

**Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study**

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**Titles:** Short- and long-term association of lipid-lowering drug treatment and cardiovascular disease by estimated absolute risk in the Second Australian National Blood Pressure study (ANBP2)

**Running head:** LLT for primary prevention of CVD in the elderly

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## **Abstract**

### **Background**

There is currently insufficient evidence to support the use of lipid-lowering drug treatment (LLT) for primary prevention of cardiovascular disease (CVD) in the elderly.

### **Objectives**

We examined the relationship of early initiation of LLT with short- and long-term all-cause and CVD mortality in persons older than 65 years in this post-hoc study from the Second Australian National Blood Pressure study (ANBP2).

### **Methods**

In- and post-trial observational study. 4257 hypertensive participants aged 65 to 84 years within Australian family practices were randomized to an angiotensin converting enzyme-inhibitor or a diuretic treatment group. After excluding participants with a prior history of CVD, the cohort was stratified into 'LLT' and 'no LLT' subgroups based on LLT status at randomization.

### **Results**

At randomization the participants had a mean age of 72 years, average blood pressure (BP) of 168/91 mmHg and estimated 5-year CVD risk of  $18.7 \pm 8.3\%$ . In the overall study population, the association of LLT with long-term (11-years) all-cause and non-CVD mortality was significant [HR 0.78 (95% CI 0.66-0.92,  $p=0.003$ ) and HR 0.70 (95% CI 0.54-0.90,  $p=0.006$ ) respectively]. Magnitudes of the association of LLT with long-term mortality and the association with short-term mortality were similar, however, no statistically significant association with short-term mortality was observed. In the subgroup analysis by baseline 5-year CVD risk, LLT participants in the highest risk tertile had a substantially lower relative risk for short-term all-cause mortality (HR 0.31, 95% CI 0.13-0.71,  $p$  for interaction 0.02), compared to those with lower estimated CVD risk. All analyses were adjusted for baseline and in-trial characteristics.

### **Conclusion**

Our study showed a strong association between LLT and reduced long-term all-cause mortality. Thus, our findings support recommendations of the use of LLT in patients over 65, particularly those with high CVD risk who were more likely to obtain additional benefits in the short-term. The findings also suggested that mortality benefits of LLT for the elderly may take longer to become evident.

### **Highlights**

- Our study supports the use of LLT for primary prevention of CVD in the elderly.
- LLT was associated with a reduced long-term all-cause mortality.
- High risk participants obtained further benefits for short-term all-cause mortality.

**Key Words:** lipid-lowering drug treatment, cardiovascular disease, primary prevention, absolute cardiovascular risk, elderly.

## Background

The global population is ageing. In 2015 there were 617 million (8.5%) people aged over 65 years and this is likely to reach 1.6 billion (17%) by 2050 <sup>1</sup>. Cardiovascular disease (CVD) remains the leading burden of disease in this age group, being 30% of the total <sup>2</sup>. Lipid-lowering drug treatment (LLT), particularly statins, plays a key role in the prevention of CVD <sup>3-5</sup>. More than 40% of the Australian and US populations aged 75 and over are currently taking LLT <sup>6,7</sup> and this number is projected to grow as most of the LLTs come off patent and are therefore available at lower cost.

Most of the evidence for benefits from the use of LLT in those 65 years or over are from trials of secondary prevention of CVD or in mixed populations of those with and without a previous history of CVD <sup>8-16</sup> whereas insufficient evidence is available to support the use of LLT for primary prevention in the elderly <sup>17-20</sup>. A systematic review and meta-analysis by Savarese et al <sup>21</sup> related predominantly to primary prevention reported no significant mortality benefit of statin treatment in individuals aged 65 and over, although there were significant reductions in myocardial infarction (MI) and stroke. The average follow-up in the studies in this analysis was 3.5 years (range: 1.0 – 5.2 years) <sup>9,13-16,22</sup>.

