REVIEW ARTICLE

Drug Safety 2001; 24 (10): 727-739
0114-5916/01/0010-0727/$22.00/0

Antihypertensive Therapy and Cancer Risk

Dirk C. Felmeden and *Gregory Y.H. Lip*

University Department of Medicine, City Hospital, Birmingham, England

Contents

Abstract

The aim of this article is to provide an overview of the available data linking antihypertensive drug therapy to cancer risk. In recent years, a number of mainly retrospective studies have reached different conclusions on the risk of cancer in patients with hypertension being treated with different antihypertensive drugs. At some point or another nearly all antihypertensive drugs have been suggested to increase the risk of cancer. Some studies have even found an association between hypertension itself and increased carcinogenesis. For calcium channel antagonists, β-blockers and α-blockers, the available evidence seems to favour a neutral effect on cancer development and death rate. For ACE inhibitors, the overall data suggest a similar neutral effect on cancer or, possibly, a small protective effect. Perhaps the strongest evidence in favour of a link, although probably weak, between cancer and antihypertensive drugs is with the diuretics. Until further solid data are available from prospective clinical trials, we suggest that the management of hypertension should continue according to current treatment guidelines with little fear of any substantial cancer risk.

Hypertension is one of the most prevalent cardiovascular risk factors in developed countries, with a substantial impact on morbidity and mortality from myocardial infarction and stroke. Antihypertensive treatment has been convincingly shown to reduce morbidity and mortality from cardiovascular and cerebrovascular events.[1-4] However, some trials failed to demonstrate a reduction in all-cause mortality, thus raising the possibility that nonvascular mortality from other causes, such as malignancy, might potentially be higher in treated patients with hypertension.

Indeed, for several years now, antihypertensive treatment or even hypertension *per se* has been linked to a increased risk of malignancy.[5] One recent review of epidemiological evidence, particularly from prospective studies, concludes that there might be a weakly but significantly increased risk of cancer in hypertension or its treatment.[5] Many classes of antihypertensive drugs have been accused of increasing this risk of cancer, but these studies were mainly case-controlled and do not withstand prospective randomised evaluation.[5-15]

The aim of this article is to provide an overview of the available data linking antihypertensive drug therapy to cancer risk. Published and unpublished data for this review were identified by searches of Medline, Embase, CancerLit and reference lists from relevant articles. Searches were concentrated upon the prevalence of cancer and antihypertensive drugs. Representative studies for various drugs and cancer in patients with hypertension were included.

1. Hypertension and Cancer

1.1 Evidence for an Association

The first prospective study to report an association between cancer risk and hypertension was performed by Dyer et al.[16] in 1975. Univariate and multivariate analyses demonstrated a relationship of systolic and diastolic blood pressure measured at study entry to subsequent 14-year mortality among 1233 White males, including subsequent mortality from lung, colon and other cancers. This association remained even after adjustment for confounders such as age, cholesterol and smoking, suggesting that high blood pressure *per se* was associated with an increased risk of death attributable to cancer.

Since then, several other studies have also verified hypertension to be a risk factor for cancer.[17-22] For example, the Western Electric Health Study reported an association between blood pressure and 17-year cancer mortality. The increase in cancer appears to be at various sites, including the kidney, colon and even the endometrium. The interaction of other risk factors, such as diabetes mellitus, obesity, smoking, age and sex, increases the complexity of this issue. The duration of hypertension seems to enhance the risk of cancer in several of the studies.[22-24]

Furthermore, Buck and Donner[18] reported a prospective observational study where the increased cancer risk was most pronounced among newly diagnosed patients with moderate or severe hypertension. However, some cancers were associated with a subsequent rise in blood pressure, suggesting that in some instances at least, the causal direction may be from cancer to hypertension, rather than the reverse.

In contrast, the Honolulu Heart Program,[25] which was a prospective observational study, failed to discover any significant association of hypertension with cancer after multivariate analysis. Similarly, a retrospective investigation from the Glasgow Blood Pressure Clinic database[26] revealed no increase in overall cancer mortality among patients with hypertension, but a significantly higher relative risk of developing renal cell cancer. In contrast, a large cohort study of nearly 1 million Americans for 7 years did not find an increased risk of fatal renal cell carcinoma in patients with hypertension.[25]

In summary, the prospect of hypertension itself being associated with a small increase in cancer is a possibility that cannot be disregarded on grounds of the presently available evidence. This however does not take into account the potential bias as a result of unpublished negative data. Furthermore, some of the evidence has been conflicting and may reflect many confounders, including differences in

population cohorts, observational periods and medical practice.

1.2 Possible Mechanisms of Carcinogenesis in Hypertension

There have been several plausible theories about possible underlying mechanism(s) linking hypertension to an increase in cancer risk.

Physiological aspects of primary hypertension include abnormalities in vascular smooth muscle proliferation, leading to increased peripheral resistance.[27] The increased proliferation of vascular smooth muscle in spontaneous hypertensive rats shows an exaggerated response to growth stimuli,[28-30] and interestingly, similar abnormalities in growth control of vascular smooth muscle in humans can be observed in cardiovascular disease.[31-33] For example, apoptosis and vascular wall remodelling have been described in hypertension.[31] Many of the abnormal pathways that have been originally discovered in neoplastic growth could be linked to carcinogenesis in hypertension.[34]

Abnormalities of carcinogen binding to DNA have been reported in lymphocytes of patients with hypertension.[35] Pero et al.[36] also reported that the number of carcinogen-induced chromosomal aberrations in lymphocytes increased linearly with the diastolic blood pressures of those individuals, and high carcinogen-induced repair synthesis was also associated with increased chromosomal damage. Thus, patients with hypertension have a greater potential for accumulating DNA damage, because of an increased chemical reactivity of lymphocytes to carcinogen exposure, than do normotensive individuals.[36] In spontaneous hypertensive rats there is an amplified but variable response to carcinogens,[37,38] although the exact underlying mechanism remain unclear.

Finally, hypertension has been associated with abnormal angiogenesis, and this pathological process seems to be increasingly related to carcinogenesis.[39,40] Interestingly, increasing evidence is also emerging for the role of angiogenesis in atherosclerotic vascular disease.[41,42]

2. Diuretics

Most classes of antihypertensive drugs have been indicted of increasing the risk of malignancies at some time or another. Diuretics, with one of the longest records of accomplishment in the treatment of hypertension, are no exception.

