RESEARCH

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Sports medicine in the spotlight—the BMJ Olympics portal

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Second generation endometrial ablation techniques are preferable to first generation techniques in the treatment of heavy menstrual bleeding. Of the second generation techniques, bipolar radio frequency and microwave ablative devices are more effective than thermal balloon and free fluid ablation. The authors of this retrospective network meta-analysis [http://www.bmj.com/content/344/bmj.e2564] on the primary outcome measures of amenorrhoea, heavy bleeding, and patients' dissatisfaction with treatment conclude that further large scale rigorous randomised trials to compare existing and emerging ablative techniques should use meaningful and standardised measures of satisfaction and menstrual bleeding and be run independently from the manufacturers of the devices.

Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial

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bmj.com

Clinical review: Telehealthcare for long term conditions (*BMJ* 2011;342:d120)

doc2doc

Would you prescribe a smartphone app for your patient? http://bit.ly/At71OG

STUDY QUESTION

In adolescents and adults with poorly controlled asthma, is mobile phone based monitoring of lung function and symptoms with feedback to patients more effective in improving asthma control and self efficacy than paper based monitoring of asthma over six months?

SUMMARY ANSWER

Improvements were seen in both arms, but there was no significant difference in the change in asthma control or self efficacy between the two groups.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Some interventions that have used mobile phone technology in asthma care have shown benefit compared with "usual care," but it is often impossible to determine whether observed benefits were because of the mobile phone intervention or the associated enhanced clinical care.
Our trial showed that mobile phone monitoring offered no clinical advantages over and above paper based monitoring when high quality clinical support services were provided to both groups.

Design

We undertook a pragmatic parallel group randomised controlled trial with analysis of costs. Central randomisation (stratified by practice, 1:1 allocation, random block sizes of two or four) ensured allocation was concealed. Researchers were blinded to allocation. Our main analysis was on an intention to treat basis.

Participants and setting

We recruited patients from primary care aged ≥12 with poorly controlled asthma (asthma control questionnaire (ACQ) score ≥1.5) and with mobile phones that supported use of the software system. All participants received clinical care and education on self management in line with national guidelines.

Primary outcomes

Our primary outcomes were changes in asthma control (ACQ) and self efficacy (knowledge, attitude, and self efficacy asthma questionnaire (KASE-AQ)) scores at six months after randomisation.

Main results and the role of chance

There was no significant difference in the improvement in asthma control between the two groups (ACQ: mean change 0.75 in mobile group *v* 0.73 in paper group, mean difference in change −0.02, 95% confidence interval −0.23 to 0.19) or self efficacy (KASE-AQ score: mean change −4.4 *v* −2.4, mean difference 2.0, −0.3 to 4.2). Treatment was stepped up in most patients in both groups, and in over half the patients in both groups asthma scores improved by more than the minimum important difference. The cost of providing the telemonitoring service meant that the mobile phone based model of asthma care was more expensive than the paper based model.

Harms

There was no significant difference between the groups in the number of acute attacks or episodes of unscheduled care.

Bias, confounding, and other reasons for caution

Although participants were obviously aware of the method of monitoring, we ensured that data collection and analysis were blinded to allocation. We handled missing data by carrying the previous result forward, which assumes that non-responders did not improve and possibly underestimates change in both groups.

Generalisability to other populations

Our multicentre trial was conducted in primary care, the setting for most asthma care in the UK. The low recruitment rate (2.4% of those invited) reflects a combination of the low response rate and our eligibility requirement that participants should have poorly controlled asthma and a compatible mobile phone system.

Study funding/potential competing interests

This study was funded by Asthma UK (project ID 07/047). Piko peak flow meters were donated by nSpire Health. HP is supported by a fellowship from the chief scientist's office of the Scottish Government.

Trial registration number

Clinical Trials NCT00512837.

