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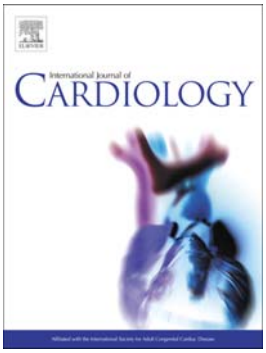

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Uptake of Evidence-based Statin Therapy among Atrial Fibrillation Patients in China: A report from the CAFR (Chinese Atrial Fibrillation Registry) Study

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Key Words: atrial fibrillation, evidence-based statin therapy, China

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ABSTRACT

Background—Atrial fibrillation (AF) is associated with increased incidence of cardiovascular disease, and hence, statin therapy is indicated in majority of AF patients.

Methods and results—We analyzed data from the Chinese Atrial Fibrillation Registry (CAFR) involving 11496 AF patients from 2011 to 2014. Practice patterns of statin therapy and factors associated with statin underuse were analyzed.

Based on the 2013 ACC/AHA cholesterol management guidelines, statins should be recommended for 67.4% (7720/11461) of AF participants in CAFR, but only 43.4% (3352/7720) with appropriate indications were taking statins. Statin underuse in AF patients was independently associated with male sex, tertiary hospital treatment, outpatient attendance, and absence of 'high risk' cardiovascular risk factors (overweight, diabetes, coronary heart disease, stroke/transient ischemic attack/peripheral embolism and hypertension).

Conclusions—A high proportion of Chinese AF patients had indications for statin

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therapy. Evidence-based statin prescribing was suboptimal in this population. Greater efforts should be made to improve a holistic approach to cardiovascular risk management in the Chinese AF population.

Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia, with 33.5 million prevalent and additional 5 million incident AF cases being reported in 2010 worldwide.[1] AF is consistently associated with a higher risk of morbidity and mortality, especially from cardiovascular conditions.[2, 3] In addition, the presence of cardiovascular comorbidities and risk factors are not uncommon in AF patients. Due to high prevalence of cardiovascular risk factors among AF patients, risk of adverse cardiovascular outcomes is also substantially higher in this group of patients.[4-6]

In the Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study, for example, AF was found to be associated with substantially increased risk of death and cardiovascular events in patients with type 2 diabetes.[7] In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, AF patients had almost 2-fold higher risk of myocardial infarction [hazard ratio 1.96, 95% confidence interval (CI), 1.52-2.52] after adjusting confounding factors.[8] More recently, incident AF was found to be associated with

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increased risk of sudden cardiac death (SCD) and non-SCD in the general population.[9] Despite this high cardiovascular risk, management of risk factors is sometimes neglected in practice, given that stroke prevention is the most feared complication of AF and much focus is directed on oral anticoagulation therapy.

Statin therapy can substantially reduce the risk of cardiovascular disease.[10] Given their high cardiovascular risk, treatment with statins may bring larger absolute risk reduction for AF patients. As the public health burden of AF in China is increasing, insights into the pattern of statin usage in AF patients will provide important information for future healthcare quality improvement.

The ongoing Chinese Atrial Fibrillation Registry (CAFR) recruited AF patients from 31 hospitals located in urban and semi-urban areas of Beijing. In this report from CAFR, we studied the use of statin therapy in this population and explored factors associated with statin underuse in clinical practice, amongst Chinese AF patients.

Methods

Study design and participants

The Chinese Atrial Fibrillation Registry (CAFR) is a prospective, multicenter, hospital-based, ongoing registry study of patients diagnosed with AF in Beijing, China. The majority of tertiary and nontertiary hospitals providing a clinical service of AF

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management in Beijing participated in this registry study. Data collected between August 2011 and July 2014 from 31 hospitals were used for analyses.

