RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

JAMES KING-HOLMES/SPL

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Diagnosis of colorectal cancer in primary care

The sooner colorectal cancer is diagnosed, the better the prognosis, but how can primary care doctors catch it early? In a systematic review, Petra Jellema and colleagues (p 795) looked at diagnostic tests that might help them to identify patients at increased risk. They identified studies in adults who consulted in primary care for non-acute lower abdominal symptoms, and they assessed the usefulness of various signs, symptoms, and blood and faecal tests. Conclusive evidence from this setting, they found, was in short supply, but combinations of symptoms and results of immunochemical faeces tests showed good diagnostic performance.

Researchers' industry affiliations and their views on the risks of rosiglitazone

CUSTOM MEDICAL STOCK/SPL

We now know that treatment with rosiglitazone has important cardiac and other risks but is still thought to convey enough benefit to be considered for at least second line use in type 2 diabetes along with metformin or a sulfonylurea. Amy T Wang and colleagues' systematic review of guidelines, meta-analyses, reviews, clinical trials, letters, commentaries, and editorials about rosiglitazone reports that authors' financial conflicts of interest were highly prevalent but under-reported, and were more common among those who stated that the drug does not increase the risk of myocardial infarction (p 799). Elsewhere in the journal, Ray Moynihan describes rosiglitazone's rise and fall and concludes that the task of analysing any drugs' complex risks and benefits "might be made easier if those studying it, prescribing it, pronouncing on it, and regulating it could do so more often in the sunshine of independence rather than the shadow of those seeking to maximise its sales" (p 785).

Breast cancer screening and mortality

As editorialist H Gilbert Welch remarked last summer "The question is no longer whether overdiagnosis occurs [through mammography], but how often it occurs... We do not know how women feel about being diagnosed at a younger age without this influencing their prognosis (those destined to die still do, those destined to survive would have done just as well if diagnosed later)" (*BMJ* 2009;339:b1425).

Karsten Juhl Jørgensen and colleagues' retrospective observational study of a natural experiment in Denmark—the gradual introduction of breast cancer screening, county by county—adds further evidence on these deaths (p 797). They found that reductions in breast cancer mortality in regions where screening had started were similar or smaller than those in non-screening areas and in women below screening age, and hence were probably not attributable to screening. This paper had already proved controversial on bmj.com (www.bmj.com/cgi/eletters/340/mar23_1/c1241) when new research by Stephen Duffy and colleagues concluded that for every two lives saved, one woman is treated unnecessarily (*Journal of Medical Screening* 2010;17:25-30)—a lower rate of overdiagnosis than previously reported. The media widely reported both papers and BBC Radio 4's *Today* programme got the two lead authors together to defend the reliability of their findings (http://news.bbc.co.uk/1/hi/health/8594940.stm). This debate looks set to run and run: in the meantime, women need good up to date information on both the benefits and harms of screening.

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl

***BMJ* policy on data sharing** Just as Ray Moynihan seeks the sunshine of independence, Tony Delamothe wants research data to be more openly exposed to the light (p 790). The *BMJ* strongly supports the view that researchers should share their raw research data, and there are good scientific and ethical reasons for doing so as long as participants' privacy is not breached without their consent. So we ask authors to include a data sharing statement at the end of each original research article such as "Data sharing: technical appendix, statistical code, and dataset available from the corresponding author at [email address or url]. Participants gave informed consent for data sharing [or ...consent was not obtained but the presented data are anonymised and risk of identification is low... or consent was not obtained but the potential benefits of sharing these data outweigh the potential harms because...] or "Data sharing: no additional data available."

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Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis

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STUDY QUESTION What is the evidence for diagnostic tests used in primary care to identify patients with an increased risk for colorectal cancer among those consulting for non-acute lower abdominal symptoms?

SUMMARY ANSWER Although symptom combinations and immunochemical faeces tests showed good diagnostic performance in referred patients, evidence in primary care populations is lacking.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Primary care physicians need to identify patients with an increased risk of colorectal cancer among all those consulting with abdominal symptoms. Most promising tests in terms of diagnostic performance are combinations of symptoms and faecal occult blood tests, especially immunochemical based tests, but these have been evaluated mainly in secondary care.

