Primary care prescribing patterns in Ireland after the publication of large hypertension trials

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What is already known about this subject

- Between 2000 and 2004, three large hypertension trials were particularly important in choice of antihypertensive drug; LIFE, ALLHAT and VALUE.
- Studies in the US and Canada have shown that subsequent prescribing patterns have been influenced through such publications.

What this study adds

- There was little or no effect of any of the trials on new antihypertensive prescribing in Ireland, except for a slight increase in new prescriptions for ACE inhibitors following ALLHAT, and calcium channel blockers following the VALUE trial.

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Keywords

antihypertensive, prescribing, trials

Received

11 September 2006

Accepted

8 January 2007

Published OnlineEarly

4 July 2007

Aims

This study assessed prescribing patterns of antihypertensive therapies (AHT) before and after the publication of the LIFE, ALLHAT and VALUE trials between 2000 and 2005.

Methods

The Irish HSE-PCRS prescribing database was used to identify those initiated any AHT. Any change 12 months before and after the trial publications was examined using a segmented regression analysis.

Results

There was little or no effect of any of the trials on new AHT prescribing, except for ALLHAT where there was an increase in new prescriptions for ACE inhibitors, and VALUE with a slight increase in prescriptions for calcium channel blockers.

Conclusions

Our findings show that there was little or no effect of any of the three clinical trials studied on new AHT prescribing patterns in Irish general practice. Future studies should assess any underlying barriers to implementing new evidence into clinical practice.

Introduction

In 2000, 26.4% or 972 million of the adult population worldwide had hypertension and half were over 50 years of age [1]. The beneficial effect of lowering blood pressure on morbidity and mortality associated with cardiovascular disease has been established, but there is debate

as to the choice of antihypertensive agent. In the last decade, the fortunes of various antihypertensive drugs have changed dramatically.

Between 2000 and 2004, three large hypertension trials were particularly important from a choice of antihypertensive drug perspective: the Losartan Intervention

for Endpoint reduction (LIFE) [2] and the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) [3] in 2002 and the Valsartan Anti-hypertensive Long-term Use Evaluation (VALUE) [4] in 2004. Although each of these trials was designed as an endpoint trial, there were also differences in the effect of various drugs in lowering blood pressure.

The LIFE study showed that for a similar level of blood pressure reduction losartan reduced events more than atenolol, a β -adrenoceptor blocker [2]. The ALLHAT trial confirmed that thiazides (chlorthalidone) controlled systolic BP as well as, and in selected sub-groups better than, both angiotensin-converting enzyme inhibitors (lisinopril) and calcium channel blockers (amlodipine) [3]. The VALUE trial, however, showed that the amlodipine-based regimen significantly reduced blood pressure further than valsartan, especially in the early period [4]. Another feature common to all studies was a demonstration of the need for polypharmacy to achieve blood pressure control.

Studies in Canada and the US have shown that such publications have influenced prescribing patterns [5, 6]. This study assesses such prescribing patterns in Ireland from January 2001 to July 2005, 12 months before and after the publication of the three major hypertension trials: LIFE, ALLHAT and VALUE.

Methods

We used the Health Service Executive Primary Care Reimbursement Services (HSE-PCRS) prescribing database from January 2000 to July 2005 in the largest Eastern Region of Ireland (approximate population 330 000). The scheme, which is means tested for those less than 70 years of age, provides free health services to about 30% of the Irish population. This study population may not be truly representative of the general population across the whole of Ireland, but the HSE-PCRS prescribing database captures more than 65% of all drugs prescribed at the primary care level.

All prescription items are coded using the WHO Anatomical Therapeutic Chemical (ATC) classification and basic demographic information (age and sex) are recorded. We identified those who had been prescribed new antihypertensive agents including angiotensin converting enzyme (ACE) inhibitors, all β -adrenoceptor blockers, thiazide-type diuretics, valsartan, losartan, calcium channel blockers, amlodipine, α -adrenoceptor blockers, and atenolol as an individual β -adrenoceptor blocker. Since diagnosis is not included in the HSE-PCRS database, we excluded those concurrently prescribed nitrates or aspirin for ischaemic heart disease, insulin and oral hypoglycaemic therapies for diabetes,

Figure 1

Relative percentage of each class of anti-hypertensive agents from January 2001 to July 2005: New prescriptions. BB β -adrenoceptor blocking drugs, TZ thiazide-like diuretics, CCB calcium channel blocking drugs, ATEN atenolol, LOSART losartan, VALSART valsartan

and loop diuretics for heart failure. New prescriptions were classified as those not having received any antihypertensive agents in the previous 12 months. Therefore, data on new prescriptions were from January 2001 onwards.

The monthly total number and relative percentage of dispensed prescriptions for each class of antihypertensive drugs were calculated for each month.

Statistical analyses

A segmented regression analysis was used to assess whether any change had occurred 12 months before and after the trial publications [7]. The change in regression slope before and after trial publication is an indication of the shift in prescribing trend. Significance at $P < 0.05$ was assumed and SAS 9.0 (SAS Institute Inc, Cary, NC) was used for all analyses.

Results

β -adrenoceptor blockers were the most frequently prescribed new antihypertensive agent in Irish primary care between January 2001 and July 2005.

