Point-of-Care Cluster Randomized Trial in Stroke Secondary Prevention Using Electronic Health Records

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Background and Purpose—The aim of this study was to evaluate whether the remote introduction of electronic decision support tools into family practices improves risk factor control after first stroke. This study also aimed to develop methods to implement cluster randomized trials in stroke using electronic health records.

Methods—Family practices were recruited from the UK Clinical Practice Research Datalink and allocated to intervention and control trial arms by minimization. Remotely installed, electronic decision support tools promoted intensified secondary prevention for 12 months with last measure of systolic blood pressure as the primary outcome. Outcome data from electronic health records were analyzed using marginal models.

Results—There were 106 Clinical Practice Research Datalink family practices allocated (intervention, 53; control, 53), with 11,391 (control, 5516; intervention, 5875) participants with acute stroke ever diagnosed. Participants at trial practices had similar characteristics as 47,887 patients with stroke at nontrial practices. During the intervention period, blood pressure values were recorded in the electronic health records for 90% and cholesterol values for 84% of participants. After intervention, the latest mean systolic blood pressure was 131.7 (SD, 16.8) mm Hg in the control trial arm and 131.4 (16.7) mm Hg in the intervention trial arm, and adjusted mean difference was −0.56 mm Hg (95% confidence interval, −1.38 to 0.26; P = 0.183). The financial cost of the trial was approximately US $22 per participant, or US $2400 per family practice allocated.

Conclusions—Large pragmatic intervention studies may be implemented at low cost by using electronic health records. The intervention used in this trial was not found to be effective, and further research is needed to develop more effective intervention strategies.


Key Words: blood pressure ▪ cholesterol ▪ electronic health records ▪ intervention studies ▪ secondary prevention ▪ stroke

Stroke represents a long-term condition that requires ongoing preventive medical care to reduce the risk of recurrence of stroke. During the first 10 years after stroke, there is nearly 40% cumulative risk of recurrence. Secondary prevention after stroke should include interventions to manage and monitor vascular risk factors including blood pressure (BP), lipid-lowering drugs, and antithrombotic treatment where appropriate, as well as efforts to control overweight, increase exercise, and reduce alcohol and smoking. Audits have revealed major deficiencies in stroke secondary prevention with ≤40% subjects achieving a systolic BP of <140 mm Hg at 6 months poststroke. Failure to use effective treatments is associated with considerable morbidity, mortality, and healthcare costs. There is a need for more effective intervention strategies to improve poststroke standards of care for secondary prevention that are relevant to routine clinical practice.

Advances in electronic health records (EHRs) offer important opportunities for more efficient implementation of clinical and cluster trials. Using EHRs from a large clinical database as a sampling frame, and source of data to evaluate trial outcomes, might offer several potential advantages, enabling the recruitment of participants and assessment of...
outcomes at only moderate cost. However, methods for delivering interventions through EHRs are relatively untested. Research is needed to provide proof of concept for the feasibility and validity of this approach. This research therefore aimed to develop methods to implement a cluster randomized trial using primary care EHRs in a large sample of participants. The research addressed the substantive primary objective of improving standards of stroke secondary prevention, comparing routine clinical practice with promotion of a more rigorous secondary prevention strategy as recommended by current guidelines. Cluster randomization was used because intervention was at the level of the family practice not the individual patient.

Methods

The study was a cluster randomized trial with family practices allocated in equal proportions to 2 trial arms.7 The study protocol was approved by the National Research Ethics Service Committee London South West (10/H0806/1). The senior partner at each participating general practice gave written informed consent on behalf of all practice practitioners to take part in the study. Treatment decisions for individual patients were at the discretion of the physician, and individual patient consent was not sought. An independent Trial Steering Committee and a Data Monitoring and Ethics Committee approved the protocol (Appendix). No interim analyses were performed.

