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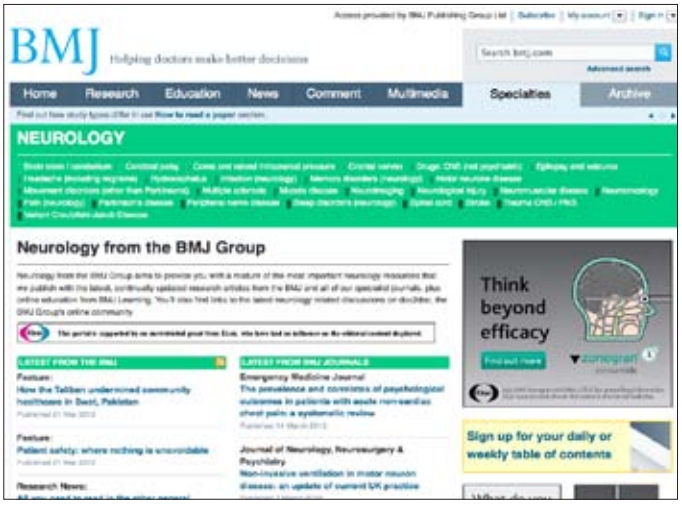
LEA PATERSON/SPL



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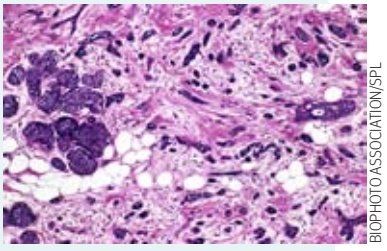

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Spironolactone and risk of incident breast cancer in women older than 55 years

In this cohort study based on data from the General Practice Database—of 290 625 female patients, older than 55 years and with no history of breast cancer—long term treatment with spironolactone for cardiovascular conditions did not increase the risk of breast cancer.

(*BMJ* 2012:345:e4505)

Reoperation rates after breast conserving surgery for breast cancer among women in England

In this retrospective study of hospital episode statistics, one in five women who had breast conserving surgery in England had a reoperation. Reoperation was nearly twice as likely when the tumour was coded with a carcinoma in situ component. Women should be informed of this reoperation risk when deciding on the type of surgical treatment of their breast cancer, say the authors.

(*BMJ* 2012:345:e4447)

Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria

In this randomised controlled trial of 170 adults admitted to hospital with stroke communication therapy had no added benefit beyond that from everyday communication in the first four months after the event. Future research should evaluate reorganised services that support functional communication practice early in the stroke pathway, say the authors.

(*BMJ* 2012:345:e4407)

Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis

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STUDY QUESTION What is the diagnostic accuracy of two "spot urine" tests for significant proteinuria or adverse pregnancy outcome in pregnant women with suspected pre-eclampsia?

SUMMARY ANSWER The maternal spot urine estimate of protein to creatinine ratio shows promising diagnostic value for significant proteinuria in suspected pre-eclampsia, but insufficient evidence exists on the use of albumin to creatinine ratio; insufficient evidence exists for either test to predict adverse pregnancy outcome.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Spot protein to creatinine ratio correlates well with 24 hour urinary protein estimation, and a cut-off value of 30 mg/mmol (0.27) has been suggested as a reasonable "rule-out test" for proteinuria above 0.3 g/day. The optimum threshold for the spot protein to creatinine ratio to detect proteinuria >0.3 g/day is between 0.30 and 0.35, giving summary sensitivity and specificity values above 0.75.

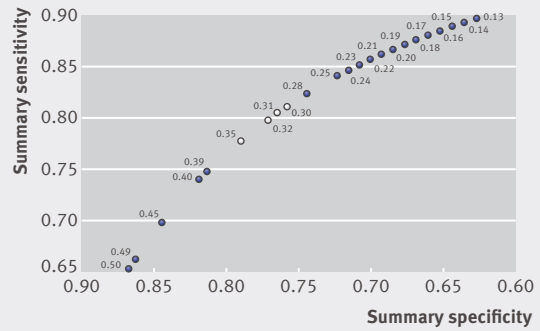
Selection criteria for studies

We searched electronic databases from 1980 to January 2011. Eligible studies were diagnostic studies, in pregnant women with hypertension, which compared the urinary spot protein or albumin to creatinine ratio with urinary protein excretion over 24 hours or adverse pregnancy outcome.

