QUALITY OF HYPERTENSION PHARMACOTHERAPY IN QUEBEC: A POPULATION-BASED STUDY

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ABSTRACT

Background
Choosing the initial pharmacotherapy for new antihypertensive users and ensuring adherence to therapy can be problematic.

Objectives
We sought to assess the quality of pharmacotherapy among new users of antihypertensives in Quebec, and to measure persistence with treatment in the short and longer term.

Methods
Using provincial administrative databases, a historical population-based study was conducted with a cohort of Quebec adults who filled their first antihypertensive prescription between January 1, 2007, and December 31, 2009. We described antihypertensive treatment for those with a diagnosis of hypertension (HTN) in the 5 years preceding initiation of drug therapy. Conformity with criteria for optimal use based on the 2006 Canadian Hypertension Education Program (CHEP) was evaluated. Persistence with treatment was estimated at 3 months, 1 year and 2 years after pharmacotherapy initiation.

Results
Among the 79,181 new antihypertensive users with HTN who started treatment between 2007 and 2009, 82.5% were first prescribed only one drug, usually an angiotensin II receptor blocker or an angiotensin-converting enzyme inhibitor and rarely a diuretic. 24.2% of newly treated hypertensive persons aged 60 or older in our sample received a beta-blocker, which is not recommended practice. The initial treatment conformed to CHEP recommendations for 72.8% of those with uncomplicated HTN. After 3 months, 69.8% of new users still persisted with their treatment. This proportion remained stable after 1 year (69.1%) and 2 years (69.2%).

Conclusion
Conformity of antihypertensive treatment with CHEP criteria, and patient persistence with therapy, was fairly high for new users in the province of Quebec. Research is needed, however, on how to further improve pharmacotherapy quality and persistence in new users.

Key Words: *Antihypertensive, guideline adherence, medication persistence, pharmacoepidemiology*

Hypertension is one of the principal risk factors for morbidity and premature mortality due to cardiovascular causes.[1,2] The prevalence of hypertension has increased from 7.9% in 1994 to 13.8% in 2005 among persons 20 years and older in Quebec.[3] A meta-analysis of trials found that antihypertensive medications are associated with a 22-27% reduction in cardiovascular events and a

10% decrease in mortality.[4] However, studies of antihypertensive prescribing practices have highlighted several shortcomings despite the availability of practice guidelines. These include lack of compliance with recommended initial treatment strategies[5], overuse of monotherapy[6,7], persistent infrequent use of fixed-dose[i] drug combinations[7], questionable combinations of antihypertensives[8], and limited use of diuretics for diabetics.[9] In addition, user adherence to antihypertensives can reduce significantly over time.[10-13]

Our principal objectives were to describe antihypertensive pharmacotherapy among adult beneficiaries of public drug insurance in Quebec in 2007-2009, and to assess the quality of newly-initiated therapies. This assessment was based on optimal use recommendations by the 2006 Canadian Hypertension Education Program (CHEP).[14] We also sought to assess medical follow-up by measuring the number of outpatient medical visits in the first year of drug therapy and treatment persistence at 3 months, 1 year and 2 years after pharmacotherapy initiation. Guidelines recommend that patients on antihypertensives be seen at least three times in the first year of treatment.[15]

METHODS

A historical study of a population-based cohort was carried out using data collected by the provincial health insurance body of Quebec, Canada (RAMQ). Information on public drug insurance plan (RPAM) beneficiaries arose from registration records. Information on dispensed prescription drugs and prescribers was extracted from the database of pharmacist services billed to RAMQ for RPAM beneficiaries. Medical services data (used for diagnoses and physician consultations) arose from dispensers' records and fee-for-service physician billing. Data were linked using unique beneficiary identifiers. These databases have been validated for research use and previously employed in pharmacoepidemiological investigations.[10,16-18]

All new users of antihypertensives between January 1, 2007 and December 31, 2009, aged 18 or older and insured by RPAM, were included in the study. The exclusion criteria were: no diagnosis of hypertension in the 5 years preceding the first antihypertensive prescription (index date) in the study period, and having a previous antihypertensive prescription in the 365 days prior to the index date. The hypertension diagnosis was identified by codes 401.0 to 405.9 of the 9th edition of the International Classification of Diseases, Ninth Revision (ICD-9). Antihypertensives included 75 different drugs registered by RAMQ, in any of the following 10 classes based on the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic classification: alpha-adrenergic agonists, direct-acting vasodilators, alpha-blockers, beta-blockers (BB), calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), aldosterone receptor antagonists, direct renin inhibitors, and diuretics.

