Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care

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STUDY QUESTION

Can one tablet containing aspirin, statin, and blood pressure lowering agents improve adherence and risk factor control compared with usual care of patients at high risk of cardiovascular disease in primary care?

SUMMARY ANSWER

Fixed dose combination treatment improved adherence to all the recommended drugs, but improvements in clinical risk factors were small and did not reach statistical significance.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Two recent long term trials indicate large improvements in self reported adherence to the recommended drugs and modest improvements in risk factor control in high risk patients receiving fixed dose combination treatment. The main findings of this trial were consistent with those of the earlier trials, and acceptability for this treatment was high among general practitioners and patients.

Design

Open label randomised controlled trial. A central randomisation service randomly assigned (1:1) participants to fixed dose combination treatment or usual care.

Participants and setting

513 adults (257 indigenous Māori) at high risk of cardiovascular disease (established disease or estimated five year risk ≥15%) from 54 general practices in New Zealand.

Primary outcomes

Self reported adherence to recommended drugs (antiplatelet, statin, and ≥2 blood pressure lowering drugs) and mean change in blood pressure and low density lipoprotein cholesterol (LDL-C) at 12 months.

Main results and the role of chance

Adherence to all four recommended drugs was greater among participants in fixed dose combination group than usual care group at 12 months (81% *v* 46%; relative risk 1.75, 95% confidence interval 1.52 to 2.03, P<0.001; number needed to treat 2.9, 95% confidence interval 2.3 to 3.7). Self reported adherence was highly concordant with dispensing data (dispensing of all four recommended drugs 79% (196/249) for fixed dose combination *v* 47% (117/248) for usual care, relative risk 1.67, 1.44 to 1.93, P<0.001). Risk factor control showed no significant improvement between the fixed dose combination and usual care groups: difference in systolic blood pressure −2.2 mm Hg (−4.5 *v* −2.3, 95% confidence interval −5.6 to 1.2, P=0.21), diastolic blood pressure −1.2 mm Hg (−2.1 *v* −0.9, −3.2 to 0.8, P=0.22), and LDL-C −0.05 mmol/L (−0.20 *v* −0.15, −0.17 to 0.08, P=0.46). At 12 months most participants found taking their prescribed medicines "very easy" or "easy" (91% fixed dose combination *v* 86% usual care, P=0.09). 90% (203/225) of participants' general practitioners stated that if they had another patient like their patient on the trial they would start them on fixed dose combination treatment if it were available.

Self reported adherence to recommended combination treatment and individual components of combination at 12 months. Values are numbers (percentages) unless stated otherwise

Drugs	Fixed dose combination (n=256)	Usual care (n=257)	Relative risk (95% CI)	P value
Antiplatelet, statin, and ≥2 blood pressure (BP) lowering drugs	208 (81)	119 (46)	1.75 (1.52 to 2.03)	<0.001
No of blood pressure lowering drugs:	n=249	n=248		
≥1	240 (96)	226 (91)	1.06 (1.01 to 1.11)	0.02
≥2	222 (89)	147 (59)	1.50 (1.34 to 1.68)	<0.001
Statin	233 (94)	220 (89)	1.05 (1.00 to 1.11)	0.06
Antiplatelet	231 (93)	205 (83)	1.12 (1.05 to 1.20)	0.0006

Harms

The number of participants with serious adverse events did not differ noticeably, overall (99 fixed dose combination *v* 93 usual care, P=0.56) or for specific organ systems. There was an excess of reported serious adverse events in some categories: hypotension (fixed dose combination 6 *v* usual care 0, P=0.01), bleeding (4 *v* 0, P=0.06), and macroalbuminuria (12 *v* 4, P=0.04). Fixed dose combination treatment was discontinued by 94 (37%) patients randomised to this group. The most commonly reported reason for discontinuation was a side effect (72%).

Bias, confounding, and other reasons for caution

The open label trial design was unavoidable, but raises the possibility of differential intensity of treatment, diagnosis, or adverse event reporting between the groups. With usual care treatment rates for antiplatelet, statin, and blood pressure lowering drugs each over 80%, the trial only had moderate statistical power and hence could not rule out either small increases or moderate decreases in risk factor levels.

