

Special Article

CONFLICT OF INTEREST IN THE DEBATE OVER CALCIUM-CHANNEL ANTAGONISTS

HENRY THOMAS STELFOX, M.D., GRACE CHUA, M.D., KEITH O'ROURKE, M.B.A., AND ALLAN S. DETSKY, M.D., PH.D.

ABSTRACT

Background Physicians' financial relationships with the pharmaceutical industry are controversial because such relationships may pose a conflict of interest. It is unknown to what extent industry support of medical education and research influences the opinions and behavior of clinicians and researchers. The recent debate over the safety of calcium-channel antagonists provided an opportunity to examine the effect of financial conflicts of interest.

Methods We searched the English-language medical literature published from March 1995 through September 1996 for articles examining the controversy about the safety of calcium-channel antagonists. Articles were reviewed and classified as being supportive, neutral, or critical with respect to the use of calcium-channel antagonists. The authors of the articles were asked about their financial relationships with both manufacturers of calcium-channel antagonists and manufacturers of competing products (i.e., beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, and nitrates). We examined the authors' published positions on the safety of calcium-channel antagonists according to their financial relationships with pharmaceutical companies.

Results Authors who supported the use of calcium-channel antagonists were significantly more likely than neutral or critical authors to have financial relationships with manufacturers of calcium-channel antagonists (96 percent, vs. 60 percent and 37 percent, respectively; $P < 0.001$). Supportive authors were also more likely than neutral or critical authors to have financial relationships with any pharmaceutical manufacturer, irrespective of the product (100 percent, vs. 67 percent and 43 percent, respectively; $P < 0.001$).

Conclusions Our results demonstrate a strong association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers. The medical profession needs to develop a more effective policy on conflict of interest. We support complete disclosure of relationships with pharmaceutical manufacturers for clinicians and researchers who write articles examining pharmaceutical products. (N Engl J Med 1998;338:101-6.)

©1998, Massachusetts Medical Society.

THE safety of calcium-channel antagonists in the treatment of cardiovascular disorders has recently become a controversial issue. A case-control study suggested a possible association between the use of calcium-channel antagonists to treat hypertension and an increased risk of myocardial infarction.¹ A meta-analysis of randomized, controlled trials in patients with ischemic heart disease and a case-control study of antihypertensive medications in the elderly raised further questions about the safety of calcium-channel antagonists.^{2,3} An intense debate followed in both the medical literature and the lay press.

A Canadian television documentary, *The Fifth Estate*, reported on Health Canada's review of calcium-channel antagonists and suggested that the public was not being adequately protected from potentially dangerous medications. The allegation that an academic advisor to the Health Protection Branch of Health and Welfare Canada (the body that reviews the safety of all pharmaceutical products) had financial relationships with manufacturers of calcium-channel antagonists raised an important question about physicians' objectivity in assessing the safety of drugs.

Physicians' interactions with pharmaceutical manufacturers are controversial. The pharmaceutical industry provides substantial financial support for both medical education and research. What is unknown is the extent to which support by the drug industry influences physicians' opinions and behavior. Limited scientific evidence suggests that physicians may be influenced by pharmaceutical promotions.⁴⁻⁷ For example, a study by Chren and Landefeld demonstrated that physicians' requests to add particular drugs to hospital formularies were associated with interactions between physicians and manufacturers.⁴

The debate about the safety of calcium-channel

From the Departments of Medicine (H.T.S., G.C., A.S.D.), Health Administration (K.O., A.S.D.), and Public Health Sciences (K.O.), University of Toronto; the Department of Medicine, Mount Sinai Hospital (A.S.D.); and the Department of Medicine, Toronto Hospital (A.S.D.) — all in Toronto. Address reprint requests to Dr. Detsky at Mount Sinai Hospital, Rm. 427, 600 University Ave., Toronto, ON M5G 1X5, Canada.

antagonists provided an opportunity to study financial conflicts of interest in medicine. Our project was designed to examine the relation between authors' published positions on the safety of calcium-channel antagonists and their financial interactions with the pharmaceutical industry.

METHODS

Study Questions

The primary question we addressed was whether there was an association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with the pharmaceutical industry. Authors were surveyed about their financial relationships with pharmaceutical manufacturers, and this information was compared with their published positions. We asked three specific questions: Were authors who supported the use of calcium-channel antagonists more likely than other authors to have financial relationships with manufacturers of calcium-channel antagonists? Were authors who criticized the use of calcium-channel antagonists more likely than other authors to have financial relationships with manufacturers of competing products (i.e., beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, and nitrates)? Were authors who supported the use of calcium-channel antagonists more likely than other authors to have financial relationships with any pharmaceutical manufacturer?