A prospective cohort study with 7.3 years follow-up <sup>23</sup> found substantial effects of early statin use (on-treatment versus no treatment at baseline) on major CVD events and all-cause mortality in the elderly ( $\geq 65$  years) without CVD at baseline. This result stands despite a possible dilution of effects due to 13% of non-drug users at baseline initiating treatment during the study. In contrast, another elderly cohort <sup>24</sup> with median follow-up at 9.1 years found no benefits for CVD or CHD events except stroke. Evidence for both short- and long-term benefits of LLT in older adults thus remains inconsistent. From patients' perspectives, other considerations in this age group impacting on chronic drug therapy are drug adherence, the possibility of adverse drug effects and the potential for consideration of medication discontinuation when other issues such as frailty and life expectancy become dominant <sup>25,26</sup>. In this current post-hoc study in a cohort of hypertensive elderly from the Second Australian National Blood Pressure study (ANBP2)<sup>27</sup>, we have examined the relationship

between the use of LLT at randomization and short- (4 year) and long-term (11 year) all-cause and CVD mortality in those aged 65 years or over.

## **Materials and methods**

We conducted a post-hoc analysis relating to a cohort from the Second Australian National Blood Pressure study (ANBP2)<sup>27</sup>. ANBP2 had an open-labelled design with blinded end-point assessment. Participants aged 65-84 years at enrolment were randomized into an angiotensin-converting enzyme treatment group (enalapril recommended) or a thiazide diuretic treatment group (hydrochlorothiazide recommended) within Australian family practices. At entry, eligible participants had an average randomized blood pressure (BP) of 160/90 mmHg or over. Short-term mortality outcomes were followed for a median 4.1 years (from 1995 to 2001) as described by Wing *et al*<sup>27</sup>. A blinded independent endpoint committee adjudicated all study endpoints. An extended observation relating to survival status was conducted to a median 10.8 years (4.1-years in-trial and 6.7 years post-trial) using linkage to the Australian National Death Index as described by Nelson *et al*<sup>28</sup> to investigate longer term all-cause or CVD mortality. In this study, fatal cardiovascular events were comprised of sudden cardiac deaths, fatal stroke, fatal myocardial infarction, and 'other' cardiovascular causes of death.

To focus on primary prevention we excluded participants who had had previous CVD events at baseline (n=705) and those who were initiated on LLT (n=1292) during the clinical trial period because we were uncertain whether they were prescribed LLT due to a CVD occurrence or an increased cholesterol level. Participants were re-stratified by LLT status at entry. Subsequently, we compared the outcomes between those who were on LLT (LLT group) and those who were not (no LLT) at randomization (baseline) regardless of their randomized treatment.

### *Subgroup by CVD risk*

To investigate how the effect of LLT was affected by baseline CVD risk, we performed a subgroup analysis stratified by tertile of 5-year predicted CVD risk score at entry. The risk score was calculated by the Framingham absolute risk equation as used in the Australian National Vascular Disease Prevention Alliance (NVDPA) guideline<sup>29</sup>. As per the guideline, participants were automatically scored at high risk (>15%) if they had systolic BP  $\geq$  180 mmHg and/or diastolic BP  $\geq$  110 mmHg, total

cholesterol > 7.5 mmol/l, diabetes and/or estimated glomerular filtration rate < 45 ml/min/1.73 m<sup>2</sup>. For participants over 75 years of age, the age value was set at 74 in the risk calculation.

