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Title: Antihypertensive drug class and dyslipidaemia: risk association among Chinese patients with uncomplicated hypertension

Running title: Dyslipidaemia in Chinese hypertensive patients

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Factors associated with dyslipidemia in Chinese patients with uncomplicated hypertension were investigated in 1,139 patients newly prescribed a single antihypertensive drug in the public primary healthcare setting in Hong Kong, where their fasting lipid profiles were measured 4 to 16 weeks after the first prescription. Multivariate logistic regression showed that thiazide users were more likely (OR 3.67, 95% C.I. 1.13, 11.88, p=0.030) to have adverse ($\geq$ 6.2mmol/l) total cholesterol (TC) compared with drugs acting on the renin angiotensin system (RAS), but the absolute difference in mean TC between thiazide users and all patients was small (0.14 mmol/l), while advanced age and male gender were also associated with some aspects of dyslipidemia.   Clinicians should be aware of the increased risk of dyslipidemia in these groups, but the mild dyslipidemic profile associated with thiazides should not in itself deter its use as a possible first-line antihypertensive agent among Chinese patients.

Dyslipidemia has been recognized as a strong predictor of cardiovascular disease[1].   There is increasing evidence that dyslipidemia is associated with[2] and possibly a causative factor in hypertension[3].   Studies on the potential predictive factors of dyslipidemia among established hypertensive patients are few, and evidence on the possible relationship between antihypertensive drug classes and dyslipidemia is mixed[4,5].   To our knowledge there are few reports on the risk factors of dyslipidemia among hypertensive patients of Chinese ethnicity.

This study examined the lipid profiles of Chinese hypertensive patients newly prescribed a single antihypertensive agent and evaluated the risk association between potential predictive factors and the occurrence of dyslipidemia.

We retrieved data from the clinical database of the Hospital Authority, Hong Kong which consists of patient demographics, clinical diagnoses, prescription details and laboratory investigation results in every out-patient consultation. Previous evaluations of this clinical tool for research purposes[6] found a high level of data completeness with respect to demographic data (100%) and prescription details (99.98%) (unpublished data). The present study included Chinese individuals residing in one large cluster which has an approximate population of 1.3 million. This cluster is further divided into 3 separate regions, namely Shatin, Tai-Po and the North district, from the most affluent to the least. Patients attending public primary care clinics for the first time who were coded by physicians with International Classification of Primary Care K86 [uncomplicated hypertension] and were newly prescribed an antihypertensive agent during the study period of January 2004 to June 2007, were included. In addition, eligible patients must have had fasting lipid profiles measured 4 to 16 weeks after prescription. Exclusion criteria included patients with: concomitant cardiovascular risks; clinical conditions which could confound the prescription choice of antihypertensive drugs (supplemental file 1); discontinuation or changes to their drug

prescription before lipid profile was measured; or prescribed at least one lipid modifying agent during the study period.   The proportions of patients with desirable, borderline and adverse levels of lipid profiles were studied for TC (<5.2; 5.2-6.1; $\geq$6.2 mmol/l), TG (<1.7; 1.7-2.2; $\geq$ 2.3 mmol/l), LDL-C (<2.6; 2.6-4.0; $\geq$ 4.1 mmol/l) and HDL-C ($\geq$ 1.5; 1.0-1.5; <1.0 mmol/l) by each major drug class.   Lipid profiles were measured after an overnight fast of 8 to 12 hours.   LDL-C was calculated using the Friedewald formula[7] but direct LDL-C was measured instead where TG level was $\geq$ 4.5 mmol/L.   Student's t-tests were used for comparison of continuous variables while chi-square tests were used for categorical variables.

Separate unconditional binary logistic regression analyses for each lipid parameter (TC [Total Cholesterol], Triglyceride [TG], Low Density Lipoprotein-Cholesterol [LDL-C] and High Density Lipoprotein-Cholesterol [HDL-C]) were conducted.   Independent predictors and covariates included patient age, gender, patient's payment status (fee-waivers vs. payers), district of residence, types of clinics attended (general vs. family medicine specialist vs. staff clinics) and the antihypertensive drug classes prescribed (thiazide diuretics, β-blockers, calcium channel blockers [CCB] and RAS-modifiers).

There were 1,139 eligible patients with a mean age of 61 years, 59.3% of which were females in the sample (supplemental file 2).   Among the four drug classes, thiazide users had the highest mean values of TC (5.38 mmol/l) and TG (1.59 mmol/l), CCB users had highest

levels of LDL-C (3.22 mmol/l) and BB users had the lowest levels of HDL-C (1.52 mmol/l).