Selection criteria for studies

PubMed and Embase were searched to September 2008. Studies were selected if the design was a diagnostic study; the patients were adults consulting because of non-acute lower abdominal symptoms; tests included signs, symptoms, blood tests, or faeces tests. In addition to primary care populations, patients consulting clinics at the interface of primary and secondary care, such as the two week referral clinics and open access outpatient clinics, were included, along with outpatient clinics if the prevalence of colorectal cancer was less than 15%.

Primary outcomes

Colonoscopy, barium enema, or clinical follow-up were considered valid reference standards for diagnosis. To inform general practitioners about the diagnostic performance of the test we presented the results as risk for colorectal cancer in case of a positive and negative test result, in addition to sensitivity and specificity. If at least four studies showed homogenous results we pooled diagnostic parameters using random effects bivariate analysis, otherwise median and range of estimates were presented.

Main results and role of chance

We included 47 studies. Only nine were performed in primary care, five in primary-secondary interface settings, and 33 in secondary care. Prevalence of colorectal cancer ranged from 0.4% to 15%.

The performance of tests in diagnosing colorectal cancer in symptomatic adult patients varied widely. Sensitivity was consistently high for age ≥50 (range 0.81-0.96, median 0.91) and the two week referral guideline (range 0.80-0.94, median 0.92), but these lacked specificity (medians 0.36 and 0.42, respectively). Specificity was consistently high for family history (range 0.75-0.98, median 0.91), weight loss (range 0.72-0.96, median 0.89), and anaemia (0.83-0.95, median 0.92), but all these tests lacked sensitivity (medians 0.16, 0.20, and 0.13, respectively). Only immunochemical based faecal occult blood tests had both reasonable sensitivity (range 0.70-1.00, median 0.95) and specificity (range 0.71-0.93, median 0.84). Combinations of symptoms might increase sensitivity without losing specificity.

Subgroup analyses showed that sensitivity of immunochemical based faecal occult blood tests was better than the guaiac based tests and better for the regular guaiac based tests than guaiac based self tests. There were indications (few studies, minimal data) that immunochemical based tests detect early Dukes's stages in all bowel locations.

Bias, confounding, and other reasons for caution

Studies were heterogeneous with respect to populations, tests, and results. For example, faecal occult blood tests differ in terms of types, number of samples, and dietary instructions. Few studies were carried out in primary care. In primary care patients with abdominal symptoms various diagnoses will be considered (including colorectal cancer, irritable bowel disease, coeliac disease) and general practitioners should identify all patients who need referral for further diagnosis. We focused on colorectal cancer, but to a clinician a positive test result (such as diarrhoea) leading to a diagnosis of inflammatory disease might also be considered a true positive result. This means that some tests will be more useful in practice than might seem from this review.

Study funding/potential competing interests

The study was supported by a grant from the Netherlands Organisation for Health Research and Development (ZonMw), The Hague, Netherlands (No 945-06-001).

SUMMARY OF FINDINGS WITH RANGES AND MEDIANS

Index test and setting	No of studies	Sensitivity (range)	Specificity (range)	Risk with positive result	Risk with negative result
Two week referral (TWR) guidelines					
TWR clinic	4	0.86-0.92	0.30-0.54	0.12-0.25	0.02-0.04
Secondary care	1	0.80-0.94	0.54-0.56	0.08-0.14	0.01-0.02
Median	—	0.92	0.42	0.14	0.03
Faecal occult blood tests					
Guaiac based:					
Primary care	1	0.57	0.90	0.18	0.02
Secondary care	13	0.33-1.00	0.72-0.94	0.07-0.59	0.00-0.07
Median	—	0.75	0.86	0.28	0.01
Immunological:					
Secondary care	8	0.70-1.00	0.71-0.93	0.07-0.59	0.00-0.05
Median	—	0.95	0.84	0.21	0.00

Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis

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STUDY QUESTION What are the effects of specific interventions for gestational diabetes on the risk of pregnancy, and perinatal and long term complications in women with gestational diabetes?

