However, the approach we adopted may still have been insufficient to address some of the barriers to secondary prevention man-

Table 3. Risk Factor Management by Experimental Group for Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Risk Factor Management</th>
<th>Intervention</th>
<th>Control</th>
<th>ARR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with antihypertensives</td>
<td>128/204</td>
<td>127/191</td>
<td>−3.74 (−13.03 to 5.67)</td>
</tr>
<tr>
<td>Treatment with anticoagulants</td>
<td>7/41</td>
<td>14/40</td>
<td>−17.93 (−35.62 to 1.23)</td>
</tr>
<tr>
<td>Appropriate alcohol use*</td>
<td>171/273</td>
<td>167/247</td>
<td>−4.97 (−13.04 to 3.23)</td>
</tr>
<tr>
<td>Receipt of written information</td>
<td>124/273</td>
<td>90/247</td>
<td>8.98 (0.05 to 17.24)</td>
</tr>
</tbody>
</table>

*Appropriate alcohol use defined as no more than 14 units/week for women or 21 units/week for men.

In the trial we defined our choice of outcome measures to reflect guidelines for best practice in poststroke risk factor management current at the time the protocol was written and these were based on receipt of treatment. Since then, the focus of best practice guidelines has changed to recommend lowering blood pressure and cholesterol in all stroke survivors. More detailed recommendations are also given on the number and use of specific antihypertensive therapies. Outcome measures derived from these recommendations such as actual blood pressure and its reduction and cholesterol control may be more sensitive in assessing the impact of the intervention. The higher than anticipated treatment rates for our main outcomes means that the sample size may not have been large enough to detect any effect of the intervention. Our inability

Table 4. Generalized Linear Model of Effect of the Intervention on Primary Outcomes Accounting for Clustering and Adjusting for Age, Sex, Ethnicity, Social Class, Prestroke Disability, and Subtype

<table>
<thead>
<tr>
<th>Risk Factor Management</th>
<th>Estimate for Effect of Being in the Intervention Arm</th>
<th>Wald 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with antihypertensives</td>
<td>−0.17</td>
<td>−0.66 to 0.26</td>
<td>0.44</td>
</tr>
<tr>
<td>Treatment with anticoagulants</td>
<td>−0.03</td>
<td>−0.47 to 0.41</td>
<td>0.88</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>−0.18</td>
<td>−0.99 to 0.63</td>
<td>0.66</td>
</tr>
</tbody>
</table>
to demonstrate any effect on clinically relevant outcomes may also reflect the problematic nature of complex interventions and the practical and methodological difficulties of conducting RCT evaluations of population interventions. It is thought that the inability of studies to demonstrate intervention effectiveness in RCTs may reflect poor theoretical and methodological development. However, development of our intervention was based on theory generated during a lengthy research phase before RCT evaluation. Other similar multicomponent interventions have demonstrated effects on risk factor management but not when evaluated by well-designed RCTs. Our parallel process evaluation embedded within the trial will be used to illuminate the reasons for the failure of our intervention.

These findings relate to an intervention delivered in 2 boroughs in inner-city London. Stroke survivors living in other rural locations may have different secondary prevention needs and may have benefited more or less from this type of intervention. The locations covered in this study also benefit from access to stroke survivors in 3 teaching hospitals with acute stroke specialist services and the intervention may have had more of an impact if delivered in areas where patients and GPs have less access to well-developed stroke services. National stroke strategies recommend that patients should receive information about stroke risk factor management and an appropriate care plan. We expected our intervention to be effective because it was theoretically designed to address these needs. The success of the quality and outcomes framework payments for GPs in improving usual care management of risk factors may partially explain the failure of our cluster trial to provide evidence of intervention effectiveness. However, quality and outcomes framework payments have only been evaluated in relation to blood pressure control, have not been evaluated in a RCT, and may not benefit those stroke survivors who do not routinely access GP services. Whether our intervention has any additional benefit for stroke survivors is less clear. Therefore, there may still be some merit in investigating this type of complex risk factor management intervention further.

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Disclosures
None.

References


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