PRESCRIBING PATTERN OF LIPID-LOWERING MEDICATIONS BEFORE AND AFTER ADOPTION OF 2013 AMERICAN COLLEGE OF CARDIOLOGY AND AMERICAN HEART ASSOCIATION GUIDELINES IN THAILAND: AN INTERRUPTED TIME SERIES ANALYSIS

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Abstract. The American College of Cardiology (ACC) and the American Heart Association (AHA) in 2013 introduced new Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013 ACC/AHA guideline) focusing on use of appropriate statins as first-line drugs to reduce risks of atherosclerotic cardiovascular diseases (ASCVD). The 2013 ACC/AHA guideline was adopted in Thailand in November 2013. Impact of the new guidelines on statin use in the country was assessed by examining changes in prescribing patterns of lipid-lowering agents (LLAs) pre- and post-2013 ACC/AHA guideline release using an interrupted time series (ITS) design with segmented regression analysis. Health records of patients ≥21 years of age were collected from three tertiary-care hospitals in Thailand. ITS analysis carried out on 1,597,346 LLA prescriptions of 133,212 patients revealed a statistically significant increase in prescribed high-intensity statins post- compared to pre-2013 ACC/AHA guideline release for all patients in the three study hospitals, including those with ASCVD, diabetes and primary LDL cholesterol ≥190 mg/dL (p-value <0.001 for all categories). In addition, post-2013 ACC/AHA guideline prescriptions transited from low- or moderate- to high-intensity statins. Thus, the significant rise in trend of prescribing high-intensity statins would suggest a positive impact on prescriber good practice in tertiary-care hospitals of Thailand as a result of adopting the 2013 ACC/AHA guideline.

Keywords: American College of Cardiology/American Heart Association 2013 guideline, atherosclerotic cardiovascular disease, diabetes, interrupted time series analysis, statin

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INTRODUCTION

Dissemination of the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults provided a new approach in cholesterol management that addressed the use of fixed-doses of statins to reduce risk of atherosclerotic cardiovascular disease (ASCVD) in adults (Stone *et al*, 2014). The new Guideline recommends appropriate "intensity" statin therapy to achieve a relative reduction in LDL cholesterol level (LDL-C): high-intensity statins in patients ≥21 years of age with ASCVD and primary LDL-C ≥190 mg/dL without clinical ASCVD, unless where high-intensity statins are contraindicated or addressed significant safety concerns; moderate to high-intensity statins for patients 40-75 years of age with diabetes, LDL-C level of 70-189 mg/dL and without clinical symptoms of ASCVD. The previous 2004 Third Report of the National Cholesterol Education Program (NCEP), Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel (ATP) III) recommends a treat-to-target for LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) (Grundy *et al*, 2004).

In Thailand, prescription of statins followed the ATP III guideline but the majority of patients do not achieve the LDL-C targets due to suboptimal statin dosing (Grundy *et al*, 2004). High-intensity statins therapy is underused in clinical practice in the country; only 26% of established myocardial infarction (MI) patients reached target LDL-C of <70 mg/dL during a three-month follow-up period using low- to moderate-intensity statins (Tungsubutra and Phongtuntakul 2015). Only 14/38 (37%) patients with ischemic stroke and diabetes prescribed low- to moderate- intensity statins achieve the target LDL-C of <70 mg/dL during a nine-month follow-up period (La-ongsuwan *et al*, 2012).

The 2013 ACC/AHA Cholesterol Managemelnt Guideline was applied in November 2013 to promote achievement of LDL-C targets (Stone *et al*, 2014). However, the effects of 2013 ACC/AHA Guideline on patterns of prescribing lipid-lowering agents (LLAs) have not been elucidated. An interrupted time series (ITS) design is a robust method to examine impacts of health policy or clinical practice guideline interventions on changes to outcomes of interests over time (Wagner *et al*, 2002). Dynamic changes in ITS are measured using a segmented regression analysis, which employs two main parameters,

changes in levels and trends, to identify differences between post-and pre-intervention implementation.

Here, ITS design with segmented regression analysis was employed to examine the changes in prescribing trends and pattern of LLAs (low-, moderate- and high-intensity statins and non-statin medications) pre- and post-adoption of 2013 ACC/AHA Guideline in the three groups of patients, namely, ASCVD , diabetic and with LDL-C ≥ 190 mg/dL, at three tertiary-care hospitals in Thailand.

MATERIALS AND METHODS

Study design

Data were obtained from medical records at three tertiary-care hospitals located in central, southern and eastern parts of Thailand for a multi-center, quasi-experimental time series analysis. Duplicated and missing data were eliminated. Random checks of data accuracy were conducted by pharmacists in all three hospitals through verification with patients' charts. Data were standardized and names of patients redacted prior to the analytical processes.

The study protocols were approved by the Ethic Committee of each of the three hospitals namely, Chonburi Hospital Institutional Review Board (Approval No. 09/61/T/h3), Suratthani Hospital Institutional Review Board (Approval No. 77/2560) and Institutional Review Board, Royal Thai Army Medical Department (Approval No. Q028h/60_exp). No prior written consent was required as the study was retrospective and all identifications of the patients were redacted.

Study population

Patients ≥21 years of age prescribed any LLA during at least one visit to the outpatient department (OPD) from 1 January 2012 to 31 July 2016 were enrolled. Exclusion criteria were patients (i) with triglyceride level >500 mg/dL and other secondary cause of hyperlipidemia (biliary obstruction, hypothyroidism diseases or nephrotic syndrome) and (ii) prescribed statin of unclear intensity or non-daily statin regimes, *eg* every other day or twice a week.

