Self-reported adherence with medication and cardiovascular disease outcomes in the Second Australian National Blood Pressure Study (ANBP2)

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ABSTRACT

Objective: To investigate whether responses to a previously validated four-item medication adherence questionnaire were associated with adverse cardiovascular events.

Design: Survey conducted among a cohort of participants in the Second Australian National Blood Pressure Study.

Setting: Australian general practice.

Participants: 4039 older people with hypertension.

Main outcome measures: All major cardiovascular events or death; first specific cardiovascular event.

Results: Subjects who adhered to their medication regimen (compared with non-adherent subjects) were significantly less likely to experience a first cardiovascular event or a first non-fatal cardiovascular event (hazard ratio [HR] for both, 0.81; 95% CI, 0.67–0.98; $P = 0.03$); a fatal other cardiovascular event (HR, 0.68; 95% CI, 0.48–0.99; $P = 0.04$); or a first occurrence of heart failure (HR, 0.58; 95% CI, 0.37–0.90; $P = 0.02$). Those who answered yes to *"Did you ever forget to take your medication?"* were significantly more likely to experience a cardiovascular event or death (HR, 1.28; 95% CI, 1.04–1.57; $P = 0.02$); a first cardiovascular event or death (HR, 1.31; 95% CI, 1.07–1.60; $P = 0.01$); a first cardiovascular event (HR, 1.34; 95% CI, 1.09–1.65; $P = 0.01$); or a first non-fatal cardiovascular event (HR, 1.35; 95% CI, 1.09–1.66; $P = 0.01$). Those who answered yes to *"Sometimes, if you felt worse when you took your medicine, did you stop taking it?"* were significantly more likely to experience a first occurrence of heart failure (HR, 2.06; 95% CI, 1.16–3.64; $P = 0.01$).

Conclusions: Subjects who adhered to their medication regimen were less likely to experience major cardiovascular events or death. The question relating to forgetting to take medication identified non-adherent subjects likely to experience a cardiovascular event or death. Clinicians could use this question to identify patients with hypertension who are likely to benefit from medication adherence strategies.

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Adherence is defined as "the extent to which a person's behaviour coincides with medical or health advice".[1] If such advice is evidence-based, non-adherence is likely to lead to adverse health outcomes. Previous studies have provided significant and useful knowledge about several determinants of non-adherence and effective interventions.[2,3]

Non-adherence to drug therapy for hypertension is acknowledged as a major contributor to the less than ideal levels of blood pressure control seen in the community.[4] However, there have been no studies of links between adherence to cardiac medication and major adverse cardiovascular outcomes.

A specific, four-question patient questionnaire has been shown to provide good specificity for drug adherence.[5] We postulated that this instrument could help doctors identify patients who did not adhere to their medication regimen and therefore were most at risk of adverse cardiovascular events or death. This would allow them to intervene with effective adherence and other preventive strategies.

METHODS

Survey

A postal survey of medication adherence was undertaken in September and October 2000 of all 6018 surviving participants in the Second Australian National Blood Pressure Study (ANBP2).[6] Non-responders were not followed up. Data relating to participants' demographic characteristics, cardiovascular risk factors, and outcomes were accessed from the ANBP2 database.

1 The Morisky instrument[5]

1. Did you ever forget to take your medication?
2. Were you careless at times about taking your medication?
3. When you felt better, did you sometimes stop taking your medication?
4. Sometimes, if you felt worse when you took your medicine, did you stop taking it?

ANBP2 was a large randomised controlled trial of therapy for hypertension (≥ 160 mmHg systolic or ≥ 90 mmHg diastolic blood pressure [if systolic blood pressure was ≥ 140 mmHg]) in men and women aged 65–84 years at trial entry: diuretic medication was compared with angiotensin-converting enzyme (ACE) inhibitors. ANBP2 participants were recruited from March 1995 to July 1998. ANBP2 closed in September 2001; the median follow-up period was 4.1 years.

Questionnaire

A short, validated patient questionnaire (the Morisky instrument; Box 1) was used to determine medication adherence.[5] The rates of all cardiovascular events, deaths or the various cause-specific events (eg, coronary events [myocardial infarction, sudden cardiac death], cerebrovascular events [stroke] and other cardiovascular events [heart failure, ruptured aortic aneurysm]) experienced by subjects were compared between those who adhered or did not adhere to their medication regimen. The adherent group were those who answered "no" to each question (or no to each question completed) and the non-adherent group were those who answered "yes" to any question. We also compared subjects according to their response to each of the four questions separately.