Trained personnel including doctors from tertiary and nontertiary hospitals enrolled unselected eligible AF outpatients and inpatients from their daily practices. Abstracted data were submitted to the CAFR registry website. Eligible patients were those aged ≥ 18 years, with AF documented via either electrocardiogram (ECG) or Holter within the past 6 months. AF was diagnosed by local investigator via the baseline 12-lead ECGs or Holter recordings. Written informed consent was obtained from each patient. Those patients with transient and reversible AF, suffering from other diseases with a life expectancy < 1 year, diagnosed with rheumatic mitral stenosis or having mitral valve prostheses were excluded.

Data collection

Patients' characteristics information, including socio-demographic data (age, gender, level of education, and medical insurance status), medical history [history of congestive heart failure, hypertension, diabetes, hyperlipidemia, prior stroke/transient ischemic attack (TIA)/peripheral thromboembolism, established coronary heart disease (any history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery), hyperlipidemia, prior bleeding], cardiovascular risk factors (smoking, alcohol consumption and body mass index), results of physical examinations, results of the latest laboratory tests, including liver

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and renal function, blood glucose and cholesterol levels, tested within 1 year or at the time of enrollment, results of electrocardiogram and echocardiogram, and medical therapies received were collected.

Definition of population with indications for statins

According to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline, statins use was recommended for four subgroups of patients: adults with atherosclerotic cardiovascular disease, adults with LDL cholesterol>190mg/dL, adults 40-79 years old with LDL cholesterol 70-189 mg/dL and diabetes, and adults with a 10-year predicted risk for atherosclerotic cardiovascular disease (ASCVD) ≥5%.[10]

In this study, ASCVD was defined as positive history of acute coronary syndromes, myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke/TIA, or peripheral arterial disease presumed to be of atherosclerotic origin. 10-year risk of ASCVD was predicted with a simplified point score model as recommended by Chinese guidelines.[11, 12] The algorithm used in this study is provided in the appendix Figure 1.

Statistical analysis

Categorical variables were shown as n(%), whereas continuous variables are shown as mean (standard deviation, SD). Continuous variables were compared using either

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the unpaired T-test or the Mann-Whitney U test, whereas categorical variables were compared using the Chi-square test. For the analysis of factors associated with non-use of statins in AF patients who have indication(s), a univariate logistic regression was first conducted by using each baseline variable as a covariate. A logistic regression model was then applied to include all the significant covariates identified in the univariate analysis. A stepdown method was used to determine the final model of the logistic regression. To investigate whether the rate of statin usage differed significantly among hospitals after considering the differences in patients' characteristics, we also fitted a generalized linear mixed model with hospital included as a random effect and tested whether the variance for the random effect was significantly different from zero. The results were shown in appendix. A *P* value <0.05 was considered statistically significant. All analyses were conducted using SAS software, version 9.2.

Ethical approval

The CAFR was reviewed and approved by the Ethics committee of Beijing Anzhen Hospital.

Results

We included 11496 patients with AF (average age 65.8 ± 12.0 years, 40.4% female), where the prevalence of patients with history of hypertension, congestive heart failure, diabetes, stroke/TIA/peripheral embolism, established coronary heart diseases and hyperlipidemia were 66.1%, 18.9%, 24.5%, 17.0%, 17.8% and 27.0%,

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respectively (Table 1). More than half (52.9%) of patients had paroxysmal AF, 38.3% with persistent AF, and the rest with newly diagnosed AF. The majority of enrolled patients (92.0%) were totally or partially covered by medical insurance. Compared to participants enrolled from tertiary hospitals, those enrolled from nontertiary hospitals were older, more likely to have comorbidities, and more likely to be smokers, had lower education status and permanent AF (Table 1).

Statin usage among those with indications

Overall, 67.4% (7720/11461) of AF patients had indication(s) for statin therapy while only 43.4% (3352/7720) patients with indication(s) were taking statin. Usage of stain varied among patients with different indications (Table 2): 57.8% (2022/3500) of those patients with a history of ASCVD were taking statin.