2.1 What Is the Evidence?

Several case-control and cohort studies have looked into the possible relationship between diuretic use and cancer risk (table I). One of the first studies suggesting that diuretic therapy might be associated with renal cell carcinoma came from a small interview-based study of 160 incident cases and age-, race- and sex-matched neighbourhood controls. In this study, diuretic use appeared to be a risk factor for cancer only in women [relative risk (RR) = 4.5, p = 0.002].[44] This was confirmed by a larger population-based case-control study of 518 cases and 1381 controls, where diuretic use was also associated with an increased risk for renal cell carcinoma among women, but not among men.[45]

Hiatt et al.[46] investigated the association between renal cell carcinoma and the use of thiazides in a case-control study of 257 cases and age- and sex-matched controls, and after adjusting for the potential confounders (smoking, body mass index, hypertension and history of kidney infection) there remained a significantly elevated RR of 4.0 [95% confidence interval (CI) 1.5 to 10.8] for renal cancer associated with thiazide use amongst women.[41] Similarly, Weinmann et al.[24] reported a population-based case-control study of 206 cases of renal cell carcinoma where the odds ratios (OR) for cancer associated with any use of a diuretic drug were 2.2 (95% CI 1.2 to 3.9) for men and 1.8 (95% CI 1.01 to 3.2) for women. Importantly, an increased duration of diuretic use and increased risk of renal cell cancer were positively associated.

In contrast, other studies have not convincingly related cancer risk to diuretics. Chow et al.[48] studied 691 renal cell cancer cases and an equal number of controls in a population-based case-control study and found that antihypertensive medication,

Table I. Diuretics and cancer

Study	Number of cases/controls	Odds ratio (CI)	Cancer type	Comments
McCredie and Stewart[43]	489 cases, 523 controls	Men: 1.82 (1.18 to 2.80) Women: 1.44 (0.97 to 2.14)	RCC, renal pelvis cancer	β-Blockers increased risk for RCC and renal pelvis cancer
Yu et al.[44]	158 cases, 158 controls	Men: 1.0 (0.36 to 2.81) Women: 4.5	RCC	
Finkle et al.[10]	191 cases, 191 controls	Women: 3.14	RCC	Risk tended to increase with dose
Kreiger et al.[45]	518 cases, 1381 controls	Men: 1.98 (1.16 to 3.37) Women: 2.46	RCC	
Hiatt et al.[46]	257 cases, 257 controls	Men: NS Women: 4.0 (1.5 to 10.8)	RCC	
Mellemgaard et al.[47]	368 cases, 396 controls	Men: 1.35 (0.81 to 2.25) Women: 1.47 (0.9 to 2.40)	RCC	
Weinmann et al.[24]	206 cases, 292 controls	Men: 2.2 (1.2 to 3.9) Women: 1.8 (1.01 to 3.2)	RCC	
Chow et al.[48]	691 cases, 691 controls	1.4 (0.8 to 2.2)	RCC	Risk associated with hypertension and diuretics (antihypertensive drugs)
McLaughlin et al.[49]	1732 cases, 2309 controls	1.4 (1.2 to 1.7)	RCC	Increased risk only after >15 years use of diuretics
Heath et al.[11]	998 904	Men: 0.8 (0.4 to 1.3) Women: 3.1	RCC	Cohort study, diuretics and antihypertensives
Mellemgaard et al.[50]	192 133	Men: 2.21 Women: 2.22	RCC	Cohort study
Prineas et al.[51]	35 192	2.6	RCC	Cohort study, postmenopausal women only
Grossman et al.[52]	Case-controlled: 10 195 Cohort: 1 226 229	Men: 1.69 (1.34 to 2.13) Women: 2.01 (1.56 to 2.67) Cohort: 2-fold	RCC	Meta-analysis of case-controlled[6,24,39-43,46,47] and cohort[7,48,49] studies

CI = confidence interval; **NS** = not significant; **RCC** = renal cell carcinoma.

including diuretics, given for non-blood pressure reducing purposes, increased cancer risk, especially among persons who reported no previous history of hypertension. Nevertheless, after adjustment for hypertension, the use of diuretics alone was associated with a statistically insignificant excess risk (OR 1.4; 95% CI 0.8 to 2.2).

The International Renal-Cell Cancer Study[49] was a large multicentre, population-based, case-control study of 1732 cases and 2309 sex- and age-matched controls, and after adjustment for hypertension, the risk for diuretics was reduced to unity, except among long term (>15 years) users. However, the risk for use of nondiuretic antihypertensive drugs remained significantly elevated and increased further with duration of use. Because of potential misclassifications of these highly correlated variables, the investigators were unable to distinguish the effects of treatment from its indication, hypertension.[49]

Overall, the evidence from case-controlled and cohort studies seems to favour the association of renal cell carcinoma and diuretic use. In a meta-analysis by Grossman et al.,[52] the patients in 3 cohort studies who were treated with diuretics were on average twice as likely to develop renal cell carcinoma than non-users of diuretics. In 9 case-controlled studies, diuretic therapy was also associated with an increased risk of renal cell carcinoma, with an overall OR of 1.55 (95% CI 1.42 to 1.71).

2.2 Is There a Real Association?

In many studies, the relationship between diuretic therapy and the risk of renal cell carcinoma became statistically not significant when corrected for possible confounders.[43,47,48,49] However, the

association remained significant and independent in other studies.[6,24,44-46] In cohort studies, the results are similarly variable. Some studies demonstrated an increased risk of renal cell carcinoma in men and women, another only in women and one failed to show any excess risk in patients with hypertension being treated with diuretics only.[7,50,51]

Case-control studies and cohort studies are at best hypothesis-generating even when several studies are combined in a meta-analysis. The latter is an important way of reducing the effects of random error, but is impossible to correct for potential bias present in the original studies, as well as publication bias. It is well known that positive results are far more likely to be published than neutral or negative results. In case-control studies and cohort studies, one of the main obstacles is the inability to exclude any confounding or unknown risk factors for renal cell carcinoma that are potentially shared by both hypertension and diuretic therapy. In many studies, data were not collected for other confounding factors like analgesia use, which is also strongly associated with an increased risk of renal cell carcinoma. [45,53] A further problem with retrospective analyses is the lack of differentiation between different thiazide diuretics or even loop diuretics. Furthermore, the dosages of diuretics used in earlier studies were much higher than the dosages of thiazide diuretics than usually prescribed nowadays, risking adverse metabolic effects without any additional antihypertensive benefits.[54]