Statistical analysis

Analyses were carried out using SAS, version 9.1 (SAS Inc, Cary, NC, USA). Cox regres-

sion using the method of Wei, Lin and Weissfeld was used to model multiple times to events within "subject", and to allow for clustering of subjects within "practitioner".[7,8] The primary outcome was defined as any cardiovascular event or death from any cause. Further analyses were performed on the time to first specific cardiovascular event. Estimates were adjusted for age and sex. Hazard ratios with 95% confidence intervals and two-sided *P* values are presented. The significance level was set at 0.05.

We also compared systolic and diastolic blood pressure measurements at baseline and after the survey (most recent measurement), and the difference between changes in blood pressure levels of adherent and non-adherent subjects to investigate whether such responses were related to adherence or non-adherence to their antihypertensive medication regimen.

2 Adjusted effect (rates are per 1000 person-years) of overall adherence with medication (Yes: *n* = 2614; No: *n* = 1298) on total cardiovascular events, deaths and cause-specific events

Outcome	Adherence response	Rate	Hazard ratio* (95% CI)	*P*†
All cardiovascular events or death from any cause	Yes	35.9	0.83 (0.69–1.00)	0.05
	No	45.3	1.00	
First cardiovascular event or death from any cause	Yes	27.5	0.83 (0.68–1.00)	0.05
	No	33.3	1.00	
First cardiovascular event	Yes	26.0	0.81 (0.67–0.98)	0.03
	No	31.9	1.00	
First non-fatal cardiovascular event	Yes	25.2	0.81 (0.67–0.98)	0.03
	No	31.1	1.00	
Fatal other cardiovascular event	Yes	9.6	0.68 (0.48–0.99)	0.04
	No	14.4	1.00	
First occurrence of heart failure	Yes	3.6	0.58 (0.37–0.90)	0.02
	No	6.3	1.00	

* Hazard ratios are adjusted for age and sex. † Only significant associations are shown. ◆

RESULTS

The characteristics of the ANBP2 cohort are reported elsewhere.[6] Replies were received from 4039 of 6018 subjects (response rate, 67%). One hundred and twenty-seven subjects answered none of the four questions, 328 answered at least one but not all four, and 3584 answered all four questions. Of the 328 subjects giving incomplete responses, 181 were categorised as adherent and 147 as non-adherent. Baseline characteristics of responders and non-responders to the questionnaire were similar; however, responders were younger, less likely to smoke, and more likely to be physically active. Baseline characteristics of the adherent and non-adherent groups were similar. Details are available from the authors.

The incidence of any cardiovascular event or death among survey responders was 39.1 per 1000 person-years, versus 99 per 1000 person-years in non-responders (hazard ratio [adjusted for age and sex as per the main study], 0.38; 95% CI, 0.33–0.42; $P < 0.0001$).

A total of 2614 subjects (67% of those who responded to any of the adherence items) were, by our definition, adherent to their medication regimen. Adherent subjects, compared with non-adherent subjects, were marginally less likely to experience a cardiovascular event or death; and were significantly less likely to experience a first cardiovascular event or first non-fatal cardiovascular event, fatal other cardiovascular event or first occurrence of heart failure (Box 2).

The effects of adherence judged by responses to each individual question were also analysed (Box 3). A response of yes to Question 1 "*Did you ever forget to take your medication?*" was associated with a significant hazard for all cardiovascular events or death from any causes; first cardiovascular event or death from any causes; first cardiovascular event; and first non-fatal cardiovascular event (Box 3). A response of yes to Question 4 "*Sometimes, if you felt worse when you took your medicine, did you stop taking it?*" was associated with a significant hazard for first occurrence of heart failure (Box 3). There were no significant effects related to whether subjects who were non-adherent were careless taking their medication, or stopped taking it because they felt better.