ASCVD patients were identified using the following criteria: (i) having an International Statistical Classification of Diseases and Related Health Problems 10th Revision Thai Modification (ICD-10 TM) (MOPH, 2017) code (G450-G453, G458-G468, I200-I201, I208-I214, I219-I221, I228-I236, I238,I240, I248-I256, I258-I259, I630-I636, I638-I639, I64, I650-I653, I658-I664, I668-I701, I7020-I7022, I7029, I703-I725, I728-I729, I740-I745, I748-I749, I770, I773, I775, I779, I790, I792, T822-T825, T827-T829, and Z951-Z955) and prescribed an antiplatelet agent (aspirin or clopidogrel), or (ii) prescribed a specific drug for ASCVD therapy (abciximab, aspirin/dipyridamole, cilostazol, eptifibatide, ticagrelor, ticlopidine, or trimetazidine) (Amsterdam *et al*, 2014; Fihn *et al*, 2014; Kernan *et al*, 2014; Levine *et al*, 2016; Phrommintikul *et al*, 2017).

Diabetes patients 40-75 years of age were identified using the following criteria: (i) having an ICD-10 TM code (E100-E149) and hemoglobin A1C (Hb A1C) ≥6.5% or fasting blood sugar (FBS) ≥126 mg/dL (Armstrong, 2017) or (ii) prescribed a hypoglycemic agent. Patients with LDL-C level ≥190 mg/dL were identified by laboratory tests during a hospital visit within the study period.

Prescribed statins are categorized as of low-, moderate- or high-intensity according to the 2013 ACC/AHA Guideline (Stone *et al*, 2014). Combination prescription is defined that of statin together with a non-statin LLA (non-statins). LLAs prescriptions from 1 January 2012 to 30 November 2013 (pre-Guideline period) and from 1 December 2013 to 31 July 2016 (post-Guideline period) were examined.

Statistical analysis

Baseline characteristics of patients are presented as percentage or mean ± SD. Trend of statins and non-statins use were determined from the proportion of patients receiving LLAs in each month. ITS data were subjected to segmented regression and autoregressive integrated moving average (ARIMA) analyses to assess trends and levels of statins and non-statins prescribed post-Guideline implementation. Autocorrelation was determined using Durbin-Watson statistics. Calculations were carried out using a Statistical Package for the Social Sciences (SPSS) program version 21 (SPSS Inc, Chicago, IL).

RESULTS

A total of 1,597,346 prescriptions for LLAs issued (92.11%, 7.20% and 0.69% for statins non-statins and combination of the two types, respectively) to 133,212 patients at three tertiary-care hospitals (52.60%, 23.59% and 23.81%) of the patients from the hospital-I, -II and -III, respectively) in Thailand from 1 January 2012 to 31 July 2016 were analyzed. Mean age of the patients was 64 years old, majority with ASCVD (26.21%), followed by diabetes (19.00%), and most prescriptions (91.95%) were for statin monotherapy (Table 1).

Following adoption of the 2013 ACC/AHA guideline, analysis using an ITS model of trends in types of LLAs and intensity category of statins prescribed revealed the following: (i) statins were still the most prescribed LLAs with increase in trend and a concomitant decrease of non-statins and combination therapy (Fig 1A); there is a significant increase in prescription trend of high-intensity statins (3.88% of different trend) compared to medium- and low-intensity categories (Fig 1B); (iii) among ASCVD with and without diabetes, there are a significant increase in high-intensity statin prescriptions (Figs 1C and 1D) and among those 21-75 years of age (Fig 1E) but to a lesser degree among >75 years of age (Fig 1F); (iv) among diabetes without ASCVD patients 40-75 years of age and elevated LDL-C <190 mg/dL (Fig 1G) and patients with primary LDL-C ≥190 mg/dL (Fig 1H), there are

Table 1

Characteristics of study population in three tertiary-care hospitals in Thailand

(1 January 2012 to 31 July 2016)

Characteristic	Number
Patient treated with LLAs	133,212
Prescription	1,597,346
Age in years, mean ± SD	64 ± 13
Type of LLAs, percent	
Statin monotherapy	91.95
Non-statin monotherapy	4.95
Statin combination therapy	3.10
Patient's health status, percent	
ASCVD	26.21
Diabetes with LDL-C <190 mg/dL without ASCVD	19.00
Primary LDL-C ≥190 mg/dL without ASCVD	11.25
Others	43.54