Primary outcome(s)

We extracted study results relating to diagnostic accuracy and synthesised them by using multivariate random effects meta-analysis methods. We used sensitivity and specificity as the primary outcome measures to determine the diagnostic value of the tests for significant proteinuria on 24 hour urine collection or adverse pregnancy outcome.

Summary receiver operating characteristics curve for constrained estimates of sensitivity and specificity for protein to creatinine ratio



Open circles indicate most promising thresholds for use, as they optimise both sensitivity and specificity (and thus give largest rectangular area below paired point to right)

Main results and role of chance

We included 20 studies, testing 2978 women. Thirteen studies examining protein to creatinine ratio for the detection of significant proteinuria were included in the multivariate analysis. Threshold values for protein to creatinine ratio ranged between 0.13 and 0.5, with estimates ranging from 0.65 to 0.89 for sensitivity and from 0.63 to 0.87 for specificity; the area under the summary receiver operating characteristics curve was 0.69. On average across all studies, the optimum threshold (optimising sensitivity and specificity combined) seems to be between 0.30 and 0.35 inclusive. However, no threshold gave a summary estimate above 80% for both sensitivity and specificity, and considerable heterogeneity existed in diagnostic accuracy across studies at most thresholds. No studies looked at protein to creatinine ratio and adverse pregnancy outcome. For albumin to creatinine ratio, meta-analysis was not possible. Results from a single study suggested that the most predictive result, for significant proteinuria, was with the DCA 2000 quantitative analyser (>2 mg/mmol), with summary sensitivity of 0.94 (95% confidence interval 0.86 to 0.98) and specificity of 0.94 (0.87 to 0.98). In a single study of adverse pregnancy outcome, results for perinatal death were a sensitivity of 0.82 (0.48 to 0.98) and a specificity of 0.59 (0.51 to 0.67).

Bias, confounding, and other reasons for caution

As with any systematic review, the analyses that are possible and the inferences that can be made from the data are limited by the quality of the primary research. Although many of the papers included adhered to many of the guidelines for reporting and methodological quality of diagnostic accuracy studies, significant limitations existed in quality of the included studies. Although 24 hour urine collection for total protein is still used for comparison of tests for proteinuria, this test is time consuming, inconvenient, and subject to errors such as incomplete collection. This comparison of tests also has little bearing on actual outcome of pregnancy. This is a limitation of the studies in our review and thus a limitation of our meta-analyses.

Study funding/potential competing interests

RKM is funded by an NIHR clinical lectureship. RR and JD are supported by funding from the MRC Hub for Trials Methodology Research at the University of Birmingham.

Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: randomised controlled trial

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STUDY QUESTION Does adding the MoleMate system (SIAscopy and primary care scoring algorithm) to the systematic application of current best practice guidelines lead to more appropriate referrals of pigmented lesions from primary to secondary care?

SUMMARY ANSWER While the systematic application of best practice guidelines and MoleMate both performed much better than reports of current practice, adding MoleMate to best practice did not increase the proportion of appropriately referred lesions; instead, the lower specificity of MoleMate led to more referred lesions.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Most referred pigmented skin lesions are benign so interventions to improve primary care clinicians' diagnostic performance and referral efficiency are needed. We found no evidence that MoleMate improved the appropriateness of referral, but best practice and MoleMate both performed better than current practice.

Design

A randomised controlled trial with individual randomisation using a block design stratified by patient's age and practitioner, with single blinded outcome measurement.