Recruitment and Allocation

Family practices in England, Scotland, or Wales were eligible for the study if they were contributing data to the Clinical Practice Research Datalink (CPRD). The CPRD is a large database that includes the EHRs of 77% of all UK general practices from 1987 to the present.7,8 There were 106 family practices, of 508 CPRD family practices invited, that gave written informed consent to participation, and these were allocated to intervention and control trial arms. Allocations were performed using anonymized practice identifiers by the study team at King’s College London, independent of CPRD. Minimization9 was used, stratifying for region, as well as practice list size. Allocations were performed in 3 batches between March and July 2012, and the intervention continued for 12 months after the date of allocation.

Intervention

The intervention was delivered to healthcare professionals during consultations and aimed to encourage adoption of the UK recommendations for secondary prevention of stroke and vascular disease.2 The content of the educational and decision support tools drew on evidence summarized in the guidelines, including reports of clinical trials and meta-analyses of clinical trials, as well as observational analyses of data from CPRD.10,11 The format of the intervention materials or prompts drew on social cognitive theory, as well as qualitative research to evaluate pilot versions of the intervention with family physicians at nonstudy practices, as reported previously.1 The prompts identified 4 key areas for change in practice: control of BP to a target value of <130/80 mmHg12,13; prescription of statins when the cholesterol level remained >4 mmol/L (155 mg/dL)15,16; recording of strokes as being caused by hemorrhage or infarction, so as to define eligibility for anticoagulant therapy;17 and prescription of antiplatelet drugs to all patients with ischemic stroke18 using clopidogrel as first-line therapy.19 Secondary prevention recommendations requiring patient behavior change, such as smoking cessation, were considered to be beyond the scope of this intervention.

The intervention included evidence-based recommendations to family physicians, external links to guidelines, and research evidence to support clinical decision making, as well as printable patient information. The intervention was delivered remotely into practices through a system known as DXS Point-of-Care, which is embedded in the practice software system that is used by CPRD family practices. The intervention was activated when the family physician consulted with a patient included on the practice stroke register. A banner then appeared in the DXS toolbar showing the King’s College London logo, together with an invitation for the physician to access the intervention materials. The numbers of banner views and prompts accessed were electronically recorded through DXS software during the intervention period. General practices in the intervention trial arm were sent a letter to provide instructions on the use of the intervention, whereas practices in the control trial arm were sent a letter that reminded them to record all stroke-related consultations and adverse events.

Eligibility and Sample Size Calculation

Participants were eligible for the intervention if they were included in the practice stroke register. Participants were included in the analysis if they were ever diagnosed with acute stroke and survived to the intervention start date. There were no exclusion criteria. In sensitivity analyses, we also evaluated all participants with incident acute stroke after the start of the current CPRD record and participants with first strokes within 2 years of the intervention start date.6 Previous research showed ≥29 patients per practice within 2 years of diagnosis, with SD of systolic BP of 19 mmHg20 and in an intraclass correlation coefficient by general practice of 0.032.21 Then, with 2-sided α of 0.05 and power of 0.8, to detect a 2.75-mm Hg difference in systolic BP, ≥99 practices were required with 50 receiving the active intervention and ≥90 in the control. The detectable difference in systolic BP will be ≥3 mm Hg.2 However, adjustment for preintervention values gave greater precision than initially anticipated.21

Data Selection and Analysis

CPRD data were included for acceptable participants with defined sex and aged ≥18 years with at least 3 primary care consultations and ≥1 year of observations available from CPRD. Participants were included in the analysis if they were eligible for the intervention if they were included in the practice stroke register. Participants were included in the analysis if they were ever diagnosed with acute stroke and survived to the intervention start date. There were no exclusion criteria. In sensitivity analyses, we also evaluated all participants with incident acute stroke after the start of the current CPRD record and participants with first strokes within 2 years of the intervention start date.6 Previous research showed ≥29 patients per practice within 2 years of diagnosis, with SD of systolic BP of 19 mmHg20 and in an intraclass correlation coefficient by general practice of 0.032.21 Then, with 2-sided α of 0.05 and power of 0.8, to detect a 2.75-mm Hg difference in systolic BP, ≥99 practices were required with 50 receiving the active intervention and ≥90 in the control. The detectable difference in systolic BP will be ≥3 mm Hg.2 However, adjustment for preintervention values gave greater precision than initially anticipated.21