Selection and Review of Articles

Authors were identified by reviewing articles on calcium-channel antagonists published between March 10, 1995, and September 30, 1996. Pertinent articles (reports of original research, reviews, and letters to the editor) were identified with the use of the Medline data base and reference lists from published articles. Seventy-seven articles were initially selected.^{1-3,8-81} Seven articles were excluded because they were primarily news related, the authors could not be identified, or the authors were officially writing on behalf of the pharmaceutical industry.⁸⁻¹⁴ Seventy articles were included in the study.^{1-3,15-81}

The articles were reviewed with the use of a predefined classification system (Table 1). Each article was classified as being supportive, neutral, or critical with respect to the use of calcium-channel antagonists. The articles were independently assessed by two of us without knowledge of the authors' survey responses. Discrepancies were discussed, and a third author was consulted if an agreement was not reached. Authors were identified and assigned a classification (supportive, neutral, or critical) according to the classification of their articles. Thirty authors had more than one article, but each author was assigned a single classification. Authors classified as neutral on the basis of one article but critical or supportive on the basis of another were classified as critical or supportive.

Survey Instrument

A survey instrument based on Chren and Landefeld's⁴ questionnaire was developed to examine the authors' financial interactions with pharmaceutical companies. The manufacturers of drugs used to manage angina and hypertension were identified. Forty companies were identified in Canada and the United States: 28 manufactured only products that compete with calcium-channel antagonists (beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, or nitrates), and 12 manufactured calcium-channel antagonists; 9 of the 12 also manufactured at least one competing product. The pharmaceutical manufacturers were listed alphabetically; the nature of their products was not revealed. For each of the 40 manufacturers, authors were asked whether they had received any of five types of funding in the past five years: support to attend a symposium (i.e., funds for travel expenses), an honorarium to speak at a symposium, support to or-

TABLE 1. CLASSIFICATION OF AUTHORS' POSITIONS ON THE SAFETY OF CALCIUM-CHANNEL ANTAGONISTS.

Critical

Emphasizes concern about safety
Recommends use of alternative medications
Criticizes authors emphasizing the safety of calcium-channel antagonists

Neutral

Concludes that there is insufficient information to assess safety
Makes no recommendation about medication use
Equitably assesses opposing views

Supportive

Emphasizes safety
Recommends continued use of calcium-channel antagonists
Criticizes authors questioning safety

ganize an educational program, support to perform research, and employment or consultation. The questionnaire and the list of manufacturers are available from the National Auxiliary Publications Service (NAPS).*

The addresses of the corresponding authors were obtained from the articles, and the addresses of coauthors were requested from the corresponding authors. All authors were mailed the survey questionnaire with a cover letter explaining the purpose of the study. Reminder letters and questionnaires were mailed to authors who did not respond to the first mailing within eight weeks.

Statistical Analysis

The strategy for the primary analysis was to answer each of the three specific study questions by determining associations between the authors' positions on the safety of calcium-channel antagonists and their reported financial relationships with pharmaceutical manufacturers. The authors' survey responses were coded according to the presence or absence of at least one relationship with a manufacturer of a calcium-channel antagonist, a manufacturer of a competing product, or any pharmaceutical manufacturer. Logistic regression was performed individually for each group of manufacturers, with the classification of the authors (supportive, neutral, or critical) treated as both strictly linear (coded as 2, 1, or 0) and nominal (unordered).⁸²⁻⁸⁴ The results are reported only as linear chi-square values and P values, since the results of the nominal analyses were similar. For the authors who reported financial relationships with pharmaceutical manufacturers, the number of relationships was assessed by linear regression.