These apparent differences in lipid parameters between drug groups were statistically

insignificant (p=0.265 to 0.881).   For all lipid parameters, the crude differences in proportion

of patients with adverse lipid profiles amongst the various drug classes did not reach

statistical significance either (p=0.213 to 0.951) (supplemental file 3).   From multivariate

regression analyses, thiazide users were 3.67 times more likely than RAS to show adverse TC

levels (OR 3.670, 95% C.I. 1.134, 11.876, p=0.030) (Table 1).   However, the absolute

difference between mean TC between thiazide users and all patients was only 0.14 mmol/l.

When compared with younger age groups, advanced age (>50 years) was found to be

positively associated with borderline high TC (OR 1.513 to 1.788, p=0.015 to 0.057) and high

TC (OR 2.493 to 2.834, p=0.002 to 0.016) but negatively associated with HDL-C (OR 0.523

to 0.626, p=0.013 to 0.042) (Table 1). Male patients were also more likely to have less than

optimal HDL-C (OR 2.535, p<0.001).

Thiazide diuretics have been shown to increase levels of TC and LDL-C by 5% to 7%

without alteration of HDL-C in the first year of antihypertensive treatment[8], while other

studies reported a decline in lipid profiles with use of diuretics[9].   Our finding that thiazides

are positively associated with adverse TC levels implies association with

hypercholesterolemia in Chinese hypertensive patients, noting that the absolute increase in

TC levels was relatively mild and comparable to Kasiske et al's study[10] which reported a similar difference in mean TC (0.12 mmol/l) between thiazide users and other antihypertensive drug classes.

Published studies on the association of age and gender with dyslipidemia are inconclusive. Increased serum cholesterol was found with increasing age by Kesteloot et al[11]. Cai et al[12] reported a rise in HDL-C with age in men only and with decreasing concentrations in women after age 50. In this study both age and gender were associated with dyslipidemia which may represent a new finding among ethnic Chinese.

Some limitations of this study should be mentioned. First, the lack of baseline lipid profiles which could act as reference values prevents before-after exposure comparisons of lipid levels. Also, we recognize the absence of ICPC coding which more accurately excludes the presence of relevant co-morbidities. Secondly, this study cannot prove causative relationships between predictor variables and lipid profiles, which can only be addressed through a prospective cohort design.

In conclusion, in the present study on Chinese subjects, thiazide use was associated with elevated cholesterol levels, but the absolute increase in TC was small. Increasing age and

male gender were also associated with increased risk of dyslipidemia. Clinicians should be

aware of these increased risks, but the mild dyslipidemic profile associated with thiazides

should not in itself deter its use as a possible first-line antihypertensive agent among Chinese

patients.

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Table 1   Independent associated factors of dyslipidemia with above borderline and adverse readings [a]