A history of type I or II diabetes or chronic kidney disease was documented with reference to the antihypertensive index date. For diabetes, this was based on (1) presence of at least one diagnostic code for diabetes or diabetic retinopathy (ICD-9 codes 250.0 to 250.9 or 362.0) in the previous 5 years, or (2) at least one prescribed drug indicated for diabetes in the previous 365 days. Kidney disease was based on (1) presence of at least one diagnostic code for chronic kidney disease (ICD-9 585.X), or (2) a service code for dialysis or hemodialysis in the 5 years prior to the index date, or (3) at least one prescribed indicative drug in the previous 365 days. A person without a history of diabetes, chronic kidney disease, atherosclerotic vascular disease and heart failure was considered to have uncomplicated hypertension. (Details on the ICD-9 codes used to assign all previous diagnoses are specified in the full report prepared by the Institut national d'excellence en santé et en services sociaux (INESSS) for the Quebec Ministry of Health).[19]

The criteria used to assess conformity of antihypertensives with optimal use are described in Table 1. In short, there were four criteria and

[i] Fixed-dose antihypertensive combinations contain two active ingredients at a specified strength. Such formulations can increase adherence to treatment for some antihypertensives.[14,20]

four assessment time points. The first three criteria were all assessed at treatment initiation (the index date) and differed according to patient conditions (i.e. uncomplicated hypertension, with diabetes or with chronic kidney disease). The last criterion was assessed at 3 months, 1 year and 2 years after the index date and only for those using a two-drug regimen at the time point in question. The criteria were based on CHEP recommendations, which have the advantage of being well-known and unchanged for monotherapy up to and including 2009.[14,20]

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TABLE 1 Optimal use criteria based on CHEP (2006)

Antihypertensive regimen and time of evaluation	Situation	Optimal antihypertensive(s)
Drug regimen at treatment initiation (index date)	Uncomplicated HTN*	TD, BB, ACE, ARB, or long-acting CCB (no BB if aged 60 or older)
	Comorbid diabetes	TD, ACE, ARB, or a long-acting DHP CCB
	Comorbid chronic kidney disease but no diabetes	ACE, or ARB singly or in combination with TD
Two-drug regimen at follow-up**	Uncomplicated HTN*	TD & ACE, TD & ARB, TD & BB, long-acting CCB & ACE, long-acting CCB & ARB, or a long-acting DHP CCB & BB

CHEP: Canadian Hypertension Education Program; HTN: hypertension; TD: thiazide diuretic; BB: beta-blocker; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; DHP: dihydropyridine; *No history of diabetes, atherosclerotic vascular disease, chronic kidney disease or heart failure (see methods); **A two-drug regimen conformed to CHEP for new users if a recommended combination was dispensed at 3 months, at 1 year or at 2 years after the index date

The number of physician consultations in the first year following initiation of treatment included all visits to a community-based medical clinic or hospital outpatient services. All other types of consultations were excluded. A person who remained insured by RPAM at the time of follow-up (3 months, 1 year, 2 years) was considered to be persisting with his/her antihypertensive treatment if at least one antihypertensive prescription (of any type) was active at that time.

Institutional ethics approval was not required since no patient contact was involved and patient and provider confidentiality was ensured.

RESULTS

We found that 946,857 RPAM beneficiaries had an antihypertensive prescription filled between January 1, 2007 and December 31, 2009, representing 37.3% of all adults insured during this 3-year period. Among these, 79,181 (8.4%) were new users of antihypertensives with a diagnosis of hypertension. The majority of new users were aged 60 or older and slightly more than half were female (Table 2).

