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Thiazide diuretic prescription and electrolyte abnormalities in primary care

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Aims
Thiazide diuretics have a number of well-documented metabolic adverse effects. The aim of this study was to estimate the frequency of hyponatraemia and hypokalaemia amongst patients taking a thiazide diuretic in primary care.

Methods
A computerized search of the electronic prescribing and laboratory records of six UK general practices was performed. Of the 32 218 adult patients identified, 3773 had received at least one prescription for a thiazide between the years 1990 and 2002.

Results
Detailed prescribing data were available for 2942 patients of whom 951 (32.3%) had a recorded check of their electrolytes. One hundred and ninety-six (20.6%) had a sodium and/or potassium concentration below the normal range. The sodium distribution had a negative skew (−1.8) and in 130 (13.7%) patients was within the hyponatraemic range. Hypokalaemia was less common, occurring in 79 (8.5%) patients. Hyponatraemia was significantly associated with increased age; the odds ratio for developing hyponatraemia in patients over 70 years was 3.87 compared with those of ≤70 years. Hypokalaemia was significantly associated with increased thiazide dose.

Conclusions
Prescription of a thiazide diuretic in primary care is associated with a high frequency of hyponatraemia and hypokalaemia. Thiazides should be prescribed at low dose and the risk of hyponatraemia, especially in the elderly, should be considered and monitored for when prescribing these agents.

Introduction

Thiazide diuretics have been used in the management of hypertension for over 50 years and their role in reducing the complications of hypertension has been clearly established. They continue to be recommended as a first-line agent in the pharmacological treatment of hypertension by guidelines from US [1] and UK [2] hypertension committees and by the National Institute for Clinical Excellence [3].

Thiazide diuretics have a number of well-documented metabolic side-effects including hyponatraemia and hypokalaemia [4]. Hypokalaemia has been most extensively investigated because of the implication that thiazide-induced hypokalaemia can increase cardiac arrythmias and sudden death. The potassium depletion seen with thiazides occurs in a dose-dependent fashion [5–7]. The use of low-dose thiazides is advocated with, if necessary, potassium

sparing diuretics to limit potassium loss [1, 2, 8]. The rates of hypokalaemia seen with low-dose chlorthalidone in the ALLHAT [9] and SHEP [10] studies were 8.5% at 4 years and 7.2% at 1 year.

Thiazide-induced hyponatraemia is less well characterized. Thiazides are a common cause of severe hyponatraemia in hospitalized patients [11] associated with a high level of morbidity and mortality [12, 13]. Inpatient studies of geriatric patients suggest that hyponatraemia is a frequent side-effect, occurring in 11% [14] to 33% [15] of patients taking a thiazide on admission. However, inpatients frequently have comorbidity and the risk of hyponatraemia in primary care, where thiazides are most frequently prescribed, is unknown.

The purpose of this study was to explore the use of primary care data accessible through the electronic patient record (EPR) system to determine the pattern of thiazide prescribing, electrolyte monitoring and the frequency of hyponatraemia and hypokalaemia in primary care patients.

Methods

A cross-sectional observational study was performed of patients aged ≥18 years from general practices in the East Midlands area of the UK. Ethics committee approval was obtained for each locality. All the practices were members of the Trent Focus Collaborative Research Network and had laboratory links at the time of the study, i.e. all clinical and diagnostic results were automatically uploaded into the medical records. Installation of the 'lab-links' at the practices ranged between 1994 and 2000. A retrospective computerized search of the EPR of each practice was performed over a 12-year time frame (1990–2002) using the MIQUEST (Morbidity Information Query and Export SynTax) computer software program. This software tool allows the extraction and aggregation of comparable data from disparate general practices and incorporates security and confidentiality safeguards [16].

