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Falling cholesterol trend at acute coronary syndrome presentation is strongly related to statin use for secondary prevention

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ABSTRACT

Background: Lifestyle changes are believed responsible for temporal trends of reduced population total cholesterol (TC), but it is uncertain whether this applies to patients with known coronary heart disease (CHD) often prescribed lipid lowering therapy (LLT). We studied temporal TC trends at presentation with acute coronary syndrome (ACS) to determine the contribution of LLT given for secondary prevention.
Methods: TC and LLT were obtained in 5592 patients in annual surveys of ACS admissions in Australia between 1999 and 2013, and annual mean trends analysed by linear and segmented regression.
Results: TC declined from 5.13 ± 1.1 to 4.53 ± 1.2 mmol/L ($p < 0.001$) and LLT (96% statin) use at presentation increased from 37.4% to 47.5% ($p = 0.005$). TC decline was greater in those on LLT vs. those not on therapy, with LLT contributing to 57% of the TC decline. The decline in TC and increase in LLT use was non-linear and much steeper in those with, than without CHD history, and LLT contributed substantially more to the TC decline (79%, $p < 0.001$ vs. 27%, $p = 0.06$ respectively). The rapid decline in TC and increase in LLT, plateauing after 2005 in those with CHD history differed markedly from trends in recent population studies, while TC trend for those without CHD history was slower, linear and consistent with population trends.
Conclusions: Declining TC level at presentation for ACS was strongly associated with increasing LLT use in those with a history of CHD, indicating that increasing uptake of LLT for secondary prevention has impacted TC changes in the new millennium.

1. Introduction

Dyslipidaemia is one of the principal risk factors for major coronary heart disease (CHD) events including death and myocardial infarction. Over the past 20–30 years, there has been a steady fall in population total cholesterol (TC) in many countries. It has been calculated that reduction in TC of as little as 1% in the population would result in a 2.5% decrease in cardiovascular disease mortality [1]. There has been an active debate about whether increase in use of lipid lowering therapy (LLT) or changes in lifestyle such as diet and physical activity are the main contributors to the declining population TC levels, with a recent study concluding that lifestyle changes were the most likely cause [2].

In patients with an acute coronary syndrome (ACS), we observed a decline in baseline TC from 4.7 mmol to 4.2 mmol in two secondary prevention interventional studies separated by four years in the last decade [3,4]. However, there is uncertainty about the precise magnitude and temporal trend of this fall in TC in recent years, and whether the fall is also more related to lifestyle than LLT changes. Defining this change

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and its relationship to changes in LLT is important as it may assist our understanding of the impact of increasing guideline adherence to LLT for secondary and/or primary prevention of ACS.

We had the opportunity to examine annual temporal trends in admission TC amongst patients presenting with an ACS between 1999 and 2013 from a continuing ACS database and relate these to changes in the use of LLT. We also reviewed published population temporal trends in TC in order to place the changes seen in patients presenting with ACS in perspective. The aim of this study was to describe the recent temporal trends in TC in patients presenting with an ACS and to determine the contribution of changes in the use of lipid lowering therapy to the observed changes in TC. We hypothesised that the changes in TC over time and the relative contribution of LLT would differ in ACS patients with and without a past history of CHD.

2. Methods

2.1. GRACE and CONCORDANCE study patients

For this study, we included patients enrolled in the Australian segment of the Global Registry of Acute Coronary Events (GRACE) study from 1999 to 2007 (9 hospitals, n = 4097) [5,6] and the Cooperative National Registry of Acute Coronary Care, Guideline Adherence, and Clinical Events (CONCORDANCE) study from 2009 to 2013 (41 hospitals, n = 3858) [7]. The CONCORDANCE database was designed to be very similar to the GRACE registry database to permit comparisons and analysis of temporal changes.

GRACE was a multinational prospective registry that described and compared patient characteristics, treatment patterns and in-hospital and post-discharge outcomes in ACS patients. Full details of the GRACE study have been published previously [5,6]. In brief, patients were eligible for enrolment if they were >18 years old, alive at presentation with a presumptive diagnosis of ACS based on history and investigations [5,6]. Patients were excluded if their ACS was precipitated or accompanied by events such as surgery, trauma and gastrointestinal bleeding [5,6]. Participating centres were encouraged to recruit the first 10–20 eligible patients each month [5,6].

CONCORDANCE is an ongoing Australian multicentre, hospital-based observational study that describes the treatments and outcomes of patients admitted with ACS and provides feedback to the hospitals involved. Full details of the CONCORDANCE methodology have been published elsewhere [7]. Inclusion and exclusion criteria for CONCORDANCE were identical and patients were recruited in a similar manner to GRACE [7].

