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Calcium Antagonists and Cancer
Is There Really a Link?

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Summary

Recent publications have raised concerns about a possible link between calcium antagonist therapy and the development of cancer. Comparisons of the methodology and results of these studies with other studies where an association between calcium antagonist therapy and cancer has not been apparent suggests that the association is most likely to be due to selection bias or chance. Clinical and biochemical studies have not produced a consistent plausible mechanism for a causative link between calcium antagonists and the development of cancer. Further prospective data that will be available from long-term morbidity and mortality trials of the use of calcium antagonists in cardiovascular diseases will be of value in establishing the safety of these drugs.

An association between calcium antagonist therapy and the risk of cancer has been reported in 2 publications by Pahor et al.[1,2] and in a recent publication by Fitzpatrick et al.[3] Both of the studies by Pahor et al.[1,2] were epidemiological cohort studies and derived from the same database. The results were obtained from a survey of older persons, entitled 'The Established Populations for Epidemiological Studies in the Elderly' (EPESE), which was supported by the US National Institute on Aging.

The EPESE study began in 1982, when regional surveys on all patients aged 65 years or older were performed in selected regions of the US. The data reported in these 2 publications were obtained from questionnaires completed during follow-up of the patients in 1988, and a record of the patients who developed cancer between 1988 and 1992. At the baseline interview in 1988, demographic data were obtained and the current use of medications, including calcium antagonists, by the patients was recorded. The subsequent development of cancer was determined from hospital files, contact with relatives, examination of obituaries in local papers and examination of death certificates.

In the first Pahor et al. publication,[1] the risk of developing cancer was compared in patients who were receiving calcium antagonists (451 patients) with those who were not receiving these drugs (4601 patients). 47 patients who were receiving calcium antagonists in 1988 developed cancer over the 4-year follow-up period, compared with 373 patients in the group not taking calcium antagonists. Patients taking calcium antagonists were 1.42 times more likely to have developed a cancer than those who did not ($p = 0.032$). The risk of developing cancer appeared even greater when the results were adjusted for potential confounding factors (hazard ratio 1.72; $p = 0.0005$). Verapamil and nifedipine were both reported to be associated with an increased risk of cancer, but diltiazem was not, despite the fact that more patients received diltiazem than the other calcium antagonists and the duration of exposure to diltiazem had been

longer. No data were presented for other calcium antagonists.

In the second Pahor et al. publication,[2] 750 patients from the EPESE study, but who received either calcium antagonists, β-blockers or ACE inhibitors for the treatment of hypertension, were compared. Over the 4 years of follow-up from 1988 to 1992, patients receiving calcium antagonists were said to be twice as likely to develop cancer as patients treated with ACE inhibitors or β-blockers ($p < 0.005$). Verapamil and nifedipine were both associated with an increased risk of cancer, while diltiazem was not, despite the fact that it was the most commonly used calcium antagonist. No data were presented for other calcium antagonists.

These 2 studies have been criticised for a number of reasons.[4] Most importantly, the use of calcium antagonists was assessed only at baseline in 1988 and it is not known how long calcium antagonist therapy was continued during the course of the study. In addition, the population was elderly (mean age 79 years) and would be expected to have a high incidence of cancer and other co-morbid conditions, although the number of cancers observed was small.

The third manuscript by Fitzpatrick et al.[3] reported the results of a prospective cohort study in 5888 men and women aged >65 years who were followed for approximately 5 years on average. The study was called the Cardiovascular Health Study and the primary aim was to investigate cardiovascular endpoints. However, data relating to hospitalisations and deaths due to cancer were also documented. Fitzpatrick et al.[3] focused on the relationship between calcium antagonist use (defined as 'any use of calcium antagonists during the follow-up period') and the incidence of breast cancer. The analysis was performed on data from 3198 postmenopausal women aged 65 to 100 years. Patients known to have breast cancer at entry to the study were excluded from the analysis. 759 women received a calcium antagonist, 20 of whom developed breast cancer. In contrast, 2439 women did not receive calcium antagonists, 55 of whom developed breast cancer. The hazard ratio for developing breast cancer in calcium antagonists users was 2.57 [95% confidence interval (CI) 1.47 to 4.49, $p = 0.0009$]. No such increase in the risk of breast cancer was seen in patients receiving β-blockers, ACE inhibitors or diuretics although, with the exception of diuretics (28 cases of breast cancer), the number of breast cancers in each of these treatment groups was small (6 to 15).