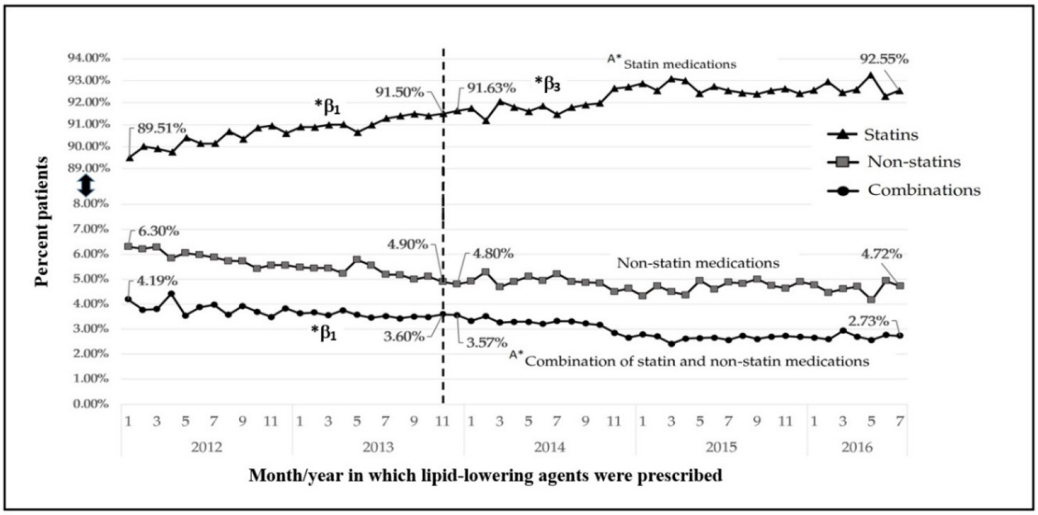
ASCVD: atherosclerotic cardiovascular diseases; LDL-C: low density lipoprotein-cholesterol; LLAs: lipid lowering agents; mg/dL: milligrams per deciliter; SD: standard deviation

increases in prescribed high-intensity statins (v) among statin-naïve ASCVD patients, there is a significant increase in prescribed high-intensity statins but to a lower extent among statin-non-naïve patients (Fig 1I); and (vi) among diabetes patients 40-75 years of age with primary LDL-C <190 mg/dL without ASCVD, there is no statistically difference in use of statins of any intensity between among statin-naïve and -non-naïve patients (Fig 1J). The numerical data are presented in Table 2.

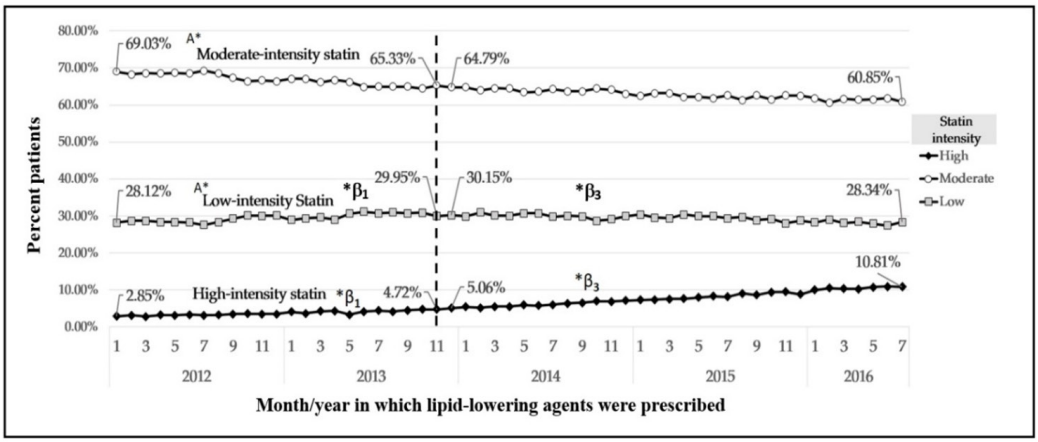
DISCUSSION

The study shows following the adoption in Thailand of the 2013 ACC/AHA guideline for LLAs in ASCVD patients, especially among those 21-75 years of age, prescription of high-intensity stains significantly increased. Although the statistically significant differences are observed only in trend changes, they do not detract from the study's reliability. However, an empirical study of Pinlac (2016) using real-world data does not show

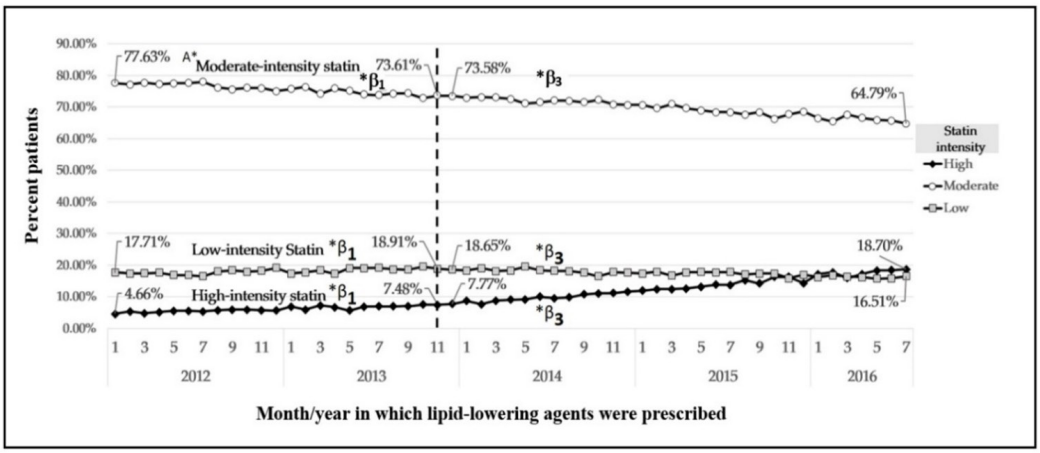
A


Percent patients
94.00%
93.00%
92.00%
91.00%
90.00%
89.00%
8.00%
7.00%
6.00%
5.00%
4.00%
3.00%
2.00%
1.00%
0.00%
89.51%
91.50%
91.63%
*β1
*β3
A* Statin medications
92.55%
Statins
Non-statins
Combinations
6.30%
4.90%
4.80%
Non-statin medications
4.72%
4.19%
*β1
3.60%
3.57%
2.73%
A* Combination of statin and non-statin medications
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