### *Statistical analysis*

The differences between the 'LLT' and 'no LLT' groups for baseline characteristics were tested by t-tests for continuous variables and Chi-square tests for categorical variables. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and corresponding 95% confidence interval (CIs) for outcomes for participants in the 'LLT' group compared with those in 'no LLT' group. Participants were followed-up from entry to the time of event (deaths) or loss of vital status or the end of the follow-up (maximum 6 years for the short-term analysis and 14 years for the long-term analysis). Those who did not have an event throughout the observed time scale were considered as censored on 30 Sep 2001 for the short-term and 31 Oct 2009 for the long-term follow-up phase. The proportional assumption was checked by a test for interaction of LLT group with time. All of the analyses were adjusted for baseline characteristics (age, sex, family history of CVD, non-HDL cholesterol, diabetes, anti-platelet use), in-trial characteristics (number of assigned in-trial BP lowering drugs), and clustered on the general practice clinic from which participants originated. Further adjustment models were tested in sensitivity analysis. In addition, we conducted subgroup analyses stratified by age, sex and diabetes at baseline to investigate the impacts of these factors on the association of LLT and mortality outcomes. The Cox regression models were used to test for interaction of treatment in the subgroup analyses. The significance of treatment effect was set to 0.05. Data management for all analyses was performed by using Stata version 12 for Windows.

## **Results**

### *Patient characteristics*

Our study included 4257 out of the original ANBP2 cohort of 6083 participants, approximately 70% of the total ANBP2 cohort. As shown in table 1, at study entry, participants had a mean age of 72 years, mean BP of 168/91 mmHg, mean plasma total cholesterol of 5.5 ± 0.9 mmol/l and HDL cholesterol of 1.4 ± 0.5 mmol/l. Compared with the 'no LLT' group, more female and younger participants were on

LLT at baseline. Also, LLT participants were more likely to have a family history of CVD, diagnosed diabetes mellitus, and be on antiplatelet and previous BP lowering drug treatment. Although these participants were on LLT, they still had higher average plasma total cholesterol level and non-HDL cholesterol. This may be attributable either to insufficient adherence to LLT or to the non-specific treatment target recommended at the time (1995-2001) for primary prevention. In general, based on the estimated risk over 5-year, all participants were at high risk of CVD – mean risk: 18.7%  $\pm$  8.3% using the Anderson equation<sup>30</sup> as per the Australian NVDPA guideline<sup>29</sup>. The estimated CVD risk score of the no LLT group (18.9%  $\pm$  8.3%) was slightly higher than the LLT group, suggesting that LLT was prescribed based on the participant's cholesterol level, not on absolute CVD risk.

Table 1. Baseline characteristics by lipid-lowering drug treatment.

	Total (N=4257)	No LLT (n=3609)	LLT (n=648)	p- value
Age (mean $\pm$ SD in years)	72.0 $\pm$ 5.0	<b>72.1 <math>\pm</math> 5.0</b>	<b>71.0 <math>\pm</math> 4.4</b>	<b>&lt;0.001</b>
Female sex n (%)	2195 (51.6)	<b>1789 (49.6)</b>	<b>406 (62.7)</b>	<b>&lt;0.001</b>
Current smoker n (%)	305 (7.2)	260 (7.2)	45 (6.9)	0.81
Systolic BP at randomization (mean $\pm$ SD, mmHg)	167.6 $\pm$ 12.6	167.7 $\pm$ 12.6	167.4 $\pm$ 12.3	0.58
Diastolic BP at randomization (mean $\pm$ SD, mmHg)	90.8 $\pm$ 8.1	90.8 $\pm$ 8.1	90.8 $\pm$ 7.9	0.89
Total cholesterol (mean $\pm$ SD, mmol/l)	5.5 $\pm$ 0.9	<b>5.5 <math>\pm</math> 0.9</b>	<b>5.8 <math>\pm</math> 1.1</b>	<b>&lt;0.001</b>
HDL cholesterol (mean $\pm$ SD, mmol/l)	1.4 $\pm$ 0.5	1.4 $\pm$ 0.5	1.4 $\pm$ 0.5	0.48
Non-HDL cholesterol (mean $\pm$ SD, mmol/l)	4.2 $\pm$ 1.0	<b>4.1 <math>\pm</math> 0.9</b>	<b>4.4 <math>\pm</math> 1.1</b>	<b>&lt;0.001</b>
BMI (mean $\pm$ SD, kg/m <sup>2</sup> )	27.0 $\pm$ 4.2	27.0 $\pm$ 4.2	27.2 $\pm$ 4.1	0.18
5-year Framingham risk score (mean $\pm$ SD, %)	18.7 $\pm$ 8.3	<b>18.9 <math>\pm</math> 8.3</b>	<b>17.8 <math>\pm</math> 8.1</b>	<b>&lt;0.001</b>
Diabetes mellitus n (%)	275 (6.5)	<b>217 (6.0)</b>	<b>58 (9.0)</b>	<b>0.01</b>
Waist circumference (mean $\pm$ SD, cm)	94.4 $\pm$ 12.1	94.6 $\pm$ 12.2	93.6 $\pm$ 11.8	0.07
W-H ratio	0.90 $\pm$ 0.08	<b>0.90 <math>\pm</math> 0.08</b>	<b>0.89 <math>\pm</math> 0.08</b>	<b>0.004</b>



