Statin Prescribing Patterns and Residual CRP Risk on Hospitalisation in a South-Western Sydney Population

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Abstract

Background: *Statins have been utilised extensively in atherosclerotic cardiovascular disease (ASCVD) to lower serum low-density lipoprotein cholesterol (LDL-C) and inhibit inflammation. However, the association between statin therapy, subclinical inflammation and associated health outcomes is poorly understood in primary care.*

Methods: *Statistical analysis was performed using primary care electronic health record (EHR) data from the electronic Practice-Based Research Network (ePBRN) to identify trends in statin prevalence and adherence in South Western Sydney (SWS). The relationship between baseline CRP and incident hospitalisation rates for all-cause and ASCVD hospitalisations was investigated in patients on statin therapy with subclinical (<10mg/L) C-reactive protein (CRP) measurements.*

Results: *Although statin use was higher in the SWS population than in a nationally representative cohort, the growth in statin use was slower than the general populace. Only 55% of individuals had good adherence (>80%). The multivariable model of factors independently associated with elevated CRP (≥2mg/L) among statin-treated people had a similar R^2 value to a similar model in a United States population. However, among statin-treated patients, elevated CRP levels were not associated with all-cause and ASCVD hospitalisations after adjustment for confounding factors.*

Conclusion: *This data reaffirms the existence of a health disparity between the SWS population and the general population, suggesting it is further widening. Patients may benefit from faster adoption of new literature and involvement in management plans. This study does not support the use of CRP as an independent marker of future hospitalisations but does validate the use of primary care EHR data in population health research.*

Research Category

Clinical characterisation

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality globally (1). Atherosclerosis, the underlying process of lipid deposition in the blood vessel intima, has become increasingly viewed as an inflammation-driven disease, characterised by subclinical inflammatory cytokine expression and immune cell involvement (2). Serum C-reactive protein (CRP) is a key inflammatory biomarker with great predictive power of ASCVD event rates, but low marginal benefit in risk stratification when incorporated with the existing framework (3-5). However, large multicentre trials suggest inflammation may be causal in ASCVD, providing a novel role for CRP in examining residual risk following anti-inflammatory therapy (6, 7). Statins are used in primary and secondary prevention of ASCVD due to their effects on the reduction of low-density lipoprotein cholesterol (LDL-C), a risk factor for ASCVD(8, 9). However, statins also have pleiotropic effects, acting as anti-inflammatory agent and reducing circulating CRP levels(10, 11). Application of these experimental

findings at the physician level involves ongoing review to ensure that the most updated guidelines translate into the treatments administered to the population. Therefore, this study will explore statin prescribing patterns in the population of South-Western Sydney (SWS) using electronic health record (EHR) data from the Electronic Practice-Based Research Network (ePBRN), and examine the potential role of on-treatment CRP level as a marker for hospitalization risk among statin-treated patients.

Methods

The ePBRN dataset consists of anonymised, computerised records sourced from a network of general practitioner (GP) clinics located in SWS(12). These are extracted and linked to hospital data using GRHANITE^{TM} and ensemble-based linkage(13, 14). Between 2012-2019, 166,590 patients visited the network and 13,689 of these patients were on lipid-lowering therapy. After selecting the first, valid, subclinical CRP measurement (<10 mg/L) for adults on statin therapy, 3224 patients remained. Patient parameters were obtained from GP and hospital records generated by treating physicians. These included demographic factors; behavioural factors; examination findings; past medical history; medication prescription data; and clinical biomarkers. Prevalence was determined for those on lipid-lowering therapy for each year from 2012-2019. Adherence to statins was determined for those who received statin prescriptions for a year or more (n=9109). Factors independently associated with CRP were determined among 3224 patients on statin therapy and validated using the United States National Health and Nutrition Examination Survey (NHANES) cohort. Hospital records of these patients were used to assess the relationship between elevated CRP and all-cause and ASCVD hospitalisations.

Results

The prevalence of statin therapy in the ePBRN cohort increased over time, and was higher in older age groups, but fell sharply in those over 85 years of age (Figure 1). There was a slight fall from 2013-2015 led by a decrease in statin use, whereas non-statin medications did not experience this fall (Figure 2). Males were prescribed statins more frequently and were prescribed higher strength statins. There was an increase in prescription rates in urban areas, but a decrease in non-urban locales. 60% of the cohort was on moderate-strength statin therapy, 35% were on high-strength therapy and less than 5% were on low-strength therapy. There was a trend towards the prescription of hydrophilic statins over time. Good adherence (>80%) was observed by 55% of the cohort.

There were 14 independent determinants of elevated CRP levels (≥2 mg/L) in a stepwise multivariable logistic regression model, including non-urban residence, hepatobiliary comorbidities, statin intensity, lipophilic statin, higher levels of alkaline phosphatase (ALP) and sodium, higher counts of monocytes, neutrophils and platelets, larger red cell distribution width (RDW), lower levels of albumin, bilirubin, chloride and a decreased estimated glomerular filtration rate (eGFR). This final multivariable model consisted of data from 2604 patients and had a Nagelkerke R^2 value of 0.187. There were also 14 independent determinants of elevated CRP in the NHANES cohort. Shared determinants included lipophilic statin use, higher levels of ALP, higher counts of monocytes and neutrophils, larger RDW and lower levels of albumin, bilirubin, and chloride. Other independent determinants of elevated CRP included female gender, smoking, higher BMI, lower calcium, higher levels of globulin and total cholesterol. Although the independent determinants slightly differed in the NHANES cohort, the final multivariable analysis included data from 3306 participants with a Nagelkerke R^2 value of 0.231.