For those with LDL-C≥190 mg/dL, 58.1% (36/62) patients were taking statin. In contrast, only 37.6% (303/807) of patients aged 40-79 years old with diabetes and LDL cholesterol=70-189 mg/dL and 29.6% (991/3351) of patients who had predicted 10-year-ASCVD risk≥5% were taking statin. Of note, 20.6% (771/3741) of AF patients with no guideline recommended indications for statin use were taking it. Among patients with statin indications, the proportion of statin usage varied from 32% to 74% in tertiary hospitals and from 33% to 75% in nontertiary hospitals (Figure 1).

Factors associated with statin usage in AF patients

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After adjusting covariates that may impact the use of statins, underuse in AF patients were found to be independently associated with male sex [odds ratio (OR) 1.15, 95%CI 1.03-1.29] and tertiary hospital treatment (OR 1.99, 95%CI 1.70-2.31), while inpatients treatment (OR 0.70, 95%CI 0.63-0.79), BMI≥28 (OR 0.80, 95%CI 0.70-0.91) and comorbidities including history of diabetes, CHD, stroke/TIA/peripheral embolism and hypertension were associated with higher likelihood of statin use. ORs of statin underuse among patients with these comorbidities were 0.74 (95%CI 0.66-0.83), 0.26 (95%CI 0.23-0.30), 0.59 (95%CI 0.52-0.67) and 0.60 (95%CI 0.53-0.69) respectively. (Table 3)

In subgroups of patients treated in tertiary and nontertiary hospitals, factors associated with non-use of statins were also analyzed by the proc glimmix model which included hospital type as a random effect, and showed consistent results (intercept *P* among tertiary hospitals: 0.3396, non-tertiary hospital: 0.2888). [see Appendix Table 1-2]

Discussion

In this contemporary large registry study of statin therapy use in patients with AF we found that statin was greatly underused in AF patients, especially in those with a 10-year predicted risk for ASCVD≥5% and those aged 40-79 years old with LDL cholesterol 70-189 mg/dL and diabetes. Conversely a substantial proportion of AF

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patients with no indication for statins were prescribed these drugs.

Several large cohort studies have noticed increased risk of adverse cardiovascular outcomes beyond stroke in AF patients, that is, cardiovascular events including heart failure, myocardial infarction, etc.[6, 13, 14] However, the importance of preventing cardiovascular events is perhaps under-emphasized in current practice. ASCVD is not an uncommon comorbidity in AF patients.[15-17] On the other hand, AF patients already receiving anticoagulation therapy still suffer from a relative high risk of ASCVD events.[14, 18] Given the increased risk of AF-associated mortality and cardiovascular complications, especially the bidirectional relationship between AF and ASCVD,[8, 19] a comprehensive and holistic management approach of all cardiovascular risk factors in AF patients is of vital importance.

Much of the focus of AF management is directed towards stroke prevention with antithrombotic therapy, as well as rate or rhythm control. Less attention is paid to the importance of cardiovascular risk factor modification. Indeed, suboptimal statin usage was observed in our study, whereby over 65% of Chinese AF patients had statin indications while less than half of them were prescribed statin. Although the underuse of evidence-based cardiac prevention therapy has been noticed in patients with coronary heart disease [20-22] and initiatives have been launched to improve this, suboptimal treatment among patients with AF has not yet got enough attention. Aside from optimal statin usage, optimal management of traditional risk factors like

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hypertension and diabetes, management of obesity and overweight, leading healthy lifestyle are of equal importance in reducing cardiovascular risk and AF management. [23] However, it is reported that only a minority of patients received indicated therapies for their comorbidities and nearly half patients hadn't have their blood pressure controlled.[24] Importantly, AF patients whose predicted 10-year-ASCVD risk ≥5% in our study were least likely to receive any statin, reflecting the practice pattern of statin use which is more likely to be based on single disease rather than considering the complexity of all comorbidities and risk factors. Over-prescribing was evident in more than 20% of AF patients without indication for statins.

