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BRIEF COMMUNICATION

LDL-cholesterol Predicts a First CHD Event in Senior Citizens, Especially so in Those With Elevated Lipoprotein(a): Dubbo Study of the Elderly

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Q4 **Objective** The analysis was designed to explore the combined effects of LDL-cholesterol and lipoprotein(a) (Lp(a)) in predicting incident coronary heart disease (CHD) in senior citizens without prior CHD.

Methods This is a prospective cohort study in Dubbo NSW which has followed 2805 men and women 60 years and older for 16 years since 1988–1989. Subjects with prior CHD (n = 607) were excluded from this analysis. Incident CHD events were identified by hospital record linkage. The contributions of LDL and Lp(a) to CHD events and their combined effects were evaluated in proportional hazards regression models.

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Results There were 689 CHD events over 16 years in a cohort of 2198 men and women without prior CHD. LDL-cholesterol (corrected for cholesterol content of Lp(a)) and Lp(a) modelled in quartile categories each independently predicted CHD, but exclusively in Quartile 4 (Q4) for each parameter. Using the combination of LDL Q1 and Lp(a) Q1 as a reference group, LDL Q4 (>4.90 mmol/L) most clearly predicted CHD in combination with Lp(a) Q4 (>276 mg/L), hazard ratio 1.95 (95%CI 1.31–2.90).

Conclusion The present findings may have important practical implications in clinical management. If Lp(a) is assessed in senior citizens without prior CHD and found to be genuinely low, elevated LDL-cholesterol may not require active intervention.

Keywords Senior citizens • Cohort study • CHD • LDL-cholesterol • Lipoprotein(a) • LDL and Lipoprotein(a) combination

Introduction

Q7 Contemporary research supports a role for lipoprotein(a) (Lp(a)) in the genesis of coronary heart disease (CHD), including cohort [1], Mendelian randomisation [2] and genome wide Q8 association studies [3]. Lipoprotein(a) is essentially a low density lipoprotein (LDL) particle bound to a glycoprotein apolipoprotein(a), a protein with some homology to plasminogen. While we have previously documented a role for elevated Lp(a) levels in predicting CHD in a cohort of senior citizens, including many with prior CHD [4], the present analysis explored the role of combinations of LDL-cholesterol and Lp(a) in predicting incident CHD in senior citizens initially free of prior CHD.

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Materials and Methods

Study Background

Q9 Baseline examinations in the Dubbo Study were performed in 1988-89, the cohort comprising all non-institutionalised residents born before 1930. Participation rate was 73% (1233 men and 1572 women). Methods and measures have been described in detail in a previous report [4]. Prior CHD was defined as previous myocardial infarction and/or angina reported by questionnaire and/or resting ECG changes. Those with prior CHD (607/2805) were excluded from the current analysis. Lipoprotein(a) was measured by a sand-
Q10 wich ELISA technique using polyclonal sheep antibody raised against purified human apolipoprotein(a) (TintElize Lp(a) Biopool Sweden). Calculated LDL-cholesterol was corrected for the approximate 30% cholesterol content of Lp(a) [5].

Q11 Coronary heart disease events over 16 years from September 1988 were included. Hospitalisation and death records were monitored continuously, with postal surveys conducted every two years to confirm vital status. Records were coded according to the *International Classification of Diseases, 9th edition* (*Clinical Modification*) (*ICD-9*) and *10th edition* (*Australian Modification*) (*ICD-10*). Coronary heart disease was defined by ICD-9 codes 410–414 and ICD-10 codes I20–25.

Statistical Methods

Lipoprotein(a) has a highly skewed distribution and was analysed in quartile categories. Where relevant, LDL-cholesterol was also modelled in quartile categories. The independent contributions of LDL and Lp(a), and finally, combinations of LDL and Lp(a) quartiles to incident CHD were examined in Cox proportional hazards regression models which included other conventional risk factors or confounders. The study has been approved by institutional ethics committees at St Vincent's Hospital Sydney, the University of NSW and University of Western Sydney. All subjects gave informed, written consent.

Results

There were 689 CHD events over 16 years in a cohort of 2198 men and women without prior CHD (31/100 subjects). Selected baseline characteristics in subjects with and without incident CHD are summarised in Table 1. Some statistically significant differences were noted, yet there was no significant difference between cases and non-cases with respect to Lp(a) analysed as a continuous variable (Mann–Whitney U test).

In the Cox model which included both LDL and Lp(a) quartiles as well as conventional risk factors and confounders, the hazard ratios (HR and 95% CIs) for prediction of CHD by LDL-cholesterol quartile were: Quartile 1 (<3.47 mmol/L) HR 1.0, reference group; Quartile 2 (3.47–4.12 mmol/L) HR 1.16 (0.93–1.45); Quartile 3 (4.13–4.90 mmol/L) HR 0.98(0.78–1.24);

Q1 **Table 1 Selected Baseline Characteristics in Subjects with and without Incident CHD During 16 Years Follow-up.**

	New CHD cases (n = 689)	Non-cases (n = 1509)
Age (years)	70.1 ± 7.2	68.0 ± 6.7*
Male (%)	46	41†
Lipoprotein(a) (mg/L)	110	105ns
LDL chol (mmol/L)	4.46 ± 1.16	4.36 ± 1.07**
LDL chol [corr for Lp(a)]	4.28 ± 1.12	4.19 ± 1.05ns
HDL chol (mmol/L)	1.31 ± 0.36	1.41 ± 0.38*
Blood Pressure Rx (%)	55	34*
BP ≥160 or 95 (%)	9	6*
Diabetes (%)	11	6*
Current smoking (%)	17	15ns
Fam history CHD (%)	36	32**

Continuous variables shown as mean ± SD (t-test), categorical variables as % (X^2), Lp(a) as median (U test): *p < 0.001, †p < 0.02, **p < 0.05, ns = not significant. We show only conventional risk factors, but many other characteristics were documented.

Quartile 4 (>4.90 mmol/L) HR 1.36(1.09–1.71) p < 0.01. The hazard ratios with respect to Lp(a) were: Quartile 1 (<51 mg/L) HR 1.0, reference group; Quartile 2 (51–110 mg/L) HR 1.16(0.93–1.45); Quartile 3 (111–276 mg/L) HR 1.09(0.87–1.38); Quartile 4 (>276 mg/L) HR 1.45(1.17–1.80) p < 0.001.

The combined effects of LDL and Lp(a) quartiles in the prediction of CHD in the Cox model are summarised in Table 2. Using the combination of LDL Q1 and Lp(a) Q1 as a reference group, LDL predicted CHD most strongly in combination with Lp(a) Q3 and Q4. Findings were essentially unchanged if the Cox model was re-calculated using uncorrected LDL cholesterol values (data not presented).

Discussion

We have confirmed that elevated LDL cholesterol and elevated Lp(a) independently predict future CHD in senior citizens without prior CHD, with excess relative risks in Q4 versus Q1 of 36% and 45% respectively. The present analysis extends this prediction further by highlighting that this increased CHD risk is most clearly seen in those citizens with LDL Q4 (>4.90 mmol/L) in combination with Lp(a) Q4 (>276 mg/L).

Few studies have explored the combined effects of LDL and Lp(a) on CHD risk. An examination of this question was recently reported from the longitudinal US Cardiovascular Health Study in older adults. In contrast to the present findings, Lp(a) was most strongly predictive of CHD in those with the lowest LDL-cholesterol (<1.8 mmol/L) [6]. However, all subjects in this US cohort had prior cardiovascular disease or other high risk conditions and many were using

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