A national, multi-centre, randomised controlled trial of the efficacy of structured care algorithm in achieving individual blood pressure targets at 26 weeks in primary care

The Valsartan Intensified Primary care ReducEtion of BP Study

Simon Stewart
Disclosures

Co-Principal Investigators *(Professor Garry Jennings & Dr Melinda Carrington)*

GP Investigators *(Australian GPs)*

Study Sponsor Novartis Pharmaceuticals Australia *(Dr Carla Swemmer & Dr Nicol Kurstjens)*

Clinical trial manager *(Ms Karen Best)*

Data Management Team *(Nerolie Stickland, Lisa Meyenn, Rebecca Perez, Sunghwa O’Mahony, Leonila Tanyag, Ann Nadonza, Eleanor Tan)*

**Scientific Advisory Board**

Prof Craig Anderson (Cardiology), Dr Fred De Looze (Primary Care), Dr Alex Brown (Indigenous Health), Prof Leonard Arnolda (Cardiology), Prof Nigel Stocks (Primary Care), Prof Louise Burrell (Endocrinology), Prof Henry Krum (Clinical Pharmacology), Dr John Amerena (Cardiology), Prof Mark Nelson (Primary Care), Prof Mark Harris (Primary Care), Prof Joseph Hung (Cardiology) & Dr Markus Schlaich (Nephrology)
Global impact of hypertension

- Hypertension - greatest contributor to preventable forms of CVD globally
- Associated with worse morbidity and mortality than any other CV risk factor\(^1\)
- Prevalence remains at historical highs (1 in 4 adults worldwide)\(^2\)
- Projected increased prevalence with ageing and more obese/metabolically challenged populations

Historically high BP in Australia

Pattern of blood pressure in Australian adults: Results from a National Blood Pressure Screening Day of 13,825 adults

Melinda J. Carrington, Garry L. Jennings, Simon Stewart
Baker IDI Heart and Diabetes Institute, Melbourne, Australia

ABSTRACT

Background: Recent national data on cardiovascular disease (CVD) risk factors in Australia are limited. Therefore, this study sought to gain a contemporary snapshot of the blood pressure (BP) profile of Australian adults.

Methods: We established 100 metropolitan and regional screening sites. Using a standardized protocol and the same automated validated BP monitor, registered nurses recorded the BP and other risk factors for CVD of self-selected volunteers on a single day.

Results: A total of 13,825 subjects (55% female; aged 48 ± 16 years) were assessed. Mean systolic and diastolic BP was 131 ± 18 and 79 ± 12 mm Hg. Overall, 34.5% had an elevated BP while 10% being treated for hypertension (HT). Elevated BP was more common in older individuals, men, and women (42% versus 27% of women), regional residents (40% versus 32% of metropolitan) and people from lower socio-economic backgrounds (30% versus 30% of higher). Overall, 50% of subjects with a history of HT had elevated BP compared to 30% without a history of HT. Adjusting for age and sex, elevated BP was independently associated with obesity (OR: 1.77, 95% CI 1.52–2.06), regional location (OR: 1.32, 95% CI 1.19–1.45) andmodifiable risk factors (OR: 1.28, 95% CI 1.12–1.43); those being treated for CVD or diabetes are less likely to have high BP.

Conclusions: In the largest study of its kind in Australia, the findings highlight the need for continued vigilance to detect, monitor and prevent elevated BP within an ageing population in whom metabolic disorders are becoming more frequent.

Crown Copyright © 2009 Published by Elsevier Ireland Ltd. All rights reserved.

1. Introduction

As a key contributor to the global increase in cardiovascular disease (CVD), high blood pressure (BP) is a readily detectable and modifiable condition that represents a major target for primary and secondary prevention programs. In 2001, high BP or hypertension (HT) was estimated to contribute to 7.5 million deaths (13.5% of total deaths) and 92 million disability-adjusted life years globally [1]. In Australia, it was the largest contributor to CVD in 2003 and explained 42% of CVD burden (7.6% of total disease burden) [2]. It is also the most commonly managed cardiovascular risk factor by primary care physicians in Australia, accounting for nine in every 100 encounters (three times that of lipid disorder management) [3].