Interestingly, we observed a statin prescription "paradox" in different level hospitals. Patients treated in tertiary hospitals were less likely to receive guideline-indicated statins. There are several possible underlying reasons for this prescription paradox. First, doctors in tertiary hospitals are busier and looking after more patients so that they had more limited time to consider the importance of statin therapy. Second, doctors in tertiary hospitals focused more on anticoagulation therapy and even more invasive and expensive interventions such as ablation therapy, whilst statin therapy is ignored. After adjusting for covariates, we found outpatients and male patients to be less likely to be prescribed statin. This is in line with our hypothesis that doctors in the outpatients department were less likely to have enough time to communicate with patients about the necessity of taking statins. Moreover, statin underuse was associated with fewer comorbid conditions and less overweight, which again

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suggests that doctors are likely to ignore statin therapy in those patients with multiple moderate increased risk factors while great increased global cardiovascular risk. We didn't find medical insurance coverage was a risk factor for stain under prescription in this study. One possible explanation is that majority of Beijing residents are covered by "medical insurance for urban residents" or "medical insurance for urban employees". Out-of-pocket expense is about 30% of the medical fee for out-of-hospital medication. For rural residents, although only 50% of in-hospital cost can be reimbursed by "new rural cooperative medical care", the costs of statins are not unaffordable as generic statins are less expensive.

Limitations

The study population was composed of AF patients recruited from hospitals in Beijing, China's capital, and might not fully represent the whole AF population in China. Since majority of the recruiting sites were high-level medical centers located in urban areas, we can assume that statin use may be poorer in other areas of the country, especially in rural areas. The importance of statin therapy and treat the AF patient as a whole person rather than a single medical problem should be more emphasized in related guidelines. Reasons for not prescribing statin in AF population were not collected and thus detailed analysis cannot be provided, including the proportion with drug intolerance. The majority of our patients were covered by health insurance and thus, drug costs are not likely to account for the substantial proportion with non-use of statins.

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Conclusions

A high proportion of Chinese AF patients had indications for statin therapy. Evidence-based statin prescribing was suboptimal in this population. Greater efforts should be made to improve a holistic approach to cardiovascular risk management in the Chinese AF population.

Funding sources

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Figure Legends

Figure 1. Statin use in different hospitals amongst AF patients with indications. Inclusion of at least 50 patients from each participating hospital was sought.

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Table 1. Baseline characteristics of the patients.

Characteristics	Tertiary (N=10029)	Nontertiary (N=1467)	Overall (N=11496)
Age (mean±SD)	65.0±12.0	70.8±10.0	65.8±12.0
Gender, male	6050/10029 (60.3)	796/1467 (54.3)	6846/11496 (59.6)
Congestive heart failure	1456/10029 (14.5)	718/1467 (48.9)	2174/11496 (18.9)
Hypertension	6432/10018 (64.2)	1157/1467 (78.9)	7589/11485 (66.1)
Diabetes	2349/10029 (23.4)	464/1467 (31.6)	2813/11496 (24.5)
Prior Stroke/TIA/Peripheral embolism	1597/10028 (15.9)	356/1467 (24.3)	1953/11495 (17.0)
Prior bleeding	472/10028 (4.7)	57/1467 (3.9)	529/11495 (4.6)
Hyperlipidemia	2620/10002 (26.2)	471/1459 (32.3)	3091/11461 (27.0)
Established CHD*	1680/10028 (16.8)	366/1466 (25.0)	2046/11494 (17.8)
Smoking			
Current	1606/9968 (16.1)	242/1461 (16.6)	1848/11429