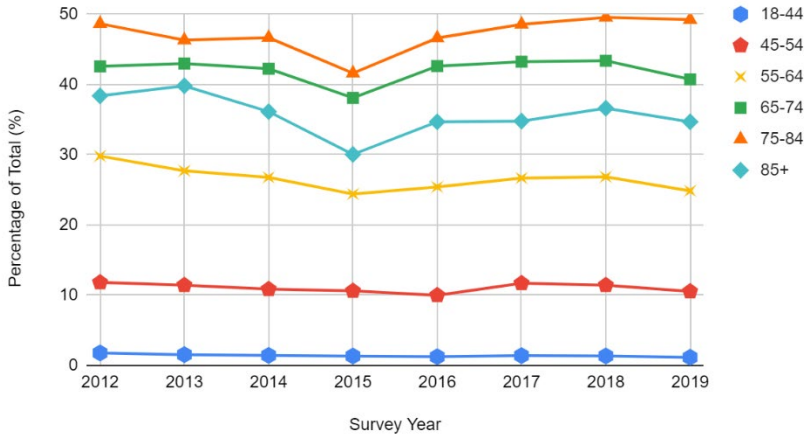

Figure 1: Trends in Prevalence of Statin Therapy by Age Group in the ePBRN Cohort

When adjusting for age and gender, an elevated CRP level was associated with a higher risk of all-cause hospitalisation at 3-month to 12-month after CRP level measurement, but not to ASCVD hospitalisations. After adjusting for independent determinants of elevated CRP levels, an elevated CRP level was not associated with either all-cause or ASCVD hospitalisations but appeared to trend toward significance. No significant differences were observed across subgroups of patients stratified by the different independent determinants of elevated CRP levels. Mediators of the relationship between elevated CRP and all-cause hospitalisations were ALP and bilirubin. Mediators between elevated CRP and ASCVD hospitalisations were non-urban residence, statin strength, statin lipophilicity, RDW, ALP and bilirubin.

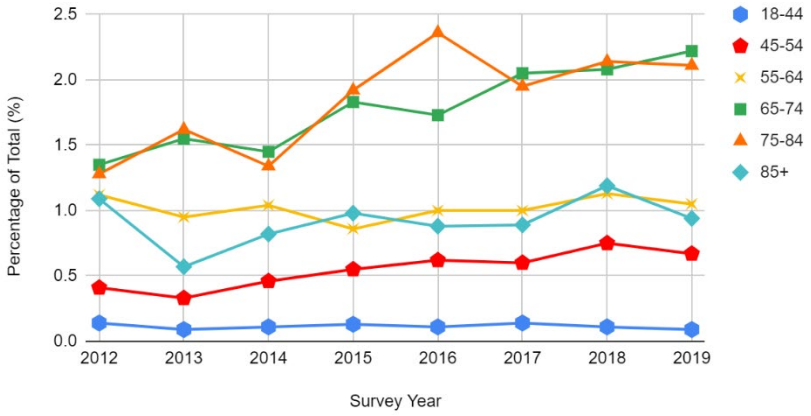

Figure 2: Trends in Prevalence of Non-Statin Lipid Lowering Therapy by Age Group in the ePBRN Cohort

Discussion

Prevalence patterns suggest that statin use is increasing in the SWS population, but the increase is slower than seen in a nationally representative cohort(15), indicating certain populations are being overlooked for treatment. The low proportion of individuals on low-intensity statin therapy may indicate that most overlooked individuals have low cardiovascular risk. Trends towards hydrophilic statins may reflect the growing body of literature favouring rosuvastatin over atorvastatin(16-18), however, this has been a slow shift. Furthermore, new evidence suggests that benefits of statin use in the elderly outweigh costs. However, this has still not translated to prescribing patterns, suggesting a significant delay in the translation of evidence to the clinic. The slight fall of statin prescriptions between 2013-2015 occurred likely due to an ABC Catalyst production critical of statins(19). Interestingly, non-statin lipid-lowering therapy remained steady in the same period, indicating that rotating therapies may be an effective compromise between patient concerns and ideal treatment. The low adherence rate indicates that presenting to the GP is a key barrier in complying with treatment, and exploratory analyses exemplified that non-urban residence was a factor that exacerbated this issue. The similarity between the R^2 value of the ePBRN and NHANES models for independent determinants of CRP validates the use of GP records to provide a proxy for the general health status of the population who visits the GP. After accounting for independent determinants of CRP, the data suggests that there is no benefit in monitoring residual risk of CRP to predict future events. A larger sample size with more accurate data on reasons for hospital admission would aide in drawing a more definitive conclusion.

Conclusions

Overall, results from this study indicate that the SWS area is still experiencing poorer health outcomes than the general population. This disparity may continue to expand as opportunities for early intervention are missed, and if statin adherence remains low. This study does not support the use of CRP in predicting incident all-cause or ASCVD hospitalisations among patients on lipid-lowering therapy due to confounding factors.

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