Original Scientific Paper

Does changing Dihydropyridine Calcium Channel Blockers for subsidy reasons affect blood pressure control?

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ABSTRACT

Objective

To describe the pattern of changes in blood pressure levels that occurred when GPs changed hypertension medication as a result of changes in calcium channel blocker (CCB) subsidy arrangements. Typically this involved changing from existing CCB medication to a different, fully subsidised CCB.

Method

New Zealand data from two subsidised visits for reviewing medication were collected on age, gender, socioeconomic status and blood pressure. Changes in blood pressure were analysed by intervention across the two visits.

Results

Repeated measures analysis of BP changes for 5 683 matched patient forms found no significant change in measurements of systolic and diastolic blood pressure, and a Wilcoxon matched pairs test on three levels of 'degree of blood pressure control'.

Conclusion

Deficiencies in claim form design, lack of standardised protocols for BP measurement, and some inconsistencies in completion of claim form items mean that these results must be interpreted cautiously. However, the analysis suggests that medication changes following reduction in subsidies paid by the government for CCBs had no significant effect on either systolic or diastolic blood pressure.

Implications

While there may be other considerations to take into effect such as the need for explanation to patients and administrative issues, changing patients from one brand of CCB to another does not appear to have a significant effect on their blood pressure.

(NZFP 2002; 29: 247–253)

Introduction

In New Zealand the Pharmaceutical Management Agency Limited (PHARMAC) manages the pharmaceutical schedule on behalf of its owner, the Health Funding Authority (HFA). A key activity of PHARMAC is the continual monitoring of pharmaceutical trends, through the Pharmaceutical and Therapeutics Advisory Committee (PTAC) and various sub-committees, and negotiating with providers of pharmaceuticals to obtain the best prices for medicines on the schedule.

PHARMAC operates a policy known as 'reference pricing' in which the lowest negotiated price for a pharmaceutical will apply to all medicines in a given therapeutic group. If a pharmaceutical company is unwilling to match the lowest market price being offered for a medicine in a given therapeutic group, then patients may face 'part charges' or 'manufacturers premiums' when they present prescriptions to pharmacies.

When reference pricing was applied to ACE Inhibitors in June 1998, PHARMAC agreed to subsidise two consultations to discuss therapy options and monitor the effect of any changes in medication. Data from claim forms submitted by GPs was analysed by an independent group (the RNZCGP Research Unit at the University of Otago).

In March 1999 PHARMAC started to apply reference pricing to Dihydropyridine Calcium Channel Blockers (DHP CCBs). PHARMAC negotiated a price for Felodipine ('Plendil', 'Agon') which set the level of the subsidy for DHP CCBs. Felodipine was fully subsidised whereas patient part charges for alternative DHP CCBs – Isradipine, Amlopidine and some forms of Nifedipine – ranged from NZ$10 to $23 per month.

DHP CCBs are not recommended as first-line treatment of hypertension, but have been found to be suitable antihypertensive agents in patients who remain hypertensive despite treatment with an ACE-inhibitor, beta-blocker or diuretics, or those with concomitant diseases that preclude the use of other antihypertensives.

Research has indicated that Felodipine produces a similar reduction of blood pressure to that obtained when other DHP CCBs are used.[1–3] In particular, studies have indicated successful switching from taking short-acting Nifedipine to once-daily Felodipine.[4,5]

PHARMAC agreed to fund up to two consultations to advise patients about their therapeutic options and monitor the effect of any changes in therapy. The RNZCGP Research Unit at the University of Auckland was contracted to provide an analysis of the data contained on the claim forms. This paper presents that analysis.

Method

There are certain caveats on data accuracy. The Research Unit had no control over experimental design or data collection. As the data presented here has not been collected in a controlled research environment we can not make any assumptions about the reliability or validity of the raw data. The accuracy of blood pressure recordings in particular can not be assessed.