There appeared to be a significant interaction between calcium antagonist use and the use of estrogen hormone replacement therapy (hazard ratio 4.48, 95% CI, 1.58 to 12.75, $p = 0.005$). However, this analysis was based on only 4 cases of breast cancer occurring in 123 patients who received both calcium antagonists and estrogens. Women who received calcium antagonists were well matched with women who received other antihypertensives or no antihypertensive except for the presence of coronary heart disease which was over 5 times more common in women receiving calcium antagonists than those not on antihypertensives and 2.5 times more common than in women receiving other antihypertensive therapy. Interestingly, when all women who developed breast cancer were compared with women who did not develop breast cancer (irrespective of whether or not they received antihypertensive therapy) the only major difference between the 2 groups was the presence of coronary artery disease (29.3% in women with breast cancer compared to 20.1% in women without).

These observations suggest that the association between calcium antagonists and breast cancer may have been confounded by an association between the presence of coronary artery disease (for which calcium antagonists are prescribed) and the presence of breast cancer. In addition, the results of the study are based on a small number of breast cancers particularly in the group receiving calcium antagonists.

There are 3 possible reasons for the increased incidence of cancer in patients receiving calcium antagonists observed in these 2 studies: (i) selection bias (the patients who developed cancer may have been more likely to require calcium antagonist therapy); (ii) calcium antagonists either caused

cancer, or promoted the growth of cancers that were already present, but not clinically apparent; and (iii) extensive analysis of the database may have led to the associations between calcium antagonist and cancer by chance.

The aim of this article is to discuss these possibilities in the light of previously published data on the associations between calcium antagonists and cancer that have been identified from a search on the Medline database back to 1965.

1. Selection Bias

The results of these studies may have resulted from selection bias because of a greater need for patients at high risk of cancer to require calcium antagonist therapy for ischaemic heart disease or hypertension. Patients who received calcium antagonists had a much higher incidence of coronary artery disease than those who did not take calcium antagonists (for example 71.2% versus 21.9%).[1] Individuals in the first study by Pahor et al.[1] also had a significantly higher incidence of heart failure, hypertension, stroke and diabetes mellitus. Cardiovascular diseases and cancers share many important common risk factors[5,6] and probably share a number of risk factors that are not readily apparent. Patients with hypertension have previously been reported to have an increased incidence of malignancy.[7]

In the first publication by Pahor et al.,[1] there was an apparent increase in the risk of developing a wide range of cancers in those patients receiving calcium antagonists. The exception was lung cancer, for which the risk appeared to be decreased in these patients. With reference to smoking habits, only information on current use was presented in this publication; 90% of patients did not smoke during the period of study, irrespective of whether or not they received calcium antagonists. No information was presented concerning smoking habits before the study period.

Patients who took calcium antagonists may have had a greater lifetime exposure to cigarettes, leading to an increased risk of coronary heart disease and cancer. A lower risk of lung cancer in the patients who received calcium antagonists may seem inconsistent with this proposal. However, lung cancer may have presented at a relatively younger age than the other cancers. Furthermore, lung cancer is associated with poor long term survival, and the patients who were at highest risk of lung cancer in this population may have already died. It is also possible that other important differences in lifestyle, such as diet, may have existed between the groups, and were not corrected for in the analysis.

Pahor et al.[1] reported an apparent dose-response relationship for the association between calcium antagonist therapy and cancer: the higher the dosage of the calcium antagonist, the greater the risk of cancer. However, this could also be explained by association between coronary artery disease and cancer resulting from common risk factors. Patients who were heavier smokers or who had the poorest diets would be expected to have more severe coronary artery disease (requiring higher dosages of drug therapy), together with a greater risk of malignancy.