Elevated BP seems to have re-emerged with an even greater effect on premature mortality and disability [3] and despite the availability of effective pharmacological treatments [4]. During the 1980s, the prevalence of high BP in Australia repeatedly declined from 38% to 20% but steadily rose again in the 1990s and early 21st Century [5–8]. The population is ageing and rates of obesity and metabolic disorders are rising [9] which may contribute to increasing rates of HT.

Australia has also experienced significant socio-demographic changes, including the overall ageing of the post-war “baby boomer” generation and widening differentials in the socio-economic status of the population, particularly metropolitan versus regional/rural communities. In Australia, regional and remote populations comprise around 32% of the 15 million adult population aged over 18 years [10].

We undertook a National Blood Pressure Screening Day to gain a contemporary “snapshot” of the BP profile of adult Australians. A key objective was to explore differences according to age, sex, geographic location, treatment for those known to have HT and socio-economic status. A secondary aim was to project the prevalence of elevated BP and obesity in adult Australians.

2. Material and methods

2.1. Participants

A total of 13,825 participants were recruited. This equates to one in every 1000 adult Australians (see Fig. 1 for a profile of the Australian population). People were offered a free BP check if they were aged over 18 years and not being treated for HT. The study was approved by the Ethics Committee of the National Health and Medical Research Council of Australia.

2.2. Methods

Blood pressure was measured using a standard automated validated oscillometric device. The device was calibrated daily to the device used by the NHFS and was assessed against the NHFS reference values. Participants were asked to fast for at least 3 h prior to BP measurement. Measurements were taken after 10 min of seated rest with the arm supported at heart level. Three measurements were obtained in the sitting position. Values were considered as systolic when systolic pressure was greater than diastolic pressure and vice versa. The highest recorded BP was noted. Participants with a systolic pressure ≥ 140 mm Hg or a diastolic pressure ≥ 90 mm Hg were considered to have BP elevated. Participants with systolic pressure ≥ 140 mm Hg or a diastolic pressure ≥ 90 mm Hg were considered to have HT.

Participants were asked to report on a range of risk factors, including smoking, alcohol intake, current medication use, physical activity, and dietary intake. Participants were asked if they had been diagnosed with HT or diabetes, as well as if they were currently taking any medications for these conditions.

Results were compared with national surveys and guidelines from the National Health and Medical Research Council of Australia, which recommend ≤ 130 mm Hg for systolic pressure and ≤ 80 mm Hg for diastolic pressure as the targets for BP control for the general population (Stage 1 HT) and ≤ 120 mm Hg for systolic pressure and ≤ 70 mm Hg for diastolic pressure as the targets for BP control for those at high risk of CVD (Stage 2 HT). Risk factors were also compared with the Age-Related National Health Survey, the National Blood Pressure Screening Day, and the Risk Factor Prevalence Survey.
Hypertension in primary care

3. Overall, 36% of patients had hypertension.

BP poorly controlled in hypertensive adults: >40% on Tx had BP that exceeded 140/90 mmHg.

Cochrane review of interventions to improve BP control in primary care⁶:

“antihypertensive drug therapy should be implemented ... by means of a vigorous stepped care approach when patients do not reach target BP levels.”

Aims & hypothesis

To evaluate the efficacy of an intensive BP management strategy relative to usual care.