A series of questions (queries) was designed to extract the following data – the date, dose and name of any thiazide prescribed within the given time frame and the date and results of electrolyte tests. Data for each practice were imported into Microsoft Access, merged and exported into SPSS as one file for analysis. Due to the complexity of the data, manual review was required to investigate the timing of the sodium and potassium concentration measurements in relation to the thiazide prescriptions.

As plasma sodium concentration did not follow a normal distribution, data were analysed by standard nonparametric tests and logistic regression in SPSS 11.01 (SPSS, Chicago, IL, USA). The 95% confidence intervals (CI) were calculated as 2.5th and 97.5th percentiles of 1000 bootstrap estimates.

Results

The total number of patients within the age group covered by the relevant general practice lists was 32 218. Of these, 3773 (11.7%) had received at least one prescription for a thiazide during the years 1990–2002. Detailed prescribing data were obtained for 2942 patients: median age 68 years (range 19–99). Further characteristics of patients prescribed a thiazide diuretic and levels of electrolyte monitoring are shown in Table 1. The number of thiazide prescriptions per patient ranged from one to 109, with 578 (19.6%) patients receiving only one prescription. The majority of patients were prescribed bendroflumethiazide (BDZ)

Table 1
Characteristics of patients prescribed a thiazide diuretic and levels of electrolyte monitoring

Age (years)	*n* (total)	*n* (male)	Median number of prescriptions	*n* (%) with check [Na^+]	*n* (%) with check [K^+]
19–29	15	2	1	0 (0)	0 (0)
30–39	86	21	2	12 (13.9)	12 (13.9)
40–49	250	63	4	44 (17.6)	44 (17.6)
50–59	569	177	6	172 (30.2)	162 (28.4)
60–69	678	266	9	255 (37.6)	251 (37.0)
70–79	771	270	12	275 (35.7)	268 (34.7)
80–89	502	168	16	171 (34.1)	171 (34.0)
>90	71	10	13	21 (29.6)	19 (26.8)
Overall	2924	959 (33.2%)	9	950 (32.5)	927 (31.7)

(2615 a daily dose of 2.5 mg, 273 a daily dose of 5 mg) with small numbers prescribed indapamide (17), metolazone (14) and other thiazides (16).

Of the 2942 patients, 488 (16.6%) had an electronically recorded sodium ($n = 486$) and/or potassium ($n = 468$) concentration prior to thiazide initiation and 951 (32.3%) had a recorded sodium ($n = 950$) and/or potassium ($n = 927$) whilst prescribed the thiazide (see Table 1). A subgroup of 140 (4.8%) patients had their electrolytes checked both prior to (within 2 years) and during thiazide prescription.

Whilst prescribed a thiazide, 36.1% of males had their sodium checked compared with 30.4% of females ($P = 0.002$). Those individuals who had their sodium checked (median age 69 years, 95% CI 68, 70) were slightly, but significantly, older than those who did not (median 67 years, 95% CI 66, 68; $P < 0.001$), and had received more prescriptions [median 19 (95% CI 18, 21) *vs.* 5 (95% CI 4, 5), $P < 0.001$]. The associations with gender and age remained when explored concurrently using binary logistic regression ($P = 0.003$ and $P < 0.001$, respectively). The same pattern is present for potassium testing: those who had a test were more likely to be male ($P = 0.007$), and were older [median age 69 years (95% CI 68, 70) *vs.* 67 years, $P < 0.001$]. Again these associations were present when tested concurrently ($P < 0.001$ and $P = 0.01$ for age and gender, respectively). The number of prescriptions for a thiazide was greater in those who had a documented potassium concentration ($P < 0.001$).

In the 488 patients with recorded electrolytes prior to thiazide initiation the sodium concentration ranged from 127 to 146 mmol l^{-1} (median 139). Twenty-four (4.9%) patients had a sodium concentration below the normal range (135–145 mmol l^{-1}). The potassium concentration ranged from 2.5 to 8.9 (median 4.3), in five (1.1%) it was below the normal range (3.5–5.3 mmol l^{-1}).