SUMMARY ANSWER Treatment for gestational diabetes, consisting of treatment for lowering blood glucose concentrations, either alone or with special obstetric care, seems to lower the risk for some perinatal complications.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Treatment of women with gestational diabetes is recommended, but controversy remains over which outcomes can be influenced. Treatment seems to have beneficial effects on some complications of pregnancy. This evidence is derived from trials for which women were selected by a two step strategy.

Selection criteria for studies

Eligible studies had to investigate specific treatment of gestational diabetes compared with usual care or "intensified" specific treatment compared with "less intensified" specific care. They also had to be randomised controlled trials and include pregnant women with an impairment of their glucose tolerance, based on the results of an oral glucose tolerance test. We carried out a full literature search of relevant research databases, publishers' databases, and the reference lists of relevant secondary literature up to October 2009.

Primary outcomes

The interventions were compared for their effect on pregnancy outcomes relevant to patients and long term outcomes.

Main results and role of chance

We found five studies comparing specific treatment with usual care. All studies used a two step approach with a glucose challenge test, screening for risk factors, or both, and a subsequent test for oral glucose tolerance. Meta-analyses did not show significant differences for most single end points judged to be of direct clinical importance. Shoulder dystocia was less common in women treated for gestational diabetes (odds ratio 0.40, 95% confidence interval 0.21 to 0.75). One study reported a major reduction of pre-eclampsia in women with specific treatment. For the surrogate end point of infants large for gestational age, a notable reduction was seen (0.48, 0.38 to 0.62).

Thirteen studies compared specific treatments of different intensities. The meta-analysis showed a significant reduction of shoulder dystocia in women with more intensive treatment (0.31, 0.14 to 0.70).

SELECTED RESULTS FROM META-ANALYSES ON MATERNAL AND NEONATAL OUTCOMES

Outcome	Specific treatment *v* usual care	Intensified *v* less intensified treatment
Shoulder dystocia	0.40 (0.21 to 0.75)	0.31 (0.14 to 0.70)
Caesarean section	0.86 (0.72 to 1.02)	1.04 (0.80 to 1.34)
Perinatal mortality	NA	0.96 (0.19 to 4.79)
Large for gestational age	0.48 (0.38 to 0.62)	NA
Small for gestational age	1.10 (0.80 to 1.51)	0.85 (0.50 to 1.44)

NA=not available because of high heterogeneity.

Bias, confounding, and other reasons for caution

The risk for bias was judged to be low for two studies comparing treatment for gestational diabetes with usual care and comparing intensive with less intensive treatment, respectively, and high for the remaining trials.

Study funding/potential competing interests

This study was commissioned by the German Federal Joint Committee. KH, KJ, EM, and AS acted as consultants for the preparation of the review. For this they were reimbursed by IQWiG. KK, RB, HB, and SL (as well as PTS, SD, SW, AS, MM, YZ, EV, CS, and SS) are employees of IQWiG.

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Breast cancer mortality in organised mammography screening in Denmark: comparative study

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STUDY QUESTION Is the previously observed 25% reduction in breast cancer mortality in Copenhagen following the introduction of mammography screening indeed the result of screening?

SUMMARY ANSWER The reductions in breast cancer mortality observed in screening regions in Denmark were similar or less than those in non-screened areas and in age groups too young to benefit from screening, and are more likely to be explained by changes in risk factors and improved treatment than by screening mammography.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Recent systematic reviews have estimated much lower reductions in breast cancer mortality than those claimed when screening was introduced. A previous Danish study claimed a large effect of screening in Copenhagen compared with unscreened regions. We used data from the whole of Denmark and five additional years of follow-up, but could not find an effect of the Danish screening programme on breast cancer mortality.