	Total Cholesterol				Triglycerides		LDL-Cholesterol				HDL-Cholesterol [b]	
	Above borderline		Adverse		Above borderline		Above borderline		Adverse		Less than optimal	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)												
<50	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
50-59	1.513 (0.988, 2.318)	0.057	2.834 (1.445, 5.557)	0.002	1.413 (0.880, 2.269)	0.152	1.008 (0.547, 1.855)	0.981	2.733 (1.003, 7.452)	0.049	0.626 (0.399, 0.984)	0.042
60-69	1.788 (1.120, 2.854)	0.015	2.493 (1.185, 5.245)	0.016	1.313 (0.776, 2.224)	0.310	1.630(0.796, 3.336)	0.181	1.791 (0.547, 5.867)	0.336	0.592 (0.362, 0.966)	0.036
≥70	1.763 (1.081, 2.876)	0.023	2.808 (1.327, 5.942)	0.007	1.195 (0.696, 2.052)	0.519	0.902 (0.449, 1.812)	0.773	1.867 (0.602, 5.789)	0.280	0.523 (0.315, 0.870)	0.013
Gender												
Female	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Male	1.004 (0.723, 1.394)	0.981	0.755 (0.467, 1.220)	0.755	1.282 (0.900, 1.827)	0.169	1.147 (0.706, 1.863)	0.579	1.176 (0.569, 2.430)	0.662	2.535 (1.778, 3.615)	<0.001
Payment status												
Fee-waivers	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Fee-payers	0.863 (0.608, 1.225)	0.410	0.777 (0.477, 1.267)	0.312	0.993 (0.681, 1.448)	0.972	0.732 (0.435, 1.230)	0.239	0.865 (0.394, 1.896)	0.717	1.122 (0.783, 1.607)	0.531
District of residence												
Shatin	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Taipo	0.630 (0.344, 1.153)	0.134	0.257 (0.096, 0.685)	0.007	0.762 (0.388, 1.497)	0.430	0.265 (0.105, 0.670)	0.005	0.183 (0.050, 0.674)	0.011	1.228 (0.631, 2.387)	0.545
North	1.052 (0.672, 1.647)	0.825	0.652 (0.361, 1.175)	0.155	0.876 (0.537, 1.431)	0.597	0.755 (0.350, 1.628)	0.474	0.437 (0.165, 1.160)	0.096	0.880 (0.544, 1.422)	0.602
Others	1.182 (0.571, 2.446)	0.653	0.916 (0.351, 2.386)	0.857	0.783 (0.365, 1.679)	0.529	1.015 (0.313, 3.296)	0.980	0.621 (0.121, 3.193)	0.569	1.014 (0.454, 2.265)	0.973
Service type												
General	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
FMSC	2.205 (1.050, 4.630)	0.037	2.669 (1.053, 6.763)	0.039	0.868 (0.404, 1.863)	0.716	0.858 (0.257, 2.867)	0.803	0.962 (1.195, 4.734)	0.962	1.167 (0.511, 2.663)	0.715
Staff clinic	1.638 (0.690, 3.886)	0.263	1.037 (0.278, 3.868)	0.957	0.598 (0.231, 1.547)	0.289	0.637 (0.169, 2.399)	0.505	1.466 (0.244, 8.797)	0.676	0.801 (0.318, 2.019)	0.639
Drug class												
RAS	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
β-blockers	1.048 (0.550, 2.000)	0.886	2.293 (0.726, 7.242)	0.157	1.132 (0.554, 2.311)	0.734	0.649 (0.241, 1.746)	0.392	1.622 (0.337, 7.799)	0.546	0.914 (0.454, 1.843)	0.802
Thiazide	1.437 (0.730, 2.825)	0.294	3.670 (1.134, 11.876)	0.030	1.204 (0.575, 2.522)	0.622	0.802 (0.289, 2.225)	0.671	0.954 (0.181, 5.036)	0.956	0.783 (0.380, 1.616)	0.508
CCB	1.317 (0.691, 2.508)	0.402	2.769 (0.870, 8.811)	0.085	1.102 (0.538, 2.255)	0.790	0.625 (0.233, 1.681)	0.352	1.535 (0.315, 7.477)	0.596	0.677 (0.335, 1.369)	0.277

(HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; FMSC: Family Medicine Specialist Clinics; CCB: Calcium Channel Blockers; RAS: drugs acting on the rennin angiotensin system.   **a:** Above borderline lipid profiles were defined as, respectively, TC $\geq$ 5.2 mmol/l; TG $\geq$ 1.7 mmol/l; LDL-C $\geq$ 2.6 mmol/l; less than optimal for HDL-C defined as $\leq$ 1.6 mmol/l; Adverse results were defined as TC $\geq$ 6.2 mmol/l; TG $\geq$ 2.3 mmol/l; LDL-C $\geq$ 4.1 mmol/l; HDL-C < 1.0 mmol/l.   **b:** None of the patients had adverse HDL-Cholesterol readings.   All adjusted Odds Ratios (OR) were adjusted for age, gender, payment status, district of residence, service types of attended clinics and drug classes as listed in table)

Table 2 Summary Table

What is known about topic

- Hypertension and dyslipidemia often coexist and there is increasing evidence that one may lead to the occurrence of another.

- There were few studies on the factors associated with dyslipidemia among patients with uncomplicated hypertension, especially in ethnic Chinese patients

- Evidence on the association of antihypertensive drug classes with dyslipidemia is presently mixed.

What this study adds

- Advanced age, male gender and use of thiazide were associated with higher risk of some aspects of dyslipidemia in hypertensive patients prescribed a single antihypertensive drug.

- Thiazide use was associated with hypercholesterolemia yet the absolute increase in total cholesterol was small

- Chinese patients with uncomplicated hypertension newly prescribed a single antihypertensive agent with these associated factors should have more meticulous screening of their lipid profiles.