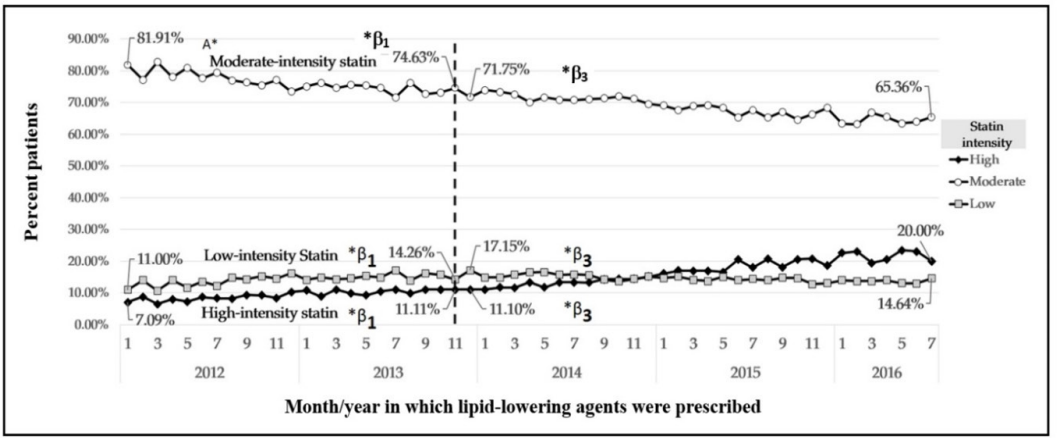
B


Percent patients
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
69.03%
A*
Moderate-intensity statin
65.33%
64.79%
60.85%
Statin intensity
High
Moderate
Low
28.12%
A*
Low-intensity Statin
*β1
29.95%
30.15%
*β3
28.34%
10.81%
2.85%
High-intensity statin
*β1
4.72%
5.06%
*β3
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

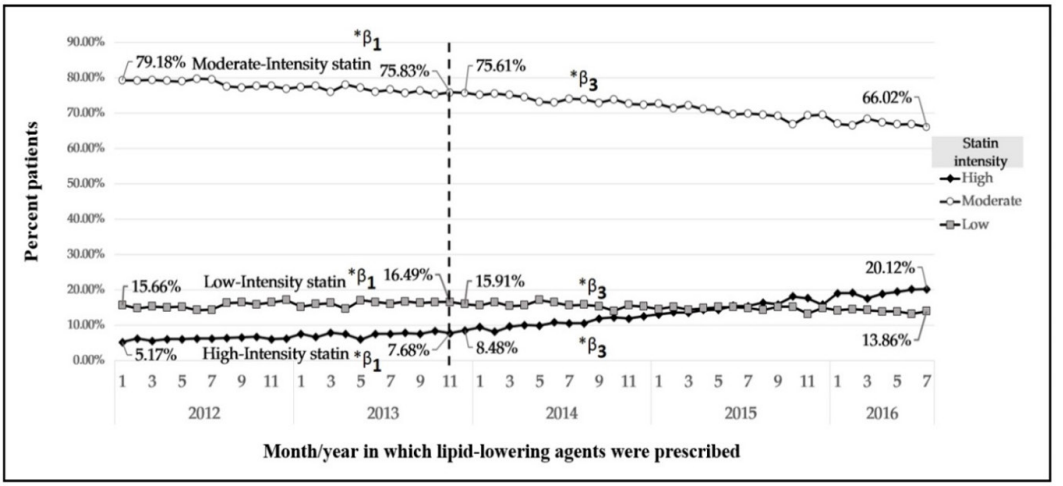
C


Percent patients
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
77.63%
A*
Moderate-intensity statin
73.61%
*β1
73.58%
*β3
64.79%
Statin intensity
High
Moderate
Low
17.71%
Low-intensity Statin
*β1
18.91%
18.65%
*β3
18.70%
4.66%
High-intensity statin
*β1
7.48%
7.77%
*β3
16.51%
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

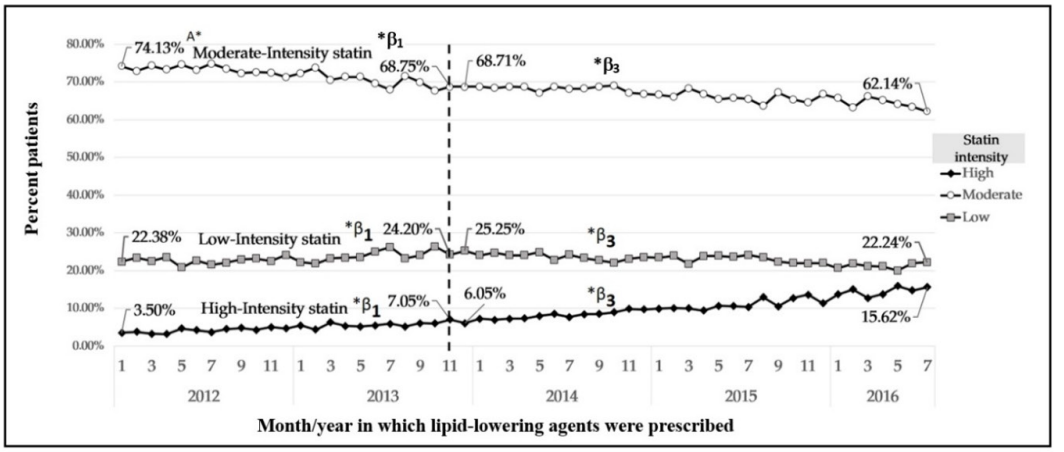
D


Percent patients
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
81.91%
A*
Moderate-intensity statin
*β1
74.63%
71.75%
*β3
65.36%
11.00%
Low-intensity Statin
*β1
14.26%
17.15%
*β3
20.00%
7.09%
High-intensity statin
*β1
11.11%
11.10%
*β3
14.64%
Statin intensity
High
Moderate
Low
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