Current alcohol consumption n (%)	3126 (73.4)	2660 (73.7)	466 (71.9)	0.34
Physically active n (%)	3332 (78.3)	2815 (78.0)	517 (79.8)	0.31
Education n (%)				0.57
Primary school	997 (23.4)	854 (23.7)	143 (22.1)	
High school not completed	1853 (43.5)	1560 (43.2)	293 (45.2)	
Competed high school or higher	1407 (33.1)	1195 (33.1)	212 (32.7)	
Socio-economic status n (%)				0.66
1st quartile (most advantaged)	1085 (25.5)	915 (25.4)	170 (26.2)	
2nd quartile	1151 (27.0)	969 (26.9)	182 (28.1)	
3rd quartile	1365 (32.1)	1171 (32.5)	194 (29.9)	
4th quartile (most disadvantage)	656 (15.4)	554 (15.4)	102 (15.7)	
Family history of CVD n (%)				<b>&lt;0.001</b>
Yes	1986 (46.7)	<b>1604 (44.4)</b>	<b>382 (59.0)</b>	
Unknown	496 (11.7)	<b>423 (11.7)</b>	<b>73 (11.3)</b>	
Random blood glucose (mean ± SD, mmol/l)	5.5 ± 1.8	5.5 ± 1.8	5.6 ± 1.9	0.33
Serum creatinine (mean ± SD, µmol/l)	90.8 ± 19.2	90.8 ± 19.2	90.8 ± 18.9	0.96
Antiplatelet use n (%)	433 (10.2)	<b>341 (9.5)</b>	<b>92 (14.2)</b>	<b>&lt;0.001</b>
Previous BP lowering treatment n (%)	2556 (60.0)	<b>2077 (57.6)</b>	<b>479 (73.9)</b>	<b>&lt;0.001</b>

LLT: lipid-lowering drug treatment, BP: blood pressure, HDL: high-density lipoprotein, BMI: body mass index, W-H ratio: waist-hip ratio, CVD: cardiovascular disease. **Bold** p<0.05

For in-trial characteristics (Table 2), there was no significant difference between the number of 'LLT' and 'no LLT' participants randomized to either ACE-I or diuretic-based therapy. However, LLT participants were more likely to receive a higher number of randomized drugs and had a lower average on-treatment diastolic BP.

Table 2. In-trial characteristics by LLT stratification.

	Total (N=4257)	No LLT (n=3609)	LLT (n=648)	p- value
Randomized to ACE-I n (%)	2117 (49.7)	1782 (49.4)	355 (51.7)	0.28

