RESEARCH PAPER

Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death

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Objective: To determine whether nicotine replacement therapy (NRT) is associated with an increased risk of acute myocardial infarction, acute stroke, or death.
Design: Self control case series analysis of data from The Health Improvement Network (THIN) to estimate the relative incidence of myocardial infarction and stroke in four 14 day periods before and after the first prescription for NRT.
Setting: THIN is a computerised general practice database.
Subjects: Patients contributing data to THIN.
Interventions: Observational study of NRT.
Main outcomes: Acute myocardial infarction, acute stroke, and death.
Results: 33 247 individuals had been prescribed NRT, of whom 861 had had a myocardial infarction and 506 a stroke. There was a progressive increase in the incidence of first myocardial infarction in the 56 days leading up to the first NRT prescription (overall incidence ratio 5.55, 95% confidence interval (CI) 4.42 to 6.98), but the incidence fell after this time and was not increased in the 56 days after starting NRT (incidence ratio 1.27, 95% CI 0.82 to 1.97). The results were similar for second myocardial infarction and stroke, and for subgroups of people with pre-existing angina and hypertension. There were 960 deaths in our cohort during a mean follow up period of 2.6 years after starting NRT, with no evidence of an increased mortality in the 56 days after the NRT prescription (incidence ratio 0.86, 95% CI 0.60 to 1.23).
Conclusions: The use of NRT is not associated with any increase in the risk of myocardial infarction, stroke, or death.

Smoking is the most common preventable cause of morbidity and premature mortality in the developed world.[1] Smoking cessation interventions, including nicotine replacement therapy (NRT), are among the most cost effective interventions available in medicine,[2–6] and guidelines from the USA, UK, and mainland Europe recommend that these interventions are made available to all smokers.[7–11] There are, however, safety concerns relating to the use of NRT in people with pre-existing cardiovascular disease arising from the pharmacological vasoconstrictor actions of nicotine,[12] and from anecdotal reports that NRT may precipitate myocardial infarction.[13] Most NRT manufacturers therefore caution against the use of NRT in patients with cardiovascular disease. Clinical trials have not reported any adverse effects in such patients,[14 15] but lack the statistical power to exclude a small, but important, increase in risk. To resolve this question it is necessary to study much larger populations.

We have used data from The Health Improvement Network (THIN), a computerised longitudinal UK general practice database to estimate the risk of myocardial infarction, stroke, and sudden death associated with the use of NRT, and have excluded the effects of the major likely confounders by using the self controlled case series method.[16 17]

METHODS

THIN contains computerised longitudinal primary care data collected in the process of routine clinical care. The dataset includes information on all prescriptions supplied by the general practitioner and all diagnoses made by or reported to the general practitioner. The data for the present study include data up to November 2003. To avoid the problems of bias and confounding associated with cohort and case–control studies we used the self controlled case series method. With this approach the incidence of an outcome during exposed and unexposed time periods is compared within-person, and thus estimates of relative incidence are derived only from subjects who are both exposed to the treatment under review and have the outcome of interest.[16 17]

Initially we extracted data for all patients with at least one prescription for NRT, and identified the start and stop dates of their THIN record and the date of their first NRT prescription. We then identified all recorded diagnoses of acute myocardial infarction and stroke and all deaths. To minimise duplicate recording of myocardial infarction and stroke diagnoses we included data from only the first diagnosis when two similar diagnoses were recorded within 28 days. We then divided the person-time as follows. To establish whether the incidence of myocardial infarction was increased after the first NRT prescription we defined four consecutive periods of 14 days starting the day after the first NRT prescription. We excluded the actual day of prescription since our previous studies have shown that repeat recording of relevant previous diagnoses may occur on the day of a prescription for a new drug.[18] To establish whether the incidence of myocardial infarctions was increased immediately before the prescription we also defined four consecutive 14 day periods running up to the first prescription. All remaining time periods were defined as the baseline time period (fig 1). We estimated the relative incidence for all eight high risk periods compared to baseline using conditional Poisson regression (GLIM version 4), adjusting for age at myocardial infarction in two year age bands. We looked for effect modification by age (coded as a binary variable above and below the age of 55 years, approximately the median), sex, formulation of NRT, date of NRT prescription (since NRT become widely available only after April 2001) and a history of angina or hypertension by stratifying our analyses by these