Nine hundred and fifty-one had recorded electrolytes whilst prescribed a thiazide (Figure 1 shows the distribution of electrolyte concentrations). The sodium concentration ranged from 110 to 147 mmol l^{-1} (median 139.0), and the potassium concentration ranged from 1.0 to 8.1 mmol l^{-1} (median 4.1). In total, 196 (20.6%) patients had a sodium and/or potassium concentration below the reference range. The characteristics and electrolyte monitoring of the patients with severe electrolyte disturbance (sodium ≤125 mmol l^{-1}, potassium ≤ 2.9 mmol l^{-1}) are shown in Table 2.

One hundred and thirty (13.7%) patients were hyponatraemic and 79 (8.5%) were hypokalaemic. Tables 3 and 4 summarize the subsequent management of these patients.

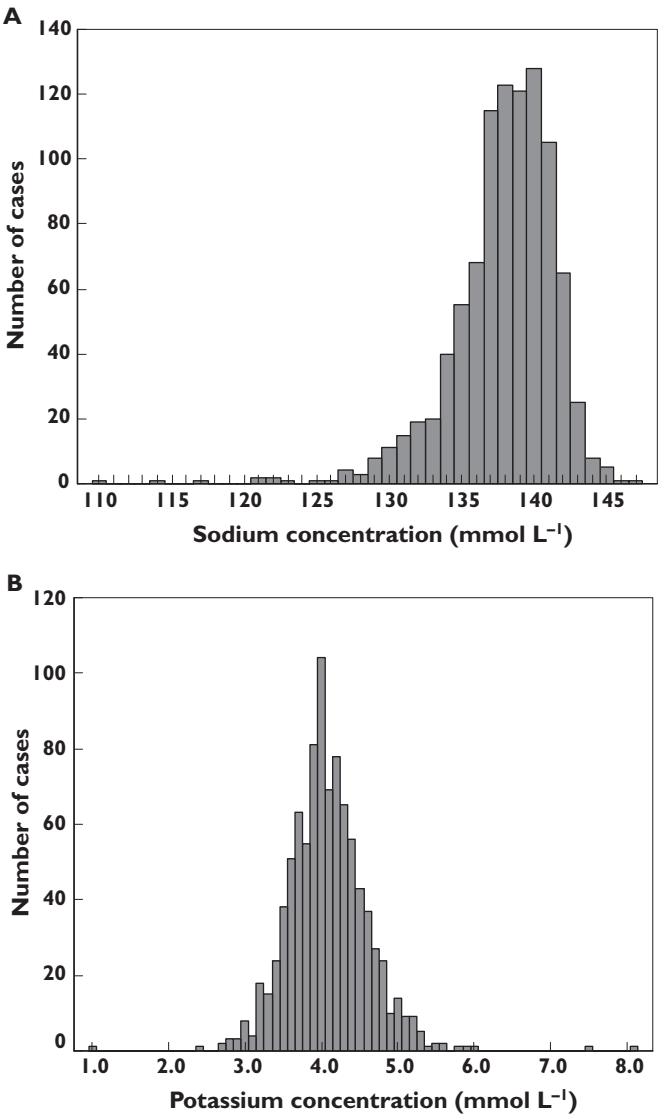

Figure 1
Histograms showing the distributions of electrolyte concentrations in patients prescribed a thiazide. (A) Sodium concentration. The distribution has skew −1.80 and kurtosis 7.54. (B) Potassium concentration

There was no association between gender and plasma sodium as a continuous variable or when the presence of hyponatraemia was considered as a binary variable. Age correlated negatively with sodium level ($P = 0.010$ using Pearson correlation), and was also significantly associated with the presence of hyponatraemia (Figure 2). Plasma potassium was not associated with gender or correlated with age. When age was accounted for in a regression model, the number of prescriptions received was also associated with hyponatraemia ($P = 0.03$). The drug prescribed (bendroflumethiazide 2.5 mg, bendroflumethiazide 5 mg, or 'other' thiazide) was not associated with plasma sodium or the presence