The rate of response to the survey was analyzed according to the classification of the authors with the use of logistic regression (linear and nominal). Agreement on the classification of the authors was assessed with Spearman's rank-correlation test. Data were analyzed with S-PLUS software.⁸⁵

RESULTS

Classification of Authors

Seventy articles (5 reports of original research, 32 review articles, and 33 letters to the editor) were included in the study; 30 were classified as support-

*See NAPS document no. 05439 for 5 pages of supplementary material. Order from NAPS, c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) \$7.75 for photocopies or \$5 for microfiche. Outside the U.S., add postage of \$4.50 for up to 20 pages, and \$1.00 for each 10 pages of material thereafter, or \$1.75 for the first microfiche and \$0.50 for each microfiche thereafter. There is a \$15 invoicing charge on all orders filled by remote payment.

ive,³²⁻⁶¹ 17 as neutral,¹⁵⁻³¹ and 23 as critical.^{1-3,62-81} Agreement on the classification of the articles by the two reviewers was initially 81 percent (agreement on 57 of the 70 articles) and increased to 96 percent (67 of 70) after the reviewers had discussed the discrepancies. A third reviewer was required to resolve the disagreement on the classification of three articles. Interobserver variation was small for the initial reviewer agreement on article classification (Spearman's rank-correlation coefficient, 0.82). Eighty-nine authors of the 70 articles were identified and assigned a classification according to that of their articles; 36 authors were classified as supportive, 19 as neutral, and 34 as critical.

Response Rates

Addresses were available for 86 of the 89 authors, and all 86 were mailed questionnaires. Three coauthors (one supportive, one neutral, and one critical) were not mailed surveys because their addresses were not provided by the corresponding authors. Of the 86 authors who were mailed surveys, 71 (83 percent) responded. Two authors (one supportive and one critical) refused to participate in the study. A total of 69 authors (80 percent) completed the survey. Table 2 shows the response rate according to the classification of the authors. Sixty-nine percent of the authors who were supportive of calcium-channel antagonists completed the survey, as compared with 83 percent of the neutral authors and 91 percent of the critical authors (P=0.02).

Study Questions

The first question we addressed was whether supporters of calcium-channel antagonists were more likely than other authors to have financial relationships with manufacturers of calcium-channel antagonists. The answer was yes. Ninety-six percent of the supportive authors had financial relationships with manufacturers of calcium-channel antagonists, as compared with 60 percent of the neutral authors and 37 percent of the critical authors (P<0.001) (Table 3).

Our second question was whether critics of calcium-channel antagonists were more likely than other authors to have financial relationships with manufacturers of competing products (beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, and nitrates). The answer was no. In fact, supportive and neutral authors were more likely than critical authors to have financial interactions with manufacturers of competing products (88 percent and 53 percent, respectively, vs. 37 percent; P<0.001).

Our third question was whether supporters of calcium-channel antagonists were more likely than other authors to have financial relationships with any pharmaceutical manufacturer. The answer was yes. One hundred percent of the supportive authors, as compared with 67 percent of the neutral authors

TABLE 2. RATES OF RESPONSE TO THE SURVEY.

VARIABLE	SUPPORTIVE	NEUTRAL	CRITICAL	CHI-SQUARE FOR LINEAR TREND	P VALUE
No. of articles	30	17	23		
No. of authors surveyed	35	18	33		
No. of respondents	24	15	30		
Response rate (%)	69	83	91	5.60	0.02

TABLE 3. AUTHORS WITH FINANCIAL RELATIONSHIPS WITH PHARMACEUTICAL MANUFACTURERS.

MANUFACTURER	SUPPORTIVE AUTHORS (N=24)	NEUTRAL AUTHORS (N=15)	CRITICAL AUTHORS (N=30)	CHI-SQUARE FOR LINEAR TREND	P VALUE FOR TREND
no. of authors (%)					
Manufacturer of calcium-channel antagonist	23 (96)	9 (60)	11 (37)	22.02	<0.001
Manufacturer of competing product	21 (88)	8 (53)	11 (37)	14.84	<0.001
Any manufacturer	24 (100)	10 (67)	13 (43)	22.68	<0.001

and 43 percent of the critical authors, had financial interactions with at least one pharmaceutical manufacturer (P<0.001).

The associations between the authors' positions on the safety of calcium-channel antagonists and the presence or absence of financial relationships with pharmaceutical manufacturers were consistent in the five categories of funding (funds for travel expenses, honorariums for speeches, support for educational programs, research grants, and employment or consultation) (Table 4). Sixty-seven percent of the supportive authors reported three or more of the five types of interactions, as compared with 40 percent of the neutral authors and 13 percent of the critical authors (P<0.001). In the group of authors who had at least one relationship with any pharmaceutical manufacturer, there were no significant associations between an author's position on the safety of calcium-channel antagonists and the mean number of relationships.