BP lowering-drug compliance n (%)	1828 (67.2)	1532 (67.3)	296 (66.2)	0.64
Average on-treatment systolic BP (mean $\pm$ SD, mmHg)	145.6 $\pm$ 9.9	145.6 $\pm$ 9.9	145.4 $\pm$ 9.6	0.49
Average on-treatment diastolic BP (mean $\pm$ SD, mmHg)	80.8 $\pm$ 5.5	<b>80.8 <math>\pm</math> 5.5</b>	<b>80.3 <math>\pm</math> 5.2</b>	<b>0.02</b>
Number of assigned in-trial BP lowering drugs n (%)				<b>&lt;0.001</b>
0	195 (4.6)	<b>175 (4.9)</b>	<b>20 (3.1)</b>	
1	2183 (51.6)	<b>1902 (53.0)</b>	<b>281 (43.4)</b>	
2	1640 (38.7)	<b>1336 (37.3)</b>	<b>304 (46.7)</b>	
$\geq 3$	216 (5.1)	<b>174 (4.9)</b>	<b>42 (6.5)</b>	

LLT: lipid-lowering drug treatment, ACE-I: Angiotensin Converting Enzyme-Inhibitor, BP: blood pressure. Bold  $p < 0.05$

#### *Association of LLT and mortality in the total cohort*

263 deaths (106 CVD deaths including 13 fatal myocardial infarction, 28 fatal stroke and 65 other CVD deaths) occurred during the in-trial period (median 4.1 years/'short-term'). These numbers increased to an overall 1250 deaths (622 CVD deaths including 124 fatal myocardial infarction, 122 fatal stroke and 376 other CVD deaths) by the end of the extended phase (median 10.8 years/'long-term'). Accumulative incidences of events according to LLT were presented in KM curves in figure 1 of the supplementary material.

In the long-term (10.8 years), LLT participants had a significantly lower adjusted risk of all-cause mortality HR 0.78 (95% CI 0.66-0.92,  $p=0.003$ ). Noticeably, most of the survival benefits were attributable to the effects on long-term non-CVD deaths HR 0.70 (95% CI 0.54-0.90,  $p=0.006$ ), particularly cancer deaths HR 0.62 (95% CI 0.44-0.88,  $p=0.007$ ) (Table 3). Also, magnitudes of the association of LLT with long-term mortality and the association with short-term mortality were similar, however, no statistically significant association on short-term mortality was observed (Table 3 and 4). In terms of CVD mortality, there was no significant difference between the LLT and no LLT groups in either the short (HR 0.86, 95% CI 0.46-1.61) or long term (HR 0.87, 95% CI 0.68-1.11).

Table 3. Association between LLT and long-term mortality in tertiles by estimated 5-year CVD risk and in the total cohort.