General practitioners received an information pack from PHARMAC describing the new CCB subsidy arrangements and sets of forms for making claims for payment for patient visits. There were two PHARMAC-designed forms to be completed to receive payment.

Data from individual patients were recorded on separate forms, each consisting of an original and two carbonised copies. The GP retained the original and sent the remaining copies to HBL for processing, together with a summary form to accompany each batch of forms.

The GP was required to indicate whether a form was for a first or second visit. The link between forms, to establish that they were for the same patient, was through the NHI number recorded on each form, or through matching by encrypted name and date of birth. In a small but significant proportion of cases both visits were recorded on the same form, with GPs creating ad hoc entries as required, for example for recording a second blood pressure.

Summary claim forms and individual patient claims were received by HBL and processed for payment. One copy was forwarded to the Research Unit, where the forms were entered into an Access database by a full-time data entry person. When large batches of data were received a second data entry person was employed on a casual basis. Only two data entry persons were employed. The accuracy of data entry was checked by a random audit of 200 claim forms (1% sample) performed by the first author (BG). One data entry error was detected, an accuracy rate of 99.5% per form, or 99.96% per field. The data entry person created separate records in the database for visits one and two if they were recorded on the same form. Analyses were performed using SAS.

Key points

- In March 1999 PHARMAC started to apply reference pricing to Dihydropyridine Calcium Channel Blockers.
- Over 5 000 paired BP recordings were available for analysis.
- Changing patients from one brand of CCB to another does not appear to have a significant effect on their blood pressure.

Results

The Research Unit entered a total of 21 747 claim forms, 14 848 for first visits, 6 893 for second visits and six that could not be classified. Data was often incomplete in claim forms. Claims were received from 2 089 different GPs. Most doctors submitted less than five claims, although some doctors submitted more than 50 claims.

The claim form allowed GPs to specify the patient's current DHP, allowing the GP to choose from the three DHP CCB that were not fully subsidised. On some claim forms this section was not completed (93), including forms on which GPs had indicated that the patient was on another DHP CCB. The distribution of DHP CCBs (not including Felodipine) in the 14 755 completed forms at the first visit was Nifedipine 8 138 (55%); Amlodipine 5 200 (35%) and Isradipine 1 417 (10%). A small number of doctors (13) indicated that their patient was already using the fully subsidised DHP CCB Felodipine

Table 1. Decision to change by current DHP CCB, first visit

Changing/DHP CCB	Amlodipine	Isradipine	Nifedipine	Totals
Yes	4190	1315	6791	12296
No	914	85	1232	2231
TOTAL	5104	1400	8023	14527

Table 2. Type of change in therapy by current DHP CCB

Type of change	Amlodipine	Israpidine	Nifedipine	All	%
Stop CCB therapy	194	51	385	631	5.0
To thiazide	77	23	149	249	2.0
To beta blocker	81	29	138	253	2.0
To ACE inhibitor	170	57	344	573	4.5
To fully subsidised DHP CCB	3650	1134	5730	10552	83.8
To other antihypertensive	112	41	183	340	2.7

The "All" column includes cases for which current CCB therapy was not recorded, thus the total (12598) is greater than the sum of the earlier columns, and greater than the number classified as changing DHP CCB therapy in the previous table (12296). The most common change in therapy by far was to replace one of the non-fully subsidised DHP CCBs with a fully subsidised DHP CCB.

Table 3. BP by current DHP CCB

DHP CCB	Systolic	Diastolic
Amlodipine	145.9	82.8
Isradipine	149.4	84.3
Nifedipine	146.1	83.1
All DHP CCBs	146.3	83.1

at the first visit, by writing a free form note on the claim form.

Table 1 shows the changes in medication that occurred at the first visit. There are some differences in the rates of changing medication, depending on which DHP CCB the patient was using. Of the 14 755 forms for which DHP CCB data were available, information on whether a change in medication was being made was available for 14 527. These differences in decision to change medication are statistically significant at p<0.0001 (c2df=2). A decision to change medication appears to be more likely for patients on Israpidine than for Amlodipine or Nifedipine.