- VIPER-BP Intervention:
  - Structured follow-up & computer assisted decisions
  - Clinical management pathways using valsartan-based therapies

- Patients exposed to the VIPER-BP Intervention will demonstrate greater BP control against their individualised BP target at 26 weeks follow up relative to patients exposed to usual care primary care management.
Eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed or currently treated hypertension</td>
<td>Severe hypertension (SBP &gt;180 mmHg)</td>
</tr>
<tr>
<td>Not achieving their BP target$^4$</td>
<td>On 3 or more anti-hypertensive agents</td>
</tr>
<tr>
<td>Requiring active pharmacological treatment</td>
<td>Contra-indications to study medication</td>
</tr>
</tbody>
</table>

National Heart Foundation of Australia Hypertension Guidelines

- $\leq 125/75$ mmHg (proteinuria)
- $\leq 130/80$ mmHg (existing CVD)
- $\leq 140/90$ mmHg (no CVD)
**VIPER Intervention:**

- Vigorous computer-assisted structured care approach including a standardized algorithm for open-label, pharmacotherapy (2 in 3 patients)

**VIPER Monotherapy**

- Valsartan 160mg per day

**VIPER Combination Therapy**

- Valsartan/HCTZ 80/12.5mg per day
- Valsartan/Amlodipine 80mg/5mg per day

- Titrate valsartan to 320mg, then add HCTZ and titrate, then consider triple or alternative therapy

- Titrate valsartan to 160mg, then titrate other component (HCTZ to 25mg or amlodipine to 10mg) then consider triple/alternative therapy

**Usual Care**

- With same BP targets according to physician discretion (1 in 3 patients)

**Primary Endpoint:** Proportion of randomized patients to achieve their individualized BP target at 26 weeks

**Study Design**

- National network of >250 General Practitioners screen hypertensive adults with elevated BP according to national guidelines for individualized BP control

- Initial run-in phase: valsartan 80mg (4 weeks)

- Stratified randomization for those still not at individual BP target

- Structured up-titration at pre-defined visits until BP targets were achieved

- 14 day BP check, if SBP ≥ 180 mmHg at any point randomize
2,337 hypertensive patients from 119 primary care clinics enrolled

2,185 (93.5%) eligible patients entered “run-in” phase

152 (6.5%) Ineligible

84 (3.8%) Rescue randomised

1562 Randomised (72%)

524 assigned to usual primary care

483 (92%) patients attended 6 week clinic review

20 (3.8%) withdrawn (no endpoint BP)

466 patients included in 26 wk primary analysis

1038 assigned to VIPER-BP intervention

945 (91%) patients attended 6 week clinic review

50 (4.8%) withdrawn (no endpoint BP)

857 patients included in 26 wk primary analysis

416 (19%) Achieved BP target

56 (2.6%) Adverse event

20 (0.9%) Investigator decision

74 (3.4%) Lost to follow-up

13 (0.6%) Protocol Deviation

40 (1.8%) Consent withdrawn

4 (0.2%) Other

678 (65%) assigned to combination therapy

360 (35%) assigned to mono-therapy therapy

N=1,323
# Study Cohort

## Demographic Profile

<table>
<thead>
<tr>
<th></th>
<th>ALL RANDOMISED (n=1562)</th>
<th>Usual Care (n=524)</th>
<th>VIPER-BP (n=1038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>963 (62%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>59 ± 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Baseline Clinical Profile at Randomisation

<table>
<thead>
<tr>
<th></th>
<th>ALL RANDOMISED (n=1562)</th>
<th>Usual Care (n=524)</th>
<th>VIPER-BP (n=1038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>131 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>301 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior hypertension</td>
<td>1045 (67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>150 ± 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>88 ± 11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Pre-specified BP Target

<table>
<thead>
<tr>
<th>BP Target</th>
<th>ALL RANDOMISED (n=1562)</th>
<th>Usual Care (n=524)</th>
<th>VIPER-BP (n=1038)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 140 / 90 mm Hg</td>
<td>449 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 130 / 80 mm Hg</td>
<td>843 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 125 / 70 mm Hg</td>
<td>270 (17%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BP response post randomisation

Mean BP by visit (all BP target groups)

Mean difference in endpoint SBP **-4.2 mmHg**
(95% CI 2.0 to 6.5) in favour of VIPER-BP group (*p*<0.001)

Mean difference in endpoint DBP **-2.6 mmHg**
(95% CI 2.4 to 2.9) in favour of VIPER-BP group (*p*<0.001)