Tertiles by estimated 5-year CVD risk	Number of event % (n)	Event (rate per 1000 person-year)		Univariate HR (95%CI)	Adjusted * HR (95%CI)
		No LLT	No LLT		
<b>All-cause mortality</b>					
1 <sup>st</sup> tertile (2-14.5%)	7.0 (297)	11.5	22.5	<b>0.51 (0.35-0.74)</b>	<b>0.64 (0.44-0.94)</b>
2 <sup>nd</sup> tertile (14.5-22.6%)	9.3 (398)	21.7	29.6	<b>0.72 (0.53-0.98)</b>	0.85 (0.62-1.16)
3 <sup>rd</sup> tertile (22.6-59.8%)	13.1 (557)	30.7	43.3	<b>0.70 (0.53-0.91)</b>	0.85 (0.65-1.11)
Total	29.4 (1252)	20.6	31.6	<b>0.64 (0.54 - 0.76)</b>	<b>0.78 (0.66-0.92)</b>
p for interaction	-	-	-	0.29	0.29
<b>CVD mortality</b>					
1 <sup>st</sup> tertile (2-14.5%)	3.3 (141)	5.9	10.5	<b>0.56 (0.33-0.95)</b>	0.74 (0.43-1.26)
2 <sup>nd</sup> tertile (14.5-22.6%)	4.6 (196)	10.9	14.5	0.74 (0.48-1.14)	0.86 (0.53-1.38)
3 <sup>rd</sup> tertile (22.6-59.8%)	6.6 (282)	17.9	21.4	0.82 (0.58-1.16)	0.98 (0.69-1.38)
Total	14.5 (619)	11.1	15.4	<b>0.71 (0.56 - 0.91)</b>	0.87 (0.68-1.11)
p for interaction	-	-	-	0.5	0.46
<b>Cancer death</b>					
1 <sup>st</sup> tertile (2-14.5%)	2.0 (87)	2.4	6.8	<b>0.35 (0.15-0.80)</b>	<b>0.40 (0.17-0.93)</b>
2 <sup>nd</sup> tertile (14.5-22.6%)	2.9 (125)	7.1	9.3	0.76 (0.44-1.29)	0.86(0.50-1.47)
3 <sup>rd</sup> tertile (22.6-59.8%)	3.7 (157)	6.9	12.5	<b>0.55 (0.32-0.95)</b>	0.62 (0.35-1.08)
Total	8.7 (369)	5.3	9.5	<b>0.55 (0.39 - 0.78)</b>	<b>0.62 (0.44-0.88)</b>
p for interaction	-	-	-	0.27	0.28
<b>Non-CVD death</b>					
1 <sup>st</sup> tertile (2-14.5%)	3.7 (156)	5.5	11.9	<b>0.46 (0.27-0.80)</b>	<b>0.57 (0.33-0.98)</b>
2 <sup>nd</sup> tertile (14.5-22.6%)	4.7 (202)	10.9	15.1	0.71 (0.46-1.09)	0.84 (0.55-1.30)
3 <sup>rd</sup> tertile (22.6-59.8%)	6.5 (275)	12.9	21.8	<b>0.58 (0.39-0.87)</b>	0.72 (0.48-1.08)
Total	14.9 (633)	9.5	16.2	<b>0.57 (0.44-0.74)</b>	<b>0.70 (0.54-0.90)</b>
p for interaction	-	-	-	0.47	0.48

LLT: lipid-lowering treatment, CVD: cardiovascular disease. \* Age, sex, family history of CVD, non-HDL-C, diabetes, anti-platelet use, clustering effect by general practice, number of assigned in-trial BP lowering drugs. Bold p<0.05.

Table 4. Association between LLT and short-term mortality in tertiles by estimated 5-year CVD risk and in the total cohort.

Tertiles by estimated 5-year CVD risk	Number of event % (n)	Event (rate per 1000 person- year)		Univariate	Adjusted *
		LLT	No LLT	HR (95%CI)	HR (95%CI)
<b>All-cause mortality</b>					
1 <sup>st</sup> tertile (2-14.5%)	1.2 (52)	7.0	9.3	0.76 (0.34-1.67)	0.92 (0.41-2.07)
2 <sup>nd</sup> tertile (14.5-22.6%)	1.8 (76)	14.7	12.5	1.17 (0.64-2.12)	1.39 (0.74-2.60)
3 <sup>rd</sup> tertile (22.6-59.8%)	3.1 (134)	6.9	24.9	<b>0.28 (0.12-0.64)</b>	<b>0.32 (0.14-0.75)</b>
Total	6.2 (262)	9.4	15.7	<b>0.60 (0.40-0.90)</b>	0.71 (0.47-1.07)
p for interaction	-	-	-	<b>0.01</b>	<b>0.02</b>
<b>CVD mortality</b>					
1 <sup>st</sup> tertile (2-14.5%)	0.4 (15)	2.0	2.8	0.70 (0.16-3.08)	1.12 (0.23-5.39)
2 <sup>nd</sup> tertile (14.5-22.6%)	0.8 (32)	7.9	5.1	1.54 (0.67-3.56)	1.78 (0.71-4.47)
3 <sup>rd</sup> tertile (22.6-59.8%)	1.3 (57)	3.5	10.4	0.33 (0.10-1.07)	0.35 (0.11-1.14)
Total	2.4 (104)	4.3	6.2	0.71 (0.39 - 1.29)	0.86 (0.46-1.61)
p for interaction	-	-	-	0.09	0.1
<b>Cancer death</b>					
1 <sup>st</sup> tertile (2-14.5%)	0.5 (23)	3.0	4.0	0.74 (0.22-2.49)	0.77 (0.23-2.55)
2 <sup>nd</sup> tertile (14.5-22.6%)	0.8 (35)	5.6	5.9	0.96 (0.37-2.48)	1.14 (0.44-3.00)
3 <sup>rd</sup> tertile (22.6-59.8%)	1.1 (48)	2.3	8.9	0.26 (0.06-1.08)	0.27 (0.06-1.18)
Total	2.5 (106)	3.6	6.3	0.58 (0.30-1.11)	0.60 (0.31-1.17)
p for interaction	-	-	-	0.26	0.28
<b>Non-CVD death</b>					
1 <sup>st</sup> tertile (2-14.5%)	0.9 (37)	5.0	6.4	0.78 (0.30-2.00)	0.85 (0.33-2.18)
2 <sup>nd</sup> tertile (14.5-22.6%)	44 (1.0)	6.8	7.4	0.91 (0.39-2.16)	1.12 (0.46-2.73)
3 <sup>rd</sup> tertile (22.6-59.8%)	1.8 (77)	3.5	14.5	<b>0.24 (0.08-0.77)</b>	<b>0.29 (0.09-0.96)</b>
Total	3.7 (158)	5.1	9.5	<b>0.53 (0.31-0.93)</b>	0.61 (0.35-1.06)
p for interaction	-	-	-	0.13	0.17