Intention to treat analysis of asthma control and quality of life in people randomised to mobile phone or paper based monitoring

	No in group	Mean (SD) score		Mean change in score (95% CI)	Mean difference of mean change (95% CI)
		Baseline	6 months		
Asthma control questionnaire					
Mobile	139	2.32 (0.73)	1.57 (0.99)	0.75 (0.61 to 0.89)	−0.02 (−0.23 to 0.19)
Paper	139	2.29 (0.77)	1.56 (1.09)	0.73 (0.57 to 0.89)	
Mini-asthma quality of life questionnaire					
Mobile	97	4.25 (0.91)	5.0 (1.32)	−0.75 (−0.94 to −0.57)	0.10 (−0.16 to 0.34)
Paper	104	4.34 (1.08)	4.99 (1.34)	−0.65 (−0.84 to −0.46)	

Effect of offering different levels of support and free nicotine replacement therapy via an English national telephone quitline: randomised controlled trial

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EDITORIAL by Chapman and Wakefield

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Response on bmj.com

"Oncologists face a real challenge when trying to develop personalized medicine through tumor sequencing.For smoking cessation, treatment must be personalized, either for NRT or for psychological support. This can be easily done"
Alain Braillon and Gérard Dubois, Public Health, 27 rue Voiture, 80000 Amiens, France.

STUDY QUESTION

Does offering either free nicotine replacement therapy (NRT) or higher intensity proactive telephone support in addition to standard quitline care increase smoking cessation rates at six months after starting quitline supported cessation attempts?

SUMMARY ANSWER

Cessation rates at six months were not improved by offering either NRT or higher intensity proactive telephone support in addition to standard quitline support.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Quitlines reach many smokers but optimum methods for providing quitline cessation support need defining. In England, where cessation support is readily available through established health services, offering free NRT or proactive counselling in addition to reactive cessation support provided by the national quitline was ineffective.

Design

A pragmatic, parallel group, 2×2 factorial, randomised controlled trial.

Participants and setting

Participants were 2591 non-pregnant smokers aged 16 or more residing in England who called the English national quitline between February 2009 and February 2010 and agreed to set a quit date. 648 were each randomised to standard support, proactive support, or proactive support with NRT, and 647 were randomised to standard support with NRT. There was no interaction between the two trialled interventions so, as intended a priori, these four treatment conditions were analysed as two intervention groups: participants offered free NRT or more intensive proactive support.

Primary outcome

Self reported smoking cessation for six or more months after starting a quit attempt.

Smoking cessation outcomes by intervention group (n=2591 for each) at six months. Values are numbers (percentages) unless stated otherwise

Outcomes	Proactive support (n=1296)	Standard support (n=1295)	Unadjusted odds ratio (95% CI)	NRT offered (n=1295)	NRT not offered (n=1296)	Unadjusted odds ratio (95% CI)
Self reported*	236 (18.2)	254 (19.6)	0.91 (0.75 to 1.11)	229 (17.7)	261 (20.1)	0.85 (0.70 to 1.04)
Carbon monoxide validated cessation†	100 (7.7)	107 (8.3)	0.93 (0.70 to 1.23)	85 (6.6)	122 (9.4)	0.67 (0.50 to 0.90)

NRT=nicotine replacement therapy.
*Primary outcome.
†Secondary outcome.

Main results and the role of chance

71.9% (798/1295) of participants offered NRT requested a supply and 70% (555/798) recalled receiving this. The median number of successfully completed telephone support phone calls to participants offered proactive support was three (two in standard support group). At six months, 17.7% (n=229) of those offered NRT reported smoking cessation compared with 20.1% (n=261) not offered this (odds ratio 0.85, 95% confidence interval 0.70 to 1.04), and 18.2% (n=236) offered proactive counselling reported smoking cessation compared with 19.6% (n=254) offered standard support (0.91, 0.75 to 1.11). Using validated outcome data changed the findings for NRT only with validated smoking cessation in 6.6% (85/1295) of those offered NRT compared with 9.4% (122/1296) not offered NRT (0.67, 0.50 to 0.90).

Bias, confounding, and other reasons for caution

Primary outcome ascertainment rates at six months were relatively low in intervention groups (54.9% to 56.7%), although ascertainment rates were higher at one month (62.4% to 68.3%) and interventions showed no positive impact on cessation at either point. It was assumed that participants who could not be contacted at six months were still smoking, a potentially conservative assumption that could mask variation in actual smoking rates. However, testing alternative assumptions for the relation between "missingness" of outcome data and actual smoking status gave similar findings. Although primary cessation outcomes were self reported, validated ones also provided no evidence of intervention effectiveness. Considering these facts together, it is apparent that biases in outcome ascertainment are possible, but there is no evidence that these were substantial.

Generalisability to other populations

Findings are most generalisable to quitlines which serve populations that have ready access to pharmaceutical and behavioural cessation support at low or no cost.