A similar selection bias could explain the higher risk of cancer in patients treated with calcium antagonists for hypertension compared with those treated with β-blockers or ACE inhibitors in the second publication.[2] In this study, the smoking habits of the patients were categorised into those who were lifelong nonsmokers, former smokers or current smokers, and smoking status was adjusted for in the analysis. However, information concerning the number of cigarettes smoked and the duration of smoking before 1988 were not presented. Patients receiving calcium antagonists may have had a greater lifelong exposure to cigarettes. It is interesting to note that data covering previous smoking habits were presented in the second publication,[2] but not in the first,[1] despite the fact that the information came from the same questionnaire. This suggests that the authors of these publications may have been a little selective in the data that they chose to include.

Hypertensive patients who had been heavier smokers may have been more likely to have re-

ceived calcium antagonists rather than β-blockers because of a higher incidence of respiratory problems associated with smoking. However, heavier smokers with chronic airways disease would also have been more likely to have received ACE inhibitors or diuretics. The incidence of cancer was not increased in patients receiving ACE inhibitors, and no data were presented concerning the incidence of cancer in patients receiving diuretics.

A similar argument can be made to explain the higher incidence of breast cancer in patients taking calcium antagonists in the study by Fitzpatrick et al.[3] Breast cancer appeared to be more common in patients with coronary artery disease, and patients with coronary artery disease were much more likely to receive calcium antagonists than patients without coronary artery disease.

2. Calcium Antagonists Causing or Promoting Cancer

If calcium antagonist therapy was the cause of the higher incidence of cancer in this population, it could only have occurred as a result of an effect on the rate of growth of cancers already present. The 4-year time span of the study is too short for any chemical to induce the formation of a new cancer and for it to grow large enough to be clinically apparent.[8,9] The increased incidence of cancer was apparent within 2 years of the commencement of follow-up.[1,2] This would require an extraordinarily potent tumour-promoting effect.

Pahor et al.[1,2] suggest that calcium antagonists may promote the growth of tumours because of an ability to inhibit apoptosis (or programmed cell death) that has been demonstrated in several *in vitro* studies.[10-12] Impaired apoptosis refers to the situation in which cancer cells continue growing when they should have died because of genetic programming. In contrast, other *in vitro* studies have reported that calcium antagonists induce apoptosis in human glioblastoma cells when used in high concentrations in the presence of cisplatin.[13] However, in laboratory studies, calcium antagonists have been shown to have a number of other effects on cancers, including a reduction in cell growth, both *in vitro*[14] and *in vivo*,[15] and reduced metastatic dissemination.[16-22]

If calcium antagonists promote tumour growth, the long term administration of these drugs to patients known to have cancers would be expected to increase tumour growth and worsen prognosis. The only study to specifically examine this possibility in humans was a cohort study of 719 patients with advanced carcinoma of the lung and colon,[23] who were free from other major life-threatening diseases, and who were followed for a mean duration of 5.8 months. 19 of these patients were coincidentally receiving long term calcium antagonist therapy (mainly nifedipine, diltiazem or verapamil) for the treatment of hypertension or chronic angina. The progression of malignant disease was significantly slower in the patients receiving calcium antagonists ($p = 0.045$). Furthermore, there was a nonsignificant trend towards improved survival in these patients ($p = 0.057$). It must be emphasised that this was a retrospective cohort study that may have been subject to selection bias, and the number of patients studied was small. However, the results are supported by studies in animals, showing enhanced regression of tumours when calcium antagonist therapy is combined with cytotoxic therapy,[24-28] albeit at doses considerably higher than those used for long term therapy in humans.

3. Possibility of a Chance Association With Malignancy

3.1 Clinical Studies with Calcium Antagonists

Larger studies have shown no association between calcium antagonist therapy and cancer. Braun et al.[29] recently published a cohort study of 11 575 patients who had a diagnosis of coronary artery disease, and who were followed for a mean period of 3.2 years. Approximately half of these patients received calcium antagonist therapy. The important differences between this study[29] and those reported by Pahor et al.[1,2] were that the patients in the study of Braun et al.[29] all had coronary artery disease, and the calcium antagonist group and control group were both well matched

for risk factors associated with coronary artery disease (and presumably with cancer). In addition, the study was much larger than those of Pahor et al.,[1,2] had an equal number of patients receiving or not receiving calcium antagonists, and the age of the population studied was considerably younger (mean age 60 years). No difference was found in the incidence of cancer during the period of follow-up between the patients receiving and those not receiving calcium antagonists (relative risk 1.0; 95% CI 0.72 to 1.40).