Results

There were 106 family practices allocated in the trial (53 control, 53 intervention; Figure I in the online-only Data Supplement). Two practices allocated to the control group left CPRD before the intervention was started. This left 51 practices in the control trial arm. There were 11391 participants with a previous stroke who survived to the trial start date. There were only 110 (1%) participants (59 control, 51 intervention) who had no days with consultations recorded during the intervention period, and 68% of patients had clinical events recorded on ≥12 days during the year.

Table 1 shows the characteristics of eligible participants in the trial arms, in comparison with 47887 participants who met the same entry criteria but were registered with nontrial CPRD family practices. The results of a significance test, contrasting data for practices in the intervention trial arm with nonstudy practices, are shown. In general, participants in the
intervention and control trial arms and participants from the nonstudy practices were similar with respect to length of time since stroke, mean age, sex, prevalence of comorbid coronary heart disease and diabetes mellitus, body mass index category, mean systolic and diastolic BP, and serum cholesterol concentration. Participants in the intervention trial arm were slightly more likely to have their stroke coded as ischemic rather than undefined.

Table 2 provides results for systolic and diastolic BP and serum total cholesterol. The median number of BP recordings in the first 15 months after intervention was 2 (interquartile range, 1 to 4) with 90% of intervention and 89% of control participants having ≥1 BP record during the intervention period. The most recent BP value was ≈46 weeks after the start of intervention. The mean values for systolic and diastolic BP were similar in each trial arm. The adjusted mean difference in BP between intervention and control trial arms was −0.56 (−1.38 to 0.26 mm Hg; P=0.183) for systolic BP and 0.00 (−0.47 to 0.49; P=0.972) for diastolic BP. The intraclass correlation coefficient by practice for systolic BP was 0.022 in the intervention period. The proportion of participants with BP controlled to <130/80 mm Hg was 28% in both trial arms (P=0.652). Total cholesterol values were recorded during the intervention period for 84% of participants. The median number of records was 1 (interquartile range, 1 to 2), and the latest record was ≈39 weeks after the start of intervention. Mean values for total cholesterol were similar in the 2 trial arms. The adjusted mean difference in total cholesterol between trial arms was −0.02 (−0.06 to 0.01; P=0.194). The proportion with total cholesterol ≤4 mmol/L (155 mg/dL) was 37% in each trial arm (P=0.990). Table I in the online-only Data Supplement presents data that explore the effect of varying the eligibility criteria for the analysis. Inclusion of all prevalent stroke cases gave 13,391 participants; inclusion of incident cases of stroke only gave 6,295 participants; inclusion of incident strokes within 2 years of the intervention start gave 1,705 participants. Mean systolic BP values were similar according to each eligibility criterion, with negligible difference between the 2 trial arms. For incident stroke cases, a P value of 0.025 was observed, but the 1-mm Hg estimated reduction in systolic BP was unlikely to have been of clinical significance.
Table 3 summarizes data for prescribing for secondary prevention. There was no difference between trial arms in the number of classes of antihypertensive drugs prescribed. There were 668 participants in the control trial arm and 746 in the intervention trial arm with elevated BP but were not prescribed antihypertensive drugs ($P=0.492$). A high proportion of participants (control, 71%; intervention, 69%) were prescribed lipid-lowering drugs. Among participants with cholesterol values >4 mmol/L (>155 mg/dL), 34% in the control trial arm and 36% in the intervention trial arm were not prescribed lipid-lowering drugs ($P=0.414$). There were 67% in the control trial arm and 59% in the intervention trial arm ($P=0.065$) who did not have type of stroke recorded after intervention, leaving eligibility for antiplatelet and anticoagulant therapy undefined. Nevertheless, a majority of participants were prescribed antiplatelet or anticoagulant therapy.