The GRACE and CONCORDANCE study datasets during the specified years included 7955 patients. TC values were available in 5592 (70.3%) of the population. TC was measured during the admission in all but 13/5592 patients during years 1999 and 2000. In those 13 patients, a value of TC known from a blood level obtained in the year prior to admission was used.

Patient-level data from the GRACE and CONCORDANCE databases were combined to perform the analyses listed below. We divided subjects into those with no prior history of CHD and those with a past history of CHD: this included prior myocardial infarction (MI)/acute coronary syndrome (25.9%), angina pectoris (32.5%), percutaneous coronary intervention (PCI) (14.2%), coronary artery bypass graft surgery (CABG) (11.1%) and ischemic cardiomyopathy (6.8%).

2.2. Literature search

A literature search for studies describing TC and LLT temporal trends in the general population was conducted on MEDLINE and EMBASE using search terms listed (see Supplementary data). A total of 33 observational studies in populations from 14 countries were identified. These trends were plotted graphically as a comparator for those obtained from the GRACE and CONCORDANCE databases. A similar search strategy for studies describing temporal trends of TC and LLT restricted to patients with ACS revealed two studies with TC trends, and five with LLT trends.

2.3. Statistical analysis

Linear, as well as segmented regression was used to explore the relationship between time and TC as well as time and LLT. Independent samples t-tests and chi-squared tests were used to compare trends in patients with, versus patients without, a history of CHD. Comparison between goodness of fit of the linear and segmented models of temporal trends was performed using an F test. Multiple regression analyses using mean LLT and age per year, as well as proportion of male patients per year and interaction term between age * sex were performed to predict TC levels. Regression analyses were performed separately for patients with CHD, patients without CHD, as well as for the total cohort. Data were analysed using SAS 9.3 and GraphPad Prism 6.

3. Results

The overall demographics and risk factor profiles of the cohorts are shown in Table 1. Patients with no CHD history were significantly younger than those with a history of CHD, but the gender distribution was identical (70% male). Patients with a history of CHD were significantly more likely to have cardiovascular risk factors of hypertension, diabetes, and dyslipidaemia, but were less likely to be current smokers. Prehospital LLT use was much higher in those with a history (60.3%) compared to those without a history of CHD (18.7%), and this LLT was almost always (96%) a statin. There was no temporal change in age or gender balance or the proportion with a history of CHD during the study period (data not shown). In the overall cohort between 1999 and 2013, TC fell from 5.13 ± 1.1 mmol/L to 4.53 ± 1.2 mmol/L ($p < 0.001$) whilst LLT use increased from 37.4% to 47.5% ($p = 0.005$) (Fig. 1). The decline in TC was not linear, and the fall was better described by a segmented line ($R^2 = 0.88$, $F = 17.3$, $p = 0.0013$ segmented line vs. single line), with an initial rapid fall followed by a plateau. There was a linear increase in LLT during the same time period.

Fig. 2 shows the temporal trend of TC in patients who were taking LLT at the time of admission, and those not prescribed LLT. TC levels declined over the study period in both groups, irrespective of LLT use prior to admission, however TC level was lower in those taking LLT in the first years of data collection and showed a greater decline over the study period compared to those not on LLT. The TC decline was statistically significant for both cohorts, but the slope of TC decline was greater in the group on LLT ($p = 0.004$). Multiple regression analysis with treatment, age and age * sex interaction indicated that amongst ACS patients overall, LLT accounted for 57% of TC decline ($R^2 = 0.57$, $p < 0.005$).

Because patients with a past history of CHD had a much higher rate of LLT use than those without prior CHD we examined the impact of CHD history on TC decline, and the relationship between trends of LLT use and TC fall in both groups (Fig. 3). TC fall and LLT rise were much steeper in those with a history of CHD compared to those without. In patients with a history of CHD, the fall in TC is again best represented by two lines ($R^2 = 0.87$, $F = 19.1$, $p = 0.009$, segmented line vs. single line) with a rapid initial decline followed by a plateau, whilst in those without a history of CHD, the decline is represented by a single line. In both groups, the increase in LLT mirrored the TC trends. After adjustment for age and sex, LLT use explained 79% of the fall in TC in the group with a history of CHD ($R^2 = 0.79$, $p < 0.001$) but accounted for only 27% of the fall in those without a history of CHD of borderline statistical significance ($R^2 = 0.27$, $p = 0.06$).

Population studies indicate that serum TC levels have been declining from 1960 to the first decade of the millennium [8–32], and LLT use in the general population has increased from 1980 to 2006 [33–36]. The fall in TC and increase in LLT in the general population from the world literature has been superimposed on the GRACE and CONCORDANCE data in Fig. 4. The decline in general population TC and increase in LLT