Participants and setting

The trial was set in 15 general practices in eastern England. We recruited adults with pigmented skin lesions not immediately detectable as benign. Patients were assessed by primary care clinicians using best practice (clinical history, naked eye examination, seven point checklist) either alone (control) or with MoleMate (intervention).

Primary outcome

Appropriateness of referral, defined as the proportion of referred lesions that were biopsied or monitored. A reference standard diagnosis was recorded for all lesions in the trial, either by histology or expert opinion, and all patients with non-referred lesions were offered a follow-up consultation 3-6 months later to confirm a benign diagnosis. Secondary outcomes related to the clinicians (diagnostic performance, confidence, learning effects) and patients (satisfaction, anxiety).

Main results and the role of chance

1297 participants with 1580 lesions were randomised: 643 patients with 788 lesions to the intervention group and 654 with 792 lesions to the control group. We found no evidence that adding MoleMate to best practice improved appropriateness of referral: intervention 56.8% *v* control 64.5%; absolute difference −8.1% (95% confidence interval −18.0% to 1.8%, P=0.12). No difference was found in the proportion of benign lesions appropriately managed in primary care (intervention 99.6% *v* control 99.2%, P=0.46), or the percentage agreement with expert decision to biopsy or monitor (intervention 98.5% *v* control 95.7%, P=0.26). However, MoleMate showed a significantly lower percentage agreement with expert assessment that the lesion was benign (intervention 84.4% *v* control 90.6%, P<0.001), and a higher proportion of lesions were referred (intervention 29.8% *v* control 22.4%, P=0.001). No melanomas were missed in the intervention group (18/18) and only one was missed in the control group (17/18). Clinicians were confident in both groups, and there was no evidence of any learning effects between groups. Patients ranked satisfaction with consultations with MoleMate higher than with best practice alone, and were not made anxious by the addition of this new diagnostic aid to best practice.

Harms

None.

Bias, confounding, and other reasons for caution

Unusually for skin cancer studies done in primary care, expert clinical diagnoses on all lesions were obtained, including those that were managed in primary care: only 2.7% (42/1573) of lesions did not have a reference standard diagnosis. We compared MoleMate with standardised best practice to obtain data on all lesions for reference standard diagnostic purposes: this meant that we did not have directly comparable data for usual care. We did not detect any improvement in diagnostic performance during the trial and therefore do not believe that contamination between trial groups through learning effects is the explanation for the high performance in the best practice group.

Appropriateness of referrals and clinicians' diagnostic performance in control and intervention groups. Values are percentages (number/number in group)

Variables	Control group	Intervention group	% difference (95% CI)	P value
No of lesions assessed	785	788		
% appropriate referral rate*	64.5 (111/172)	56.8 (130/229)	−8.1 (−18.0 to 1.8)	0.11
% appropriately managed in primary care†	99.2 (588/593)	99.6 (535/537)	0.5 (−0·6 to 2·0)	0.46
% agreement with expert decision to take biopsy or monitor (sensitivity)†	95.7 (111/116)	98.5 (130/132)	2.8 (−1.8 to 7.4)	0.26
% agreement with expert assessment that lesion benign (specificity)†	90.6 (588/649)	84.4 (535/634)	−6.2 (−9·9 to −2·6)	<0.001
Volume referred†	22.4 (176/785)	29.8 (235/788)	7.4 (3·1 to 11·7)	0.001

*Difference adjusted for clustering of lesions within patients; difference unadjusted for clustering is −7.8% (95% confidence interval −17.4% to 1.8%, P=0.12).
†Unadjusted for clustering of lesions within patients.

Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study

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STUDY QUESTION What is the risk of systemic adverse events associated with intravitreal injections of vascular endothelial growth factor (VEGF) inhibiting drugs?

SUMMARY ANSWER Intravitreal injections of ranibizumab and bevacizumab were not associated with significant risks of ischaemic stroke, acute myocardial infarction, venous thromboembolism, or congestive heart failure.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Intravenous administration of VEGF inhibitors for cancer has been associated with several adverse vascular events, but clinical trials have been inconclusive regarding the risks associated with the smaller doses used to treat age related macular degeneration. This study using linked population based administrative healthcare data found no significant vascular risks associated with intravitreal VEGF inhibitors.