Once a decision had been made to change DHP CCB therapy, the GP was asked to indicate what the change would be, from a possible six choices (Table 2).

Mean systolic and diastolic blood pressure were plotted for first visit, including distribution of blood pressure measurements by age and gender. Most cases fell in the '60–79' age range, with small numbers in the '<40' and '80+' groups. Females appeared to have a consistently higher systolic BP. In addition the trend to increasing systolic with age is accompanied with an increase in pulse pressure (systolic – diastolic BP). The increase in BP with increasing age and the higher systolic BP in females were both statistically significant (p<.001, Sheffé post hoc tests). BP classified by current DHP CCB (Table 3) also gave statistically significant differences (one-way ANOVA, p<.05). The slightly higher BPs recorded for Isradipine (p<.001, Sheffé post hoc tests) may explain the earlier finding that a change in medication was more likely on Isradipine than other DHP CCB medication.

The distribution of DHP CCBs (not including Felodipine) in the completed forms (2 703 out of 6 893 second visit forms) at the second visit was Nifedipine 1 426 (53%); Amlodipine 959 (35%) and Isradipine 318 (12%). A number of doctors indicated that their patient had changed onto Felodipine (329). General practitioners could also change medication at the second visit. As with the first visit, the most common change in therapy recorded at the second visit was to replace one of the non-fully subsidised DHP CCBs with a fully subsidised DHP CCB at the second visit.

The distribution of blood pressure measurements at the second visit by age and gender demonstrated the same pattern as observed in the first visit data with widening pulse pressures and a persistently higher systolic BP in females. Increasing BP with age group and the higher systolic BP in females were statistically significant (p<.001, Sheffé post hoc tests).

The changes in BP across the two studies were analysed first in an in-

Table 4. Pattern of changes in therapy across both visits

	SECOND VISIT					
FIRST VISIT	**Stop CCB**	**Thiazide**	**ß blocker**	**ACE inhibitor**	**Fully sub. CCB**	**Other**
Stop CCB	70	2	2	4	50	7
Thiazide	2	25	2	2	13	2
ß blocker	3	0	29	2	7	2
ACE inhibitor	3	0	1	78	20	3
Other	6	2	3	0	19	25

GPs recorded what action they took at each visit. This table records the pattern of changes when the data were available for both visits. Example: 13 patients were started on a fully subsidised CCB at the first visit, then switched to a thiazide at the second visit.

Table 5. Change in BP, matched pairs

Variable	Mean	T	Std error	p-value
systolic	+0.28	1.07	0.26	0.284
diastolic	-0.45	-3.01	0.15	0.002

dependent t-test analysis, and then in a general linear model, controlling for age and gender. A t-test analysis showed a significant increase in systolic BP of 1 mm Hg in the second visit compared with first, however subsequent analyses showed that after controlling for age group and gender this difference disappeared. Many patients attended the first visit but not the second. The second visit forms were thus a biased subset of the first. This makes interpretation difficult, for example – would the non attenders at a second visit tend to have higher or lower BPs?

A repeated measures analysis on matched patient forms is a much more powerful analysis, which was then conducted. A total of 5 683 second forms could be matched with a first form, from the total of 6 893 second forms. With matched data, analyses were performed on the differences in BP measurements for each patient, or in changes in degree of BP control.