Is the association between diuretics and renal cancer at all possible? On the whole, the effects of treatment with diuretics and other nondiuretic antihypertensive drugs on renal cell cancer risk are small. Both hypertension and use of antihypertensive drugs are closely associated with diuretic use, and because of potential misclassification of highly correlated events it may be impossible to disentangle fully the effects of these separate exposures. Several possible underlying mechanisms have nevertheless been hypothesised. The renal cell carcinoma originates from the renal tubular cell, which is also the target of the thiazide diuretics. It is conceivable that the constant chemical stimulation may have a low carcinogenic effect. This is of particular importance as hydrochlorothiazide, a cyclic imide compound, can be converted in the stomach to a mutagenic nitroso derivative.[55,56] Indeed, experimental data from animal studies suggest that diuretic treatment may result in nephropathy and renal adenomas.[57] Similar treatment caused tubular cells to exhibit tumour markers, as well as causing cell degeneration and death in the distal convoluted tubule.[58]

Diuretics may particularly increase the risk of renal cell carcinoma in women.[43,44-46] This increased risk has been postulated to be attributable to many reasons, for example an increase in estrogen levels,[10,59] but Lindblad et al.[53] found an increased risk of renal cell carcinoma in women following oophorectomy and demonstrated a protective effect of the oral contraceptive pill. Several potential mechanisms have been suggested for the potential sex-specific effect of diuretic-induced renal cell carcinoma. First, compared with men, women are prescribed diuretics far more often, perhaps because of the higher frequency of ankle oedema.[60] Secondly, animal data demonstrated that estrogen replacement in oophorectomised rats enhances the thiazide effect on the distal convoluted tubule.[61]

Three studies showed an association between the duration of diuretic therapy and increased risk of renal cell cancer.[24,47,49] However, lower average daily dosages of diuretics had a higher carcinogenic effect, somewhat contradicting the possibility of a cumulative dose effect of diuretics.[46] The carcinogenicity of diuretics is, if present, probably low grade, thus requiring prospective trials to last for more than 5 years, which is not common practice for most clinical trials. This kind of data will not be available in the near future. Ongoing studies such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[62] and analysis of the recently terminated Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) should provide further valuable information. However, the planned follow-up is still not

sufficiently long to answer the question of a relationship between diuretic use and risk of cancer, and it is doubtful if trials of the required length will ever be performed.

3. Calcium Channel Antagonists

Calcium channel antagonists have been used to treat hypertension for more than 2 decades. Some suspicion has been raised that these agents might be related to increased risk of heart attacks, Parkinson's disease, cognitive dysfunction, intra-operative and gastrointestinal bleeding.[63-67] Recently, some studies have even suggested that calcium channel antagonists might be associated with an increased risk of malignancy (table II).

3.1 What Is the Evidence?

In a 4-year follow-up of 750 people with hypertension using either β-blockers, ACE inhibitors or calcium channel antagonists, the RR of cancer for the calcium channel antagonists was 2.02 (95% CI 1.16 to 3.54) compared with β-blockers, even after adjusting for several confounders (age, sex, race, smoking, body mass index and number of hospital admissions not related to cancer).[14] In a similar prospective cohort study of 5052 people, Pahor et al.[69] reported that the incidence of cancer in patients treated with calcium channel antagonists compared with those not taking calcium channel antagonists was higher (RR 1.72; 95% CI 1.27 to 2.34), after adjustment for confounding factors. Fitzpatrick et al.[70] reported 75 women with incident invasive breast carcinoma who were retrospec-

Table II. Calcium channel antagonists (CAA) and cancer

Study	Number of cases/controls	Odds ratio (CI)	Cancer type	Comments
Jick et al.[68]	446 cases, 1750 controls	1.27 (0.98 to 1.63)	All	Cohort study of patients with hypertension compared with β-blocker users
Pahor et al.[69]	451 cases, 4601 controls	1.72 (1.27 to 2.34)	Most common	Prospective cohort study, significant dose-response gradient
Pahor et al.[14]	750 patients with hypertension	2.02 (1.16 to 3.54)	Most common	Prospective study
Fitzpatrick et al.[70]	3198 cases	2.57 (1.47 to 4.49)	Breast	Observational study, risk increased in combination with estrogens
Braun et al.[71]	5611 cases, 5543 controls	1.07 (0.83 to 1.37)	All	Prospective cohort study
Hole et al.[72]	2297 cases, 2910 controls	1.01 (0.84 to 1.18)	Fatal and nonfatal	Retrospective study
Meier et al.[73]	3706 cases, 14 155 controls	0.9 (0.7 to 1.2)	Breast	Retrospective case-controlled
Sorensen et al.[74]	23 167 users	1.04 (0.98 to 1.11)	Breast, colon	Population based cohort study
Stahl et al.[75]	391 cases, 1050 controls	Case-control: 1.05; longitudinal: 1.1	Fatal	Prospective case-control study and longitudinal study
Rosenberg et al.[76]	9513 cases, 6492 controls	1.1 (0.9 to 1.3)	Overall, 23 specific	Case-controlled study
Olsen et al.[77]	17 911 cases	All cancers: 1.0; colon: 0.8 (0.5 to 1.1)	All	Prospective observational study, short follow-up (up to 3 years)
Trenkwalder et al.[78]	137 cases, 354 controls	1.12 (0.7 to 1.8)	Fatal and nonfatal	Prospective cohort study, 3-year follow-up
Dong et al.[79]	11 201 patients	*vs* active control: 1.20 (0.60 to 2.42) *vs* placebo: 0.73 (0.39 to 1.39)	Fatal and nonfatal	Meta-analysis of prospective trials comparing verapamil *vs* active control and placebo
Michels et al.[80]	18 635 female nurses	1.25 (0.91 to 1.72)	All fatal and nonfatal cancer	Self-reported use of CCA

CI = confidence interval.

tively assessed for drug usage, and an elevated risk of breast carcinoma was associated with use of calcium channel antagonists (RR 2.57; 95% CI 1.47 to 4.49).