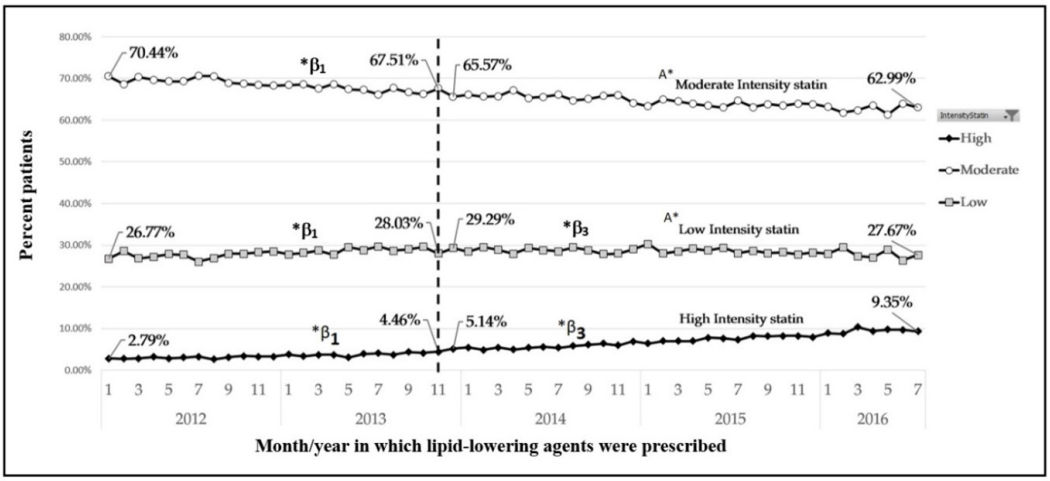
E


Percent patients
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
*β1
79.18%
Moderate-Intensity statin
75.83%
75.61%
*β3
66.02%
15.66%
Low-Intensity statin
*β1
16.49%
15.91%
*β3
20.12%
5.17%
High-Intensity statin
*β1
7.68%
8.48%
*β3
13.86%
Statin intensity
High
Moderate
Low
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

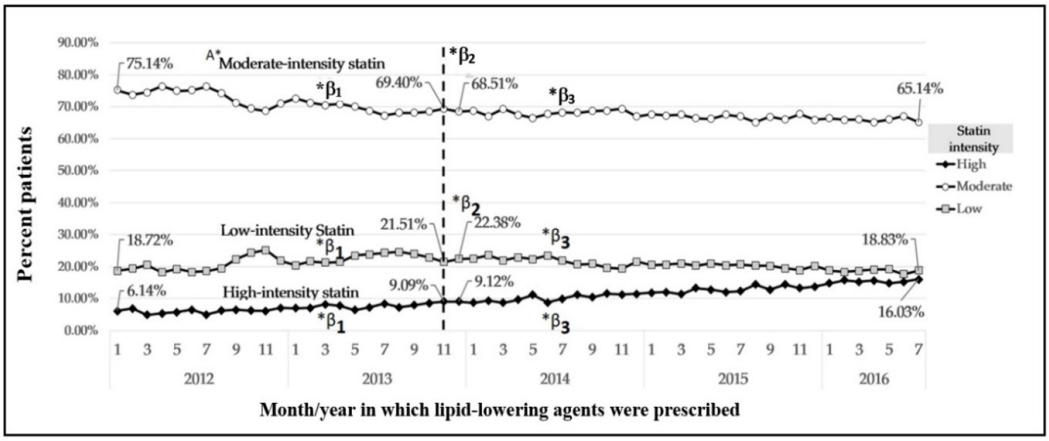
F


Percent patients
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
74.13%
A*
Moderate-Intensity statin
*β1
68.75%
68.71%
*β3
62.14%
22.38%
Low-Intensity statin
*β1
24.20%
25.25%
*β3
22.24%
3.50%
High-Intensity statin
*β1
7.05%
6.05%
*β3
15.62%
Statin intensity
High
Moderate
Low
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