TABLE 2 Distribution of new antihypertensive users with HTN according to user characteristics and year

Characteristic	Year of treatment initiation*				Total (2007-2009)	
	2007		2009			
	n	%	n	%	n	%
Age (years)						
18-29	343	1.2	319	1.3	983	1.2
30-44	2,010	7.0	1,636	6.8	5,447	6.9
45-59	6,555	22.9	5,536	23.0	18,184	23.0
60-74	12,823	44.8	10,859	45.1	35,430	44.7
75-84	5,589	19.5	4,515	18.8	15,228	19.2
≥85	1,308	4.6	1,200	5.0	3,909	4.9
Sex						
Female	15,652	54.7	13,176	54.8	43,256	54.6
Male	12,976	45.3	10,889	45.2	35,925	45.4
RPAM insurance category**						
Adherent	9,289	32.4	8,097	33.6	26,021	32.9
Elderly (65 years +)	16,215	56.6	13,566	56.4	44,797	56.6
Receiving financial aid†	3,124	10.9	2,402	10.0	8,363	10.6
Comorbid type I or II diabetes						
Yes	4,336	15.1	3,618	15.0	11,928	15.1
No	24,292	84.9	20,447	85.0	67,253	84.9
Comorbid chronic kidney disease						
Yes	334	1.2	303	1.3	965	1.2
No	28,294	98.8	23,762	98.7	78,216	98.8
TOTAL	28,628	100.0	24,065	100.0	79,181	100.0

HTN: hypertension; *For brevity we do not present the detailed results for 2008, which did not differ significantly; **Public drug insurance plan; †The official name of this category is *"prestataire d'une aide financière de dernier recours"*

TABLE 3 Distribution of new antihypertensive users with HTN according to antihypertensive class first received and year

Class of hypertensive received* or multidrug therapy	Year of treatment initiation**				Total (2007-2009)	
	2007		2009			
	n	%	n	%	n	%
Centrally acting drug	220	0.8	251	1.0	711	0.9
Direct-acting vasodilators	5	0.0	2	0.0	10	0.0
Alpha-blockers	52	0.2	37	0.2	122	0.2
Beta-blockers	3,263	11.4	2,517	10.5	8,722	11.0
Calcium channel blockers	3,706	12.9	3,131	13.0	10,227	12.9
Angiotensin-converting enzyme inhibitors	5,559	19.4	4,195	17.4	14,289	18.0
Angiotensin II receptor blockers	6,163	21.5	6,001	24.9	18,528	23.4
Aldosterone receptor antagonists	44	0.2	25	0.1	112	0.1
Direct renin inhibitors	0	0.0	14	0.1	14	0.0
Diuretics	4,783	16.7	3,572	14.8	12,563	15.9
Two-drug regimens	4,021	14.0	3,559	14.8	11,490	14.5
≥3-drug regimens	812	2.8	761	3.2	2,393	3.0
Total	28,628	100.0	24,065	100.0	79,181	100.0

HTN: hypertension; *Results are presented according to drug class for single drug regimen at treatment initiation. The 10 classes are based on the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic classification**;****For brevity we do not present the detailed results for 2008, which did not differ significantly

Description of antihypertensive pharmacotherapy

The majority of new antihypertensive users (82.5%) received a single drug regimen at therapy initiation. Of these, 15.9% used a diuretic. Multidrug regimens, either fixed-dose or separate combinations, were observed at the start of therapy for 17.5% (Table 3). At 2 years after treatment initiation, 37.9% of users were on multidrug therapy (not shown in Table).

Table 3 shows that ACE inhibitors and particularly ARBs were the most often used. These two classes were also the most often represented in multidrug regimens, especially in conjunction with diuretics (not shown in Table). Among those on a multidrug regimen at treatment initiation, the proportion of persons receiving an ACE inhibitor, an ARB and a diuretic was 35.1%, 47.9% and 78.8%, respectively, in the most recent year (2009) (not shown in Table). Slightly more than half of new users on multidrug regimens received fixed-dose combinations at 2 years (not shown in Table).

Conformity with optimal use criteria

Table 4 shows the conformity of pharmacotherapy with optimal use criteria. Across the 3 years of the study, initial pharmacotherapy conformed to the criteria for 72.8% of new antihypertensive users with uncomplicated hypertension. Conformity was lower among new users with diabetes (62.6%) and was particularly low for those with chronic kidney disease but no diabetes (28.2%). For those on a two-drug regimen at 3 months, 1 year and 2 years after treatment initiation, pharmacotherapy conformed to optimal use criteria for just over 80% of users.