Participants and setting

This study was conducted on all Danish women recorded in the Cause of Death Register and Statistics Denmark between 1971 and 2006 for Copenhagen, where mammography screening started in 1991, and Funen county, where screening was introduced in 1993. The rest of Denmark (about 80% of the population) served as an unscreened control group.

Design, size, and duration

We used Poisson regression analyses adjusted for changes in age distribution to compare the annual percentage change in breast cancer mortality in areas where screening was used with areas where it was not used during 10 years before screening was introduced and for 10 years after screening was in practice (starting five years after introduction of screening).

Main results and the role of chance

In women who could benefit from screening (ages 55-74 years), we found a mortality decline of 1% per year in the screening areas (relative risk (RR) 0.99, 95% confidence interval (CI) 0.96 to 1.01) during the 10 year period when screening could have had an effect (1997-2006). In women of the same age in the non-screening areas, there was a decline of 2% in mortality per year (RR 0.98, 95% CI 0.97 to 0.99) in the same 10 year period. In women who were too young to benefit from screening (ages 35-55 years), breast cancer mortality during 1997-2006 declined 5% per year (RR 0.95, CI 0.92 to 0.98) in the screened areas and 6% per year (RR 0.94, CI 0.92 to 0.95) in the non-screened areas. For the older age groups (75-84 years), there was little change in breast cancer mortality over time in both screened and non-screened areas. Trends were less clear during the 10 year period before screening was introduced, with a possible increase in mortality in women aged less than 75 years in the non-screened regions.

Bias, confounding, and other reasons for caution

Our study was observational, but our findings are robust because the Danish population is homogeneous, opportunistic screening is very rare in Denmark, and the expected effect was large.

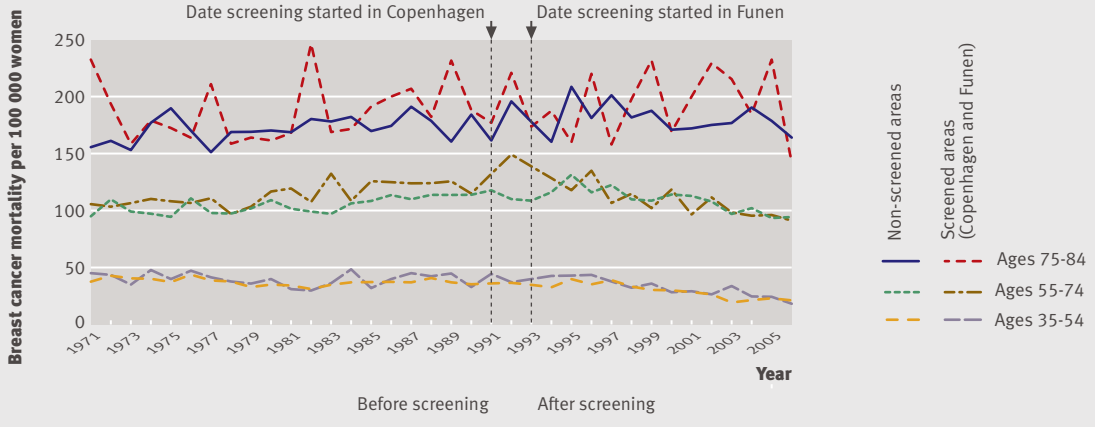
Generalisability to other populations

The levels of breast cancer mortality in screened and unscreened age groups before and after screening is similar to that in other European countries, including those with the longest running, most comprehensive programmes such as the United Kingdom and Sweden.

Study funding/potential competing interests

No funding was received for this research. The authors have no competing interests.

UNADJUSTED BREAST CANCER MORTALITY FOR SCREENED AND NON-SCREENED AREAS



This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1241

Epidemiology of rib fractures in older men: Osteoporotic Fractures in Men (MrOS) prospective cohort study

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bmj.com

Read rapid response by Pekka A Kannus and Teppo NL Järvinen from Tampere, Finland: "Falling, not osteoporosis, is the strongest risk factor for rib fracture"—and have your say on bmj.com

This article is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1069

STUDY QUESTION

Are rib fractures (the most common clinical fracture in older men) osteoporotic fractures and are they associated with important consequences?