Another case-controlled study[30] examined the relationship between cancer and calcium antagonist, ACE inhibitor or β-blocker therapy in 446 patients with cancer and 1750 healthy individuals. The data were obtained from the UK General Practice Research Database, and the study population was restricted to patients with at least a 4-year medical history recorded on computer. The cases and controls were well matched for age (mean age 71.6 and 71.3 years, respectively), smoking status, body mass index and duration of hypertension. However, there were no data concerning the presence of comorbid conditions such as ischaemic heart disease or chronic airways disease. The relative risk of cancer was calculated for calcium antagonists and ACE inhibitors, using β-blockers as the reference therapy.

In this study,[30] there was a trend towards an increased incidence of cancer with calcium antagonists, which was not statistically significant (relative risk 1.17; 95% CI 0.98 to 1.63). There was no significant association between the duration of calcium antagonist therapy and the incidence of cancer, but patients receiving high dosages of calcium antagonists had the highest incidence of cancer, an incidence that was significantly greater than that observed for β-blockers (relative risk 1.71, 95% CI 1.06 to 2.78). Interestingly, the relative risk for lung cancer also appeared to be higher in patients receiving ACE inhibitors compared with those receiving β-blockers.

Smoking status was unknown in 25% of the healthy individuals and 29% of the patients with cancer in this study,[30] and there was no information concerning the number of cigarettes smoked or the duration of smoking in either group. Thus, it is possible that patients who were heavier smokers and who had significant chronic airways disease and a higher risk of cancer were preferentially prescribed calcium antagonists or ACE inhibitors rather than β-blockers for the treatment of hypertension.

In a 3-year randomised, double-blind comparison of the calcium antagonist isradipine and the diuretic hydrochlorothiazide in 883 patients with hypertension, the incidence of cancer appeared to be lower with isradipine (2.94 per 100 patients) than with hydrochlorothiazide (4.53 per 100 patients), but the difference was not statistically significant ($p = 0.21$).[31]

A prospective, randomised, controlled clinical trial compared the effects of nifedipine therapy with those of placebo in 1632 elderly Chinese patients with hypertension, who were treated for a mean period of 30 months.[32] A trend towards a reduction in the occurrence of new malignancies was observed with nifedipine, which did not achieve statistical significance (relative risk 0.24, 95% CI 0.05 to 1.13). However, the number of new malignancies observed was small.

A recent study by Olsen et al.[33] compared the incidence of cancer in 17 944 individuals who received calcium antagonists and who were followed for up to 2 years with the incidence expected from population data. 412 cancers occurred in the patients while 413.9 were expected. The standardised incidence ratio was 1.00 (95% CI 0.90 to 1.10). Although the follow-up period of this study was relatively short, the number of patients studied was large. The results did not suggest an association between calcium antagonists and cancer.

3.2 Clinical Studies With Other Cardiovascular Drugs

Calcium antagonists are not the first cardiovascular drugs to face allegations of causing malignancy. Associations between cardiovascular drugs and malignancy have even been reported from prospective, randomised clinical trials in which selection

bias would not normally be considered likely to occur. Sporadic associations may occur by chance, particularly in trials that are not specifically designed to examine the effects of a drug therapy on cancer.

However, under certain circumstances, selection bias may still occur. In the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials,[34,35] which compared the effects of enalapril therapy with those of placebo on the treatment of left ventricular dysfunction in 6797 patients over a period of approximately 3 years, an apparent increase in the number of gastrointestinal malignancies was observed in the patients receiving enalapril. It has been argued that the patients who received enalapril and who subsequently had less severe heart failure were more likely to be investigated for possible malignancies.[35] In the UK Medical Research Council trial of the treatment of hypertension in older adults,[36] atenolol therapy was associated with a significantly higher risk of developing bronchial cancer than thiazide or placebo. This was refuted in subsequent studies.[37]

4. Conclusion

A consideration of the results of laboratory and animal experiments, and the results of the 4 available cohort studies and other clinical data, suggest that either selection bias or association by chance are the most likely explanations for the reported relationship between calcium antagonist therapy and cancer in the 2 papers by Pahor et al.[1,2] and the publication by Fitzpatrick et al.[3] Furthermore, the results of these studies cannot be generalised to all calcium antagonists, as no association was found between diltiazem therapy and the development of cancer in the Pahor et al.[1,2] papers. The study by Fitzgerald et al.[3] was too small to allow conclusions about the hazard ratio for individual calcium antagonists to be made.