Table 2
Characteristics and management of patients with severe electrolyte disturbance whilst prescribed a thiazide diuretic

Age, years	Sex	Electrolytes pre thiazide, mmol l^{-1}	Thiazide daily dose	Time to electrolyte check, months	Na^+, mmol l^{-1}	K^+, mmol l^{-1}	Thiazide stopped	Electrolytes post thiazide, mmol l^{-1}	Repeat electrolytes on thiazide, mmol l^{-1}
Hyponatraemic and hypokalaemic									
56	M	No record	BDZ 2.5 mg	3	110	1.0	Yes	Na^+ 127, K^+ 3.3	N/A
81	F	Na^+ 143, K^+ 3.8	BDZ 2.5 mg	3	117	2.8	Yes	Na^+ 137, K^+ 4.4	N/A
Hyponatraemic									
47	F	No record	BDZ 2.5 mg	14	121	4.0	Yes	Na^+ 139	N/A
52	M	No record	BDZ 2.5 mg	44	122	3.9	Yes	Na^+ 139	N/A
53	F	No record	BDZ 2.5 mg	44	121	4.6	No	N/A	No record
55	M	No record	BDZ 2.5 mg	10	122	4.6	Yes	Na^+ 134	N/A
77	F	No record	BDZ 2.5 mg	6	123	4.9	No	N/A	No record
78	F	Na^+ 137	BDZ 2.5 mg	4	125	4.0	No	N/A	Na^+ 127
79	F	No record	BDZ 2.5 mg	13	114	–	Yes	Na^+ 134	N/A
Hypokalaemic									
50	F	No record	BDZ 2.5 mg	88	137	2.4	Yes	K^+ 3.3	N/A
64	M	No record	BDZ 5.0 mg	4	139	2.9	No	N/A	No record
67	F	No record	BDZ 5.0 mg	5	140	2.9	Yes	No record	N/A
72	M	No record	MET 5.0 mg	21	142	2.7	No	N/A	K^+ 3.5
78	F	No record	BDZ 2.5 mg	22	140	2.8	No	N/A	K^+ 3.6
86	F	No record	BDZ 2.5 mg	90	139	2.8	Yes	No record	N/A
90	M	K^+ 3.8	BDZ 2.5 mg	16	136	2.9	No	N/A	K^+ 3.5
93	F	No record	BDZ 5.0 mg	86	135	2.7	Yes	K^+ 5.3	N/A

BDZ, Bendroflumethiazide; MET, metolazone; N/A, not applicable.

Table 3
Management and further electrolyte monitoring of patients prescribed a thiazide with hyponatraemia on initial testing

Initial Na^+, mmol l^{-1}, on thiazide	*n*	Thiazide stopped, *n*	Repeat Na^+ off thiazide, *n*	Repeat Na^+, mmol l^{-1}		Thiazide continued, *n*	Repeat Na^+ on thiazide, *n*	Repeat Na^+, mmol l^{-1}	
≤125	9	6	6	126–130	1	3	1	126–130	1
				131–134	2				
				Normal	3				
126–130	27	10	7	≤125	1	17	9	126–130	3
				126–130	1			131–134	5
				131–134	1			Normal	1
				Normal	4				
131–134	94	9	3	Normal	3	85	28	131–134	12
								Normal	16

Patients are divided into those with mild (sodium 131–134 mmol l^{-1}), moderate (sodium 126–130 mmol l^{-1}) and severe hyponatraemia (sodium ≤ 125 mmol l^{-1}).