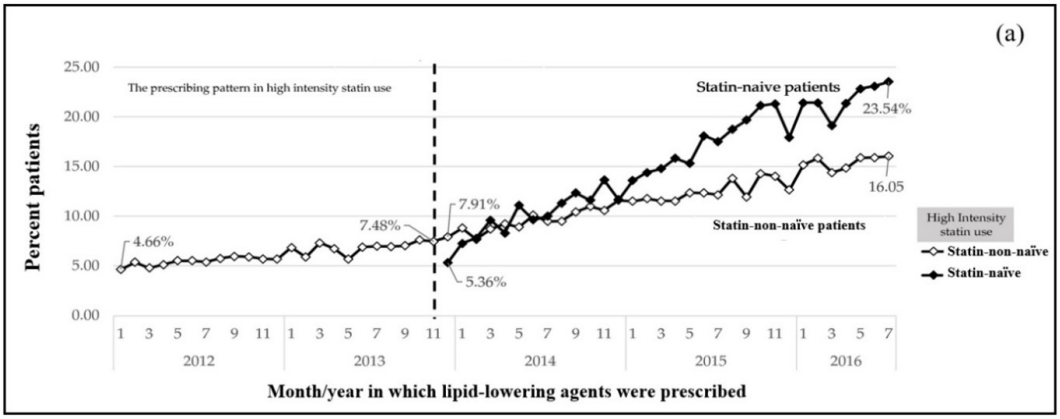
G

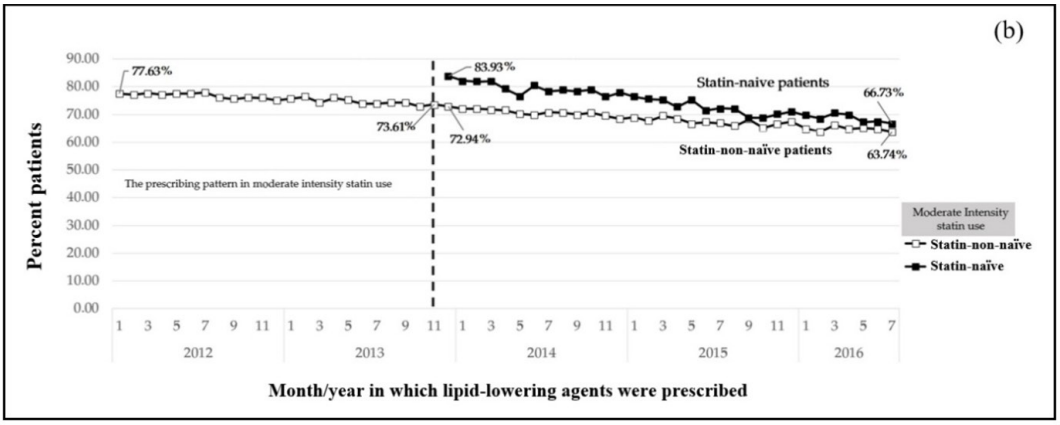

Percent patients
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
70.44%
*β1
67.51%
65.57%
A* Moderate Intensity statin
62.99%
26.77%
*β1
28.03%
29.29%
*β3
A* Low Intensity statin
27.67%
2.79%
*β1
4.46%
5.14%
*β3
High Intensity statin
9.35%
IntensityStatin
High
Moderate
Low
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

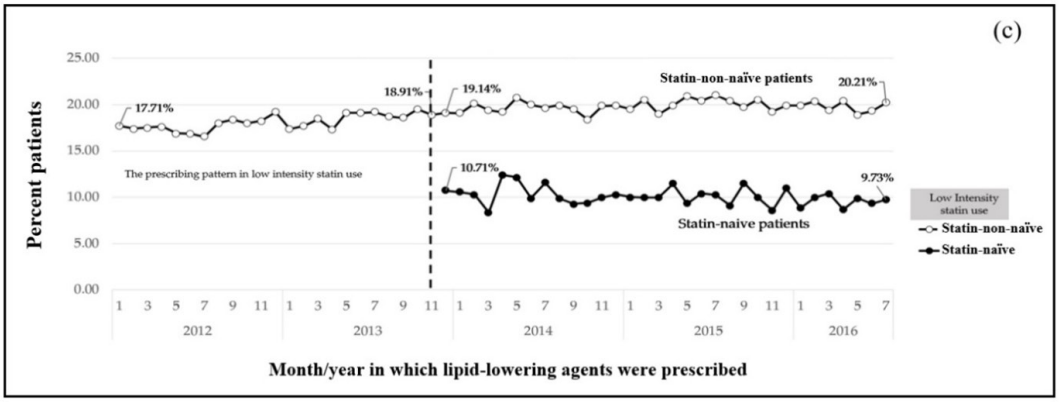
H


Percent patients
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
75.14%
A* Moderate-intensity statin
*β1
69.40%
*β2
68.51%
*β3
65.14%
18.72%
Low-intensity Statin
*β1
21.51%
*β2
22.38%
*β3
18.83%
6.14%
High-intensity statin
*β1
9.09%
9.12%
*β3
16.03%
Statin intensity
High
Moderate
Low
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

I


(a)
Percent patients
25.00
20.00
15.00
10.00
5.00
0.00
The prescribing pattern in high intensity statin use
Statin-naive patients
23.54%
16.05
7.91%
7.48%
4.66%
5.36%
Statin-non-naïve patients
High Intensity statin use
Statin-non-naïve
Statin-naïve
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed


(b)
Percent patients
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
77.63%
83.93%
Statin-naive patients
66.73%
73.61%
72.94%
Statin-non-naïve patients
63.74%
The prescribing pattern in moderate intensity statin use
Moderate Intensity statin use
Statin-non-naïve
Statin-naïve
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed


(c)
Percent patients
25.00
20.00
15.00
10.00
5.00
0.00
17.71%
18.91%
19.14%
Statin-non-naïve patients
20.21%
The prescribing pattern in low intensity statin use
10.71%
9.73%
Statin-naive patients
Low Intensity statin use
Statin-non-naïve
Statin-naïve
1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7 9 11 1 3 5 7
2012
2013
2014
2015
2016
Month/year in which lipid-lowering agents were prescribed