Table 4 shows the same measures divided by trial arm and category of intervention uptake. During the 12-month intervention period, use of the intervention materials was low to moderate. There were 14 family practices that did not access the intervention. In the remaining practices, the number of accesses was between 19 and 91 for practices in the highest quartile of utilization. There was no evidence for a trend in outcomes according to level of intervention utilization. There were no adverse events. The study was 1 of 2 cluster randomized trials that were completed through a grant of £338,335 from the Wellcome Trust and Research Councils’ joint initiative on electronic patient records. The cost of this trial to the
fundiers amounted to £169/168 or $15 (US $22) per eligible participant or £1600 (US $2400) per family practice allocated.

Discussion

Main Findings

An important purpose of the research was to advance methods to implement intervention studies in stroke using EHRs, aiming to provide proof of concept for this methodological approach. We provide evidence that many of the processes of trial implementation can be implemented successfully using EHRs. We were able to recruit family practices from the network of practices contributing EHRs data to the CPRD. Practices participated in the trial on the basis of informed consent, but we showed that participating practices and patients were similar to those of practices that did not agree to take part in the study, suggesting limited scope for volunteer bias.

We analyzed outcomes for a large sample of >10,000 patients with previous acute stroke. Outcomes were evaluated from EHRs with key measures being recorded and analyzed for a high proportion of participants. Interventions were installed remotely at intervention trial arm practices, and use of the intervention was monitored electronically. However, the low utilization and lack of effectiveness of the trial intervention indicate that more research must be done to develop effective intervention strategies before this approach to delivering cluster trials can be considered entirely successful.

The substantive topic addressed in the trial was stroke secondary prevention with the primary outcome of systolic BP. The trial intervention itself was not associated with improvement in clinical outcome measures assessed to follow-up. About a quarter of intervention practices seem not to have accessed the intervention information. Evidence from a qualitative process evaluation suggested this resulted from physicians’ lack of awareness of the intervention. This was a pragmatic trial at the point of care in routine clinical practice, with the effectiveness of the intervention being evaluated in the same conditions in which it might be applied in routine clinical practice. The delivery of the trial intervention closely resembled the circumstances in which a similar intervention might be rolled out into usual healthcare settings. A more intensive strategy to promote utilization of the intervention might have resulted in improved intervention fidelity and effectiveness. It may be preferable to identify nonresponsive practices early, so that these could then be actively targeted to enhance their adherence to the intervention. However, such strategies would tend to vitiate the naturalistic approach to intervention implementation and reduce the external validity of the trial results.

Table 4. Risk Factor Control Measures by Category of Intervention Utilization

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<tr>
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<tbody>
<tr>
<td>No. of intervention accesses</td>
<td>...</td>
<td>0</td>
<td>2 to 7</td>
<td>8 to 18</td>
<td>19 to 91</td>
<td></td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>131.7</td>
<td>131.7</td>
<td>131.6</td>
<td>130.2</td>
<td>132.0</td>
<td>0.146</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg</td>
<td>74.5</td>
<td>74.6</td>
<td>74.9</td>
<td>74.1</td>
<td>75.2</td>
<td>0.881</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.4</td>
<td>4.3</td>
<td>4.4</td>
<td>4.3</td>
<td>4.4</td>
<td>0.189</td>
</tr>
</tbody>
</table>

Figures are frequencies (column percent) except where indicated. BP indicates blood pressure.

Strengths and Limitations

This study had the strengths of a large sample drawn from a large nationally representative data source. The trial drew on clinical data for analysis. Practices participating in the CPRD are required to confirm to specified standards of data quality. Awareness of the trial might have itself promoted better data recording. Nevertheless, we observed several limitations of the data including, for example, a high proportion of patients with unspecified subtype of stroke and a smaller number with BP values not recorded during the intervention period. From an explanatory perspective, these limitations of the data reduce the capacity of the study to provide an accurate assessment of intervention efficacy. However, from a more pragmatic perspective, the data closely resemble those available to clinicians in routine clinical practice, strengthening the external validity of our trial results. The evaluation was naturalistic in the sense that the intervention was delivered in a manner that closely resembled the way in which an intervention might be rolled out into routine clinical practice. This has the merits that, had the intervention been effective or of benefit to physicians, it could readily be scaled up to provide sustainable population coverage. However, the low-cost intervention was also lacking in the intensity required to achieve changes in clinical practice in a condition that some practitioners may regard as routine.