Study funding/potential competing interests

The English Department of Health funded most aspects of the study (and paid for NRT); views are those of the authors. The UK Centre for Tobacco Control Studies (UKCTCS) provided additional funding to complete follow-up and analysis. We thank the British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, and the National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, for funding.

Trial registration number

ClinicalTrials.gov NCT00775944.

Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study

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EDITORIAL by Camporota and Hart

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STUDY QUESTION

Is volume limited and pressure limited (lung protective) mechanical ventilation associated with survival in patients during two year follow-up after acute lung injury?

SUMMARY ANSWER

Lung protective mechanical ventilation is associated with a substantial long term survival benefit for patients with acute lung injury. The absolute risk reduction in two year mortality ranged from 4.0% to 7.8%.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Survivors of critical illness, such as acute lung injury, are at increased risk of mortality for years after hospital discharge. Use of lung protective mechanical ventilation during critical illness was associated with a substantial two year survival benefit for patients with acute lung injury.

Participants and setting

Participants were 485 consecutive mechanically ventilated patients with acute lung injury receiving routine medical care in 13 intensive care units at four hospitals in Baltimore, United States.

Design, size, and duration

This research was designed as a prospective cohort study, analysed using time varying Cox regression analysis, to evaluate the association of lung protective ventilation and survival over two year follow-up.

Main results and the role of chance

The 485 participants contributed data for 6240 eligible ventilator settings, as measured twice daily, of which 41% were adherent to lung protective mechanical ventilation. Of these 485 patients, 311 (64%) died within two years, with substantially increasing mortality over the first year after the onset of acute lung injury (44% mortality at 30 days, 52% at 90 days, and 62% at one year). After adjusting for the total duration of mechanical ventilation and other relevant covariates, for each additional adherent ventilator setting the hazard of mortality decreased by 3% over two years (0.97, 95% confidence interval 0.95 to 0.99, P=0.002). The estimated absolute risk reduction in two year mortality for a prototypical patient with 50% adherence to lung protective ventilation was 4.0% (0.8% to 7.2%, P=0.012) and with 100% adherence was 7.8% (1.6% to 14.0%, P=0.011) compared with a 49.7% baseline mortality under the assumption of no adherence to lung protective ventilation. Mean tidal volume showed a linear relation with two year survival, with an 18% relative increase in mortality for each 1 mL/kg of predicted body weight increase in average tidal volume (adjusted hazard ratio 1.18, 95% confidence interval 1.07 to 1.31, P=0.001).

Bias, confounding, and other reasons for caution

Cause-effect inferences and generalisability of these results are potentially limited because this was an observational study carried out in four teaching hospitals in one city.

Generalisability to other populations

Given the relatively limited number of exclusion criteria and the routine clinical practice setting of this study, the results may be generalisable to patients with acute lung injury in other clinical settings but not to other types of mechanically ventilated patients without acute lung injury.

Study funding/potential competing interests

This study was funded by the National Institutes of Health (grant No P050HL73994; K23GMO71399) and the Canadian Institutes of Health Research. We have no competing interests.

Selected predictors from multivariable Cox regression analysis of two year survival for patients with acute lung injury

Predictor	Adjusted hazard ratio (95% CI)	P value
No of ventilator settings adherent to lung protective ventilation	0.97 (0.95 to 0.99)	0.002
Duration of mechanical ventilation	1.01 (1.00 to 1.02)	0.182
Age	1.03 (1.02 to 1.04)	<0.001
Charlson comorbidity index	1.07 (1.02 to 1.12)	0.006
Daily sequential organ failure assessment score	1.20 (1.16 to 1.25)	<0.001
Cumulative fluid balance in intensive care unit, per litre	1.02 (1.01 to 1.03)	<0.001

Response on bmj.com "Needham and colleagues present much needed data regarding long term hard outcomes in this day and age of acute lung injury management, which reflects 'effectiveness' rather than 'efficacy' of lung protective mechanical ventilation. Kudos to them on a well-designed observational prospective multi-centre cohort study" Wassim H Fares, assistant professor of medicine, Yale University, Department of Medicine, Pulmonary and Critical Care, 15 York Street, LCI-105, New Haven, CT, USA 06510

doc2doc Discuss in our respiratory medicine forum http://bit.ly/J4BzVT

Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study

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STUDY QUESTION

What are the risk factors for dying from imported malaria in the United Kingdom once acquired?