Generalisability to other populations

A major strength of this trial is that it tested the strategy of fixed dose combination treatment in a pragmatic primary care setting.

Study funding/potential competing interests

The trial was funded by project grants from several organizations (see full paper on bmj.com for details).

Trial registration number Australian New Zealand Clinical Trial Registry ACTRN12606000067572.

Time to treatment with recombinant tissue plasminogen activator and outcome of stroke in clinical practice: retrospective analysis of hospital quality assurance data with comparison with results from randomised clinical trials

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- Editorial: Hyperacute stroke care and NHS England's business plan (*BMJ* 2014;348:g3049)
- Views & reviews: Thrombolysis in acute ischaemic stroke: example of a health divide? (*BMJ* 2010;340:c45)
- Practice: Should more patients with acute ischaemic stroke receive thrombolytic treatment? (*BMJ* 2009;339:b4584)

STUDY QUESTION

Does thrombolytic therapy for acute ischaemic stroke have a similar time dependent benefit/risk ratio in clinical practice to that seen in pooled analyses of randomised clinical trials?

SUMMARY ANSWER

In patients with acute ischaemic stroke treated with thrombolytic therapy in routine clinical practice, the time dependent odds ratios for mortality and favourable early outcome are close to the values found in a pooled analysis of randomised clinical trials.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Pooled analysis of randomised clinical trials of recombinant tissue plasminogen activator in patients with stroke has shown a time related decreasing benefit/risk ratio with increasing time between onset of stroke and treatment up to 4.5 hours. In an unselected cohort of patients with acute ischaemic stroke in clinical practice, there was also a clear association between shorter onset to treatment with thrombolytic therapy and better functional outcome, suggesting a similar magnitude to that observed in clinical trials.

Participants and setting

All 148 hospitals involved in acute stroke care in a large federal state in southwest Germany with 10.4 million inhabitants. Data from 84 439 (of 109 284) patients with acute ischaemic stroke were analysed: 10 263 (12%) were treated with thrombolytic therapy and 74 176 (88%) were not treated.

Design

A retrospective cohort study using data from a large scale comprehensive population based state-wide stroke registry in Germany.

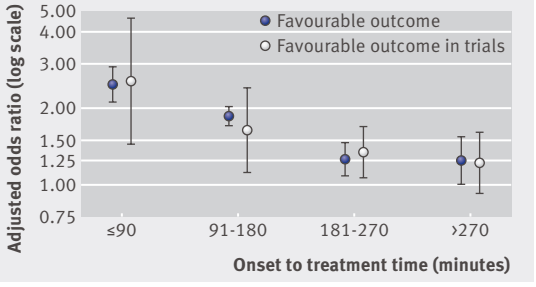
Primary outcome

The primary endpoint was the dichotomised score on a modified Rankin scale at discharge ("favourable outcome" score 0 or 1 or "unfavourable outcome" score 2-6) analysed by binary logistic regression. As a co-primary endpoint an ordinal logistic regression analysis (shift analysis) was used. Patients receiving thrombolytic therapy were categorised according to time from onset of stroke to treatment.

Main results and the role of chance

After adjustment for characteristics of patients, hospitals, and treatment, recombinant tissue plasminogen activator was associated with better outcome in a time dependent pattern. The number needed to treat ranged from 4.5 (within the first 1.5 hours after onset) to 18.0 (up to 4.5 hours),

Odds ratio for favourable outcome (logistic regression analysis) and comparisons with trials



while mortality did not vary up to 4.5 hours. Patients treated with thrombolytic therapy beyond 4.5 hours showed a significantly better outcome in a dichotomised analysis (odds ratio 1.25, 95% confidence interval 1.01 to 1.55), but the mortality risk was higher (1.45, 1.08 to 1.92). The odds ratios for good outcome in clinical practice were comparable with those observed in a pooled analysis of randomised clinical trials of alteplase for acute stroke.