In contrast, in a large prospective study of 18 635 female nurses who were followed up for 6 years, 852 women were newly diagnosed with cancer and 335 women died of cancer: the RR of dying from cancer associated with the self-reported use of calcium channel antagonists was 1.25 (95% CI 0.91 to 1.72) after adjusting for several confounders,[80] which was not statistically significant. Similarly, another case-control drug surveillance study analysed 9513 patients with incident cancer of various sites and 6492 controls, and found that calcium channel antagonist use was unrelated to the overall risk of any cancer (RR 1.1; 95% CI 0.9 to 1.3),[76] although there was an increased risk for renal cancer (RR 1.8; 95% CI 1.1 to 2.7). A larger study using the Danish Cancer Registry with 17 911 patients receiving prescriptions of calcium channel antagonists found 412 cancers amongst users of calcium channel antagonists compared with 414 expected from county-specific incidence rates of cancer, suggesting the lack of any excess risk.[77] A recent and much larger case-control analysis of 3706 postmenopausal women who were diagnosed with incident breast cancer and 14 155 matched control women found no increased risk of breast cancer in women who used calcium channel antagonists (OR 0.9; 95% CI 0.7 to 1.2), ACE inhibitors (OR 1.0; 95% CI 0.7 to 1.5) or β-blockers (OR 1.0; 95% CI, 0.8 to 1.2) when compared with non-users of antihypertensive drugs.[73]

In the Department of Health Hypertension Care Computing Project (DHCCP), 11 663 patients with treated hypertension were recruited in a matched case-control study and a longitudinal study of survival, comparing 391 cases of cancer with 1050 controls; there was no increased cancer mortality in this population with the use of calcium channel antagonists.[75] Similarly, a further large cohort study using record linkage between a population-based prescription database, the Danish Cancer Registry and the Danish Death Registry, which included 23 167 users of calcium channel antagonists, found 967 incident cases of cancer, resulting in a standardised incidence ratio of 1.04 (95% CI 0.98 to 1.11), which was close to that expected in the Danish population.[74] In a retrospective analysis from the Glasgow Blood Pressure Clinic of 2297 patients who were prescribed calcium channel antagonists, the relative risk of cancer was virtually identical when compared with calcium channel antagonist non-users.[72] Three smaller studies analysing data on more than 10 000 patients with follow–up of up to 10 years exhibited no significant increase in risk of fatal or nonfatal cancer when compared with non-users.[61,71,78] A systematic review of all published randomised controlled trials of 11 201 patients in 39 trials who were receiving verapamil found no increased risk of cancer, cancer-related deaths or all-cause mortality.[79]

The nested case-controlled cohort study of Jick et al.[68] based on 446 cases of cancer and 1750 controls found that the RR estimates for all cancers in calcium channel antagonist users was 1.27 (95% CI 0.98 to 1.63). There was also no evidence of cumulative risk with duration of use of calcium channel antagonists.

3.2 Is There a Real Association?

There appears to be no substantial association between the use of calcium channel antagonists and the incidence rate of cancer or cancer mortality. Nonetheless, none of the above mentioned studies are based on a prospective randomised controlled design, resulting in some susceptibility to bias.

The best way of avoiding possible bias is a prospective randomised trial. Some evidence is available from the Systolic Hypertension in Europe (Syst-Eur) trial, where 4695 patients were randomly assigned to nitrendipine, with the possible addition of enalapril and hydrochlorothiazide, or matching placebos.[81] At 2 years of follow-up (which is still continuing), the use of calcium channel antagonists resulted in a 31% ($p < 0.001$) reduction of all cardiovascular end-points and in a trend[3] to reduced cancer mortality, although statistically not significant.

Table III. ACE inhibitors and cancer

Study	Number of cases/controls	Odds ratio (CI)	Cancer type	Comments
Lever et al.[82]	Men: 752; women: 807	Men: 0.80 (0.56 to 1.11) Women: 0.63 (0.41 to 0.93)	female sex–specific, lung	Retrospective cohort study of hypertensive patients, greatest benefit if follow-up >3 years
SOLVD Investigators[83]	Enalapril 2111, placebo 2117	1.59 (0.90 to 2.82)	Gastrointestinal	Prospective double-blind trial
Jick et al.[68]	446 cases, 1750 controls	0.79 (0.58 to 1.06)	All	Retrospective cohort study, ACE inhibitors *vs* β-blockers
Yusuf et al.[84]	9297 high risk patients	1.03 (0.85 to 1.26)	Death from noncardiovascular cause	All cause mortality, RR 0.84 (p = 0.005)

CI = confidence interval; **RR** = relative risk; **SOLVD** = Studies of Left Ventricular Dysfunction.

The cohort studies from the groups of Pahor, Furberg and Psaty [4,69,70] appear to be main ones associating calcium channel antagonists with an increased cancer risk. These studies were based on questionnaire follow-up and were not prospectively randomised; thus, correction for possible confounders is virtually impossible. However, larger cohort studies and even prospective trials have failed to unearth a convincing correlation between the use of calcium channel antagonists and cancer risk. Generally, in the studies with larger numbers, the RR approaches 1.0 with narrower confidence intervals.

4. ACE Inhibitors

4.1 What Is the Evidence?

It remained largely unnoticed that in the prospective Studies of Left Ventricular Dysfunction (SOLVD) study, patients with left ventricular dysfunction treated with enalapril showed a slightly higher incidence of malignancy than those receiving placebo (OR 1.59; CI 0.90 to 2.82) [table III].[83] In this study, there were 38 gastrointestinal cancers in the enalapril group compared with 22 in the placebo group (OR 1.7). Since the SOLVD study, several case reports have related ACE inhibitors to malignancies. For example, pemphigus vulgaris, which can be associated with internal malignancies, is a known adverse effect of captopril. One case report linked enalapril for the first time to pemphigus vegetans with a simultaneously occurring internal malignancy.[8] In a further case report, Kaposi's sarcoma appeared 8 months after the start of captopril treatment in a 70-year-old woman with rheumatoid arthritis. A marked reduction of cutaneous and gastric lesions occurred when captopril was stopped, suggesting a possible relation between Kaposi's sarcoma and the ACE inhibitors.[13,15] A later study however showed inhibition of angiogenesis in Kaposi's sarcoma by captopril, casting some doubt over the previous case reports.[85]