SUMMARY ANSWER

Elderly people, tourists, and those not born in countries with endemic malaria are at greatest risk of dying from imported malaria in the UK, with additional risk if presenting in UK regions where malaria is rarely seen, or in the month of December.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In the UK falciparum malaria is a common cause of fever in the returning traveller, mainly affecting individuals of African heritage visiting friends and relatives.
This study shows that, once malaria is acquired, individuals born in non-endemic areas bear the brunt of mortality, particularly the elderly, and those presenting in December or in regions where malaria is seldom treated.

Participants and setting

We analysed all cases of, and deaths from, *Plasmodium falciparum* malaria reported to the UK Malaria Reference Laboratory between 1987 and 2006.

Design

This observational study used national data. Malaria is a notifiable infectious disease in the UK, so clinicians have to report cases by law to the national reference laboratory.

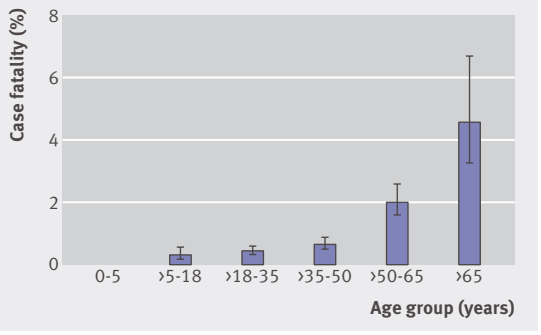
Primary outcome

We aimed to identify risk factors associated with death from imported falciparum malaria. Potential factors analysed were age (divided into groups), sex, tourist versus traveller visiting friends and relatives in a country with endemic malaria, presentation by calendar month, reported use of effective malaria chemoprophylaxis versus reported use of no prophylaxis, birth in an African country with endemic malaria versus birth elsewhere, and country and region visited, and presenting UK region.

Main results and the role of chance

Of the 25 054 patients notified with *P falciparum* infection, 184 died, giving a case fatality of 0.73%. Mortality increased steadily with increasing age, rising to 4.6% (25 deaths/548 cases) in those over 65 years old, and the adjusted odds ratio of dying of malaria for >65 year olds was 10.68 (95% CI 6.4 to 17.8, P<0.001) compared with 18–35 year olds (see figure). Mortality among infants and children was low, with no deaths in those <5 years old and a case fatality of 0.33% in those aged 5–18 years.

Mortality from imported falciparum malaria in UK by age



Tourists had a greater case fatality (3.0% (81/2740)) than those visiting friends and relatives in their country of origin (0.32% (26/8077)). Case fatality was particularly high in individuals visiting the Gambia (3.9% (28/726)) compared with any other west African country (0.4% (58/13 448) (χ^2 test, P<0.001; adjusted odds ratio of death 4.7 (2.7 to 8.1), P<0.001).

There was a striking seasonal peak in deaths, with 2.6% mortality among cases notified in December (49/1922) compared with 0.6% (135/23 132) across all other months (χ^2, P<0.001). There was a clear trend in mortality based on the UK region where the patient presented, which was inversely correlated with number of cases seen (linear regression R^2=0.72, P<0.001). The highest case fatality of 8.4% (10 deaths) was in a region where only 119 cases were seen, whereas the lowest (0.3%) was in the region with the most cases (15 993) (adjusted odds ratio of death 18.2 (8.6 to 38.3), P<0.001).

Bias, confounding, and other reasons for caution

Although we controlled for likely confounding factors, residual confounding cannot be excluded. Capture-recapture data suggest that 66% of cases of falciparum malaria in the UK are reported. The reporting of deaths known to be due to malaria is likely to be more complete than that of non-fatal cases. Certain data are likely to be associated with recall bias in fatal cases.

Generalisability to other populations

The characteristics of the patients in our study were similar to those of travellers from other European and North American studies, and our results can probably be generalised to other developed countries where malaria is not endemic.

Study funding/potential competing interests

The Malaria Reference Laboratory is funded by the UK Health Protection Agency.

Cost effectiveness of alternative planned places of birth in woman at low risk of complications: evidence from the Birthplace in England national prospective cohort study

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STUDY QUESTION For women at "low risk" of complications, what is the most cost effective planned place of birth?