Bias, confounding, and other reasons for caution

Data were collected as routine data for quality assurance. We adjusted for known confounders between groups of patients treated and not treated with thrombolytic therapy, but we cannot completely exclude other residual confounding.

Generalisability to other populations

The federal state where this analysis was performed has implemented a three level system for the treatment of acute stroke with local or regional stroke units and comprehensive stroke centres.

Study funding/potential competing interests

Internal research funds from the departments of neurology, University of Heidelberg, Heidelberg and Mannheim Campus. CG holds a scholarship of the young scientists programme of the German network Health Services Research Baden-Wuerttemberg. The sources of funding had no role in study design, data collection, analyses, interpretation, and decision to submit the article for publication. RK, PR, MGH, and WH have received fees for presenting at meetings and/or travel compensation from pharmaceutical companies and are/were chairs of or involved with trials of thrombolytic therapy and are involved in national or international quality assurance programmes. IB is the project leader at the quality assurance institution.

Evaluation of safety of A/H1N1 pandemic vaccination during pregnancy: cohort study

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- Research: Influenza A/H1N1 MF59 adjuvanted vaccine in pregnant women and adverse perinatal outcomes: multicentre study (*BMJ* 2013;346:f393)
- Research: Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark (*BMJ* 2012;344:e2794)
- Research: Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study (*BMJ* 2010;340:c1279)

STUDY QUESTION

What is the risk of adverse maternal, fetal, and neonatal outcomes associated with administration of an MF59 adjuvanted A/H1N1 vaccine during pregnancy?

SUMMARY ANSWER

No increased risk of either fetal or birth outcomes was seen following vaccination, whereas a limited increase in the prevalence of gestational diabetes and eclampsia was observed.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The effect of MF59 adjuvanted A/H1N1 vaccine on "hard" pregnancy outcomes, such as gestational diabetes, eclampsia, and congenital malformations, has rarely been explored. The findings of this study add to the available body of evidence on the safety of the MF59 adjuvanted pandemic vaccine in pregnancy.

Participants and setting

All singleton deliveries occurring in the resident population of the Lombardy region of Italy were eligible for the study. We retrieved data on exposure to A/H1N1 pandemic vaccine, potential confounders, and pregnancy and birth outcomes from regional electronic health archives. We used the following databases: birth registry, pandemic vaccination, hospital discharges, drug prescriptions, and clinical investigations. All databases were linkable through a unique, anonymised, personal identifier. Main maternal outcomes included type of delivery, admission to intensive care unit, eclampsia, and gestational diabetes. Fetal and neonatal outcomes included perinatal deaths, small for gestational age births, and congenital malformations.

Design, size, and duration

In this historical cohort study, we retrieved 86 171 eligible pregnancies between 1 October 2009 and 30 September 2010, in women aged at least 12 and up to 55 years. We used a propensity score matched analysis to compare the risk of adverse outcomes between vaccinated (n=6131) and non-vaccinated (n=23 987) women. We did a sensitivity analysis on the matched cohort to investigate the potential protective role of the "healthy vaccinee effect," excluding all outcomes occurring in the two weeks after the vaccination date (and the index date in the non-vaccinated women).

Main results and the role of chance

We found no difference in terms of spontaneous deliveries (adjusted odds ratio 1.02, 95% confidence interval 0.96 to 1.08) and admissions to intensive care units (0.95, 0.47 to 1.88), whereas a limited increase in the prevalence of gestational diabetes (1.26, 1.04 to 1.53) and pre-eclampsia/eclampsia (1.19, 1.02 to1.39) was seen in vaccinated women. Rates of fetal and neonatal outcomes were similar in vaccinated and non-vaccinated women. A slight increase in congenital malformations, although not statistically significant, was present in the exposed cohort (adjusted odds ratio 1.14, 0.99 to 1.31). The sensitivity analysis did not alter the risk estimates.