LLT: lipid-lowering treatment, CVD: cardiovascular disease. \* Age, sex, family history of CVD, non-HDL-C, diabetes, anti-platelet use, clustering effect by general practice, number of assigned in-trial BP lowering drugs. Bold p<0.05.

#### *Association of LLT and mortality in a subgroup by 5-year estimated CVD risk*

In the subgroup analysis by estimated absolute CVD risk at baseline (Tables 3 and 4), heterogeneity was found for short-term all-cause mortality, but no other

outcomes. In the highest risk tertile, LLT group had a reduced risk of short-term all-cause mortality (HR 0.32, 95% CI 0.14-0.75) with p for interaction of 0.02, compared to the low and moderate risk tertiles. There was no effect seen in other outcomes in the short or long-term.

### *Sensitivity analysis*

In subgroup analyses stratified by age, sex and diabetes status at baseline (Table 1 and 2 in Supplementary), regarding long-term and short-term associations between LLT and mortality outcomes, the associations were not statistically different among stratified subgroups. In a further adjusted model, we added characteristics that were statistically different (W-H ratio and previous BP lowering treatment) between the LLT group, systolic BP and diastolic BP at randomization in the adjusted model. The results were similar to the adjusted model, and no substantial difference was recorded.

### **Discussion**

In this post-hoc analysis of ANBP2, we found a positive association between LLT with long-term all-cause, non-CVD and cancer mortality, but the protective association with CVD mortality did not reach statistical significance. For short-term outcomes, no significant association was recorded, although the magnitudes of the associations (HRs) were similar to the long-term effects.

Our long-term findings are consistent with the long-term ASCOT-LLA trial<sup>31</sup> and a 7.3-year observational study<sup>23</sup>. All three studies found a significant reduction in all-cause mortality and a non-significant reduction in CVD mortality. Surprisingly, similar to our study, ASCOT-LLA also observed a significant benefit on long-term non-CVD deaths (HR 0.85, 95%CI 0.73-0.99). Our study recorded a substantial benefit of LLT on cancer deaths, whereas ASCOT-LLA reported a non-significant effect on cancer deaths (HR 0.92, 95%CI 0.76-1.12), but a significant effect on deaths related to infectious or respiratory diseases (HR 0.64, 95% CI 0.42-0.97). The ANBP2 study did not record these outcomes, so we were unable to include these in this analysis. A limitation of our findings is that cancer deaths in both the short- and long-term may be confounded by the status of diagnosed cancer at entry. If the prevalence of diagnosed cancer at study entry were equally distributed between LLT and no LLT group, our results would support findings from previous studies showing

a substantial reduction of cancer-related deaths by statin treatment in participants either with pre-existing cancer or no cancer<sup>32,33</sup>. In contrast, two meta-analyses<sup>5,34</sup> of large randomised controlled trials showed no beneficial effect of statins on cancer-related deaths. Yet, most of these RCTs had a high proportion of participants with previous CVD.