Table 4
Management and further electrolyte monitoring of patients prescribed a thiazide with hypokalaemia on initial testing

Initial K^+, mmol l^{-1}, on thiazide	*n*	Thiazide stopped, *n*	Repeat K^+ off thiazide, *n*	Repeat K^+, mmol l^{-1}		Thiazide continued, *n*	Repeat K^+ on thiazide, *n*	Repeat K^+, mmol l^{-1}	
≤ 2.9	10	6	4	3.3–3.4	2	4	3	Normal	3
				Normal	2				
3.0–3.2	30	2	2	Normal	2	28	17	3.3–3.4	6
								Normal	11
3.3–3.4	39	3	2	Normal	2	36	11	3.3–3.4	2
								Normal	9

Patients are divided into those with mild (potassium 3.3–3.4 mmol l^{-1}), moderate (potassium 3.0–3.2 mmol l^{-1}) or severe hypokalaemia (potassium ≤ 2.9 mmol l^{-1}).

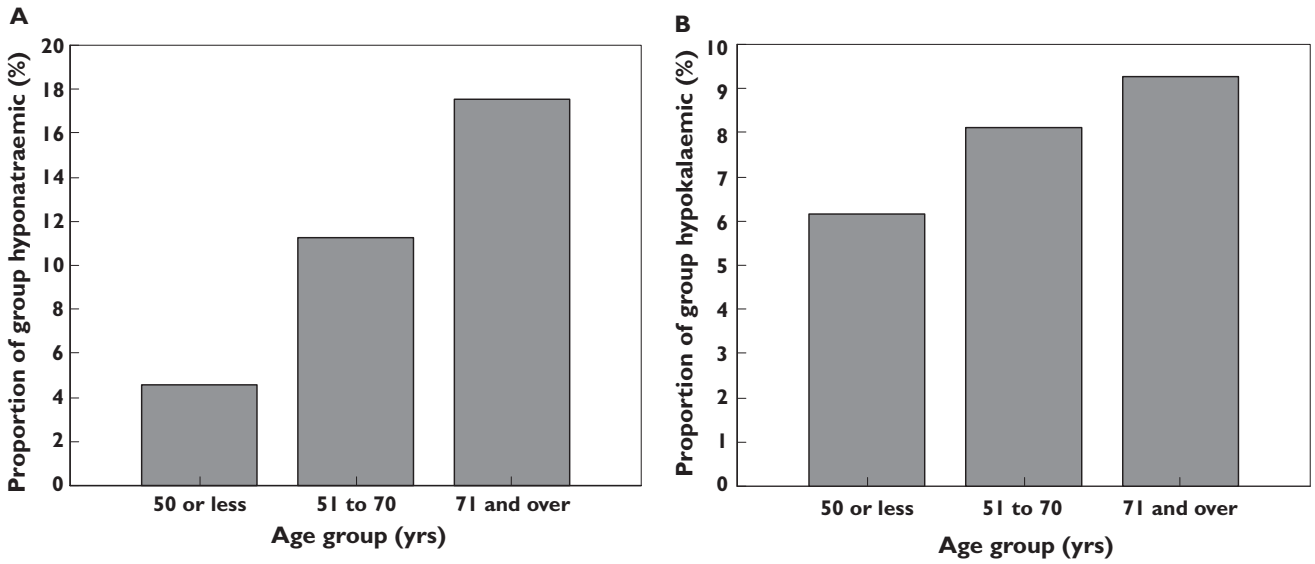

Figure 2
Electrolyte disturbance according to age in patients prescribed a thiazide. (A) Hyponatraemia (≤50 years, *n* = 66; 51–70, *n* = 445; >71 years, *n* = 439). (B) Hypokalaemia (≤50 years, *n* = 65; 51–70, *n* = 438; >71 years, *n* = 435). Age was significantly associated with hyponatraemia ($P = 0.007$), there was no significant association with hypokalaemia

of hyponatraemia (Figure 3). Potassium concentration was, however, significantly affected by the drug prescribed, with median potassium concentrations for patients on bendroflumethiazide 2.5 mg daily, bendroflumethiazide 5 mg daily, or another thiazide being: 4.1 mmol l^{-1}, 3.95 mmol l^{-1}, and 3.75 mmol l^{-1} ($P = 0.004$), respectively. Similarly, drug type was associated with hypokalaemia as a binary outcome ($P = 0.007$).