DISCUSSION

Our study was designed to examine financial conflicts of interest in the debate over calcium-channel antagonists. The results demonstrate a strong association between authors' opinions about the safety of

TABLE 4. AUTHORS' FINANCIAL RELATIONSHIPS WITH PHARMACEUTICAL MANUFACTURERS.

INTERACTION AND MANUFACTURER	SUPPORTIVE AUTHORS (N=24)	NEUTRAL AUTHORS (N=15)	CRITICAL AUTHORS (N=30)	CHI-SQUARE FOR LINEAR TREND	P VALUE FOR TREND
	% of authors				
Support to attend symposium					
Manufacturer of calcium-channel antagonist	67	33	20	12.39	0.002
Manufacturer of competing product	50	27	13	8.84	0.01
Any manufacturer	67	47	27	8.87	0.01
Honorarium to speak at symposium					
Manufacturer of calcium-channel antagonist	71	27	13	19.82	<0.001
Manufacturer of competing product	62	40	13	14.66	<0.001
Any manufacturer	75	40	17	19.62	<0.001
Support for educational program					
Manufacturer of calcium-channel antagonist	46	20	7	11.92	0.003
Manufacturer of competing product	37	13	10	6.16	0.04
Any manufacturer	50	20	10	11.26	0.003
Research funding					
Manufacturer of calcium-channel antagonist	79	33	17	22.45	<0.001
Manufacturer of competing product	50	33	20	5.45	0.07
Any manufacturer	87	40	20	26.09	<0.001
Employment or consultation					
Manufacturer of calcium-channel antagonist	21	33	7	2.13	0.07
Manufacturer of competing product	21	33	17	0.19	0.46
Any manufacturer	25	33	17	0.60	0.45

calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers. Supportive authors were much more likely than critical authors to have financial associations with manufacturers of calcium-channel antagonists, as well as with manufacturers of other products. Conversely, critical authors were much less likely to be financially associated with manufacturers of competing products.

Limitations of the Study

The results of this study need to be interpreted within the context of its limitations. First, the survey instrument used was simple and perhaps imperfect. Author–manufacturer relationships were assessed simply as being present or absent. No estimates of monetary value were assigned to the relationships to assist in quantification. We also realized later that the authors' business interests in pharmaceutical companies (e.g., equities) were not assessed. The most serious weakness of the survey instrument, however, was that it provided only self-reported data on financial relationships. Independent verification of these relationships would be very difficult. Self-reporting could potentially have biased the study results since the authors were more likely to underreport than overreport interactions with manufacturers. Most of the critical authors (91 percent) completed the survey, and we believe it is unlikely that they underreported their financial relationships, as compared with the other authors. The supportive authors had a lower response rate (69 percent), yet all the sup-

portive authors who responded to the survey reported a financial relationship with at least one manufacturer. We therefore believe that self-reporting is unlikely to have significantly influenced our study findings.

Second, we were unable to determine the temporal relation between authors' published opinions and their financial interactions with pharmaceutical manufacturers. The authors may have formulated their opinions after having financial interactions with drug manufacturers. However, it is equally plausible that the pharmaceutical companies sought relationships with clinicians and researchers who had already expressed favorable opinions of their products.

Guidelines for Disclosing Conflicts of Interest

The medical profession has failed to develop and enforce strict guidelines for disclosing conflicts of interest. Furthermore, many conflicts of interest may go unrecognized. In our study, the majority of authors (63 percent) had a financial relationship with either a manufacturer of a calcium-channel antagonist or a manufacturer of a competing product. However, only 2 of the 70 articles included in the study disclosed the authors' potential conflicts of interest.^{41,53} Clearly, our current disclosure policies are inadequate.

We propose a disclosure mechanism in the form of a questionnaire for authors: a simple two- or three-page document, similar to the one used in our study, listing pharmaceutical manufacturers and in-

quiring about specific financial relationships with them. A questionnaire posing simple, concrete questions facilitates the disclosure of conflicts of interest. With this approach, ambiguity and accidentally missed conflicts, as recently noted in the *New England Journal of Medicine*,⁸⁶ would be avoided. Editorial staff would be in possession of all information on potential conflicts of interest and would be able to make an appropriate decision about disclosure for each article published.

