Polytherapy with two or more antihypertensive drugs to lower blood pressure in elderly Ontarians. Room for improvement

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BACKGROUND: Although guidelines now recommend polytherapy to achieve blood pressure targets, little is known about which antihypertensive drugs are combined in clinical practice.

OBJECTIVE: To examine current practices for the coprescribing of antihypertensive agents.

METHODS: A population-based cohort study was performed using linked administrative databases on all Ontario residents 66 years of age or older who were newly treated for hypertension between July 1, 1994, and March 31, 2002, and did not have diabetes or other relevant comorbidities. All patients were followed for two years to determine which antihypertensives were prescribed concurrently.

RESULTS: Of the 166,018 patients in the described cohort, 1819 (1%) were prescribed a combination therapy tablet as their first-line therapy. The number of patients prescribed antihypertensive polytherapy within the first two years of diagnosis increased from 2071 (21%) of the 9825 hypertensive patients starting treatment in the second half of 1994 to 2578 (37%) of the 6988 hypertensive patients beginning treatment in the first quarter of 2002 ($P < 0.0001$). Overall, 11,003 (27%) of polytherapy prescriptions were for drugs without additive hypotensive effects when combined and this proportion did not change over time.

CONCLUSIONS: Although there has been an increase in the use of polytherapy in elderly hypertensive patients without comorbidities in Ontario over the past decade, more than one-quarter of the two drugs prescribed together have not been proven to have additive hypotensive effects. Because this likely contributes to suboptimal blood pressure control rates, future guidelines and educational programs should devote increased attention to the choice of optimal polytherapy combinations.

Key Words: Antihypertensive prescribing patterns; High blood pressure; Hypertension; Polytherapy

Polychimiothérapie composée d'au moins deux antihypertenseurs pour abaisser la pression artérielle chez les personnes âgées en Ontario : Place à l'amélioration

CONTEXTE : Bien que la polychimiothérapie soit recommandée dans les lignes directrices pour faciliter l'atteinte des valeurs cibles de la pression artérielle, on connaît peu de choses sur l'association des antihypertenseurs en clinique.

BUT : L'étude avait pour but d'examiner la pratique actuelle en matière d'emploi concomitant des antihypertenseurs.

MÉTHODE : Une étude de cohorte, fondée sur une population, a été menée à partir du recoupement de plusieurs bases de données administratives concernant toutes les personnes âgées d'au moins 66 ans, demeurant en Ontario, nouvellement traitées pour de l'hypertension artérielle entre le 1^{er} juillet 1994 et le 31 mars 2002 et non atteintes de diabète ou d'autres maladies concomitantes, liées à la première affection. Les patients ont été suivis pendant deux ans pour permettre de déterminer quels antihypertenseurs étaient prescrits en association.

RÉSULTATS : Au total, 166 018 patients ont été inclus dans la cohorte en question; sur le nombre, 1819 (1 %) patients ont été soumis à la polychimiothérapie orale comme traitement de première intention. Le nombre de patients qui ont reçu une ordonnance de polychimiothérapie antihypertensive au cours des deux années suivant la pose du diagnostic est passé de 2071 (21 %) sur les 9825 hypertendus ayant commencé le traitement au cours de la seconde moitié de 1994 à 2578 (37 %) sur les 6988 hypertendus ayant commencé le traitement au cours du premier trimestre de 2002 ($p < 0,0001$). Sur l'ensemble des ordonnances de polychimiothérapie, 11 003 (27 %) l'étaient pour des médicaments dépourvus d'effet hypotenseur additif lorsqu'ils étaient employés en association, et la proportion n'a pas changé au fil du temps.

CONCLUSIONS : Bien que le recours à la polychimiothérapie ait augmenté chez les personnes âgées hypertendues, non atteintes de maladies concomitantes, en Ontario, au cours de la dernière décennie, plus du quart des traitements prescrits, composés de deux médicaments ne produisaient pas d'effet hypotenseur additif avéré. Comme cela conduit vraisemblablement à une maîtrise sous-optimale de la pression artérielle, il faudrait que les futures lignes directrices et les nouveaux programmes de formation comportent un volet sur le choix des médicaments susceptibles d'association afin de composer une polychimiothérapie optimale.

Clinical trials, meta-analyses (1,2) and guidelines (3-5) have focused primarily on first-line therapy choices in recommending particular drug classes for individuals with hypertension. As a result, pharmacoepidemiological studies have also focused on monotherapy treatment choices (6). However, large clinical trials have documented that to achieve currently recommended blood pressure targets, two or more drugs are required in most patients (7-10).