Figure 1 shows the relative percentage of new prescriptions for each class of antihypertensive agent. There was no significant change in new prescriptions for either atenolol ($P = 0.29$) or losartan ($P = 0.44$) before and after the publication of the LIFE trial in February 2002. The use of ACE inhibitors continued rising even after the publication of the ALLHAT study in December 2002 and the change in rate before and after the trial publication was significant (change in slope = 0.003,

Figure 2

The distribution of the number of newly initiated antihypertensive agents over time. % monotherapy (■); % dual therapy (■); % 3+ therapy (□)

SE = 0.002, $P = 0.0098$). There were no significant changes for either amlodipine ($P = 0.72$) or thiazide-type diuretics ($P = 0.64$). New prescriptions of valsartan did not change significantly after the VALUE trial ($P = 0.81$). However, there was a significant change in the percentage of new calcium channel blocker prescriptions before and after the VALUE trial publication (change in slope = 0.002, SE = 0.0007, $P = 0.0085$), but not for amlodipine prescribing in particular ($P = 0.108$).

There was a five-fold increase in valsartan prescriptions in July 2005 relative to January 2001, which was proportionately higher than for any other antihypertensive agent, where little or no relative change was observed, except for losartan at 1.6-fold increased prescribing. Figure 2 shows a proportional increase in polypharmacy in newly treated hypertensive patients relative to a decline in monotherapy over time.

Discussion

Our study showed no apparent statistically significant changes in new prescriptions following the publication of the three large hypertension trials except for the ALLHAT trial, where there was a significant increase in new prescriptions for ACE inhibitors, and the VALUE trial where there was an increase in use of all calcium channel blockers. Our study excluded patients with heart failure. The influence of earlier trials, particularly the HOPE trial [8], on the use of ACE inhibitors in patients at cardiovascular risk is more likely. A similar explanation could be attributed to the EUROPA trial [9] that reinforced the beneficial effect of ACE inhibitors especially on low-risk patients unlike the high-risk patients recruited in the HOPE trial [8].

When the ratio of individual drugs was examined in July 2005 relative to January 2001, valsartan prescrip-

tion rates had the greatest proportionate increase of five-fold from a very low baseline rate, compared with the little or no proportionate increase in other therapies except losartan (a 1.6 fold increase). Such a pattern may reflect the power of marketing of valsartan rather than the impact of clinical trials. However, the reported fewer side-effects of angiotensin receptor blocking drugs, such as lower cough incidence, are also more likely to influence the prescribing pattern.

There was a general trend, although not statistically significant, of increased prescribing of amlodipine following the VALUE trial. This trial found a greater blood pressure reduction with amlodipine, as opposed to the valsartan based regimen, which is of particular interest as commercial promotion following the VALUE study concentrated on valsartan. Another 'outcome' of this, and earlier studies, is a growing appreciation that to achieve blood pressure control, patients are more likely to receive multiple antihypertensive therapies. A similar trend in the use of polypharmacy was also observed in our study.

When the ALLHAT study was published in December 2002, the findings of this trial were not actively promoted in primary care in Ireland and prescriptions for thiazides continued to decline. The promotion of thiazides in the US and Canada was based on equal effectiveness for cardiovascular disease prevention, lower cost and the higher risks of other vascular endpoints for other antihypertensive drugs [5, 6]. However, in Ireland there was no cost implication in the HSE-PCRS scheme which provides free health services to 30% of the Irish population.

In contrast to the LIFE and VALUE studies, ALLHAT was not industry supported and received no secondary promotion through advertisements for the individual products in Ireland. Furthermore, the population studied in the ALLHAT trial included 35% Black and 19% Hispanic and this may not represent the Irish hypertensive population.

Previous publications have indicated limited change in physician practice following the publication of clinical trial findings [10]. Results of randomized controlled trials on cardiovascular drug prescribing patterns have categorically pointed out that more incentives are needed to effect change [11]. Reports on the influence of practice guidelines on physician behaviour indicate that there is suboptimal adherence to guidelines [12]. As with any behaviour, professional behaviour is difficult to change. Health authorities have issued guidelines to doctors that address these issues. However, it is not easy to change prescribing practices, and research has shown that issuing guidelines has only limited effects [13, 14].

Attitudes and lack of knowledge among physicians are likely to be the main barriers to adhering to these recommendations [15].

Nonetheless, a few published guidelines might have influenced the clinical practice in Ireland. For example, in 2000/2001 MIMS (Monthly Index of Medical Specialties) published an abbreviated version of the British Hypertension Society (BHS) guidelines with β -adrenoceptor blocking drugs and thiazides as drugs of first choice. Again, in 2002/2003 ISH/WHO and European guidelines suggested ACE inhibitors, angiotensin receptor blocking drugs, β -adrenoceptor blocking drugs, calcium channel blockers or thiazides as all drugs of first choice. By 2004 the BHS introduced the ABCD algorithm [16].

In addition to changing clinical guidelines, several other factors may influence the pattern of prescribing. Examples include the cardiovascular risk factor profile of the individual patient, the presence of target organ damage, the presence of other coexisting disorders, variation in individual patient response to drugs from different classes, the strength of the evidence, and socioeconomic factors [17]. Furthermore, pharmaceutical promotion may have a direct influence on the prescribing practices of physicians [18].

The recent ASCOT study showed that the amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen [19]. The National Institute of Clinical Excellence in the UK recently recommended that β -adrenoceptor blockers should not be the first line of treatment for hypertension, particularly in those diagnosed with diabetes [20]. In a subanalysis of our data, in those with diabetes, we found no significant change in newly initiated prescriptions for atenolol or losartan before and after the LIFE study.

In conclusion, our findings showed that there was little or no effect of any of the three clinical trials studied on new prescribing patterns of new antihypertensive therapy in primary care in Ireland. However, there was an increase in new prescriptions for ACE inhibitors following ALLHAT, and an increase in calcium channel blockers following the VALUE trial. It is therefore important to undertake qualitative studies to understand the behavioural patterns among the general practitioners, as well as to understand the underlying barriers to implementing new evidence into clinical practice.

We thank the HSE-PCRS for access to the data on which the study is based and the Irish Heart Foundation for funding.

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