SUMMARY ANSWER For both nulliparous and multiparous low risk women, planned birth at home was the most cost effective option, but for nulliparous women planned home birth was also associated with an increase in adverse perinatal outcome.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Robust evidence on the cost effectiveness of planned birth in alternative settings is needed. For nulliparous low risk women, planned home birth generates incremental cost savings but with increased adverse perinatal outcomes; for multiparous low risk women, it generates incremental cost savings with no significant effect on perinatal outcomes. For maternal outcomes, planned birth at home was always most cost effective.

Main results
Total mean costs per low risk woman before the onset of labour were £1631 in obstetric units, £1461 in alongside midwifery units, £1435 in free standing midwifery units, and £1067 at home (equivalent to about €1950, $2603; €1747, $2332; €1715, $2290; and €1274, $1701). After adjustment for confounding, planned birth in non-obstetric units was cost saving. Adjusted savings averaged £134, £130, and £310 for planned births in alongside midwifery units, free standing midwifery units, and home, respectively. Being multiparous or married was associated with reduced costs, while birth after 40 weeks' gestation, being overweight or obese, and maternal age of 30 or more were each associated with increased costs.

In multiparous low risk women, planned home birth had a 100% probability of being the most cost effective option across all cost effectiveness thresholds between £0 and £100 000. For low risk nulliparous women the probability of planned home birth being the most cost effective option reduced to 0.63 at a cost effectiveness threshold of £20 000 and 0.35 for births in a free standing midwifery unit. The incremental cost effectiveness ratios and net benefit statistics for adverse perinatal outcome avoided in low risk women according to planned place of birth are shown in the table. Planned birth at home was always the most cost effective option when maternal outcomes were considered.

Design
This economic evaluation was conducted alongside a national prospective cohort study that included 64 538 low risk women who gave birth from April 2008 to April 2010. Data on use of resources were captured from the start of care in labour and included immediate after birth care or higher level postnatal or neonatal care when this was received.

Source of effectiveness
The main exposure was planned place of birth at the start of care in labour and the primary measure of effectiveness was a composite measure of perinatal mortality and specified intrapartum related morbidity.

Data sources
Clinical outcomes were estimated from the cohort study. Primary data were collected for key resource profiles. Unit costs were estimated with a combination of primary and secondary research methods.

Results of sensitivity analysis
Sensitivity analyses showed that the mean incremental cost effectiveness ratios were relatively robust to variations in overheads and staffing costs attributed to labour care but were sensitive to unit occupancy rates

Limitations
Some components of the unit cost data collection had to be modelled with data from secondary sources. The time horizon did not include lifetime costs associated with adverse perinatal outcome. The study did not assess cost effectiveness for the mother and baby combined. Broader aspects of antenatal and community based postnatal care were not included.

Study funding/potential competing interests
The study was jointly funded by the Department of Health's Policy Research Programme and the National Institute of Health Research Service Delivery and Organisation.

Incremental cost effectiveness ratios and net benefit statistics for primary outcome (adverse perinatal outcome avoided*) for all women at low risk of complications according to planned place of birth: home, freestanding midwifery unit (FMU), or alongside midwifery unit (AMU) with obstetric unit as reference

	Home	FMU	AMU
Cost difference (95% CI)	−565 (−591 to −538)	−196 (−229 to −163)	−170 (−199 to −141)
Difference in adverse perinatal outcome avoided (95% CI)	−0.00007 (−0.0014 to 0.0013)	0.0004 (−0.0010 to 0.0019)	0.0005 (−0.0007 to 0.0019)
Mean ICER†	7 950 356	−431 873	−296 400
Quadrant on cost effectiveness plane	South west	South east	South east
Mean net benefit (95% CI) by cost effectiveness threshold:			
£20 000	592 (547 to 639)	263 (211 to 315)	167 (111 to 224)
£30 000	593 (535 to 654)	270 (205 to 334)	174 (99 to 244)

*Composite of perinatal mortality and specified neonatal morbidities: stillbirth after start of care in labour, early neonatal death, neonatal encephalopathy, meconium aspiration syndrome, brachial plexus injury, fractured humerus, or fractured clavicle.
†95% CI not provided because bootstrapped replicates of incremental cost effectiveness ratios fell across more than one quadrant of cost effectiveness plane.

Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database

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STUDY QUESTION Is the risk of cancer higher among patients who have ever used angiotensin receptor blockers compared with those who used only angiotensin converting enzyme (ACE) inhibitors?