In terms of the short-term outcomes, our findings on all-cause and CVD mortality are consistent with a previous meta-analysis by Savarese<sup>21</sup> who reported a non-significant effect of LLT on all-cause mortality with an RR 0.94 (95% CI 0.86-1.04;  $p=0.21$ ) and on CVD mortality with an RR 0.91 (95% CI 0.69-1.20;  $p=0.49$ ) with a mean follow-up of 3.5 years (range: 1 to 5.2 years). However, in our study, the protective association for all-cause mortality reached statistical significance in the long-term analysis with the median follow-up time of 10.8 years, suggesting that differences in mortality may take longer to accrue.

In the subgroup analysis by CVD risk, LLT showed a greater effect on short-term all-cause mortality in the highest risk tertile, compared to other lower risk groups. We did not find any significant difference in the low or moderate risk groups regarding other trial endpoints. In contrast to our results, the Cholesterol Treatment Trialists (CTT) Collaborators<sup>5</sup> observed a substantial reduction of all-cause mortality on the total cohort 0.91 (95%CI 0.85-0.97) but a non-statistically significant heterogeneity ( $p$  for trend=0.2) among risk subgroups (5-year risk at baseline <5%,  $\geq 5\%$  and <10%,  $\geq 10\%$  and <20%,  $\geq 20\%$  and <30%,  $\geq 30\%$ ). The CTT meta-analysis included participants at both middle and old age.

## Limitations

Due to the nature of the post-hoc observational design, our findings are open to residual confounding, and thus should be interpreted with caution. The results are also only based on one study, so are limited by low power. Another limitation of our study is missing details of LLT at baseline and in the post-trial period including reason for prescription, dose, duration and adherence to treatment. Compared to the 'no LLT' group, LLT participants had a substantially higher total cholesterol and were more likely to have previous BP lowering and antiplatelet use, to be diabetic and to have a family history of CVD suggesting that they were at higher underlying baseline risk. Covariate adjustment has limited ability to control for 'confounding by indication'. In the subgroup analysis by estimated CVD risk, age, sex and diabetes at baseline

(Supplementary table 1), the magnitudes of the association between LLT and mortality were similar in stratified groups, except that the association between LLT and short-term all-cause mortality varied according to estimated CVD risk. The association between LLT and other short-term or long-term mortality was found to be independent of age, sex, diabetes and estimated CVD risk. Furthermore, confounding by indication would be expected to bias in favor of higher mortality in the LLT group. A final point is that the risk algorithm is for untreated populations in both groups, but underestimation should affect those in the LLT group to a greater extent as they were on lipid-lowering therapy.

In conclusion, our study supports the early use of LLT in those 65 years or over due to the association with long-term benefits on all-cause mortality, although the short-term benefits are likely to be evident only in the high-risk population. The findings suggest that the mortality benefit of LLT for the elderly may take longer to become evident.

**Competing interests:**

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**Contributors:** MRN and CR are responsible for the study conception and data archive. CLBH and EKC performed the analyses and CLBH drafted the manuscript. MB, CR, JD provided substantial support on statistical analyses. LMHW is the



principle investigator in ANBP2. All authors contributed to the interpretation of data, critically revised the manuscript and approved the final version.

**Ethics approval:** ANBP2 was approved by the ethics committee of the Royal Australian College of General Practitioners and the post-trial cohort by the Monash University Standing Committee on Ethics in Research Involving Humans. The current cohort study was performed on non-identifiable dataset, thus an ethics approval was unnecessary.

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