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			(16.2)
Former	1604/9968 (16.1)	332/1461 (22.7)	1936/11429 (16.9)
None	6758/9968 (67.8)	887/1461 (60.7)	7645/11429 (66.9)
Alcohol			
Current	1901/9958 (19.1)	235/1461 (16.1)	2136/11419 (18.7)
Former	1177/9958 (11.8)	205/1461 (14.0)	1382/11419 (12.1)
None	6880/9958 (69.1)	1021/1461 (69.9)	7901/11419 (69.2)
BMI (mean±SD)	25.4±3.7	25.3±3.8	25.4±3.7
Type of AF			
First time of diagnose	691/10029 (6.9)	323/1467 (22.0)	1014/11496 (8.8)
Paroxysmal	5620/10029 (56.0)	463/1467 (31.6)	6083/11496 (52.9)
Persistent	3718/10029 (37.1)	681/1467 (46.4)	4399/11496 (38.3)
Completed higher education	3032/8281 (36.6)	117/1450 (8.1)	3149/9731 (32.4)

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Types of health insurance			
None	825/10029 (8.2)	93/1467 (6.3)	918/11496 (8.0)
Partially	7906/10029 (78.8)	1284/1467 (87.5)	9190/11496 (79.9)
100%	1298/10029 (12.9)	90/1467 (6.1)	1388/11496 (12.1)
Type of healthcare			
Outpatients	4923/10029 (49.1)	377/1467 (25.7)	5300/11496 (46.1)
Inpatients	5106/10029 (50.9)	1090/1467 (74.3)	6196/11496 (53.9)

Values are n/N (%), unless otherwise indicated.

BMI indicates body mass index; TIA, transient ischemic attack; CHD, coronary heart disease;

* Established Coronary heart disease includes history of myocardial infarction, history of percutaneous coronary intervention and history of coronary artery bypass grafting

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Table 2. Statin use and prevalence of indications for statin use among CAFR Study participants

Participants Subgroups	Tertiary		Nontertiary		*P*
	With indication	Taking statin	With indication	Taking statin	
History of ASCVD*	2881	1619/2881 (56.2%)	619	403/619 (65.1%)	<0.001
LDL-C ≥190 mg/dL	56	32/56 (57.1%)	6	4/6 (66.7%)	0.653
Diabetes, LDL-C 70-189 mg/dL, 40-75y	697	241/697 (34.6%)	110	62/110 (56.4%)	<0.001
10-year-ASCVD risk≥5%	2895	777/2895 (26.8%)	456	214/456 (46.9%)	<0.001
Any indication for statin therapy	6529	2669/6529 (40.9%)	1191	683/1191 (57.4%)	<0.001
No indication for statin therapy	3469	660/3469 (19.0%)	272	111/272 (40.8%)	<0.001

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* History of atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

LDL-C indicate low-density lipoprotein cholesterol.

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Table 3. Factors associated with no statin use in AF patients who have indications

Characteristics	n/N(%)	Crude OR (95%CI)	Adjusted OR (95%CI)
Age			
<75	2952/5161 (57.2)	1.00 (reference)	-
≥75	1416/2570 (55.1)	0.92 (0.84,1.01)	-
Gender			
Female	2678/4578 (58.5)	1.00 (reference)	1.00 (reference)
Male	1690/3159 (53.5)	1.23 (1.12,1.35)	1.15 (1.03,1.29)
Education			
Higher education	1193/1949 (61.2)	1.00 (reference)	-
Lower education	2529/4607 (54.9)	0.77 (0.69,0.89)	-
Hospital level			
Nontertiary	508/1191 (42.6)	1.00 (reference)	1.00 (reference)

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Characteristics	n/N(%)	Crude OR (95%CI)	Adjusted OR (95%CI)
Tertiary	3860/6529 (59.1)	1.94 (1.72,2.20)	1.99 (1.70,2.31)
Diabetes			
No	3091/5178 (59.7)	1.00 (reference)	1.00 (reference)
Yes	1277/2559 (49.9)	0.67 (0.61,0.74)	0.74 (0.66,0.83)
BMI			
BMI < 28	3107/5348 (58.1)	1.00 (reference)	1.00 (reference)
BMI ≥ 28	781/1491 (52.4)	0.79 (0.71,0.89)	0.80 (0.70,0.91)
Established CHD			
No	3713/5685 (65.3)	1.00 (reference)	1.00 (reference)
Yes	654/2044 (32.0)	0.25 (0.22,0.28)	0.26 (0.23,0.30)
Stroke/TIA/Peripheral embolism			
No	3406/5783 (58.9)	1.00 (reference)	1.00 (reference)
Yes	962/1951 (49.3)	0.68 (0.61,0.75)	0.59 (0.52,0.67)