SUMMARY ANSWER There was no evidence that angiotensin receptor blocker exposure was associated with an increased risk of cancer overall and we were able to rule out a large effect. Observed increased risks for breast and prostate cancer were small in absolute terms, and the lack of association with duration of treatment meant that non-causal explanations could not be excluded.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Data from randomised clinical trials have suggested an increased risk of cancer with angiotensin receptor blockers, but the most recent and comprehensive meta-analysis found no association; however trial data can lack power, follow-up, and generalisability. In a large population based study of angiotensin receptor blockers in routine use in which 45% of patients had at least five years of follow-up, we found no overall association with cancer; we detected small absolute risk increases for breast and prostate cancer, but the results did not support a causal effect.

Participants and setting

We included new users of angiotensin receptor blockers or ACE inhibitors with at least one year of initial treatment from UK primary care practices contributing to the General Practice Research Database.

Rate of any and specific cancers by treatment and adjusted hazard ratios in people with hypertension taking angiotensin receptor blocker (ARB) or angiotensin converting enzyme (ACE) inhibitor

	Total cancers	Total person time	Rate per 1000 person years (95% CI)	Adjusted HR (95% CI)*
Any cancer				
Ever used ARB	5077	385 101	13.2 (12.8 to 13.6)	1.03 (0.99 to 1.06)
ACE inhibitor use only	15126	1 157 222	13.1 (12.9 to 13.3)	1.00
Lung cancer				
Ever used ARB	422	385 101	1.1 (1.0 to 1.2)	0.84 (0.75 to 0.94)
ACE inhibitor use only	1722	1 157 222	1.5 (1.4 to 1.6)	1.00
Breast cancer				
Ever used ARB	780	221 072	3.5 (3.3 to 3.8)	1.11 (1.01 to 1.21)
ACE inhibitor use only	1631	523 186	3.1 (3.0 to 3.3)	1.00
Prostate cancer				
Ever used ARB	700	164 029	4.3 (4.0 to 4.6)	1.10 (1.00 to 1.20)
ACE inhibitor use only	2325	634 035	3.7 (3.5 to 3.8)	1.00
Colon cancer				
Ever used ARB	384	3 85 101	1.0 (0.9 to 1.1)	1.02 (0.91 to 1.16)
ACE inhibitor use only	1132	1 157 222	1.0 (0.9 to 1.0)	1.00

*Adjusted for age, sex, BMI, smoking, alcohol, diabetes (with or without metformin/insulin use), hypertension, heart failure, statin use, index of multiple deprivation score, calendar year.

Design, size, and duration

377 649 individuals were included in a cohort study, covering the period 1995-2010 We explored the effects of ever exposure to angiotensin receptor blockers (compared with ACE inhibitor use only) and cumulative duration of use with time updated covariates in Cox models, adjusted for potential confounders. Absolute changes in risk were predicted from a Poisson model incorporating the strongest determinants of cancer risk from the main analysis.

Main results and the role of chance

Follow-up ended a median of 4.6 years after the start of treatment; 20 203 cancers were observed. There was no evidence of any increase in overall cancer risk among those ever exposed to angiotensin receptor blockers (adjusted hazard ratio 1.03, 95% confidence interval 0.99 to 1.06; P=0.10). Among specific cancers, there was some evidence of an increased risk of breast and prostate cancer (1.11, 1.01 to 1.21, P=0.02; and 1.10, 1.00 to 1.20, P=0.04; respectively), which in absolute terms corresponded to an estimated 0.5 and 1.1 extra cases, respectively, per 1000 person years of follow-up among those with the highest baseline risk. Longer duration of treatment did not seem to be associated with higher risk (P>0.15 in each case). We observed a decreased risk of lung cancer (0.84, 0.75 to 0.94), but no effect on colon cancer (1.02, 0.91 to 1.16, P=0.70).

Bias, confounding, and other reasons for caution

Patients were not randomised, but comparison against a drug class with similar indications (ACE inhibitors) should have reduced confounding by indication. We adjusted for a wide range of potential confounders: age, sex, body mass index (BMI), diabetes and metformin/insulin use, hypertension, heart failure, statin use, socioeconomic status, alcohol, smoking, and calendar year. Despite long follow-up relative to many other studies, we cannot rule out that an important effect might operate at still longer timescales.

Generalisability to other populations

Our clinical data were not restricted to any particular subgroup so results should be generalisable within the UK and to similar populations elsewhere.

Study funding/potential competing interests

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