These limited data are in contrast to greater evidence suggesting the lack of cancer risk with the ACE inhibitors. In the recent large-scale Heart Outcomes Prevention Evaluation (HOPE) trial, a total of 9297 high risk patients treated with ramipril or placebo for a mean of 5 years had similar numbers of deaths from noncardiovascular causes in both groups (RR 1.03; CI 0.85 to 1.26; p = 0.74).[84] Several other retrospective studies investigating the possible association between various antihypertensive drugs and cancer risk failed to discover an increased risk with ACE inhibitor use.[14,73,75] The possible carcinogenicity of ACE inhibitors was further questioned when Jick et al.[68] demonstrated a reduction in malignancies comparing ACE inhibitors to β-blockers (RR 0.79; CI 0.58 to 1.06), although this decrease was not statistically significant, perhaps because of small numbers. The Scottish retrospective cohort study by Lever et al.,[82] who compared 1559 patients taking ACE inhibitors and 3648 on other antihypertensive drugs, demon-

strated a risk reduction for female sex–specific and lung cancers (RR 0.72; CI 0.55 to 0.92).

4.2 Mechanisms

The overall evidence so far would suggest that ACE inhibitors have a neutral effect on cancer risk in hypertension, and might even reduce that risk.

Some animal studies have reported that captopril inhibits angiogenesis and growth rate of experimental tumours, thus possibly suppressing the development and growth of new cancer.[86-88] Mitotic activity of human mammary ductal carcinoma cells is also inhibited by captopril, and the underlying mechanism seems to be captopril-induced generation of the cytotoxin H_2O_2, inhibiting proliferation of tumour cells.[89] There is also some evidence that blockade of the renin-angiotensin system may interfere with angiogenesis, at least in hypertension.[40]

5. β-Blockers

β-Blockers are widely used in hypertension, and seem to be equivalent to diuretics in their effects on stroke and coronary heart disease prevention.[2,90-91] Until recently this drug class had a clean track record with regard to possible association with increased cancer risk. However, a population-based case-control study of kidney cancer in New South Wales, Australia, changed this view.[48] McCredie et al.[43] reviewed 489 cases of renal cell cancer and 147 cases of renal pelvic cancer, who were compared with 523 controls: patients using regular β-blockers had an increased risk for renal cell cancer and renal pelvic cancer, with a RR of 1.5 to 1.8.

Since then, 2 further studies failed to demonstrate an increased risk of cancer with the β-blockers (table IV). In an analysis of 6528 patients with hypertension from the Glasgow Blood Pressure clinic, incident and fatal cancers were not significantly increased in male or female patients taking atenolol.[26] Furthermore, the DHCCP[75] only observed 5 cancer-related deaths in 99 patients treated with β-blockers (RR 0.719; CI 0.26 to 1.98).

In summary, there are insufficient data to suggest that β-blocker use in hypertension is associated with an increase in cancer risk.

6. Other Antihypertensive Drugs

One of the first antihypertensive drugs thought to be related to an increased risk of cancer was the rauwolfia alkaloids, which was treatment of choice in the past. Three retrospective investigations revealed an increased risk of breast cancer in patients with hypertension taking the rauwolfia derivative reserpine.[7,12,92] However, an observational study[93] and a prospective study demonstrated no significantly increased effect of reserpine on breast cancer.[16] The overall evidence to suggest an increased risk of cancer in association with rauwolfia alkaloids is not persuasive and further studies are unlikely because these agents do not form part of modern antihypertensive treatment.

There has been one case report linking methyldopa to a drug-associated immunoblastic lymphadenopathy.[6] Indeed, several forms of immunological changes have been observed with methyldopa therapy, such as haemolytic anaemia, lupus and thrombocytopenia. In another retrospective study of only 82 patients with biliary carcinoma, a higher than expected prevalence of methyldopa therapy was found.[9] It appears that the electrophilic reactive metabolites of methyldopa can potentially be

Table IV. β-Blockers and cancer

Study	Number of cases/controls	Odds ratio (CI)	Cancer type	Comments
Hole et al.[26]	6528 patients with hypertension	NS	All	Retrospective analysis, age- and sex-matched controls
McCredie and Stewart[43]	489 cases of RCC, 147 renal pelvic cancer, 523 controls	1.5 to 1.8	RCC, renal pelvis cancer	Retrospective case-controlled
Stahl et al.[75]	99 receiving β-blockers	0.719 (0.26 to 1.98)	All	Case-control study

CI = confidence interval; **NS** = not significant; **RCC** = renal cell carcinoma.

involved in carcinogenesis. However, a large prospective observational case-controlled study examined 11 663 patients, 425 of whom were treated with methyldopa resulting in 34 cancer-related deaths: the risk for cancer deaths was virtually identical with that of the control group (RR 0.986; CI 0.65 to 1.49).[75]

In an experimental study investigating the effects of α_1-adrenoceptor antagonists on prostate cancer cell growth, there was a significant inhibition of tumour growth.[94] These findings demonstrate the ability of doxazosin and terazosin to suppress prostate cancer cell growth *in vitro* and *in vivo* by inducing apoptosis, without affecting cell proliferation, in keeping with a 'cancer protective' effect.[94]

7. Discussion

Over recent years almost every antihypertensive drug class has been associated with an increased cancer risk. However, close examination of the available evidence suggests that the vast majority of data originates from retrospective case-controlled cohort studies with small absolute numbers and wide confidence intervals. In addition, the major disadvantage of retrospective cohort studies is their susceptibility to bias. For example, recall bias would make patients with renal cell carcinoma more likely to recollect taking diuretics than those with diseases unrelated to the kidney. Furthermore, retrospective studies may not have collected all data relevant for such analysis. For example, retrospective investigation of drug registries would not allow for over-the-counter analgesics, such as the nonsteroidal anti-inflammatory drugs, which have also been associated with renal cancer.[95]

Some groups have been pooled the data of several studies in meta-analyses to improve statistical power. Meta-analysis is an important way of reducing uncertainty attributable to random error, but this does not prevent nor correct for bias present in the original studies. Additionally, publication bias is of major importance, as negative results tend to be less likely to be published and hence the data used in the meta-analysis is at danger of being incomplete, consequently resulting in positive findings. Meta-analysis also cannot correct for statistical confounders. In particular, the effects of antihypertensive drugs and hypertension itself, which has also been associated with cancer, are difficult to disentangle.