Bias, confounding, and other reasons for caution

We took five main categories of potential confounders into account: demographic characteristics of the mothers, socioeconomic status, history of previous pregnancy(ies), history of selected comorbidities and drugs at pregnancy onset, and healthcare use. No data were available on alcohol use, smoking status, body mass index, over the counter drugs, and multivitamin supplementation.

Generalisability to other populations

Although not previously recommended on a large scale, vaccination against pandemic influenza was deemed an appropriate intervention to prevent adverse outcomes during pregnancy. In comparison with the past, future vaccination campaigns targeted at pregnant women will rely on more sound evidence on the safety of vaccine.

Study funding/potential competing interests

Only public employees of the national or regional health authorities were involved in conceiving, planning, and conducting the study; no additional funding was received.

Pregnancy, fetal, and neonatal outcomes: propensity score matched analysis

Outcomes	No (%) of cases		Adjusted odds ratio (95% CI)
	Unvaccinated (n=23 987)	Vaccinated (n=6131)	
Pre-eclampsia/eclampsia	715 (3.0)	219 (3.6)	1.19 (1.02 to 1.39)
Gestational diabetes	444 (1.9)	144 (2.3)	1.26 (1.04 to 1.53)
Perinatal death	77 (0.3)	21 (0.3)	1.06 (0.65 to 1.71)
Small for gestational age	2307 (9.6)	562 (9.2)	0.95 (0.86 to 1.04)
Congenital malformations	945 (3.9)	276 (4.5)	1.14 (0.99 to 1.31)

Relation between surgeon volume and risk of complications after total hip arthroplasty: propensity score matched cohort study

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STUDY QUESTION

Is there a cut point in annual surgeon volume associated with increased risk for complications after primary elective total hip arthroplasty, and, if so, can we quantify this risk?

SUMMARY ANSWER

In a cohort of first time recipients of total hip arthroplasty, we found that patients operated on by surgeons who had performed 35 or fewer procedures in the year before the index arthroplasty were at increased risk for dislocation and early revision.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Though there is a general consensus that increased surgeon volume is associated with a reduced risk of complications, there is a lack of consensus around what constitutes a "low" annual volume. This study showed that in patients undergoing total hip arthroplasty, the risks for dislocation and early revision increased by about 48% and 44%, respectively, when they were operated on by surgeons with annual volumes ≤35 procedures.

Participants and setting

Patients in Ontario, Canada, who underwent a first primary elective total hip arthroplasty during 2002-09.

Design, size, and duration

This was a propensity score matched cohort study. We included 6716 patients who were operated on by a surgeon who had carried out ≤35 such procedures in the 365 days before the index surgery. We successfully matched each (1:1) to a patient who received arthroplasty from a surgeon who had carried out more than 35 procedures in the 365 days before the surgery using a propensity score that included several variables, including age, sex, comorbidity, various socioeconomic indicators, and hospital volume (standardized difference <10% for all variables).

Main results and the role of chance

Patients with hip replacement carried out by a surgeon with an annual volume of ≤35 procedures had a higher rate of dislocation (1.9% *v* 1.3%; P=0.006) and revision (1.5% *v* 1.0%; P=0.03) within two years of their surgery. The numbers needed to harm for dislocation and revision were 172 (95% confidence interval 164 to 182) and 204 (193 to 217), respectively. These recipients were at higher risk of both dislocation (hazard ratio 1.48, 95% confidence interval 1.21 to 1.80; P<0.001) and revision (1.44, 1.15 to 1.80; P=0.001) compared with those whose surgeons had an annual volume of more than 35 procedures.

Bias, confounding, and other reasons for caution

We could not control for smoking or body mass index (BMI). Both these factors, however, are strongly associated with other factors that were measured and balanced between matched groups, including diabetes, hypertension, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, frailty, and various socioeconomic indices.

Generalisability to other populations

The technique used here can be applied to various populations for any surgical procedure. Its use, however, requires the availability of population based data, the ability to accurately determine the volume for each operating surgeon in the year before the surgery, and specific patient level data including comorbidity and sociodemographic variables.

Study funding/potential competing interests

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Probability of specific complications *v* surgeon volume