It should also be noted that this database used by Pahor et al.[1,2] has been used to report an apparent association between calcium antagonist therapy and mortality,[38] and between calcium antagonist therapy and gastrointestinal bleeding.[1] This suggests that the data may have been used to search for multiple relationships, increasing the likelihood of chance associations.

While selection bias or association by chance appear to be the most likely explanations for the relationship between calcium antagonist therapy and cancer, continued surveillance of the incidence of cancer in prospective clinical trials involving calcium antagonists would clearly be prudent. Further prospective data will be available shortly from long term morbidity and mortality trials of the use of calcium antagonists for the treatment of hypertension, for example, Systolic Hypertension in the Elderly Long-Term Lacidipine Trial (SHELL), Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Systolic Hypertension in Europe Trial (SYST-EUR).

References

1. Pahor M, Guralnik JM, Ferrucci L, et al. Calcium-channel blockade and incidence of cancer in aged populations. Lancet 1996; 348: 493-7
2. Pahor M, Guralnik JM, Salive ME, et al. Do calcium channel blockers increase the risk of cancer? Am J Hypertens 1996; 9: 695-99
3. Fitzpatrick AL, Daling JR, Furberg CD, et al. Use of calcium channel blockers and breast carcinoma risk in postmenopausal women. Cancer 1997; 80: 1438-47
4. Walker AM, Stampfer MJ. Observational studies of drug safety. Lancet 1996: 348: 489
5. Saracci R, Trichopoulos D. Aetiological leads. In: Peckham M, Pinedo HM, Veronesi V, editors. Oxford textbook of oncology. Oxford: Oxford University Press, 1995: 167-74
6. Framer JA, Grotto A Jr. Dyslipidemia and other risk factors for coronary artery disease. In: Braunwald E, editor. Philadelphia: Saunders, 1997: 1126-60
7. Dyer AR, Stamler J, Berkson DM, et al. High blood-pressure: A risk factor for cancer mortality? Lancet 1975; 1 (7915): 1051-6
8. Bel Buono R, Wright N. The growth of human tumors. In: Peckham M, Pinedo HM, Veronesi V, editors. Oxford textbook of oncology. Oxford: Oxford University Press, 1995: 3-11
9. Yuspa SH, Shield S. Etiology of cancer: chemical factors. In: DeVita VT, Hellman S, Rosenberg SA, editors. Principles and practice of oncology. Philadelphia: Lippincott-Raven, 1997: 185-202
10. Connor J, Sawczuk IS, Benson MC, et al. Calcium channel antagonists delay regression of androgen-dependent tissues and suppress gene activity associated with cell death. Prostate 1988; 13: 118-30
11. Juntti Berggren L, Larsson O, Rorsman P, et al. Increased activity of L-type Ca^{2+} channels exposed to serum from patients with type I diabetes. Science 1993; 261: 86-90
12. Ray SD, Kamendulis LM, Gurule MW, et al. Ca^{2+} antagonists inhibit DNA fragmentation and toxic cell death induced by acetaminophen. FASEB J 1993; 7: 453-63