To assess whether treatment with a thiazide was likely to be responsible for these associations, we analysed data for the subgroup of 140 patients for whom electrolytes were available before and during prescription. The percentage change in sodium concentration (Figure 4) whilst on a thiazide was significantly correlated with age ($P = 0.001$, Pearson correlation) but was not related to gender ($P = 0.886$) or the number of prescriptions ($P = 0.37$). The odds ratio for developing hypon-

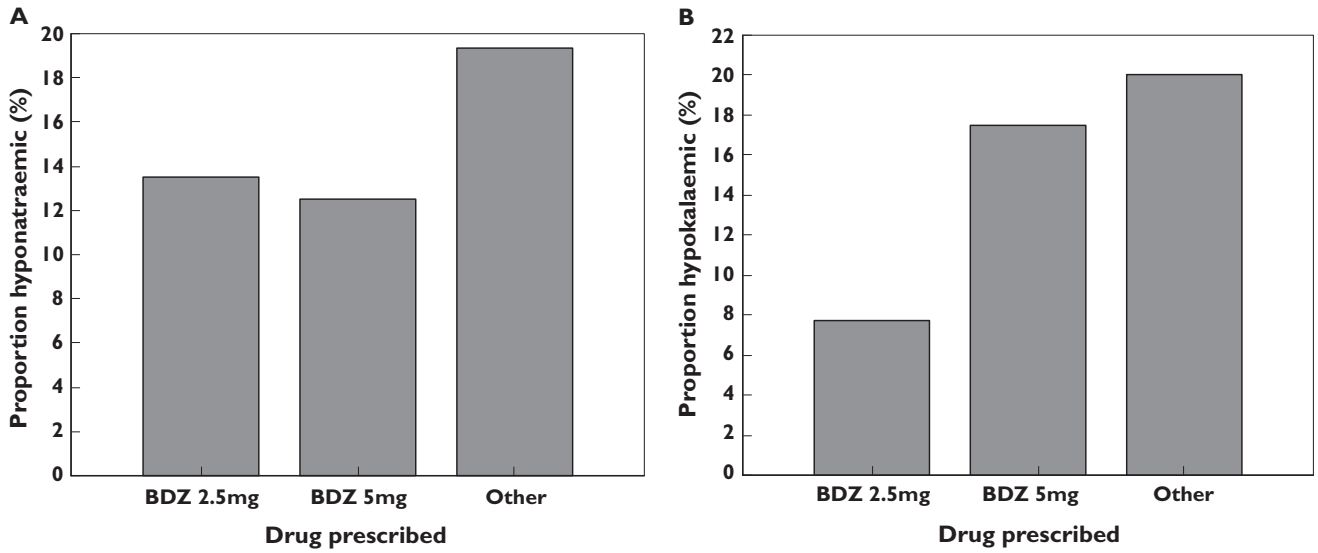

Figure 3

Incidence of electrolyte disturbance according to thiazide prescribed. (A) Hyponatraemia (BDZ 2.5 mg, $n = 880$; BDZ 5.0 mg, $n = 40$; other, $n = 31$). (B) Hypokalaemia (BDZ 2.5 mg, $n = 857$; BDZ 5.0 mg, $n = 40$; other, $n = 30$). There was significant association with the thiazide prescribed and both potassium concentration ($P = 0.004$) and hypokalaemia ($P = 0.007$) but no significant association with hyponatraemia