Participants and setting

Using population based healthcare databases from Ontario Canada, we identified 91 378 adults aged 66 years or older with a history of retinal disease diagnosed by a physician between 1 April 2006 and 31 March 2011.

Design, size, and duration

We used a nested case-control design to assess the relation between several adverse cardiovascular outcomes and exposure to intravitreal injections of either ranibizumab or bevacizumab.

Primary outcome(s), risks, exposures

Cases were patients admitted to hospital with a primary diagnosis of ischaemic stroke, acute myocardial infarction, venous thromboembolism, or congestive heart failure. For each outcome, we matched cases with up to five randomly selected controls and used conditional logistic regression to assess the relation with exposure to intravitreal injection of ranibizumab or bevacizumab in the previous 180 days. The primary analysis compared outcomes in patients who received either ranibizumab or bevacizumab with those who were not exposed to either drug. Secondary analyses directly compared the two agents against one another and assessed outcomes in subgroups with and without diabetes.

Main results and the role of chance

We identified 1477 cases of ischaemic stroke, 2229 of acute myocardial infarction, 1059 of venous thromboembolism, and 2623 of congestive heart failure. We were able to successfully match 95% of cases to five controls. In our primary analysis, we found no statistically significant association between the four outcomes and exposure to either bevacizumab or ranibizumab (see figure). Similarly, a secondary analysis comparing exclusive users of bevacizumab and of ranibizumab showed no differences in risk (adjusted odds ratios for bevacizumab versus ranibizumab as reference: 1.03 (95% confidence interval 0.67 to 1.60) for ischaemic stroke, 1.23 (0.85 to 1.77) for acute myocardial infarction, 0.92 (0.51 to 1.69) for venous thromboembolism, and 1.35 (0.93 to 1.95) for congestive heart failure). Findings were consistent for all but one outcome in subgroup analyses.

Bias, confounding, and other reasons for caution

Like all observational studies, our study was vulnerable to possible residual confounding or hidden bias. We used several approaches to limit the potential for these problems, but we cannot rule out residual confounding by unknown or unmeasured factors. Other reasons for caution include adverse events that did not lead to hospital admission or emergency department visit not being captured and the potential for misclassification of exposure to bevacizumab because of its off-label use for retinal disease. Finally, although our estimates generally showed no increased or decreased risk with the use of intravitreal VEGF inhibitors, the confidence intervals include some potentially clinically relevant differences in risk, especially in the subgroup analyses.

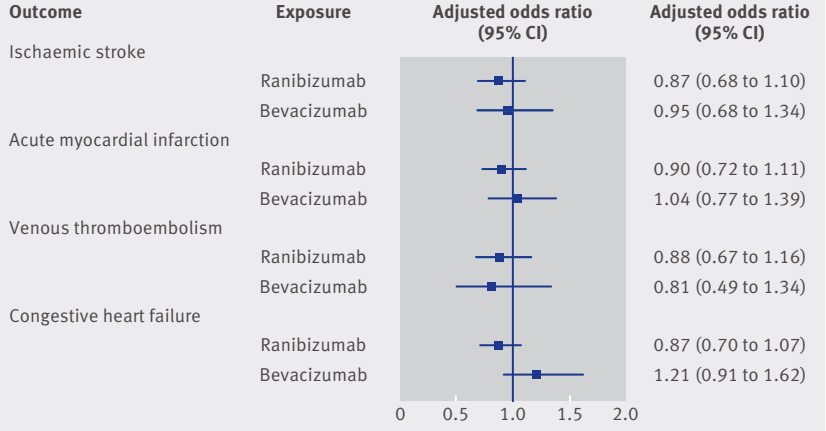
Generalisability to other populations

This analysis used administrative healthcare data for a large population in a setting with universal healthcare. Results are probably generalisable to similar groups of patients.