Comparison With Other Studies

In a previous study, our group used stroke register data to provide individualized information on patient’s risk factor status, combined with evidence-based recommendations to reduce risk, to family physicians responsible for delivery of ongoing care after stroke. However, this approach to intervention was not found to be effective. Another study used discharge orders at the end of the patient’s stay in hospital to improve preventive care with modest evidence of effect. A recent review, including 162 randomized trials, found that computer-delivered reminders generally had limited impact on practitioners’ behavior, consistent with our findings. Roshanov et al. found that interventions that required physicians to actively negate advice offered, before this could be disregarded, were more effective than other types of computer-delivered interventions.

Conclusions

This study has contributed to developing efficient methods to deliver a point-of-care cluster randomized trials in stroke secondary prevention. The research showed that practice recruitment and allocation can be completed, with the inclusion of a large sample of individual stroke participants. Interventions
may be delivered remotely and used by physicians. Relevant outcomes may be evaluated from EHRs. The substantive results of the trial showed that the intervention was not associated with changes in BP, total cholesterol, and drug use; this emphasizes the importance of developing more effective behavior change interventions that can be delivered remotely to health professionals. However, despite the lack of intervention effect in this trial, we think that the trial has a positive outcome in offering a methodological approach to evaluation that may provide a powerful tool for future intervention trials in stroke and other long-term conditions.

Appendix

Data Monitoring Committee: Sarah Meredith (Chair), Sally Kerry, Elizabeth Murray.

Trial Steering Committee: Jonathan Mant (Chair), John Robson, Andrew Haywood, Nanik Pursani.

Acknowledgments

We thank Tim Foster and colleagues at DXS (United Kingdom) Ltd for facilitating the implementation of the intervention through DXS Point-of-Care.

Sources of Funding

The study was supported by the Joint Initiative in Electronic Patient Records and Databases in Research, a partnership between the Wellcome Trust, Medical Research Council, Economics and Social Research Council, and Engineering and Physical Sciences Research Council. M.C. Gulliford and Drs Dregan, Rudd, and Wolfe were supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy’s and St Thomas’ National Health Service (NHS) Foundation Trust and King’s College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. CPRD has received funding from government departments, research councils, charities, universities, contract research organizations, and pharmaceutical companies. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Medicines and Healthcare products Regulatory Agency (MHRA).

Disclosures

None.

References

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Stroke. 2014;45:2066-2071; originally published online June 5, 2014; doi: 10.1161/STROKEAHA.114.005713
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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**Supplementary Table I: Sensitivity analysis of eligibility criteria showing numbers of eligible participants and systolic blood pressure after intervention.**

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Control trial arm (Freq.)</th>
<th>Intervention trial arm (Freq.)</th>
<th>Adjusted(^a) mean difference in systolic blood pressure (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants with acute stroke ever diagnosed</td>
<td>5,516</td>
<td>5,875</td>
<td>-0.56 (-1.38 to 0.26)</td>
<td>0.183</td>
</tr>
<tr>
<td>Participants with incident acute stroke diagnosed more than one year after start of current CPRD record</td>
<td>3,219</td>
<td>3,076</td>
<td>-1.01 (-1.99 to -0.12)</td>
<td>0.025</td>
</tr>
<tr>
<td>Participants with incident acute stroke diagnosed within two years of intervention start date</td>
<td>835</td>
<td>870</td>
<td>-0.07 (-1.70 to 1.56)</td>
<td>0.935</td>
</tr>
</tbody>
</table>

\(^a\) adjusted for age, gender and comorbid diabetes or coronary heart disease and clustering by family practice
Supplementary Figure I.

Flow diagram charting participants’ progress through the trial.