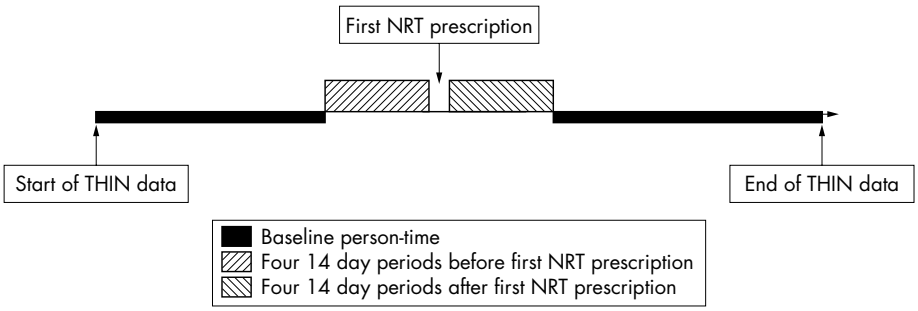

Figure 1 Pictorial representation of case series analysis. NRT, nicotine replacement therapy; THIN, The Health Improvement Network.

variables. We used the same methods for our acute stroke analysis.

For our mortality analyses we initially calculated the crude death rate after the first prescription for NRT. We then repeated our case series analyses, but restricted the person time in these analyses to the time after the first prescription.

The power for case series analyses comes from the number of events and relative proportion of exposed time.[17] We estimated that with 350 cases of myocardial infarction exposed to NRT, we would have more than 90% power to detect a rate ratio of 1.5 or greater, and with 200 cases of stroke, we would have more than 90% power to detect a rate ratio of 1.75 or greater.

RESULTS

We identified 33 247 patients with at least one prescription for NRT between June 1985 and November 2003. The mean age of these people was 44.5 years and 14 516 (44%) were male. The most common NRT formulation for the first prescription was a patch (n = 25 596, 77%), followed by gum, lozenges, and microtablets (n = 5421, 16%), inhalers (n = 1614, 5%), and nasal spray (n = 616, 2%). For the patch users 18 065 (71%) were prescribed a high dose patch (≥ 15 mg), 6025 (24%) a medium strength patch (10–14 mg), and 1506 (6%) a low dose patch (< 10 mg). For the gum users 995 (27%) were given 4 mg gum and 2648 (73%) 2 mg gum.

Among the 33 247 NRT users 861 had at least one recorded diagnosis of myocardial infarction, and among these people 146 had a second recorded diagnosis and 27 a third. In addition 506 people had at least one recorded diagnosis of stroke, and among these people 103 had a second diagnosis and 30 a third. Among these two subsets of patients the median years of follow up data was 12 years (interquartile range 7–14 years) and the distributions of NRT formulations and doses were similar to that seen in the total population. The mean age at first NRT prescription for patients with myocardial infarction was 58.0 years and 560 (65%) were male. The mean age at first NRT prescription for patients with a stroke was 60.4 years and 227 (55%) were male.