Allowing for these shortcomings, the available data are not convincing for an association between antihypertensive drugs and an increased cancer risk. Certainly for calcium channel antagonists, β-blockers and α-blockers, the available evidence seems to favour a neutral effect on cancer development and death rate. For ACE inhibitors, the overall data suggest a similar neutral effect on cancer or, possibly, a small protective effect. Perhaps the strongest evidence in favour of a link between cancer and antihypertensive drugs is with the diuretics. The potential cancer-inducing effects of diuretics, if at all present, are probably low-grade. Until further solid data are available from prospective clinical trials that are adequately powered and have sufficiently long follow-up, we suggest that the management of hypertension should continue with the main drug classes according to current treatment guidelines,[96,97] with little fear of any substantial cancer risk.

Acknowledgements

We acknowledge the support of the City Hospital NHS Trust Research and Development programme for the Haemostasis, Thrombosis and Vascular Biology Unit.

References

1. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. Arch Intern Med 1998; 158 (7): 741-751
2. Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ 1992; 304 (6824): 405-12
3. Staessen J, Bulpitt C, Clement D, et al. Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. BMJ 1989; 298 (6687): 1552-6
4. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. BMJ 1986; 293 (6555): 1145-51
5. Hamet P. Cancer and hypertension. An unresolved issue. Hypertension 1996; 28 (3): 321-4

6. Ahmad S. Lymphoma and methyldopa therapy. J Am Geriatr Soc 1995; 43 (8): 941-2
7. Armstrong B, Stevens N, Doll R. Retrospective study of the association between use of rauwolfia derivatives and breast cancer in English women. Lancet 1974; II (7882): 672-5
8. Bastiaens MT, Zwan NV, Verschueren GL, et al. Three cases of pemphigus vegetans: induction by enalapril – association with internal malignancy. Int J Dermatol 1994; 33 (3): 168-71
9. Broden G, Bengtsson L. Biliary carcinoma associated with methyldopa therapy. Acta Chir Scand Suppl 1980; 500: 7-12
10. Finkle WD, McLaughlin JK, Rasgon SA, et al. Increased risk of renal cell cancer among women using diuretics in the United States. Cancer Causes Control 1993; 4 (6): 555-8
11. Heath Jr CW, Lally CA, Calle EE, et al. Hypertension, diuretics, and antihypertensive medications as possible risk factors for renal cell cancer. Am J Epidemiol 1997; 145 (7): 607-13
12. Heinonen OP, Shapiro S, Tuominen L, et al. Reserpine use in relation to breast cancer. Lancet 1974; II (7882): 675-7
13. Larbre JP, Nicolas JF, Collet P, et al. Kaposi's sarcoma in a patient with rheumatoid arthritis – possible responsibility of captopril in the development of lesions [see comments]. J Rheumatol 1991; 18 (3): 476-7
14. Pahor M, Guralnik JM, Salive ME, et al. Do calcium channel blockers increase the risk of cancer? Am J Hypertens 1996; 9 (7): 695-9
15. Puppin Jr D, Rybojad M, de la Chapelle C, et al. Kaposi's sarcoma associated with captopril. Lancet 1990; 336 (8725): 1251-2
16. Dyer AR, Stamler J, Berkson DM, et al. High blood-pressure: a risk factor for cancer mortality? Lancet 1975; I (7915): 1051-6
17. Raynor Jr WJ, Shekelle RB, Rossof AH, et al. High blood pressure and 17-year cancer mortality in the Western Electric Health Study. Am J Epidemiol 1981; 113 (4): 371-7
18. Buck C, Donner A. Cancer incidence in hypertensives. Cancer 1987; 59 (7): 1386-90
19. Goldbourt U, Holtzman E, Yaari S, et al. Elevated systolic blood pressure as a predictor of long-term cancer mortality: analysis by site and histologic subtype in 10,000 middle-aged and elderly men. J Natl Cancer Inst 1986; 77 (1): 63-70
20. Khaw KT, Barrett-Connor E. Systolic blood pressure and cancer mortality in an elderly population. Am J Epidemiol 1984; 120 (4): 550-8
21. Svardsudd K, Tibblin G. Mortality and morbidity during 13.5 years' follow-up in relation to blood pressure: the study of men born in 1913. Acta Med Scand 1979; 205 (6): 483-92
22. Wannamethee G, Shaper AG. Blood pressure and cancer in middle-aged British men. Int J Epidemiol 1996; 25 (1): 22-31
23. Taylor JO, Cornoni-Huntley J, Curb JD, et al. Blood pressure and mortality risk in the elderly. Am J Epidemiol 1991; 134 (5): 489-501
24. Weinmann S, Glass AG, Weiss NS, et al. Use of diuretics and other antihypertensive medications in relation to the risk of renal cell cancer. Am J Epidemiol 1994; 140 (9): 792-804
25. Yano K, McGee D, Reed DM. The impact of elevated blood pressure upon 10-year mortality among Japanese men in Hawaii: the Honolulu Heart Program. J Chronic Dis 1983; 36 (8): 569-79
26. Hole DJ, Hawthorne VM, Isles CG, et al. Incidence of and mortality from cancer in hypertensive patients. BMJ 1993; 306 (6878): 609-11
27. Folkow B. Physiological aspects of primary hypertension. Physiol Rev 1982; 62 (2): 347-504
28. Tremblay J, Hadrava V, Kruppa U, et al. Enhanced growth-dependent expression of TGF beta 1 and hsp70 genes in aortic smooth muscle cells from spontaneously hypertensive rats. Can J Physiol Pharmacol 1992; 70 (4): 565-72
29. Hadrava V, Tremblay J, Hamet P. Abnormalities in growth characteristics of aortic smooth muscle cells in spontaneously hypertensive rats. Hypertension 1989; 13 (6 Pt 1): 589-97
30. Paquet JL, Baudouin-Legros M, Marche P, et al. Enhanced proliferating activity of cultured smooth muscle cells from SHR. Am J Hypertens 1989; 2 (2 Pt 1): 108-10
31. Hamet P, deBlois D, Dam TV, et al. Apoptosis and vascular wall remodeling in hypertension. Can J Physiol Pharmacol 1996; 74 (7): 850-61
32. Hamet P, Richard L, Dam TV, et al. Apoptosis in target organs of hypertension. Hypertension 1995; 26 (4): 642-8
33. Hamet P. Proliferation and apoptosis of vascular smooth muscle in hypertension. Curr Opin Nephrol Hypertens 1995; 4 (1): 1-7
34. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972; 26 (4): 239-57
35. Norden A, Schersten B, Thulin T, et al. Hypertension related to DNA repair synthesis and carcinogen uptake. Lancet 1975; II (7944): 1094
36. Pero RW, Bryngelsson C, Mitelman F, et al. High blood pressure related to carcinogen-induced unscheduled DNA synthesis, DNA carcinogen binding, and chromosomal aberrations in human lymphocytes. Proc Natl Acad Sci U S A 1976; 73 (7): 2496-500
37. Ueda N, Kondo M. Chromosome aberrations induced by 7,12-dimethylbenz[a]-anthracene in bone marrow cells of spontaneously hypertensive rats (SHR) and control Wistar Kyoto (WKY) rats: time course and site specificity. J Natl Cancer Inst 1984; 73 (2): 525-30
38. Mehta RS, Gunnett CA, Harris SR, et al. High fish oil diet increases oxidative stress potential in mammary gland of spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 1994; 21 (11): 881-9
39. le Noble FAC, Staessen FRM, Hacking WJG, et al. Angiogenesis and hypertension. J Hypertens 1998; 16: 1563-72
40. Belgore F, Blann AD, Li-Saw-Hee FL, et al. Plasma levels of vascular endothelial growth factor and its soluble receptor Flt-1 in essential hypertension. Am J Cardiol 2001; 87 (6): 805-7
41. Belgore F, Lip GYH, McCollum CN, et al. Vascular endothelial growth factor (VEGF) and soluble VEGF receptor (sFlt-1) levels in coronary artery disease and peripheral artery disease. Blood Coagul Fibrinolysis 1999; 10: 536
42. Hojo Y, Ikeda U, Zhu Y, et al. Expression of vascular endothelial growth factor in patients with acute myocardial infarction. J Am Coll Cardiol 2000 Mar 15; 35 (4): 968-73
43. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales, Australia. II. Urologic disease, hypertension, obesity, and hormonal factors. Cancer Causes Control 1992; 3 (4): 323-31
44. Yu MC, Mack TM, Hanisch R, et al. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. J Natl Cancer Inst 1986; 77 (2): 351-6
45. Kreiger N, Marrett LD, Dodds L, et al. Risk factors for renal cell carcinoma: results of a population-based case-control study. Cancer Causes Control 1993; 4 (2): 101-10
46. Hiatt RA, Tolan K, Quesenberry Jr CP. Renal cell carcinoma and thiazide use: a historical, case-control study (California, USA). Cancer Causes Control 1994; 5 (4): 319-25