TABLE 4 Distribution of new antihypertensive users with HTN according to conformity of treatment with optimal use criteria* and year

Conformity of treatment with optimal use criteria according to situation	Year of treatment initiation**				Total	
	2007		2009		(2007-2009)	
	n	%	n	%	n	%
Drug regimen at treatment initiation						
Uncomplicated HTN†						
Conforms	13,165	73.0	11,304	73.1	36,622	72.8
Does not conform	4,871	27.0	4,149	26.9	13,654	27.2
HTN and diabetes						
Conforms	2,734	63.1	2,250	62.2	7,463	62.6
Does not conform	1,602	36.9	1,368	37.8	4,465	37.4
HTN and chronic kidney disease, no diabetes						
Conforms	67	27.8	58	27.9	193	28.2
Does not conform	174	72.2	150	72.1	492	71.8
Two-drug regimens among new users with uncomplicated HTN						
At 3 months						
Conforms	2,034	82.3	1,856	85.0	5,868	84.0
Does not conform	436	17.7	328	15.0	1,114	16.0
At 1 year						
Conforms	2,602	82.1	555	84.6	5,651	82.8
Does not conform	566	17.9	101	15.4	1,176	17.2
At 2 years						
Conforms	2,897	81.7	n/a	n/a	3,634	82.5
Does not conform	650	18.3			773	17.5

HTN: hypertension; n/a: at the time of data extraction, 2-year follow-up data were not available for new users of antihypertensives in 2009; *according to CHEP [Canadian Hypertension Education Program] (2006); **For brevity we do not present the detailed results for 2008, which did not differ significantly; †No history of diabetes, atherosclerotic vascular disease, chronic kidney disease or heart failure (see Methods).

Persistence with treatment and medical follow-up
At 3 months after treatment initiation, 69.8% of new users were still persisting with their antihypertensive pharmacotherapy. This proportion remained stable at 1 year (69.1%) and 2 years (69.2%). Finally, 55.7% of new antihypertensive users had 3 or more physician consultations as outpatients in the year following treatment initiation. This proportion was 51.7% in 2007 and 57.8% in 2009.

DISCUSSION

An important proportion of the Quebec population covered by public prescription drug insurance receive antihypertensives: almost 2 in 5. In our 3-year study period (2007-2009), slightly more than 79,000 of these persons were new users with a diagnosis of hypertension in the previous 5 years. The vast majority of new users (more than 80%) were initially treated with a single antihypertensive, which was most frequently either an ARB or an ACE inhibitor. These classes were also the most often used in multidrug regimens, including the simpler, fixed-dose combinations. We found that conformity with CHEP recommendations for optimal use at therapy initiation was fairly high (nearly 75%) for those with uncomplicated hypertension. However, conformity was lower among those with diabetes and was particularly low for those with chronic kidney disease but no diabetes.

A previous cohort study of 97,042 new antihypertensive users aged 50 to 64 years at cohort entry with uncomplicated hypertension in Quebec found that 94% started treatment with a single drug in the period 1998 to 2000.[10] It is likely that updates to the CHEP guidelines since 2006 explain the lower use of monotherapy in our study (82.5%): in 2008, and in 2009 for diabetics, CHEP recommended two first-line agents as initial treatment when arterial systolic and diastolic pressure are more than 20 mmHg and 10 mmHg, respectively, away from target levels.[20,21] Considering that many persons require multidrug regimens to regulate their blood pressure, more frequent use of fixed-dose combination therapies is likely to improve hypertension control while facilitating adherence to treatment.[6,7] Increased prescription of these combination therapies over time has also been observed elsewhere in Canada, but such regimens still represented the minority of antihypertensive treatments in 2006, at 10.9%.[7.]