We believe that the pharmaceutical industry has an important and constructive role in academic medicine. Pharmaceutical manufacturers provide important support for both medical education and research. We also believe that medical journals risk severely limiting the pool of experts available to debate medical issues if they restrict the publication of articles by clinicians and researchers with conflicts of interest. Physicians and researchers simply need to disclose their financial relationships with pharmaceutical manufacturers appropriately. Medical professionals should be able to evaluate the merit of individual articles in the light of the authors' disclosure of conflicts of interest.

The extent to which the pharmaceutical industry influences clinicians' and researchers' opinions cannot be determined by the results of our study. We believe that the authors we surveyed expressed their own opinions and were not influenced by financial relationships with pharmaceutical manufacturers. However, it is our opinion that scientific authors are naive about public perceptions concerning such relationships. We wonder how the public would interpret the debate over calcium-channel antagonists if it knew that most of the authors participating in the debate had undisclosed financial ties with pharmaceutical manufacturers. The medical profession needs to develop a strong policy governing conflict of interest. Full disclosure of relationships between physicians and pharmaceutical manufacturers is necessary to affirm the integrity of the medical profession and maintain public confidence.

This study received no financial support from the pharmaceutical industry. Dr. Stelfox has no financial relationships with the pharmaceutical industry; he has attended numerous Department of Medicine educational rounds sponsored by pharmaceutical manufacturers. Dr. Chua has received funding for travel from both manufacturers of calcium-channel antagonists and manufacturers of competing products. Mr. O'Rourke has no financial relationships with the manufacturers of calcium-channel antagonists or the manufacturers of competing products; he has attended industry-sponsored functions when invited by clinicians. Dr. Detsky has received honorariums for speeches and consulting fees from manufacturers of calcium-channel antagonists and manufacturers of competing products; he has received research grants from Rhone-Poulenc Rorer Pharmaceuticals, Searle, and SmithKline Beecham Pharmaceuticals.

We are indebted to Drs. D.A. Redelmeier and M. Desreux for their help in revising the manuscript.

REFERENCES

1. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995;274:620-5.
2. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326-31.
3. Pahor M, Guralnik JM, Corti MC, Foley DJ, Carbonin P, Havlik RJ. Long-term survival and use of antihypertensive medications in older persons. *J Am Geriatr Soc* 1995;43:1191-7.
4. Chren M, Landefeld C. Physicians' behavior and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary. *JAMA* 1994;271:684-9.
5. McKinney WP, Schiedermayer DL, Lurie N, Simpson DE, Goodman JL, Rich EC. Attitudes of internal medicine faculty and residents toward professional interaction with pharmaceutical sales representatives. *JAMA* 1990;264:1693-7.
6. Orłowski JP, Wateska L. The effects of pharmaceutical firm enticements on physician prescribing patterns: there's no such thing as a free lunch. *Chest* 1992;102:270-3.
7. Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. *Am J Med* 1982;73:4-8.
8. Macdonald G. Are calcium antagonists safe? *Lancet* 1995;346:768.
9. Schubert T. Risks and benefits of calcium antagonists. *Lancet* 1995;346:961.
10. Horton R. Bayer accused of disinformation. *Lancet* 1995;346:891-2.
11. Barnett AA. FDA committee rules calcium-channel blockers safe. *Lancet* 1996;347:313.
12. Marwick C. FDA gives calcium channel blockers clean bill of health but warns of short-acting nifedipine hazards. *JAMA* 1996;275:423-4. [Erratum, *JAMA* 1996;275:1638.]
13. MacCarthy EP. Dear doctor . . . regarding calcium channel blockers. *JAMA* 1996;275:518.
14. Calcium-channel blockers: managing uncertainty. *Lancet* 1996;348:487.
15. Dargie HJ. Calcium-channel blockers and the clinician. *Lancet* 1996;348:488-9. [Erratum, *Lancet* 1996;348:694.]
16. Stryer DB, Lurie P, Bero LA. Dear doctor . . . regarding calcium channel blockers. *JAMA* 1996;275:517.
17. Walker AM, Stampfer MJ. Observational studies of drug safety. *Lancet* 1996;348:489.
18. Lip GYH, Beevers DG. Antagonism to calcium antagonists. *Lancet* 1996;347:1761.
19. Goodman S. Update on the calcium antagonist controversy: the Furberg meta-analysis revisited: scientific update. No. 120-06. Toronto: St. Michael's Hospital Division of Cardiology, 1996.
20. Fagan TC. Calcium antagonists and mortality: another case of the need for clinical judgment. *Arch Intern Med* 1995;155:2145.
21. Buring JE, Glynn RJ, Hennekens CN. Myocardial infarction associated with antihypertensive drug therapy. *JAMA* 1996;275:517.
22. Poole-Wilson PA. Are calcium antagonists safe? *Lancet* 1995;346:769-70.
23. Walker AM, Johnson ES. Bias in case-control studies of calcium antagonists. *Am J Cardiol* 1996;78:380.
24. Ferrari R. Prognosis of patients with unstable angina or acute myocardial infarction treated with calcium channel antagonists. *Am J Cardiol* 1996;77:22D-25D.
25. Mehta JL, Subramanian VB. Calcium blockers and risk of myocardial infarction and coronary heart disease mortality. *Circulation* 1996;93:1472.
26. Opie LH. Risks and benefits of calcium antagonists. *Lancet* 1995;346:961.
27. Frohlich ED, Zanchetti A. Antihypertensive therapy: safety and efficacy of drugs and publications. *Hypertension* 1996;27:317-8.
28. Gordon RD. Calcium antagonists and gastrointestinal haemorrhage: the balancing act. *Lancet* 1996;347:1056.
29. Smith GN. Calcium channel blockers and myocardial infarction. *J Fam Pract* 1996;42:30-2.
30. Horton R. Spinning the risks and benefits of calcium antagonists. *Lancet* 1995;346:586-7.
31. Ghali WA, Hershman WY. Meta-analysis and bouillabaisse. *Ann Intern Med* 1996;125:518-9.
32. Elliott HL, Epstein M, Haller H, Mancica G. Safety of calcium antagonists. *Lancet* 1995;346:1421.
33. Rafflenbeul W. Nifedipine trials. *Circulation* 1996;93:1473-4.
34. Feeman WE Jr. Myocardial infarction associated with antihypertensive drug therapy. *JAMA* 1996;275:515.
35. Parmley WW. A delayed answer to the calcium blocker question. *J Am Coll Cardiol* 1996;27:510-1. [Erratum, *J Am Coll Cardiol* 1996;27:1820.]