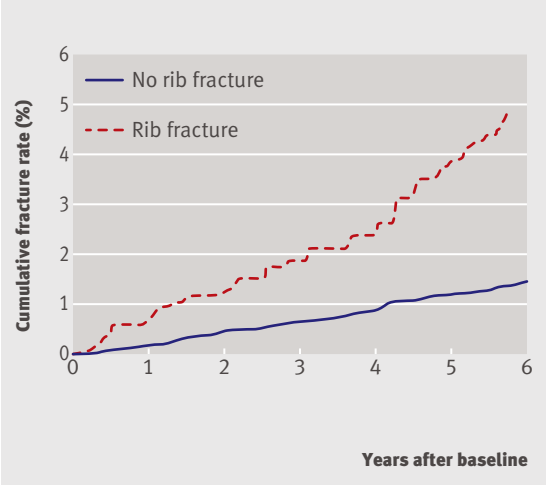
SUMMARY ANSWER

Men with a history of rib fracture had similar characteristics to men with osteoporosis, including frequent falls and a twofold increased risk of future fracture of the hip, wrist, or rib.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Men with a previous rib fracture were older and had lower bone mineral density, more falls, and more impaired activities of daily living than did men without a rib fracture history; they had a significantly increased risk of a new radiologically confirmed fracture at the hip, wrist, or rib independent of multiple other risk factors.

CUMULATIVE INCIDENCE OF RIB FRACTURE AMONG MEN WITH AND WITHOUT BASELINE HISTORY OF RIB FRACTURE



Participants and setting

Community dwelling men were recruited from six sites in the United States in 2000-2.

Design, size, and duration

This was a prospective study of 5995 men aged 65 or above; 99% of surviving participants answered mailed questionnaires about falls and fractures every four months for a mean 6.2 (SD 1.3) year follow-up. Incident fractures reported were validated radiographically.

Main results and the role of chance

The incidence of rib fracture was 3.5 per 1000 person years; 24% (n=126) of all incident non-spine fractures were rib fractures. Independent risk factors for an incident rib fracture were age 80 or over, low bone mineral density, difficulty with instrumental activities of daily living, and a baseline history of rib or chest fracture. A history of rib or chest fracture carried at least a twofold increased risk of an incident rib fracture (multiply adjusted hazard ratio 2.71, 95% confidence interval 1.86 to 3.95), hip fracture (2.05, 1.33 to 3.15), and wrist fracture (2.06, 1.14 to 3.70). The figure shows the greater cumulative incidence of fracture among men with a baseline history of rib fracture compared with those with no such history. Only 14/82 men reported treatment with bone specific drugs after their incident rib fracture.

Bias, confounding, and other reasons for caution

Although chance is always a possible explanation for associations observed in epidemiological studies, the consistent associations of well accepted risk factors for osteoporosis with past and new rib fractures seem much more likely to be evidence that rib fractures are osteoporotic fractures. The use of radiographically defined rib fractures as an outcome underestimates the number of new rib fractures but precludes misclassification. Rib fractures that did not lead to a radiograph would have been missed, because only confirmed rib fractures were included. Some classification error is likely for the unvalidated baseline history of rib fracture, but selective recall bias or misclassification of baseline covariates is less problematic in a prospective study.

Generalisability to other populations

Participants were recruited mainly from population based lists of men who were eligible on the basis of age, and they are in general representative of the geographical areas from which they were recruited. They may have been healthier than non-participants, given volunteer bias.

Study funding/potential competing interests

The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the National Center for Research Resources, and National Institutes of Health Roadmap for Medical Research provide support under the following grant numbers: U01 AR45580, U01 AR45614, U01 AR45632, U01 AR45647, U01 AR45654, U01 AR45583, U01 AG18197, U01-AG027810, and UL1 RR024140.

Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review

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FEATURE, p 785

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STUDY QUESTION

Is there an association between article authors' views on the risk of myocardial infarction with rosiglitazone and the authors' financial conflicts of interest and, if so, what is the prevalence of financial conflicts of interest?