Although the previous Quebec study found the same drug classes were the five most frequently used monotherapies as we observed, their results differed somewhat from ours in terms of frequency: 27% of new users received an ACE inhibitor (versus 17% in our study), 25% a diuretic (vs. 15%), 15% a BB (vs. 11%), 14% a CCB (vs. 13%) and 13% an ARB (vs. 25%).[10] An increase in the level of evidence in favour of ARBs over time and lower frequency of cough as a side effect of ARBs when compared to ACE inhibitors has likely led to greater use of ARBs at the expense of ACE inhibitors, diuretics, and BBs.[22,23]

Conformity with optimal use criteria and medical follow-up
The finding that nearly three-quarters of new antihypertensive users during the 3 years of our study had an initial treatment that conformed to CHEP recommendations is encouraging. Physicians in Quebec appear to know and apply these guidelines, as observed elsewhere in Canada.[7] The CHEP guidelines, however, are much more flexible for uncomplicated hypertension than 2008 recommendations from British Columbia (GPAC)[24], the national American education program on hypertension active during our study period[25], the clinical guide from the Institute for Clinical Systems Improvement (USA)[26], and the conclusions of 2009 Cochrane systematic reviews.[27,28] All of these sources recommend starting treatment of uncomplicated hypertension with a thiazide diuretic. If this criterion were applied to our study, only 12.9% of initial therapies would conform to optimal use (Supplementary Table 1).

The more frequent use of ARBs than ACE inhibitors as initial therapy for persons diagnosed with hypertension in our study is not incompatible with CHEP recommendations.[14] However, such a practice contradicts both GPAC and NICE which suggest an initial ACE inhibitor followed by an ARB if intolerant to the first drug.[24,29,30] ARBs are

most costly than ACE inhibitors, but are similarly effective.[31]

The levels of conformity with CHEP recommendations for diabetics and particularly for those with chronic kidney disease were lower than for those with uncomplicated hypertension. The optimal use criteria for antihypertensives are more restrictive for the first two groups: BBs are not recommended for diabetics and only ACEI inhibitors or ARBs are suggested in cases of chronic kidney disease. In addition, it is interesting to note that 24.2% of newly treated hypertensive persons aged 60 or older in our sample received a BB, which is not recommended practice. The measurement of such use is one of the quality indicators (related to safety) for hypertension proposed in INESSS's recent guide for first-line health professionals and managers working in chronic illness.[32] Future educational efforts should focus on these patients as they are at greater risk of non-optimal hypertensive therapy.

Regarding subsequent combination therapies in uncomplicated hypertension, these conformed to CHEP recommendations for at least 82.5% of users. Conformity for two-drug regimens would decrease by an absolute 8 to 11% if the optimal use criteria were based on GPAC rather than CHEP (Supplementary Table 1).

We found that the proportion of new users with 3 or more medical consultations in the year following treatment initiation increased over the study period, but remained at less than 60% in 2009. This increase occurred despite known difficulties in access to physicians in Quebec. Our figures need to be interpreted with caution since, firstly, follow-up of hypertensives may have been conferred to other health professionals (nurses, pharmacists) and, secondly, we did not have access to information on the reason(s) for consultations.

Persistence with antihypertensive treatment

Our results indicate that around 70% of new users persisted with any antihypertensive pharmacotherapy at 3 months, 1 year and 2 years after treatment initiation. The previous Quebec cohort study found that 75% of 21,011 new users with uncomplicated hypertension between 50 and 64 years of age were still persisting with their antihypertensive therapy after 6 months[10]; this proportion decreased to 55% after 3 years. In comparison, a second Quebec study of new users found persistence proportions of 88.6 to 92.9%, depending on antihypertensive class, after 2 years, when both initial treatment and changes to therapy were considered.[11] Although an association between better adherence to pharmacotherapy and older age has been noted[33], the analysis by Lachaine and colleagues actually included hypertensives less than 50 years old. The variation observed between the three Quebec studies, then, is likely mostly due to differences in methodology rather than sample.

STRENGTHS and LIMITATIONS

This study has several strengths. First, our cohort was population-based and included all persons covered by public drug insurance, thus offering high representation of individuals newly treated with antihypertensives in the province of Quebec. Second, such database studies offer the advantages of efficiency in terms of time and cost, potential richness of information, and absence of biases associated with community surveys, related to recall, non-response and sample attrition.[34,35.] Third, our quality criteria were based on well-known recommendations that have not changed for monotherapy up to and including 2009.[14,20] In addition, the databases employed in our study have been repeatedly validated for pharmacoepidemiological research[17,18,36] and are being increasingly utilized to evaluate medication use.