47. Mellemgaard A, Niwa S, Mehl ES, et al. Risk factors for renal cell carcinoma in Denmark: role of medication and medical history. Int J Epidemiol 1994; 23 (5): 923-30
48. Chow WH, McLaughlin JK, Mandel JS, et al. Risk of renal cell cancer in relation to diuretics, antihypertensive drugs, and hypertension. Cancer Epidemiol Biomarkers Prev 1995; 4 (4): 327-31
49. McLaughlin JK, Chow WH, Mandel JS, et al. International renal-cell cancer study. VIII. Role of diuretics, other anti-hypertensive medications and hypertension. Int J Cancer 1995; 63 (2): 216-21
50. Mellemgaard A, Moller H, Olsen JH. Diuretics may increase risk of renal cell carcinoma. Cancer Causes Control 1992; 3 (4): 309-12
51. Prineas RJ, Folsom AR, Zhang ZM, et al. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. Epidemiology 1997; 8 (1): 31-6
52. Grossman E, Messerli FH, Goldbourt U. Does diuretic therapy increase the risk of renal cell carcinoma? Am J Cardiol 1999; 83 (7): 1090-3
53. Lindblad P, McLaughlin JK, Mellemgaard A, et al. Risk of kidney cancer in among patients using analgesics and diuretics: a population based cohort study. Int J Cancer 1993; 55: 5-9
54. Carlson JE, Kober L, Torp-Pedersen C, et al. Relation between dose of bendrofluazide, anihypertensive effect, and adverse biochemical effects. BMJ 1990; 300: 975-8
55. Lijinsky W, Epstein SS. Nitrosamines as environmental carcinogens. Nature 1970; 225 (227): 21-3
56. Gold B, Mirvish SS. N-Nitroso derivatives of hydrochlorothiazide, niridazole, and tolbutamide. Toxicol Appl Pharmacol 1977; 40 (1): 131-6
57. Lijinsky W, Reuber MD. Pathologic effects of chronic administration of hydrochlorothiazide, with and without sodium nitrite, to F344 rats. Toxicol Ind Health 1987; 3 (3): 413-22
58. Loffing J, Loffing-Cueni D, Hegyi I, et al. Thiazide treatment of rats provokes apoptosis in distal tubule cells. Kidney Int 1996; 50 (4): 1180-90
59. Wolf DC, Goldsworthy TL, Donner EM, et al. Estrogen treatment enhances hereditary renal tumor development in Eker rats. Carcinogenesis 1998; 19 (11): 2043-7
60. Klungel OH, de Boer A, Paes AH, et al. Sex differences in antihypertensive drug use: determinants of the choice of medication for hypertension. J Hypertens 1998; 16 (10): 1545-53
61. Verlander JW, Tran TM, Zhang L, et al. Estradiol enhances thiazide-sensitive NaCl cotransporter density in the apical plasma membrane of the distal convoluted tubule in ovariectomized rats. J Clin Invest 1998; 101 (8): 1661-9
62. Sever PS, Dahlof B, Poulter NR, et al. Rationale, design, methods and baseline demography of participants of the Anglo Scandinavian Cardiac Outcomes Trial. Ascot Investigators. J Hypertens 2001; 19: 1139-47
63. Errea-Abad JM, Ara-Callizo JR, Aibar-Remon C. Drug-induced parkinsonism. Clinical aspects compared with Parkinson disease [Spanish]. Rev Neurol 1998; 27 (155): 35-9
64. Jonas M, Goldbourt U, Boyko V, et al. Nifedipine and cancer mortality: ten-year follow-up of 2607 patients after acute myocardial infarction. Cardiovasc Drugs Ther 1998; 12 (2): 177-81
65. Sleight P. Calcium antagonists during and after myocardial infarction. Drugs 1996; 51 (2): 216-25
66. Wagenknecht LE, Furberg CD, Hammon JW, et al. Surgical bleeding: unexpected effect of a calcium antagonist. BMJ 1995; 310 (6982): 776-7
67. Maxwell CJ, Hogan DB, Ebly EM. Calcium-channel blockers and cognitive function in elderly people: results from the Canadian Study of Health and Aging [published erratum appears in CMAJ 1999 Nov 30; 161 (11): 1396]. CMAJ 1999; 161 (5): 501-6
68. Jick H, Jick S, Derby LE, et al. Calcium-channel blockers and risk of cancer. Lancet 1997; 349 (9051): 525-8
69. Pahor M, Guralnik JM, Ferrucci L, et al. Calcium-channel blockade and incidence of cancer in aged populations. Lancet 1996; 348 (9026): 493-7
70. Fitzpatrick AL, Daling JR, Furberg CD, et al. Use of calcium channel blockers and breast carcinoma risk in postmenopausal women. Cancer 1997; 80 (8): 1438-47
71. Braun S, Boyko V, Behar S, et al. Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. Benzafibrate Infarction Prevention (BIP) Study Research Group. J Am Coll Cardiol 1998; 31 (4): 804-8
72. Hole DJ, Gillis CR, McCallum IR, et al. Cancer risk of hypertensive patients taking calcium antagonists. J Hypertens 1998; 16 (1): 119-24
73. Meier CR, Derby LE, Jick SS, et al. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. Arch Intern Med 2000; 160 (3): 349-53
74. Sorensen HT, Olsen JH, Mellemkjaer L, et al. Cancer risk and mortality in users of calcium channel blockers. A cohort study. Cancer 2000; 89 (1): 165-70
75. Stahl M, Bulpitt CJ, Palmer AJ, et al. Calcium channel blockers, ACE inhibitors, and the risk of cancer in hypertensive patients: a report from the Department of Health Hypertension Care Computing Project (DHCCP). J Hum Hypertens 2000; 14 (5): 299-304
76. Rosenberg L, Rao RS, Palmer JR, et al. Calcium channel blockers and the risk of cancer. JAMA 1998; 279 (13): 1000-4
77. Olsen JH, Toft Sorensen HT, Friis S, et al. Cancer risk in users of calcium channel blockers. Hypertension 1997; 29 (5): 1091-4
78. Trenkwalder P, Hendricks P, Hense HW. Treatment with calcium antagonists does not increase the risk of fatal or non-fatal cancer in an elderly mid-European population: results from STEPHY II. Starnberg Study on Epidemiology of Parkinsonism and Hypertension in the Elderly. J Hypertens 1998; 16 (8): 1113-6
79. Dong EW, Connelly JE, Borden SP, et al. A systematic review and meta-analysis of the incidence of cancer in randomized, controlled trials of verapamil. Pharmacotherapy 1997; 17 (6): 1210-9
80. Michels KB, Rosner BA, Walker AM, et al. Calcium channel blockers, cancer incidence, and cancer mortality in a cohort of U.S. women: the nurses' health study. Cancer 1998; 83 (9): 2003-7
81. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997; 350 (9080): 757-64
82. Lever AF, Hole DJ, Gillis CR, et al. Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? Lancet 1998; 352 (9123): 179-84
83. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327 (10): 685-91
84. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342 (3): 145-53
85. Vogt B, Frey FJ. Inhibition of angiogenesis in Kaposi's sarcoma by captopril. Lancet 1997; 349 (9059): 1148