Although the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure does not recommend particular drug combinations (3), both British (11) and Canadian (12) guidelines recommend combining drugs with different mechanisms of action as per the Birmingham algorithm (13-15). The Birmingham algorithm advocates the coprescribing of drug classes that are not only supported by

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a pathophysiological rationale, but that also have extensive clinical evidence to support their additive hypotensive effects – not surprisingly, all of these combinations are also available as combination products, with both drugs in a single tablet (13,14,16-20). These include thiazide diuretics with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers; beta-blockers with calcium channel blockers; and calcium channel blockers with ACE inhibitors or angiotensin receptor blockers. For other drug combinations, there is controversy over whether they have additive hypotensive effects (21-33), and the combinations do not have regulatory approval to be combined in a single tablet for the purposes of blood pressure lowering (13,17-19). Both the British Hypertension Society and the Canadian Hypertension Education Program endorse the combining of two antihypertensive drugs with proven additive hypotensive effect and advise against the use of unproven drug combinations in the absence of compelling indications arising from comorbid conditions, such as heart failure (11,12).

Several clinical trials (34-36) and meta-analyses (37,38) have documented that initial therapy of uncomplicated hypertension with a beta-blocker results in less prevention of cardiovascular events than is seen with other therapies. It remains controversial whether this lower effectiveness is limited to elderly patients (39), is explained merely by less blood pressure lowering effectiveness with beta-blockers (which may be partially addressed by using a higher dose) or whether the reduced effectiveness is also seen when beta-blockers are used as second-line or 'add-on' therapy. The extent to which beta-blockers are used as add-on therapy in hypertension treatment in elderly patients is unknown. Recently, Wald and Law (40) advocated the use of combination therapy in the treatment of hypertension, and suggested that a polypill containing fixed combinations of drugs may be the best option for cardiovascular disease prevention in patients older than 55 years of age. While this suggestion generated a storm of negative feedback on the *British Medical Journal's* rapid response Web site, one of the potential advantages of a polypill – that antihypertensive drugs combined in the polypill would be proven to have additive properties for blood pressure-lowering efficacy – was neglected by respondents. Of course, the extent to which this may represent an advantage of the polypill depends on how commonly physicians prescribe antihypertensive drug combinations that are not additive in their effects. Given the paucity of studies examining physician prescribing practices when combining two (or more) antihypertensive drugs in clinical practice, we designed the present study to examine which drugs were coprescribed when polytherapy was used in older individuals newly treated for hypertension.

METHODS

Details of how four Ontario administrative databases were linked (consisting of all hospital visits, outpatient physician visits, vital statistics and complete prescribing data) to construct a cohort of newly treated hypertensive individuals without comorbidities (and the list of conditions and comorbidities for which patients were excluded from the cohort) were published previously (6). In brief, the present cohort consisted of all Ontario residents 66 years of age or older who received a new prescription for an antihypertensive agent between July 1, 1994, and March 31, 2002, and did not have diabetes mellitus or another condition for which an antihypertensive drug may be prescribed for a nonblood pressure-lowering indication (such as coronary disease, heart failure or renal dysfunction). All patients were followed for two years after their initial antihypertensive prescription to determine antihypertensive polytherapy. Each prescription was assumed to last 100 days, and polytherapy was defined as the addition of another antihypertensive drug class

within 100 days from the date of the last prescription for the initial antihypertensive drug class prescribed. Combination agents that consisted of drugs from two different subclasses were separated and counted as one prescription in each respective subclass when assessing polytherapy. Annual proportions of patients treated with polytherapy were calculated and compared between years. χ^2 testing was performed to assess for significant trends.

For the purposes of the present report, the focus was on five major antihypertensive drug classes: thiazide and thiazide-like diuretics (hereafter referred to as diuretics), beta-blockers, ACE inhibitors, calcium channel blockers and angiotensin receptor blockers. Appropriate drug combinations were defined as those that have theoretical basis and/or randomized trial evidence of an additive hypotensive effect. These include: diuretics with beta-blockers, ACE inhibitors or angiotensin receptor blockers; beta-blockers with calcium channel blockers; and calcium channel blockers with ACE inhibitors or angiotensin receptor blockers. Drug combinations defined as 'not recommended' do not have additive hypotensive effects on a theoretical basis and do not have conclusive trial evidence supporting an additive hypotensive effect. These include: diuretics with calcium channel blockers; beta-blockers with ACE inhibitors or angiotensin receptor blockers; and ACE inhibitors with angiotensin receptor blockers.