However, several limitations of our data should be noted. Our data capture dispensed drugs in the ambulatory setting and thus exclude medications received in hospital, through clinical trials and samples. Only one diagnosis was recorded per billing and no measurement of arterial pressure was provided. For medical visits, only consultations which led to a fee-for-service were counted. Since we only used CHEP's recommendations from 2006 as the source of optimal use criteria, some practices may have been misclassified; however, the existence of only minor changes in CHEP's later versions leads us

to believe that similar levels of conformity would have been reached if we had considered more recent guidelines. We believe that these limitations do not significantly affect the validity of our findings.

FUTURE DIRECTIONS

Although the level of conformity with the CHEP 2006 recommendations in our study was fairly high overall, it would be informative to examine whether greater interdisciplinarity of initial treatment and follow-up services is associated with better application of practice guidelines and adherence to therapy, especially among people with diabetes and with chronic kidney disease. Further research could employ quality of care indicators related to increased use of diuretics and ACE inhibitors in both single and combined therapies, and decreased recourse to ARBs. It would also be worthwhile to study other elements of antihypertensive treatment not evaluable using RAMQ databases. Indicators recently developed by INESSS provide an opportunity in this regard.

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Disclosures
The authors do not have any conflicts of interest to disclose.

Supplementary Table 1 Distribution of new antihypertensive users with a diagnosis of HTN according to conformity of treatment with optimal use based on CHEP or GPAC recommendations* and year of treatment initiation

Conformity of treatment according to origin of recommendations and situation	Year of initial treatment**								Total (2007-2009)			
	2007				2009							
	CHEP		GPAC		CHEP		GPAC		CHEP		GPAC	
	n	%	n	%	n	%	n	%	n	%	n	%
Drug regimen at treatment initiation												
Uncomplicated HTN†												
Conforms	13,165	73.0	2,407	13.4	11,304	73.1	1,889	12.2	36,622	72.8	6,458	12.9
Does not conform	4,871	27.0	15,629	86.7	4,149	26.9	13,564	87.8	13,654	27.2	43,818	87.2
HTN and diabetes‡												
Conforms	2,734	63.1	2,734	63.1	2,250	62.2	2,250	62.2	7,463	62.6	7,463	62.6
Does not conform	1,602	36.9	1,602	36.9	1,368	37.8	1,368	37.8	4,465	37.4	4,465	37.4
HTN and chronic kidney disease, no diabetes												
Conforms	67	27.8	54	22.4	58	27.9	54	26.0	193	28.2	165	24.1
Does not conform	174	72.2	187	77.6	150	72.1	154	74.0	492	71.8	520	75.9
Two-drug regimens among new users with uncomplicated HTN												
At 3 months												
Conforms	2,034	82.3	1,871	75.7	1,856	85.0	1,647	75.4	5,868	84.0	5,308	76.0
Does not conform	436	17.7	599	24.3	328	15.0	537	24.6	1,114	16.0	1,674	24.0
At 1 year												
Conforms	2,602	82.1	2,321	73.3	555	84.6	500	76.2	5,651	82.8	5,002	73.3
Does not conform	566	17.9	847	26.7	101	15.4	156	23.8	1,176	17.2	1,825	26.7
At 2 years												
Conforms	2,897	81.7	2,527	71.2	n/a	n/a	n/a	n/a	3,634	82.5	3,144	71.4
Does not conform	650	18.3	1,020	28.8					772	17.5	1,262	28.6

HTN: hypertension; n/a: at the time of data extraction, 2-year data were not available for new users of antihypertensives in 2009 ; *CHEP: Canadian Hypertension Education Program; GPAC: Guidelines and Protocols Advisory Committee (British Columbia) ; **For brevity we do not present the detailed results for 2008, which did not differ significantly from those for 2007 and 2009; †No history of diabetes, atherosclerotic vascular disease, chronic kidney disease or heart failure (see methods section for more details) ; ‡The recommendations based on CHEP and GPAC were the same.

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