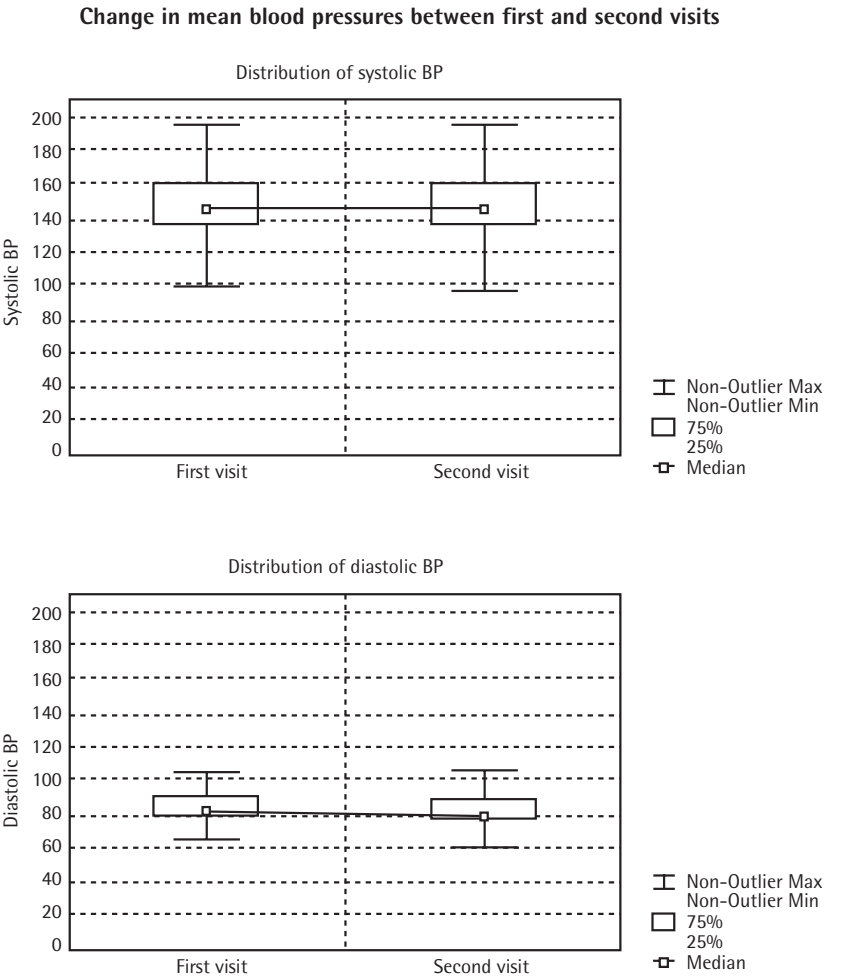
Of the 5 683 patients included in this analysis, GPs indicated they would change therapy at the first visit for 5 008 patients and at the second visit for 1 748 patients. Using matched patient forms it is possible to describe the sequence of therapy changes, if any, that occurred across the two visits (Table 4). It would appear that, for example, of the 46 patients changed to a thiazide at the first visit, 13 of them were changed to a fully subsidised CCB at the second visit, and only two were changed to a beta-blocker.

The matching of claims permits analyses to be performed on BP changes across the two visits. Matching substantially reduces measurement error due to patient variation. Blood pressures were analysed separately for systolic (5 007 patients) and diastolic (5 010 patients) measurements by paired t-tests in the first instance. The test is that the change in BP (systolic or diastolic, second visit reading minus first visit reading) is not zero. The results are summarised in Table 5. It can be seen that there was no significant change in systolic BP, but there a clinically small (0.45 mm Hg) but statistically significant drop in diastolic BP (Figure 1).

A more sophisticated analysis was conducted in which change in systolic and diastolic blood pressure was modelled by a general linear model in SAS PROC GLM. The model assumes that these differences are approximately normally distributed (they are) and tests the hypotheses that age (continuous variable), gender, socio-economic status (as measured by a dummy variable for Community Service Card (CSC) holding) have no effect on the size of the change in blood pressure. Complete data was available for 4 150 of the 5 683 matched second forms.

Neither age, gender nor CSC holding had any effect upon the differences in systolic BP observed between the two visits. However the analysis for difference in diastolic BP shows that even after controlling for

Figure 1. Comparison of BP across visits, matched data



Data is from 5 683 patients who attended for two visits and could be matched.