Mean and standard error bars encapsulated within symbols
Primary Endpoint: BP @ 26 weeks

18% increased probability of achieving minimal BP ≤ 140/90 mm Hg (52% vs. 61% - RR 1.18, 95% 1.07 to 1.31) in favour of VIPER-BP (p<0.001)

31% increased probability of achieving primary endpoint of individual BP target control (29% vs. 37% - RR 1.31, 95% 1.11 to 1.54) in favour of VIPER-BP (p=0.004)
Absolute CV risk scores showed a greater reduction in the VIPER-BP intervention arm.

<table>
<thead>
<tr>
<th>Change in absolute CV risk score from baseline</th>
<th>USUAL PRIMARY CARE</th>
<th>VIPER-BP INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change</td>
<td>-2.6 ± 4.5%</td>
<td>-3.7 ± 4.5%</td>
</tr>
</tbody>
</table>

P < .001
Predictors: Individual BP control

Variable | Relative risk (95% CI)
---|---
Age | 1.00 (1.00 to 1.01)
Sex (male vs. Female) | 0.81 (0.70 to 0.94)
Treatment (Mono vs UC) | 1.19 (0.97 to 1.46)
Treatment (Combo vs UC) | 1.33 (1.12 to 1.58)
All VIPER-BP vs UC | 1.28 (1.09 to 1.51)
Treatment (Thiazide combo vs UC) | 1.42 (1.15 to 1.75)
Treatment (Amlodipine combo vs UC) | 1.28 (1.05 to 1.55)
Triple vs. Non-triple therapy | 0.73 (0.56 to 0.96)
Baseline Systolic BP | 0.99 (0.98 to 0.99)
Baseline Diastolic BP | 0.99 (0.98 to 0.99)
Days post-randomisation | 1.00 (1.00 to 1.01)
BP target (130/80 vs 125/75) | 1.97 (1.41 to 2.76)
BP target (140/90 vs 125/75) | 4.29 (3.11 to 5.93)
Absolute risk score | 0.99 (0.98 to 1.00)
Ethnicity (Caucasian vs non-Caucasian) | 1.12 (0.92 to 1.36)
BMI | 0.97 (0.95 to 0.98)
CVD vs No CVD | 0.88 (0.72 to 1.08)
Diabetes vs No diabetes | 0.63 (0.51 to 0.80)
Depression (Arrol scale) vs No depression | 0.97 (0.83 to 1.13)
Depression (CES-D scale) vs No depression | 0.77 (0.62 to 0.96)
RRMA (increase by one unit) | 1.08 (1.02 to 1.15)
Location (Metro vs Rural/regional) | 0.86 (0.67 to 1.12)
GP sex | 1.15 (0.95 to 1.38)
Practice nurse | 1.50 (1.30 to 1.73)
Super clinic | 0.63 (0.55 to 0.73)
Projected real-world impact

Men (n=7235)

Women (n=7884)
Limitations

- Individual randomisation = GP contamination in usual care.
- Un-blinded BP measurements and records.
- Short term BP control – need for further follow-up for hard CVD end-points.
- Influence of non-pharmacological treatments.
- Tested in limited pharmacotherapy range (ARBs).
- Potential for *white coat hypertension*.
- Research orientated GPs – with translation to broader primary care environment unknown.
Conclusions

- Large pragmatic primary care management trial.
- VIPER-BP Study builds on –
  - Primary care surveillance studies
  - Disease management/automated decision support tools (CUPID)
- Use of an intensified decision support management strategy over 26 weeks achieved:
  - sig. greater BP control rates compared to usual care
  - sig. increased odds of achieving individual BP control
  - sig. reduction in absolute cardiovascular risk
- Potential longer-term prevention of CVD events.
- Strong potential for real-world application.
Frequency of adverse events post-randomisation (20 most common)

Pattern of adverse events was as expected.

Small increase in dizziness, peripheral oedema and fatigue in VIPER-BP arm (combination arm).