RESULTS

The cohort consisted of 166,018 newly treated elderly hypertensive patients who did not have diabetes or other comorbidities (such as heart failure or coronary disease) that would mandate treatment with a particular antihypertensive drug class. Initial monotherapy drug choices in this cohort were previously reported (41) – the most common monotherapy prescriptions were for ACE inhibitors (29% of all initial prescriptions) and diuretics (40% of all initial prescriptions).

Of the 166,018 patients in the cohort, 1819 (1%) were prescribed a combination therapy tablet as first-line therapy. Within two years of initial therapy, the number of patients prescribed two drug classes concurrently to control blood pressure increased from 1992 of all 9825 (20%) hypertensive patients first treated in 1994 to 2184 of the 6988 (31%) first treated in 2002 ($P<0.0001$) (Figure 1). Approximately 73% (29,439) of the two-drug combinations were compatible with the Birmingham algorithm and Canadian Hypertension Education Program recommendations, and this proportion did not change between 1994 and 2002 ($P=0.45$). Being prescribed an appropriate combination of two drugs occurred with a frequency that was greater than predicted by chance (29,439 [73%] versus 60% predicted, $P<0.0001$). Overall, polytherapy within the first two years of diagnosis increased from 21% of the 9825 hypertensive patients starting treatment in the second half of 1994 to 37% of the 6988 hypertensive patients beginning treatment in the first quarter of 2002 ($P<0.0001$); the use of three or more drugs at the same time increased more than threefold (from 138 [2%] to 345 [6%], $P<0.0001$) between 1994 and 2002 (Figure 1).

Choice of second antihypertensive drug class for add-on therapy

The drug classes chosen as the add-on drug for patients being treated with two antihypertensive drugs were stable over time; the most frequent add-on drugs were diuretics (13,436 [39%]), ACE inhibitors (8327 [24%]), calcium channel blockers (6388 [19%]) and beta-blockers (5779 [17%]).

Change in polytherapy combinations

Overall, the ACE inhibitor plus diuretic combination was the most frequently used two-drug combination in all years that were

Figure 1 Elderly hypertensive patients in Ontario prescribed monotherapy versus polytherapy, 1994 to 2002. Note that data for 1994 and 2002 only contain information from the third and fourth quarters and the first quarter, respectively

studied, increasing from 547 (29%) in the 1994 cohort to 766 (35%) in the 2002 cohort ($P < 0.0001$) (Figure 2). The use of diuretics with beta-blockers declined over time from 281 (15%) to 236 (11%) ($P < 0.0001$), as did the coprescribing of calcium channel blockers with beta-blockers, from 206 (11%) to 116 (5%) ($P < 0.0001$), as well as calcium channel blockers with ACE inhibitors, from 341 (18%) to 255 (12%) ($P < 0.0001$).

Of the nonrecommended two-drug combinations, the most frequent in all years of the present study were calcium channel blockers with diuretics, which declined from 353 (18%) of all two-drug coprescriptions in 1994 to 287 (13%) in 2002 ($P < 0.0001$) and beta-blockers with ACE inhibitors, which increased from 189 (10%) of all coprescriptions in 1994 to 261 (12%) in 2002 ($P < 0.0001$).

The overall use of beta-blockers in two-drug combination therapy declined from 35% in 1994 to 30% in 2002 ($P < 0.0001$). With the exception of the ACE inhibitor plus beta-blocker combination, all combinations with a beta-blocker declined.

DISCUSSION

In patients with hypertension and no comorbidities, the reduction in clinical events is directly related to the reduction in blood pressure (42). However, over one-quarter of all second drugs added to treatment regimens for elderly hypertensive patients in our study was for drugs that have not been proven to provide additive effects to the first-line therapy prescribed for those patients (4,11,12). This may result in suboptimal blood pressure lowering in these patients and may contribute to the poor blood pressure control rates reported in surveys from a variety of countries (43). Furthermore, even in 2002, 28% of Ontario elderly patients with uncomplicated hypertension received a two-drug combination that included a beta-blocker. Although the role of beta-blockers in combination therapy is currently unclear, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and other trials have demonstrated that beta-blocker-based therapies do not reduce cardiovascular events to the same extent as other therapeutic strategies, particularly in elderly patients with uncomplicated hypertension (34-36). It is important that almost 40% of add-on therapy was with a diuretic, which is the least expensive antihypertensive class.