Table 6. GLM model of change in diastolic BP, including treatment change (TYPE)

Factor	SS	Degree of Freedom	MS	F	p
Intercept	1977.8	1	1977.830	18.31883	.000019
AGE	397.9	1	397.864	3.68505	.054973
SEX	327.0	1	326.990	3.02861	.081885
TYPE	9056.5	5	1811.291	16.77632	.000000
CSC	26.7	1	26.726	.24754	.618842
SEX*TYPE	1397.7	5	279.547	2.58919	.024045
SEX*CSC	7.6	1	7.550	.06993	.791453
TYPE*CSC	406.0	5	81.206	.75214	.584412
SEX*TYPE*CSC	90.9	5	18.181	.16840	.974263
Error	432840.0	4009	107.967		

"TYPE" classifies the therapeutic manoeuvre, e.g. change to beta blocker, thiazide etc. 'CSC' is the New Zealand 'Community Services Card' a health resources targeting mechanism measuring household income adjusted for family size, a surrogate for socio-economic deprivation.

age, gender and CSC the significant difference in the earlier t-test analysis remains, with a significant age effect. The value of 'R-square' (not reported) for these analyses is notable. It may be interpreted as a measure of the proportion of the total variation in the dependent variable (change in systolic or diastolic BP) that may be explained by the variables in the model. Both these models explain less than 1% of the variation in blood differences across the two visits.

The above analysis was then extended to include 'type of change' (e.g. 'stop CCB', 'change to beta blocker') to the model. Of the 5 683 patients in the analysis BP differences could be calculated for approximately 5 000 patients – BP was often not recorded, and sometimes either the systolic or diastolic BP was unrecorded or illegible. As may be expected, the type of change in medication was very highly significant as a determinant of change in systolic and diastolic BP when added to the above full model (p<.00001 in both cases). When adjustments are made for age, gender and CSC status 'type of change' remained a very significant predictor of difference in systolic and diastolic BP (Tables 6 and 7).

Blood pressure (systolic and diastolic) increased for patients who had their CCB medication stopped at the first visit, changed to a thiazide, changed to a beta-blocker or changed to an ACE inhibitor but decreased slightly for those patients changed to a fully subsidised DHP CCB.

An alternative analysis was conducted by considering BP profile in three groups, controlled (systolic<= 150 and diastolic <=90), 'moderately uncontrolled' (systolic 150-<170 or diastolic 90-<100) and uncontrolled

Table 7. GLM model of change in systolic BP, including treatment change (TYPE)

Factor	SS	Degree of Freedom	MS	F	p
Intercept	14102.	1	14101.51	40.90511	.000000
AGE	90.	1	89.60	.25989	.610220
SEX	13.	1	12.86	.03730	.846873
TYPE	39337.	5	7867.40	22.82146	0.000000
CSC	738.	1	737.69	2.13986	.143593
SEX*TYPE	601.	5	120.18	.34862	.883388
SEX*CSC	331.	1	331.47	.96151	.326865
TYPE*CSC	3220.	5	644.04	1.86822	.096471
SEX*TYPE*CSC	1116.	5	223.17	.64735	.663549
Error	1381361.	4007	344.74		

Legend – see Table 6

Table 8. Change in BP control by therapy change at first visit

Type of change in BP treatment	Systolic	N	Diastolic	N	Direction of BP change *	p-value
Stop CCB	**+14.22**	215	**+6.05**	214	Worse control	.0000
Thiazide	**+4.10**	95	**+2.76**	95	Worse control	.0100
Beta blocker	+2.21	91	+0.77	90		.5112
ACE inhibitor	**+6.82**	218	**+2.29**	218	Worse control	.0000
Fully subsidised DHP CCB	**-0.94**	4286	**-1.07**	4289	Better control	.0110
Other therapy	+0.22	102	+1.24	104		.5918
ALL GROUPS	+0.28	5007	**-0.45**	5010		0.3448

*Bold results are sig at p<.005 * direction of BP change is calculated from (improvements less deteriorations), weighting by magnitude of change does change this classification for any group. Reported p-value is for Wilcoxin categories as ranks matched pairs analysis.*