The incidence ratios for the first myocardial infarction increased progressively in the period leading up to the first NRT prescription (fig 2), such that in the 14 days immediately before the prescription, patients were 8.51 times (95% confidence interval (CI) 5.96 to 12.14) more likely to have a myocardial infarction (table 1). Overall in the 56 days before first prescription the incidence ratio for myocardial infarction was 5.55 (95% CI 4.42 to 6.98). After the first NRT prescription the incidence ratios fell progressively and, although there was an increased risk of myocardial infarction during the first 14 days, overall the risk of myocardial infarction during the 56 days after starting treatment was not increased (incidence ratio 1.27, 95% CI 0.82 to 1.97). The incidence of acute stroke was also increased in the period leading up to the first NRT prescription (fig 3), and overall during the 56 days before first prescription by an incidence ratio of 3.59 (95% CI 2.56 to 5.03). In the 56 days after starting treatment there was no significant increase in risk (incidence ratio 1.30, 95% CI 0.77 to 2.19), although there was an isolated increase in the risk during the final quarter of this period. There was no evidence of effect modification by age or sex on either outcome (table 2), but stratification of the data by history of angina suggests that the risk of having either a myocardial infarction or a stroke in the period preceding the first NRT prescription was higher in people with no previous history of angina (table 3). There was no evidence that an increase in the incidence of either myocardial infarction or stroke occurred after the prescription of any particular formulation of NRT, or that the results differed for people prescribed NRT before or after April 2001

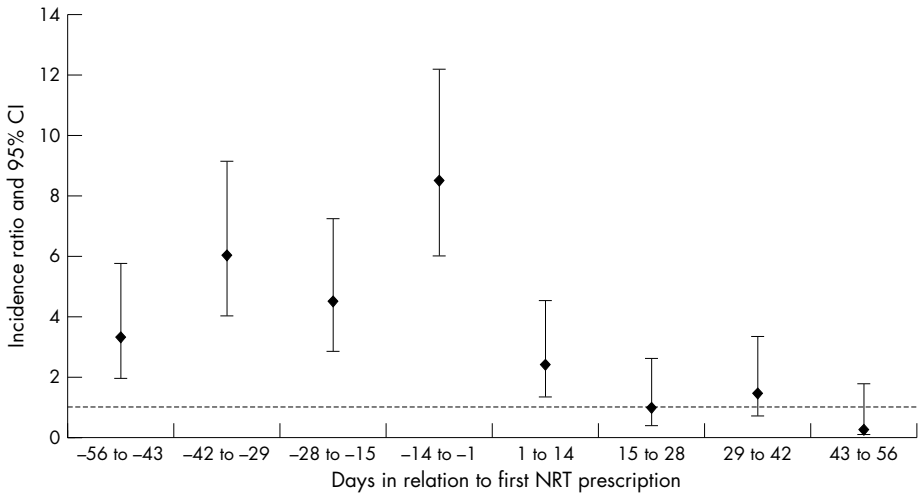

Figure 2 Temporal relationship between the relative incidence of acute myocardial infarction and first prescription for NRT.

Table 1 Case series analysis for relative incidence of myocardial infarction immediately before and after first prescription for nicotine replacement therapy

	Myocardial infarction analysis			Stroke analysis		
Time period	Number of MIs	Relative incidence	95% CI	Number of strokes	Relative incidence	95% CI
Days before NRT						
43–56	13	3.29	1.89 to 5.71	4	1.49	0.55 to 3.99
29–42	24	6.02	3.99 to 9.09	8	2.93	1.45 to 5.93
15–28	18	4.48	2.80 to 7.18	17	6.17	3.78 to 10.09
1–14	33	8.51	5.96 to 12.14	10	3.72	1.97 to 7.02
Total	88	5.55	4.42 to 6.98	39	3.59	2.56 to 5.03
Days after NRT						
1–14	10	2.39	1.28 to 4.48	2	0.69	0.17 to 2.75
15–28	4	0.97	0.36 to 2.59	3	1.03	0.33 to 3.21
29–42	6	1.47	0.66 to 3.29	3	1.03	0.33 to 3.21
43–56	1	0.24	0.03 to 1.74	7	2.47	1.16 to 5.24
Total	21	1.27	0.82 to 1.97	15	1.30	0.77 to 2.19
All other time	752*			452†		

*431 events precede 56 days before NRT, 11 events of day of NRT prescription, and 310 events more than 56 days after prescription.
†243 events precede 56 days before NRT, 8 events of day of NRT prescription, and 201 events more than 56 days after prescription.
CI, confidence interval; MIs, myocardial infarctions; NRT, nicotine replacement therapy.

(table 4). Although the numbers were smaller the results were similar when we repeated the analyses using second myocardial infarction and stroke as the outcomes.