86. Volpert OV, Ward WF, Lingen MW, et al. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. J Clin Invest 1996; 98 (3): 671-9
87. Hii SI, Nicol DL, Gotley DC, et al. Captopril inhibits tumour growth in a xenograft model of human renal cell carcinoma. Br J Cancer 1998; 77 (6): 880-3
88. Bouck N, Campbell S. Anti-cancer dividends from captopril and other inhibitors of angiogenesis. J Nephrol 1998; 11 (1): 3-4
89. Small Jr W, Molteni A, Kim YT, et al. Mechanism of captopril toxicity to a human mammary ductal carcinoma cell line in the presence of copper. Breast Cancer Res Treat 1999; 55 (3): 223-9
90. Medical Research Council Working Party. Medical Research Council trial of treatment of mild hypertension: principle results. BMJ 1985; 291: 97-104
91. The IPPPSH Collaborative Group. Cardiovascular risk and risk factor in a randomised trial of treatment based on the beta-blocker oxprenolol: the international prospective primary prevention study in hypertension. J Hypertens 1985; 3: 379-92
92. Boston Collaborative Drug Surveillance Program. Reserpine and breast cancer: report from the Boston Collaborative Drug Surveillance Program. Lancet 1974; II (7882): 669-71
93. Curb JD, Hardy RJ, Labarthe DR, et al. Reserpine and breast cancer in the Hypertension Detection and Follow-Up Program. Hypertension 1982; 4 (2): 307-11
94. Kyprianou N, Benning CM. Suppression of human prostate cancer cell growth by alpha1-adrenoceptor antagonists doxazosin and terazosin via induction of apoptosis. Cancer Res 2000; 60 (16): 4550-5
95. Gago-Dominguez M, Yuan JM, Castelao JE, et al. Regular use of analgesics is a risk factor for renal cell carcinoma. Br J Cancer 1999; 81 (3): 542-8
96. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999 Feb; 17 (2): 151-83
97. Ramsay LE, Williams B, Johnston GD, et al. Guidelines for management of hypertension: report of the third working party of the British Hyppertension Society. J Human Hypertens 1999; 13: 569-92

Correspondence and offprints: Professor *Gregory Y.H. Lip*, University Department of Medicine, City Hospital, Dudley Road, Birmingham B18 7QH, England.
E-mail: g.y.h.lip@bham.ac.uk