(systolic >=170 or diastolic >=100). The classification algorithm first checks if either systolic >=170 or diastolic >=100. If either condition is true the patient has 'uncontrolled' hypertension. Next the algorithm checks if systolic <=150 and diastolic <=90. If both these conditions hold the patient has 'controlled' blood pressure. Otherwise the patient has 'moderately uncontrolled' hypertension. A three by three table can be used to summarise the transition between categories for patients and analysed by considering only the changes in control (the off-diagonal elements). The ordinality of the data (the fact that a change from controlled to uncontrolled is more significant than a change from controlled to 'moderately uncontrolled'), can be considered in a Wilcoxon matched pairs test, regarding the categories as ranks. There are no significant changes in this table (p=0.35). The p-values for a Wilcoxon matched pairs test for the changes in distribution of BP control observed for each type of therapeutic manoeuvre made at the first visit is presented in Table 8. The overall pattern of changes is not statistically significant. However, for subgroups (type of change in therapy) the results are consistent with the earlier analysis using the actual BP measurements.

Discussion

This analysis must be interpreted bearing in mind all earlier caveats regarding accuracy of data collection. Deficiencies in claim form design, lack of standardised protocols for BP measurement, and some inconsistencies in interpretation of claim form items mean that these results must be reported cautiously.

Despite these shortcomings over 5 000 paired BP recordings are available for analysis. However, the validity of any analysis based upon pairs of single BP recordings needs to be considered carefully.

Because it is well known that there is a degree of variability between BP measurements, in many practices two or three BP readings may be taken to assess the value. Studies indicate that the BP of an individual approaches stability after the second measure and hence two readings are likely to be sufficient in diagnosed hypertensive patients established on medication.[1,2] Initial BP readings may be elevated in some patients through the 'white coat' effect, but this is less likely to occur in a population of established hyptertensive patients regularly monitored by their own GP. It is unknown whether the BP levels recorded by GPs in this study are derived from one or more readings taken during a consultation, although it can be

presumed that where the reading is as anticipated, a GP might decide one reading will suffice, but may repeat the measure if the result is unexpected. However even assuming that only one reading was taken at each visit, the degree of variability from taking single readings is likely to be the same for either visit, and given the large sample size, this should not have produced any significant error in our comparisons analysis.

The most common change in medication reported at the first visit was a shift from existing DHP CCB to a fully subsidised DHP CCB. It would be incorrect to deduce from this that GPs were not following the present recommendation to commence treating mildly elevated BP with thiazides and beta-blockers. Although it is possible that patients were inappropriately being prescribed DHP CCBs, it is also possible that DHP CCBs were already being used as second or third line therapy. In this case a change to a fully subsidised DHP CCB would be expected to be the most common therapeutic manoeuvre at the first visit. The increases in BP observed when patients were changed onto other therapeutic agents gives some support to this possibility.

We have not attempted a cost-benefit analysis of the change in the DHP CCB funding environment. The sustainability of the levels of BP recorded after changes in therapy has not been assessed in this analysis, and an investigation of the non-drug costs faced by patients, (e.g. transport, time off work) has not been possible. In subsequent time periods, in which extra consultation subsidies are not payable, and assuming that blood pressures remain unchanged from those reported, the policy change has reduced state expenditure on DHP CCBs, without detrimentally affecting the control of hypertension.

Conclusion

The overall conclusion of this analysis is that there was no clinically significant increase in either systolic or diastolic blood pressure as a result of the reduction in subsidies paid by the government for DHP CCBs. This result is based on the most rigorous statistical analysis possible with the available data, repeated measures of blood pressure on matched patients across the two visits. This conclusion is supported by analysis of both continuous BP measurements, and by an analysis of combined systolic and diastolic BP measurements into a 'degree of control' classification.

While there may be other considerations to take into effect such as the need for explanation to patients and administrative issues, changing patients from one brand of CCB to another does not appear to have a significant effect on their blood pressure.

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