J

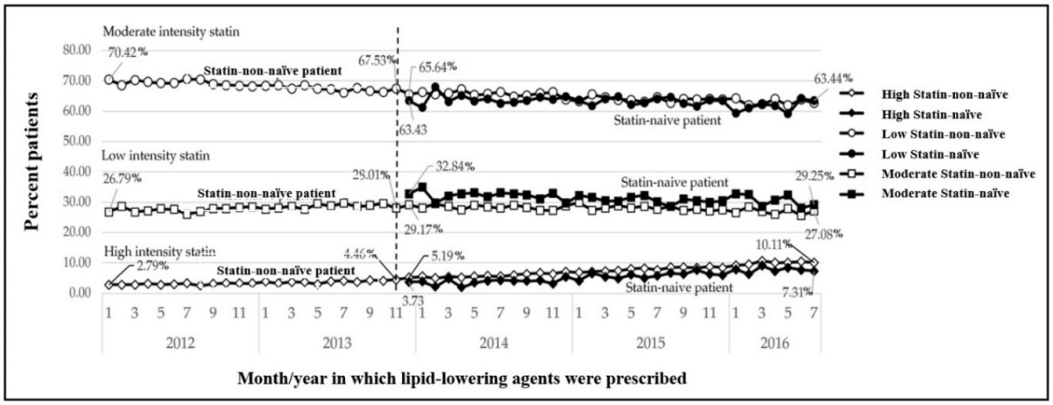


Fig 1 - Trends in prescriptions of patients for (A) lipid-lowering agents (LLAs) and (B) statins; for statins among ASCVD patients (C) without diabetes, (D) with diabetes, (E) 21-75 years of age, (F) >75 years of age; for statins among diabetes patients (G) 40-75 years of age, with primary LDL-C <190 mg/dL and without ASCVD; for statins among patients (H) with primary LDL-C ≥190 mg/dL and without ASCVD; for statins among (I) statin-naïve and statin-non-naïve ASCVD patients; for statins among (J) statin-naïve and -non-naïve diabetes patients 40-75 years of age, with primary LDL-C <190 mg/dL and without ASCVD.

The data were obtained from 1,597,346 prescriptions of LLAs issued to 133,212 patients at three tertiary-care hospitals in Thailand from 1 January 2012 to 31 July 2016. Dash vertical line indicates boundary between pre- and post-adoption in Thailand of the 2013 American College of Cardiology/American Heart Association Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

Statin-naïve: patient did not receive statin prior to being prescribed LLAs; statin-non-naïve: patient received statin(s) prior to being prescribed LLAs.

Fig 1I(a): high- intensity statin: Fig 1I(b): moderate- intensity statin; Fig 1I(c): low-intensity statin

*: significant difference in autocorrelation; *β1, significant difference in baseline trend; *β2, significant difference in intercept value; *β3, significant difference in trend change (slope) (p-value <0.05)

Table 2

Interrupted time series analysis of prescriptions for lipid-lowering agents from three tertiary-care hospitals in Thailand (1 January 2012 to 31 July 2016)

Category of patients prescribed lipid-lowering agents[#]		ARIMA model			
		Baseline level (β0)	Baseline trend (β1)	Intercept (β2)	Trend change (slope) (β3)
A	Statins	19,727.44*	49.78*	-177.73	-36.65*
	Non-stains	1377.98*	-10.27*	-25.81	8.01*
	Combinations	879.76*	-4.12*	-27.16	-2.02
B	High-intensity statin	543.25*	18.58*	-3.21	23.90*
	Moderate-intensity statin	14,161.13*	-13.30	-79.69	-7.59
	Low-intensity statin	5,661.04*	42.05*	-107.38	-57.05*
C	High-intensity statin	200.05*	7.01*	-12.67	11.87*
	Moderate-intensity statin	3,363.55*	10.48*	46.05	-18.19*
	Low-intensity statin	725.90*	9.09*	-3.46	-12.07*
D	High-intensity statin	56.04*	2.41*	-4.96	2.08*
	Moderate-intensity statin	647.69*	3.34*	33.89*	-5.38*
	Low-intensity statin	97.00*	2.69*	5.89	-3.32*
E	High-intensity statin	157.83*	4.72*	-9.29	9.46*
	Moderate-intensity statin	2,366.69*	8.19*	15.11	-14.91*
	Low-intensity statin	441.21*	5.15*	-12.75	-7.01*

Table 2 (cont)

Category of patients prescribed lipid-lowering agents[#]		ARIMA model			
		Baseline level (β0)	Baseline trend (β1)	Intercept (β2)	Trend change (slope) (β3)
F	High-intensity statin	42.19*	2.30*	-3.49	2.40*
	Moderate-intensity statin	997.60*	2.23*	32.19	-3.28*
	Low-intensity statin	285.32*	3.90*	9.73	-5.05*
G	High-intensity statin	112.87*	3.15*	13.05	4.06*
	Moderate-intensity statin	3,095.64*	-6.32*	-22.95	0.51
	Low-intensity statin	1179.16*	5.04*	-8.58	-7.01*
H	High-intensity statin	85.85*	4.88*	-12.98	2.32*
	Moderate-intensity statin	1,330.81*	13.04*	-86.29*	-6.83*
	Low-intensity statin	320.52	10.99*	-55.56*	-11.93*

[#]From Fig 1; *p-value <0.05, comparing among the three statin intensities using interrupted time series with autoregressive integrated moving average (ARIMA) model

a change in level, but it must be taken into account that when applying interventions in treatment guideline a lag time is to be expected before the effect of implementation can be discerned. In addition, a significant increase in numbers of prescribed high-intensity statins among the naïve ASCVD patients was observed, in agreement with a previous report (Valentino, 2016).