Overall in our cohort there were 960 deaths after the first prescription for NRT during a mean follow up period of 2.62 years, and this is equivalent to approximately seven deaths per week. During the 56 days after starting treatment there were 33 deaths, marginally below the expected level, and our case series analysis gave a relative incidence of death during this period compared to later periods of 0.86 (95% CI 0.60 to 1.23).

DISCUSSION

This is the largest study of the safety of NRT reported to date and includes data from more than 30 000 NRT users. Our findings demonstrate that overall there is no increased risk of myocardial infarction, stroke, or death in the 56 days after the first prescription for NRT. We did find evidence of an increased incidence of myocardial infarction and stroke in the 56 days before the first NRT prescription, however, suggesting that NRT is currently being prescribed shortly after myocardial infarctions and strokes.

The main strengths of our study are its large size, the long duration of patient follow up, and the detailed information available on prescriptions. The potential weaknesses of the study are the validity of the outcome data, the extent to which people prescribed NRT actually used the treatment, and the use of NRT purchased without a prescription over the counter. The validity of myocardial infarction diagnoses in the UK General Practice Research Database, a general practice dataset which is similar to THIN and which has considerable overlap of information with THIN, has been validated previously and, as for many other diagnoses, been found to be high.[19 20] We do not know what proportion of patients prescribed NRT actually used the treatment, and this is a problem common to most pharmacoepidemiological studies, but a previous study of antibiotic prescriptions, another short term treatment, has shown that most people prescribed these drugs use them and we have no reason to believe that the situation will be different with NRT.[21] We did not know the overall duration of NRT use for individual patients, but since the majority of patients do not carry on using NRT for the recommended period of 12 weeks we chose to study the eight week period after prescription. Since some patients may be prescribed NRT for longer periods of time we checked the robustness of this decision by repeating our analyses including periods of 12 weeks and one year after the prescription and the results were the same.

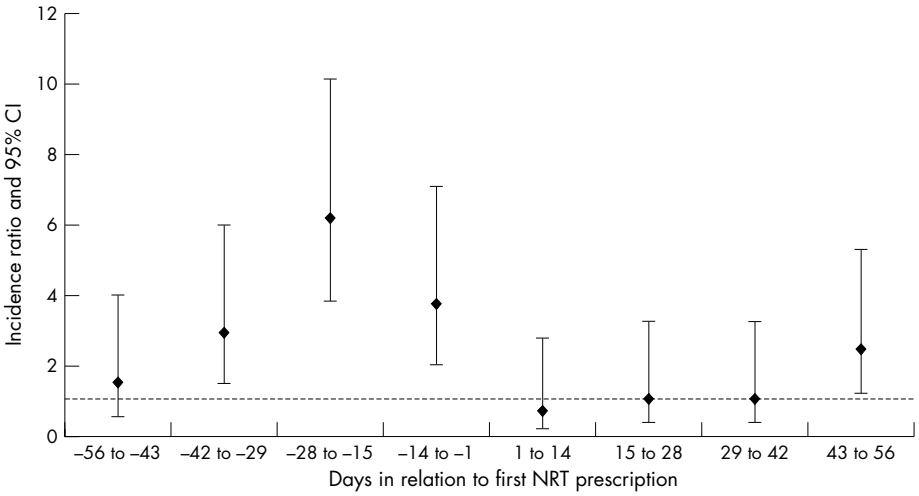

Figure 3 Temporal relationship between the relative incidence of acute stroke and first prescription for NRT.