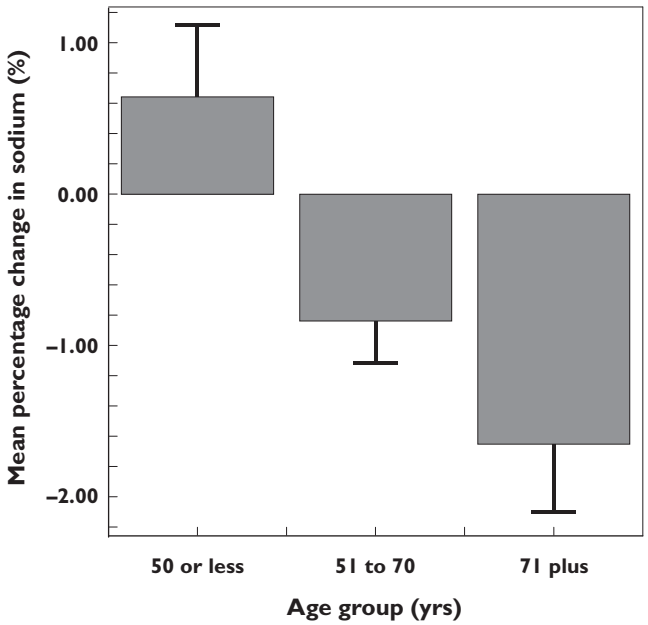

Figure 4

Mean percentage change in sodium concentration following thiazide prescription according to age. Standard error of mean shown. Change in sodium concentration correlated significantly with age ($P = 0.001$)

atraemia is 3.87 (95% CI 2.49, 6.00) in those over 70 when compared with those of ≥70 years. As there were only five individuals who were not on bendroflumethiazide 2.5 mg, the change in sodium by drug was not analysed. Gender, age and sodium level were not significantly associated with percentage change in potassium level.

Discussion

In this study we have used electronic patient record data to determine the frequency of electrolyte imbalance in a large population of primary care patients prescribed a thiazide diuretic under everyday circumstances. Our data show a high level of thiazide prescribing in primary care (11.7% of the population received one or more thiazide prescription during the study period) and that 20.6% of the patients with electrolyte monitoring were hypokalaemic and/or hyponatraemic whilst prescribed a thiazide.

A recent systematic review of the scope and quality of EPR data identified that prescribing data are generally accepted to be of high quality [18]. The use of the MIQUEST software enabled collection of electronic prescribing data from disparate primary care databases, giving a large patient population for analysis. The main limitation of the search method was that data relating to comorbidity and coprescribing were not collected. Therefore, it is possible that patients considered to have

a high risk of electrolyte disturbance or with suggestive symptoms may have been more likely to have their electrolytes checked. Also, the search will not have included patients in whom a thiazide was considered but not selected due to pre-existing electrolyte disturbance.

The majority of patients were prescribed, in line with current recommendations [1–3], a low-dose thiazide; most frequently bendroflumethiazide 2.5 mg a day. Ten percent were prescribed higher doses. Only one-third of patients had an electronic recording of their sodium or potassium whilst prescribed a thiazide. In other words, the majority of patients did not have a check of their electrolytes. This figure may be a slight underestimate as the search will not have detected those patients who had electrolytes checked before automatic upload of laboratory results was available or those who had electrolytes checked in secondary care. The patients with an electrolyte check were slightly older, were more likely to be male and, using number of prescriptions as a surrogate, had been prescribed a thiazide for a longer duration.

Despite being less well characterized in previous studies, hyponatraemia was seen more frequently than hypokalaemia in this primary care population; 13.7% of the patients on a thiazide were hyponatraemic. The sodium distribution had a negative skew but the median sodium concentration was the same as in the population with a sodium check prior to thiazide initiation. This finding is consistent with the lack of generalized reduction in sodium concentration seen in the large trials using long-term thiazides [19–21]. It suggests a subgroup of individuals is susceptible to this adverse event. Studies have implicated increasing age, female sex and low body weight [12, 17, 22–25] as clinical risk factors for thiazide-induced hyponatraemia. We found no association with female sex but a significant association with increased age, those over 70 years being at over triple the risk of hyponatraemia compared with those younger than 70. A dose-dependent effect for hyponatraemia was not seen, the study had over 90% power to detect a difference in sodium concentration of ≥ 3 mmol l^{-1} with drug dose. The hyponatraemia was identified on the first electrolyte check in the majority of patients but in 20% it was detected on subsequent samples. Our findings suggest that when prescribing a thiazide, especially in the elderly, regular checks of sodium concentration should be performed.