Following the 2013 ACC/AHA guideline release, although the trend in prescribing high-intensity statins in patients with ASCVD >75 years of age and in diabetes patients without clinical ASCVD was low, it still in accordance with the recommended 2013 Guideline. In ASCVD patients >75 years of age, the 2013 Guideline strongly recommends use moderate-intensity in place of the high-intensity statins as there is no clear evidence of an additional reduction in ASCVD events from high-intensity statin therapy in this population. Among these elderly populations, the potential benefits in ASCVD risk-reduction by high-intensity statin therapy has to be balanced by safety concerns, such as adverse drug events and drug-drug interactions.

The 2013 ACC/AHA guideline recommends moderate-intensity statin therapy in diabetic patients 40-75 years of age, although there is an opinion that the high-intensity statin therapy for this group of patients who have an estimated 7.5% 10-year risk of ASCVD (Stone *et al*, 2014)

Prescription of non-statins and combinations of statins and non-statins were infrequent during the period of this study and gradually decreased after adoption of 2013 ACC/AHA guideline. These observations were consistent with report of a limitation in reduction of ASCVD risk relative to potential adverse effects from routine prevention of ASCVD (Stone *et al*, 2014)

The study suffers from two limitation. Firstly, missing data were common and an ITS analysis cannot be undertaken when ≥10% of data go astray (Velicer and Colby, 2005). For ICD-10 TM and laboratory data used in the study, missing data were found in <15% of patients' records and the validity of the available data were strengthen using an amalgamation of ICD-10-TM code stored in electronic databases, prescription records and/or the laboratory data to categorize the patients into target groups. Incomplete data resulted in <10% of patients being unclassified. And secondly, prescribing trends of LLAs after July 2016 were not examined to avoid confounding factors from the effects of the 2016 American College of Cardiology (ACC) statement (Writing Committee *et al*, 2016) and the 2016 Royal College Physicians of Thailand (RCPT) Clinical Practice Guideline on Pharmacologic Therapy of Dyslipidemia for Atherosclerotic Cardiovascular Disease Prevention (Thai Atherosclerosis Society, 2017). Effects of these guidelines on prescribing

patterns of intensive statins and combinations of statins and non-statins warrant further studies.

In summary, the study finds adoption of the 2013 ACC/AHA guideline promoted appropriate changes in prescriptions of lipid-lowering medications, especially the statins. A significant increase in prescribed high-intensity statins concomitant with decrease in non-statins prescriptions, and transiting of low- and moderate-intensity to high-intensity statins were observed. The significant rise in trends of prescribing high-intensity statins after adoption of the 2013 ACC/AHA guideline is indicative of a positive impact on prescriber good practice in tertiary-care hospitals of Thailand.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

Amsterdam EA, Wenger NK, Brindis RG, *et al*. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 130: e344-426.

Armstrong C. ADA updates standards of medical care for patients with diabetes mellitus. *Am Fam Physician* 2017; 95: 40-3.

Fihn SD, Blankenship JC, Alexander KP, *et al*. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2014; 130: 1749-67.

Grundy SM, Cleeman JI, Merz CN, *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004; 44: 720-32.

Kernan WN, Ovbiagele B, Black HR, *et al*. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45: 2160-236.

La-ongsuwan S, Soraphong TC, Bunrukchai K, Jaemsuk K. Goal achievement of low-density lipoprotein cholesterol levels in patients with ischemic stroke and hyperlipidemia at Prasat Neurological Institute. *Thai Pharm*

Health Sci J 2012; 7: 155-61.

Levine GN, Bates ER, Blankenship JC, *et al*. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *J Am Coll Cardiol* 2016; 67: 1235-50.

Ministry of Public Health (MOPH). International Statistical Classification of Disease and Related Health Problems, Tenth Revision Thai Modification, 2017 [cited 2018 Aug 10]. Available from: URL: http://www.phoubon.in.th/download/icd10tmSim.pdf [in Thai]

Phrommintikul A, Krittayaphong R, Wongcharoen W, *et al*. Management of atherosclerosis risk factors for patients at high cardiovascular risk in real-world practice: a multicentre study. *Singapore Med J* 2017; 58: 535-42.

Pinlac PAV, Silawan T, Tempongko SB, *et al*. Interrupted time series analysis using segmented regression of premature mortality from noncommunicable disease among Filipinos. *Southeast Asian J Trop Med Public Health* 2016; 47: 810-21.

Stone NJ, Robinson JG, Lichtenstein AH, *et al*. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129 (25 Suppl 2): S1-45.

Thai Atherosclerosis Society. 2016 RCPT clinical practice guideline on pharmacotherapy of dyslipidemia for atherosclerotic cardiovascular disease prevention, 2017 [cited 2017 Jun 11]. Available from: URL: http://www.thaiheart.org/images/column_1487762586/2016%20RCPT%20Dyslipidemia%20Clinical%20Practice%20Guideline.pdf

Tungsubutra W, Phongtuntakul B. Achievement of LDL-cholesterol goal with statins after an st segment elevation myocardial infarction. *J Med Assoc Thai* 2015; 98: 129-36.

Valentino M, Al Danaf J, Panakos A, Ragupathi L, Duffy D, Whellan D. Impact of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines on the prescription of high-intensity statins in patients hospitalized for acute coronary syndrome or stroke. *Am Heart J* 2016; 181: 130-6.

Velicer WF, Colby SM. A comparison of missing-data procedures for ARIMA time series analysis. *Educ Psychol Meas* 2005; 65: 596-615.

Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; 27: 299-309.

Writing Committee, Lloyd-Jones DM, Morris PB, *et al*. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2016; 68: 92-125.