Study funding/potential competing interests

The study was funded by the Canadian Institutes of Health Research and the Ontario Ministry of Health and Long-Term Care's drug innovation fund.

Risk of adverse events after intravitreal injections of vascular endothelial growth factor inhibitors



Impact of age and sex on primary preventive treatment for cardiovascular disease in the West Midlands, UK: cross sectional study

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STUDY QUESTION What is the impact of age and sex on prescription of antihypertensive drugs and statins for primary prevention of cardiovascular disease in primary care?

SUMMARY ANSWER While prescription of antihypertensive drugs increased with age, the use of statins declined in people aged ≥74, despite their increased risk of cardiovascular disease. Previously described under-treatment of women in secondary prevention of cardiovascular disease was not observed for primary prevention.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Age inequalities exist in prescription of statins in elderly patients with existing cardiovascular disease. These inequalities also exist in those eligible for primary preventive treatment, in whom prescribing trends for statins seem to closely follow guidelines, which do not offer clear guidance for elderly patients.

Participants and setting

All 41 250 records of patients aged >40 registered at 19 general practices in the West Midlands, UK, were included in this analysis. Of these, 36 679 (89%) had no history of cardiovascular disease and therefore could be considered for primary preventive treatment.

Design

Cross sectional study of anonymised patient records.

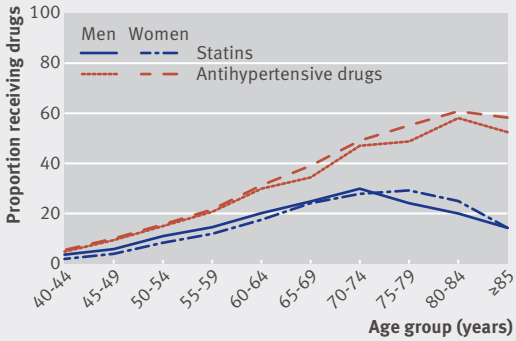
Primary outcome

The proportion of patients with no history of cardiovascular disease prescribed antihypertensive drugs or statins, or both, subdivided by age and sex.

Main results and the role of chance

Data were available for all patients included in this study. The proportion receiving antihypertensive drugs increased with age (from 5% (378/6978) aged 40-44 to 57% (621/1092) aged ≥85) as did the proportion taking statins up to the age of 74 (from 3% (201/6978) aged 40-44 to 29% (675/2367) aged 70-74). In those aged 75 and above, the odds of receiving a prescription for a statin (relative to the 40-44 age group) decreased with every five year increment in age (odds ratio 12.9 (95% confidence interval 10.8 to 15.3) at age 75-79 to 5.7 (4.6 to 7.2) at age ≥85; P<0.001). There were no consistent differences in prescribing trends by sex.

Proportion of patients prescribed primary preventive drug treatment in each age group by sex



Bias, confounding, and other reasons for caution

We could not account for contraindications to drug treatment, general practitioner's judgment in individual cases, or patient's choice. In addition, all patients were included in this analysis, regardless of their calculated absolute cardiovascular risk score. If we had done the analysis taking account of risk, the association of older age with non-use of preventive treatment would have been more marked. We did not use risk calculators because they have not been validated for people over the age of 75.

Generalisability to other populations

For the purposes of this study, the West Midlands is representative of the national picture. The area has similar mortality rates in people aged 75 and over compared with the national picture. While it is difficult to interpret whether the low use of preventive treatments (particularly statins) in older people reflects appropriate or inappropriate care, it is clear that more research is needed to inform practice in primary prevention and to examine developing age inequalities to see how best to treat elderly people.

Study funding/potential competing interests

This work forms part of a larger programme on stroke prevention in primary care supported by the National Institute for Health Research (RP-PG-0606-1153). JPS and SS are funded by the National Institute for Health Research Birmingham and Black Country Collaboration for Leadership in Applied Health Research and Care. RJMcM holds an NIHR career development fellowship.