36. Habib GB. Are calcium antagonists harmful in hypertensive patients? Distinguishing hype from reality. *Chest* 1995;108:3-5.
37. Kaplan NM. Do calcium antagonists cause myocardial infarction? *Am J Cardiol* 1996;77:81-2.
38. Frohlich ED. Recent media reports of potential risks from calcium antagonists. *J La State Med Soc* 1995;147:343.
39. Epstein M. Calcium antagonists should continue to be used for first-line treatment of hypertension. *Arch Intern Med* 1995;155:2150-6.
40. Tijssen JGP, Hugenholtz PG. Critical appraisal of recent studies on nifedipine and other calcium channel blockers in coronary artery disease and hypertension. *Eur Heart J* 1996;17:1152-7.
41. Brown MJ. Are calcium antagonists safe? *Lancet* 1995;346:768-9.
42. Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and myocardial infarction: a hypothesis formulated but not yet tested. *JAMA* 1995;274:654-5.
43. Mancia G, van Zwieten PA. How safe are calcium antagonists in hypertension and coronary heart disease? *J Hypertens* 1996;14:13-7.
44. Messerli FH. Case-control study, meta-analysis, and bouillabaisse: putting the calcium antagonist scare into context. *Ann Intern Med* 1995;123:888-9.
45. Pilotto A, Leandro G, Franceschi M, Di Mario F, Valerio G. Antagonism to calcium antagonists. *Lancet* 1996;347:1761-2.
46. Messerli FH, Opie LH, Chambers R. Long-term safety of calcium antagonists: reassessment of the Furberg hypothesis. *J Am Coll Cardiol* 1996;27:Suppl A:319A. abstract.
47. Poole-Wilson PA. The calcium antagonist controversy; implications beyond drug prescription. *Eur Heart J* 1996;17:1131-3.
48. Rafflenbeul W. Nifedipine in acute coronary syndromes: Furberg's refrain revisited. *Eur Heart J* 1996;17:1147-52.
49. Phillips BG, MacFarlane LL, Carson DS. Calcium-channel blockers and risk of myocardial infarction — more hype than harm. *Am J Health Syst Pharm* 1995;52:1460-2.
50. Ryden L, Malmberg K. Calcium channel blockers or beta receptor antagonists for patients with ischaemic heart disease: what is the best choice? *Eur Heart J* 1996;17:1-3.
51. Kaplan NM. Do calcium antagonists cause cancer? *Lancet* 1996;348:541.
52. Lucas BD Jr, Hilleman DE. Media sensationalism of clinical trials: freedom of information or potential for causing patient harm? *Ann Pharmacother* 1995;29:629-31.
53. Kaplan NM. Dear doctor . . . regarding calcium channel blockers. *JAMA* 1996;275:518.
54. Lichtlen PR. Nifedipine study. *Circulation* 1996;93:1472.
55. *Idem*. Risks and benefits of calcium antagonists. *Lancet* 1995;346:962.
56. Kloner RA. Nifedipine in ischemic heart disease. *Circulation* 1995;92:1074-8.
57. Messerli FH. Are calcium antagonists safe? *Lancet* 1995;346:767-8.
58. Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. *Circulation* 1995;92:1068-73.
59. Monge JC. Safety of antihypertensive therapies: a series of interactive panels — are calcium channel blockers safe? Scientific update. No. 120-13. Toronto: St. Michael's Hospital Division of Cardiology, 1996.