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Characteristics	n/N(%)	Crude OR (95%CI)	Adjusted OR (95%CI)
Hypertension			
No	1254/1855 (67.6)	1.00 (reference)	1.00 (reference)
Yes	3107/5873 (52.9)	0.54 (0.48,0.60)	0.60 (0.53,0.69)
Congestive heart failure			
No	3551/5968 (59.5)	1.00 (reference)	-
Yes	817/1765 (46.3)	0.59 (0.53,0.65)	-
Health insurance			
100% covered	608/1042 (58.3)	1.00 (reference)	-
Partially covered	3434/6154 (55.8)	0.91 (0.80,1.04)	-
None	326/541 (60.3)	1.09 (0.89,1.34)	-
Smoking			
No	3672/6511 (56.4)	1.00 (reference)	-
Yes	678/1181 (57.4)	1.04 (0.92,1.18)	-
Alcohol			

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Characteristics	n/N(%)	Crude OR (95%CI)	Adjusted OR (95%CI)
No	3562/6384 (55.8)	1.00 (reference)	-
Yes	782/1299 (60.2)	1.21 (1.07,1.36)	-
Form of treatment			
Outpatients	2225/3532 (63.0)	1.00 (reference)	1.00 (reference)
Inpatients	2143/4202 (51.0)	0.61 (0.56,0.67)	0.70 (0.63,0.79)

BMI indicates body mass index; TIA, transient ischemic attack; CHD, coronary heart disease.

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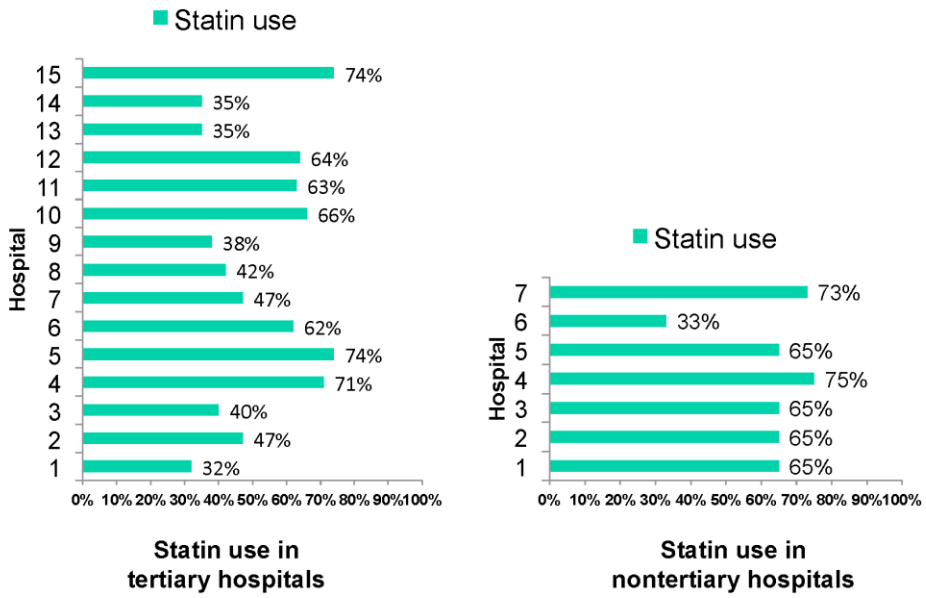

Figure 1

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