Unadjusted comparisons of baseline and post-survey systolic and diastolic blood pressure measurements by overall adherence showed that subjects adhering to their medication had a lower mean systolic blood pressure (0.7 mmHg) and a significantly greater fall in mean systolic blood pressure compared with those who were non-adher-

3 Adjusted effect (rates are per 1000 person-years) of response to each question on total cardiovascular events, deaths and cause-specific events

Outcome	Adherence response	Rate	Hazard ratio* (95% CI)	*P*†
Did you ever forget to take your medication? Yes: *n* = 902; No: *n* = 2953				
All cardiovascular events or death from any cause	Yes	50.3	1.28 (1.04–1.57)	0.02
	No	35.2	1.00	
First cardiovascular event or death from any cause	Yes	36.3	1.31 (1.07–1.60)	0.01
	No	27.1	1.00	
First cardiovascular event	Yes	35.2	1.34 (1.09–1.65)	0.01
	No	25.6	1.00	
First non-fatal cardiovascular event	Yes	34.3	1.35 (1.09–1.66)	0.01
	No	24.8	1.00	
Sometimes, if you felt worse when you took your medicine, did you stop taking it? Yes: *n* = 418; No: *n* = 3246				
First occurrence of heart failure	Yes	8.3	2.06 (1.16–3.64)	0.01
	No	4.1	1.00	

* Hazard ratios are adjusted for age and sex. † Only significant associations are shown. ◆

ent to medication (1.4 mmHg; $P = 0.02$). Paradoxically, although subjects who reported that they did not forget to take their medication had a lower mean diastolic blood pressure (0.1 mmHg), the fall in diastolic blood pressure they experienced was significantly less (0.8 mmHg; $P = 0.02$) than that in non-adherent subjects.

DISCUSSION

We found that responses to a four-item questionnaire were likely to identify individuals with a higher risk of major adverse cardiovascular events, including death. Non-adherence was significantly associated with a first cardiovascular event; a first non-fatal cardiovascular event; a fatal other cardiovascular event; and a first occurrence of heart failure (Box 2). Non-adherence was also associated, although with marginal significance, with all cardiovascular events or death from any cause (the primary endpoint for ANBP2) and a first cardiovascular event or death from any cause.

Of the four questions we asked the subjects, the one relating to forgetting to take medication seemed to best identify non-adherent subjects likely to experience a cardiovascular event or death. Furthermore, comparisons of baseline and first systolic and diastolic blood pressure readings after the survey for adherent and non-adherent subjects, as well as the responses to the individual questions, suggested that subjects who reported being adherent were truly more adherent.

Non-adherence to drug therapy is a major contributor to failure to control hypertension in the general community. Detection and measurement of non-adherence in clinical practice is difficult.[9] The strategies developed to identify this problem usually involve surrogate measures such as pill count, pharmacy records or blood pressure recordings, rather than hard endpoints such as major adverse cardiovascular events. However, pill counts are not accurate with long-term medications, and patients do not bring their medication packs with them at the time of consultation.[10] Pharmacy records have shown good validity, but are rarely used for a variety of professional, acceptability and organisational reasons.[11]

We used a specific short four-question patient questionnaire — the Morisky instrument — which has been shown to provide good specificity.[5] We found that responses to these questions correlated with cardiovascular events or death in participants in the ANBP2 hypertension trial. We chose the Morisky instrument for its practicality and utility. Other validated tools are available but are more complex. For example, the Hill–Bone Compliance Scale has 14 items and the COMpliance Praxis Survey (COMPASS) has 12 items.[12,13]

Our study was a survey conducted among a cohort of subjects participating in the ANBP2. All data were collected prospectively for the ANBP2. The cross-sectional data collected in our survey were compared with cardiovascular disease endpoint data collected up to that point and until the end of the trial (ie, retrospectively and prospectively). The usual biases associated with the use of retrospective data were minimised, as the data were collected prospectively for the purpose of the clinical trial.

The response rate was 67%. Subsequent mail-outs did not occur because these items were attached to a substudy questionnaire (which did not have funding for further mail-outs). In ANBP2, the vital status was known for all but two of the cohort of 6083 after a median follow-up of 4.1 years.

Our finding that the cardiovascular disease event rate of non-responders was more than twice that of responders suggests that a confounding factor may have been that some ANBP2 participants were too ill to respond. We also found some small but significant differences in the distributions of a range of baseline characteristics of responders compared with non-responders.

In conclusion, subjects who adhered to their medication regimen were marginally less likely to experience some types of cardiovascular events. Of the four questions asked, the first one *"Did you ever forget to take your medication?"* identified participants significantly more likely to experience a cardiovascular event or death. A clinician asking this question therefore may be able to identify individuals who may benefit from effective drug adherence strategies.

COMPETING INTERESTS

None identified.

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