SUMMARY ANSWER

Financial conflicts of interest were highly prevalent, had unexpectedly low disclosure rates, and were more common among authors who stated that rosiglitazone does not increase risk of myocardial infarction.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Over the past decade, various studies have shown an association in published articles between conflicts of interest and pro-industry conclusions. This has led to demands for increased transparency and policies on disclosures of conflicts of interest. Despite apparent progress, our study demonstrates that conflict of interest reporting is still low, and that an association between financial conflicts of interest and pro-industry conclusions still exists.

Selection criteria for studies

On 10 April 2009, we searched Web of Science and Scopus for articles citing and commenting on either of two index publications that contributed key data to the "rosiglitazone controversy" (a meta-analysis of small trials and a subsequent large trial). Articles had to comment on rosiglitazone and the risk of myocardial infarction. Guidelines, meta-analyses, reviews, clinical trials, letters, commentaries, and editorials were included.

For each article, we sought information about the authors' financial conflicts of interest in the report itself and elsewhere (that is, in all publications within two years of the original publication and online). Two reviewers blinded to the authors' financial relationships independently classified each article as presenting a favourable (that is, rosiglitazone does not increase the risk of myocardial infarction), neutral, or unfavourable view on the risk of myocardial infarction with rosiglitazone and on recommendations on the use of the drug.

Primary outcomes

The primary outcomes were the presence of financial conflicts of interest and their relation to the article authors' position on the risk of myocardial infarction with rosiglitazone—that is favourable, neutral, or unfavourable—and the continued use of rosiglitazone.

Main results and role of chance

Of the 202 included articles, 108 (53%) had a conflict of interest statement. Ninety authors (45%) had financial conflicts of interest. Authors who had a favourable view of the risk of myocardial infarction with rosiglitazone were more likely to have financial conflicts of interest with manufacturers of antihyperglycaemic agents in general, and with rosiglitazone manufacturers in particular, than authors who had an unfavourable view (rate ratio 3.38, 95% CI 2.26 to 5.06 and 4.29, 2.63 to 7.02, respectively). There was likewise a strong association between favourable recommendations on the use of rosiglitazone and financial conflicts of interest (3.36, 1.94 to 5.83). These links persisted when articles rather than authors were used as the unit of analysis (4.69, 2.84 to 7.72), when the analysis was restricted to opinion articles (6.29, 2.15 to 18.38) or to articles in which the rosiglitazone controversy was the main focus (6.50, 2.56 to 16.53), and in articles published both before and after the Food and Drug Administration issued a safety warning for rosiglitazone (3.43, 0.99 to 11.82 and 4.95, 2.87 to 8.53, respectively).

Bias, confounding, and other reasons for caution

Although two independent reviewers determined authors' positions on the safety of rosiglitazone, our findings are dependent on non-objective judgments. We were also unable to comment on the implications of the strength of the financial association (that is, assign monetary magnitude to the relationships) or whether observed association reflects ghostwriting in publications related to rosiglitazone.

Study funding/potential competing interests

No funding was required for this study, and none of the authors has any competing interests to declare.

AUTHOR POSITION ON ROSIGLITAZONE SAFETY AND FINANCIAL CONFLICTS OF INTEREST

	Risk of myocardial infarction with rosiglitazone			
	Favourable (n=31)	Neutral (n=84)	Unfavourable (n=65)	Rate ratio (95% CI)*
Any manufacturer	29 (94)	32 (38)	18 (28)	3.38 (2.26 to 5.06)
Rosiglitazone manufacturer†	27 (87)	25 (24)	13 (20)	4.29 (2.63 to 7.02)
Pioglitazone manufacturer†	20 (65)	31 (30)	14 (22)	3.96 (2.45 to 6.39)
None	2 (6)	52 (62)	47 (72)	—

Values are numbers (percentages) unless otherwise indicated.
*Comparing favourable versus unfavourable views.
†Categories not mutually exclusive.

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