13. Kondo S, Yin D, Morimura T, et al. Combination therapy with cisplatin and nifedipine induces apoptosis in cisplatin-sensitive and cisplatin-resistant human glioblastoma cells. Br J Cancer 1995; 71: 282-9
14. Yonoda T, Kitamura M, Ogawa T, et al. Control of VX_3 carcinoma cell growth in culture by calcium, calmodulin and prostaglandins. Cancer Res 1985; 45: 396-405
15. Taylor JM, Simpson RU. Inhibition of cancer cell growth by calcium channel antagonists in the athymic mouse. Cancer Res 1992; 52: 2413-8
16. Onoda JM, Diglio C, Taylor JD, et al. Antimetastatic effect of the calcium channel blocker dilantizem [abstract]. Proc Ann Meet Am Assoc Cancer Res 1984; 25: 351
17. Honn KV, Onoda JM, Diglio CA, et al. Inhibition of tumor cell-platelet interactions and tumor metastasis by the calcium channel blocker, nimodipine. Clin Exp Metastasis 1984; 2: 61-77
18. Onoda JM, Sloan BF, Taylor JD, et al. Calcium channel blockers: inhibitors of tumor cell-platelet-endothelial cell interactions. In: Hemostatic mechanisms and metastases. Hunn KV, Sloane BF, editors. Boston (MA): Martinus Nijhoff, 1984: 244-58
19. Honn KV, Onoda JM, Diglio CA, et al. Calcium channel blockers: potential antimetastatic agents. Proc Soc Exp Biol Med 1983; 174 (1): 16-9
20. Bando H, Yamashita T, Tsubura E. Effects of antiplatelet agents on pulmonary metastases. Gann 1984; 75 (3): 284-91
21. Gastpar H, Ambrus JL, Ambrus CM. Platelet aggregation inhibitors in the prevention of metastasis in neoplastic disease: a review of experimental and clinical investigations. J Med 1981; 12: 15-33
22. Tsuruo T, Iida H, Makishima F, et al. Inhibition of spontaneous and experimental tumor metastasis by the calcium antagonist verapamil. Cancer Chemother Pharmacol 1985; 14: 30-3
23. Zacharski LR, Moritz TE, Haakenson CM, et al. Chronic calcium antagonist use in carcinoma of the lung and colon: a retrospective cohort observational study. Cancer Invest 1990; 8: 451-8
24. Tsuruo T, Iida H, Nojiri M, et al. Circumvention of vincristine and adriamycin resistance *in vitro* and *in vivo* by calcium influx blockers. Cancer Res 1983; 43 (6): 2905-10
25. Slater LM, Murray SL, Wetzel MW, et al. Verapamil restoration of daunorubicin responsiveness in daunorubicin-resistant Ehrlich ascites carcinoma. J Clin Invest 1982; 70 (5); 1131-4
26. Tsuruo T, Iida H, Naganuma K, et al. Promotion of verapamil of vincristine responsiveness in tumor cell lines inherently resistant to the drug. Cancer Res 1983; 43 (2): 808-13
27. Slater L, Murray S, Wetzel M, et al. Verapamil potentiation of VP-16-213 in acute lymphatic leukemia (ALL) *in vivo* and reversal of pleiotropic drug resistance (PDR) [abstract]. Proc Ann Meet Am Assoc Cancer Res 1985; 26: 336
28. Onoda JM, Jacobs JR, Taylor JD, et al. Cisplatinum and nifedipine: synergistic cytotoxicity against murine solid tumors and their metastases. Cancer Lett 1986; 30: 181-8
29. Braun S, Boyko V, Behar S, et al. Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11,575 patients. JACC 1996; 28 (1): 7-11
30. Jick H, Jick S, Derby LE, et al. Calcium-channel blockers and risk of cancer. Lancet 1997; 349: 525-8
31. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the multicenter isradipine diuretic atherosclerosis study (MIDAS). JAMA 1996; 27: 785-91
32. Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). J Hypertens 1996; 14: 1237-45
33. Olsen JH, Storensen HT, Friis S, et al. Cancer risk in users of calcium channel-blockers [abstract]. Pharmacoepidemiol Drug Saf 1997; 6 (Suppl. 2): 31
34. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325 (5): 293-302
35. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. N Engl J Med 1992; 327: 685-91
36. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 1992; 304: 405-12
37. Hole DJ, Hawthorne VM, Isles CG, et al. Incidence of and mortality from cancer in hypertensive patients. BMJ 1993; 306: 609-11
38. Pahor M, Guralnik JM, Corti MC, et al. Long term survival and use of antihypertensive medications in the elderly. J Am Geriat Soc 1995; 43 (11); 1191-7

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