Table 2 Case series analysis stratified by sex and age

	Myocardial infarction analysis			Stroke analysis		
	Events	Relative incidence	95% CI	Events	Relative incidence	95% CI
Males						
1–56 days before NRT	59	5.74	4.33 to 7.60	19	3.06	1.89 to 4.95
1–56 days after NRT	13	1.21	0.69 to 2.12	9	1.42	0.72 to 2.79
Females						
1–56 days before NRT	29	5.33	3.58 to 7.94	20	4.29	2.66 to 6.90
1–56 days after NRT	8	1.40	0.68 to 2.86	6	1.13	0.49 to 2.60
Younger than 55 years of age						
1–56 days before NRT	45	6.84	4.94 to 9.49	14	4.09	2.29 to 7.29
1–56 days after NRT	9	1.28	0.65 to 2.52	4	1.08	0.40 to 2.98
55 years or older						
1–56 days before NRT	43	4.45	3.21 to 6.16	25	3.27	2.15 to 4.97
1–56 days after NRT	12	1.21	0.67 to 2.16	11	1.36	0.73 to 2.51

It is likely that some smokers in our study obtained NRT ''over the counter''. If this is the case then some of the time currently included in our analyses as unexposed baseline time is incorrectly classified and should in fact be exposed time. Most patients who use NRT bought over the counter do so for only short periods of time and sustained long term use of NRT is rare.[22] This means that if any misclassification of myocardial infarctions is present then the number of events involved will be small relative to the total number of events in the baseline period and so this will have only a negligible impact on the baseline incidence of myocardial infarction. It is therefore very unlikely that the presence of over the counter prescribing had any appreciable effect on our findings.[23] People who only access NRT over the counter tend to be younger and to have smoked less than those who obtain a prescription for NRT,[24] and they may differ in other ways as well. This means that our findings should not be directly extrapolated to people solely using NRT purchased over the counter. The available evidence suggests that most people who purchase NRT over the counter receive advice on indications and contraindications from their pharmacist and read the product information leaflet.[25] It therefore seems unlikely to us that patients using NRT bought over the counter will represent a subset of people at high risk of cardiovascular disease or that the use of NRT will be less safe in this setting.

We used the case series method to overcome many of the confounding problems arising from inter-person comparisons in case–control studies of adverse drug effects.[16 17] In addition we specifically looked for evidence of confounding by indication by investigating the relative incidence of each outcome before and after prescriptions for NRT. Our results demonstrate that quit attempts involving NRT do tend to occur shortly after acute vascular events. This may be because the acute event increases the determination of patients to stop smoking and/or the event provokes a review of the cardiovascular risk profile by health professionals and a more active management of modifiable factors. After the first prescription for NRT, however, we found no evidence of an overall increase in the incidence of myocardial infarction or stroke, with the exception of isolated increases in the risk of myocardial infarction during the first and second week and the risk of stroke in the seventh and eight week. In absolute terms for myocardial infarction this amounted to an additional six cases among 33 247 exposed people during the first two weeks after the NRT prescription. Since this was offset by a decreased risk of myocardial infarction during weeks 7 and 8, overall there was no significant increase in the risk of myocardial infarction after the NRT prescription. The increased risk of stroke during weeks 7 and 8 is inconsistent with the general pattern of data and is most likely to be a chance finding.

We found no evidence that the safety profile of NRT differed according to sex, formulation of NRT, and previous medical history of angina or hypertension. In general the mean age at myocardial infarction and stroke in this study is lower than the national rate for the UK, and this probably reflects the prescribing practice for NRT, but we found no evidence that age modified our results. In April 2001 NRT became available in the UK through standard National

Table 3 Case series analysis stratified by previous history of angina and hypertension

	Myocardial infarction analysis			Stroke analysis		
	Events	Relative incidence	95% CI	Events	Relative incidence	95% CI
Previous history of angina						
1–56 days before NRT	12	2.61	1.44 to 4.75	1	0.56	0.08 to 4.14
1–56 days after NRT	4	0.88	0.32 to 2.39	1	0.52	0.07 to 3.80
No history of angina						
1–56 days before NRT	76	7.19	5.58 to 9.26	38	4.13	2.92 to 5.83
1–56 days after NRT	17	1.51	0.92 to 2.47	14	1.43	0.83 to 2.47
History of hypertension						
1–56 days before NRT	16	3.61	2.14 to 6.09	12	2.69	1.47 to 4.93
1–56 days after NRT	11	2.48	1.33 to 4.60	3	0.66	0.21 to 2.09
No history of hypertension						
1–56 days before NRT	72	6.34	4.91 to 8.20	27	4.23	2.81 to 6.37
1–56 days after NRT	10	0.84	0.44 to 1.57	12	1.72	0.95 to 3.11