Figure 2 Use of proven efficacious polytherapy combinations in elderly hypertensive Ontarians, 1994 to 2002. Note that data from 1994 and 2002 only contain information from the third and fourth quarters and the first quarter, respectively. ACE Angiotensin-converting enzyme

The main strength of our study is that the data reflect longitudinal prescribing to the population of Ontario older than 65 years of age who were newly prescribed antihypertensive therapy and did not have diabetes or cardiovascular comorbidities. Our findings are congruent with a recently published analysis of the National Health and Nutrition Examination Survey (NHANES) 1988 to 1994 and NHANES 1999 to 2002 data demonstrating that the use of polytherapy to treat hypertension in patients without comorbidities is increasing in the United States (from 29% in 1988 to 36% in 2002) and that the most common two-drug combination is an ACE inhibitor with a diuretic (44). While our data confirmed the NHANES analyses in another geographic locale, our study also extended the NHANES findings, because it was longitudinal and enrolled only newly treated patients, while the NHANES analyses were cross-sectional and included a mix of new and chronic diagnoses. We were thus able to examine serial prescriptions over time to determine the sequence with which drugs were combined (proving that diuretics were the most frequently added second-line agent) and the frequency with which polytherapy was prescribed within the first two years of diagnosis.

The coprescription of calcium channel blockers with diuretics was the most common nonrecommended polytherapy combination used in our study cohort. Some may cite the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (45) as evidence in support of the combination of a calcium channel blocker with a diuretic. However, it is important to note that although patients randomly assigned to amlodipine followed by hydrochlorothiazide in the VALUE trial had greater reduction in blood pressure than patients randomly assigned to valsartan followed by hydrochlorothiazide, the VALUE trial was not designed to examine the additive hypotensive effects of the combinations. Indeed, the greatest reduction in blood pressure in the VALUE trial was during a period in which patients were on initial monotherapy, and the blood pressure differences between the study groups narrowed during combination therapy (45). Other studies have refuted the additive hypotensive effect of this combination (21,23,25,27-29,32). Although edema is the most frequent adverse effect of calcium channel blockers and the addition of a diuretic may reduce this effect (46-50), it is important to remember that calcium channel blockers are natriuretic, and the mechanism of edema formation is not related to retention of salt and water (48-51). It is likely that primary care physicians are unaware of the evidence supporting optimum drug combinations to lower blood pressure.

To avoid confounding by indications for specific antihypertensive combinations, patients were excluded in our study for the following rationale: strong clinical trial evidence supporting the combination of beta-blockers with ACE inhibitors in patients who have had a myocardial infarction or have congestive heart failure (52-54). By the same token, although the combination of an ACE inhibitor with an angiotensin receptor blocker may have clinical advantages in patients with renal disease and proteinuria despite a less than additive hypotensive effect (55), patients with renal disease or diabetes were also excluded from our study.

Although we reported antihypertensive prescribing practices in a large, representative and population-based sample of all elderly adults newly treated for hypertension in Canada's most populated province over the past decade, there are limitations to the use of administrative databases. Principally, we do not have blood pressure readings, the reasons why physicians chose to prescribe one drug over another are not recorded in administrative data, and our sample includes only those patients who filled their prescription for antihypertensive drugs. However, although these limitations would be fatal flaws for any study attempting to extrapolate from these data to report hypertension incidence or prevalence rates, these limitations do not directly impact our question of interest: ie, which drugs do physicians choose to combine when treating their hypertensive patients? Indeed, our use of administrative data collected on all Ontario residents allowed us to avoid the problems with small samples, selection bias and measurement bias, which commonly afflict cohort studies. We also did not have all the information on the duration of prescriptions, and it is possible that our assumption of each prescription lasting 100 days may have led to an overestimate of the number of polytherapy prescriptions. As well, administrative

data do not provide information on adherence rates, which if low, can also lead to an overestimate of polytherapy antihypertensive use. Nevertheless, the same methods were applied to each year throughout the study, and it is reasonable to assume that prescription duration and adherence did not change significantly throughout the study period.

CONCLUSIONS

Although the use of polytherapy to treat hypertension has been increasing over time, approximately one-quarter of antihypertensive drug combinations prescribed by clinicians are suboptimal and this proportion has remained stable over the past decade. Furthermore, almost one-third of elderly patients receiving polytherapy are treated with combinations that include a beta-blocker, although this has been declining slowly over time. To this point, most guidelines and continuing medical education programs on hypertension have focused on making the diagnosis and choosing initial monotherapy. Our data suggest that future guidelines and programs should emphasize appropriate polytherapy combinations in an effort to optimize the control of blood pressure and the reduction in cardiovascular disease in elderly hypertensive individuals.

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