In the majority of cases the hyponatraemia was mild and on repeat testing, normalized. Moderate (sodium <130 mmol l^{-1}) or severe (sodium <125 mmol l^{-1}) hyponatraemia was seen in 35 (3.7%) of the patients tested. Of the patients in whom the thiazide was discontinued, the sodium concentration normalized in the majority on repeat testing. Whilst this may represent regression towards the mean, all except one of the patients who continued thiazide treatment remained hyponatraemic, suggesting that spontaneous normalization is unlikely if the thiazide is continued.

The increased morbidity and mortality associated with hyponatraemia relates to both the sodium concentration and how rapidly the condition develops [26]. Thiazide-induced hyponatraemia typically occurs within 2–12 days of drug initiation [27], although it can occur at any point during thiazide use [21]. It usually develops over days, although more acute falls in sodium concentration have been described [28, 29]. Chronic hyponatraemia is generally asymptomatic until the sodium concentration falls below 125 mmol l^{-1} [26]. Approximately 1% of the patients in this study dropped their sodium concentration below 125 mmol l^{-1} and it is likely that they will have been symptomatic and some may have required hospital admission.

Hypokalaemia was seen in 8.52% of those tested, which is comparable to the frequency seen in large-scale studies with low-dose thiazides [9, 10]. Unlike sodium, the potassium distribution did not have a negative skew. However, the median potassium concentration was lower than in the population with prethiazide level; this is consistent with a generalized potassium lowering effect. The risk of hypokalaemia with bendroflumethiazide was dose dependent as previously reported [19]. The prescription of a thiazide other than bendroflumethiazide was also associated with increased hypokalaemia but the numbers of each individual thiazide in this group were small. There was no association with gender and no significant association with age.

Most cases had mild or moderate hypokalaemia and continued to be prescribed a thiazide; on repeat testing the potassium had increased or was normal in all patients. Just over 1% of the patients tested had severe hypokalaemia (potassium <3.0 mmol l^{-1}); in the majority the thiazide was discontinued and in those who continued the thiazide the potassium concentration was normal on repeat. From the data collected it is not possible to determine whether the observed improvements were spontaneous or due to the addition of potassium sparing diuretics or potassium supplements.

The evidence linking thiazide-induced hypokalaemia and cardiac arrhythmias or cardiac death is conflicting. Several studies have shown no increase in cardiac arrhythmias [30, 31], whereas others have shown an association with ventricular arrhythmias and/or cardiac

arrest [32–34]. In one study the increase in arrhythmias was only in patients with a serum potassium level below 3.1 mmol l^{-1} [35]. It has been proposed that the limited benefit thiazides provide against coronary heart disease events compared with stroke is due to adverse effects of the drug [8]. A recent analysis of the participants who became hypokalaemic in the SHEP study supports this: the participants who were hypokalaemic at 1 year did not experience the reduction in cardiovascular events achieved amongst those who were normokalaemic [6].

In conclusion, the interrogation of electronic patient records using MIQUEST queries shows potential for detecting adverse drug reactions in primary care. Hyponatraemia and hypokalaemia are common in primary care patients prescribed a thiazide. Patients on higher doses of thiazides are at particular risk of hypokalaemia and elderly patients are at particular risk of hyponatraemia. The use of low-dose thiazides and regular electrolyte monitoring is advised to reduce the risk and increase the detection and treatment of these electrolyte abnormalities.

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Conflict of interest: None declared.

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