Table 4 Case series analysis stratified by NRT formulation and date of prescription

	Myocardial infarction analysis			Stroke analysis		
	Events	Relative incidence	95% CI	Events	Relative incidence	95% CI
Patch users						
1–56 days before NRT	53	4.10	3.05 to 5.50	23	2.67	1.73 to 4.12
1–56 days after NRT	17	1.30	0.80 to 2.12	13	1.41	0.80 to 2.48
Gum, lozenge, microtablet users						
1–56 days before NRT	19	8.09	4.86 to 13.47	11	6.28	4.07 to 216.6
1–56 days after NRT	2	0.79	0.19 to 3.24	1	0.54	0.07 to 3.94
Inhaler and nasal spray users						
1–56 days before NRT	16	16.64	8.93 to 31.01	5	8.35	2.95 to 23.62
1–56 days after NRT	2	2.01	0.48 to 8.48	1	1.74	0.22 to 13.39
Prescription before April 2001						
1–56 days before NRT	19	4.27	2.64 to 6.90	12	4.51	2.53 to 8.36
1–56 days after NRT	5	1.04	0.42 to 2.55	0		
Prescription after April 2001						
1–56 days before NRT	69	6.07	4.62 to 7.97	27	3.07	2.04 to 4.62
1–56 days after NRT	16	1.38	0.83 to 2.30	15	1.62	0.51 to 2.77

Health Service prescriptions, but before this time it was not routinely available. In our dataset the majority of prescriptions (75%) were after 1 April 2001. It is possible that the 8336 smokers who were prescribed NRT before 2001 were either highly motivated to stop smoking or deemed by their primary care doctor to be at high risk, but our analyses have demonstrated that this does not appear to impact on the safety profile of NRT.

Our results therefore provide good evidence against an increase in risk of myocardial infarction or stroke in patients using NRT in the first 56 days after the treatment is started, and this is consistent with the limited data available from clinical trials.[14 15] Our analyses also demonstrate clearly that there is no increased risk of death associated with the use of NRT, providing further important reassurance about the safety of NRT.

In summary, our results suggest that the use of nicotine replacement as a routine therapy for the management of smoking cessation is safe and is not associated with an increased risk of myocardial infarction, stroke, or sudden death. Theoretical concerns over the safety of NRT in relation to these adverse outcomes can therefore probably be discounted, particularly when the alternative for most smokers is to continue to smoke. Patients with pre-existing cardiovascular disease represent one of the groups most likely to benefit from smoking cessation and our results should encourage the use of NRT in these individuals.

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What this paper adds

Nicotine replacement therapy (NRT) is an effective treatment for smoking cessation. Concerns exist, arising from case reports and pharmacological data, that NRT may precipitate acute cardiovascular events. The results of this observational study of 33 247 first time users of NRT suggests that this treatment does not increase the risk of acute myocardial infarction or acute stroke, even in people with pre-existing cardiovascular disease.

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Competing interest statement: The division of Statistics at the Open University is in receipt of a CASE PhD studentship partly funded by GlaxoSmithKline. In the past John Britton has received sponsorship from GlaxoSmithKline and Richard Hubbard has received sponsorship from Bayer to attend international respiratory medicine conferences, but both have declined all such sponsorship for the last five years. John Britton has received an honorarium from a third party organisation but originating from GlaxoSmithKline for speaking at an invited conference on smoking cessation management guidelines in 2002 and has acted as a consultant to several companies involved in smoking cessation therapies. There are no other competing interests for any of the other authors.

Ethics approval: The study protocol for this paper was reviewed and approved by the GPRD Scientific and Ethical advisory Group.
Work attributed to: Division of Epidemiology and Public Health, Nottingham University.

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The Lighter Side