60. Messerli FH. Meta-analysis and bouillabaisse. *Ann Intern Med* 1996;125:519.
61. *Idem*. Whatever happened to the calcium antagonist controversy? *J Am Coll Cardiol* 1996;28:12-3.
62. Furberg CD, Psaty BM. Nifedipine trials. *Circulation* 1996;93:1474.
63. *Idem*. Corrections to the nifedipine meta-analysis. *Circulation* 1996;93:1475-6.
64. *Idem*. Nifedipine in patients with heart disease. *Circulation* 1996;93:1473.
65. Furberg CD, Pahor M, Psaty BM. The unnecessary controversy. *Eur Heart J* 1996;17:1142-7.
66. Hardell L, Axelson O, Fredrikson M. Antihypertensive drugs and risk of malignant diseases. *Lancet* 1996;348:542.
67. Furberg CD, Psaty BM. Calcium antagonists: antagonists or protagonists of mortality in elderly hypertensives? *J Am Geriatr Soc* 1995;43:1309-10.
68. Horton R. Are calcium antagonists safe? *Lancet* 1995;346:770.
69. Furberg CD, Psaty BM. Should dihydropyridines be used as first-line drugs in the treatment of hypertension? The con side. *Arch Intern Med* 1995;155:2157-61.
70. Pahor M, Guralnik JM, Salive ME, Corti M-C, Havlik RJ. Do calcium antagonists cause cancer? *Lancet* 1996;348:541-2.
71. Cooper RS, Freeman V. Myocardial infarction associated with antihypertensive drug therapy. *JAMA* 1996;275:515-6.
72. Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik RJ. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996;347:1061-5.
73. Cooper RS. Risks and benefits of calcium antagonists. *Lancet* 1995;346:961.
74. Tierney WM. Meta-analysis and bouillabaisse. *Ann Intern Med* 1996;125:519.
75. Pahor M, Guralnik JM, Ferrucci L, et al. Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996;348:493-7.
76. Gifford RW Jr. Are calcium antagonists safe? *Cleve Clin Med* 1995;62:348-50.
77. Yusuf S. Calcium antagonists in coronary artery disease and hypertension: time for reevaluation? *Circulation* 1995;92:1079-82.
78. Blandino DA. Myocardial infarction associated with antihypertensive drug therapy. *JAMA* 1996;275:516.
79. Psaty BM, Koepsell TD, Weiss NS, et al. Dear doctor . . . regarding calcium channel blockers. *JAMA* 1996;275:518-9.
80. Psaty BM, Heckbert SR, Koepsell TD, et al. Myocardial infarction associated with antihypertensive drug therapy. *JAMA* 1996;275:516.
81. Psaty BM, Sevick MA. Antagonism to calcium antagonists. *Lancet* 1996;347:1761.
82. Barlow RE, Bartholomew DJ, Bremner JM, Brunk HD. Statistical inference under order restrictions: the theory and application of isotonic regression. Chichester, England: John Wiley, 1972.
83. Cox DR, Snell EJ. Analysis of binary data. London: Chapman & Hall, 1989.
84. Agresti A. Categorical data analysis. New York: John Wiley, 1990.
85. S-PLUS guide to statistical and mathematical analysis. Seattle: Statistical Sciences, 1995.
86. Angell M, Kassirer JP. Editorials and conflicts of interest. *N Engl J Med* 1996;335:1055-60.