Front. Med. 2019, 13(6): 713–722
https://doi.org/10.1007/s11684-018-0661-9

RESEARCH ARTICLE

Long-term effects of various types of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on changes in glomerular filtration rate in Korea

Seo Yeon Baik[1,*], Hyunah Kim[2,*], So Jung Yang[1], Tong Min Kim[1], Seung-Hwan Lee[3], Jae Hyoung Cho[3], Hyunyong Lee[4], Hyeon Woo Yim[5], Kun-Ho Yoon[1,3], Hun-Sung Kim (✉)[1,3]

[1]*Department of Medical Informatics, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea;* [2]*College of Pharmacy, Sookmyung Women's University, Seoul 04310, Republic of Korea;* [3]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea;* [4]*Clinical Research Coordinating Center, Catholic Medical Center, The Catholic University of Korea, Seoul 06591, Republic of Korea;* [5]*Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea*

Abstract **Few long-term follow-up studies have compared the changes in renal function according to the type of statin used in Korea. We compared the long-term effects of statin intensity and type on the changes in the glomerular filtration rate (GFR). We extracted data of patients who took statin for the first time. We analyzed whether or not different statins affect the changes in GFR at 3 months after baseline and 4 years after. We included 3678 patients and analyzed the changes in GFR. The GFR decreased by 3.2% ± 0.4% on average 4 years after the first statin prescription, indicating statistically significant deterioration (from 83.5 ± 0.4 mL/min/1.73 m^2 to 79.9 ± 0.4 mL/min/1.73 m^2, $P < 0.001$). When comparing the GFR among different statins, significant differences were observed between atorvastatin and fluvastatin (−5.3% ± 0.7% vs. 1.2% ± 2.2%, $P < 0.05$) and between atorvastatin and simvastatin (−5.3% ± 0.7% vs. −0.7% ± 0.8%, $P < 0.05$). In pitavastatin (odds ratio [OR]= 0.64, 95% confidence interval [CI]= 0.46–0.87, $P < 0.005$) and simvastatin (OR = 0.69, 95% CI = 0.53–0.91, $P < 0.008$), the GFR rate that decreased by < 60 mL/min/1.73 m^2 was significantly lower than that of atorvastatin. Regarding long-term statin intake, GFR changed with the type of statin. This work is the first in Korea to compare each statin in terms of changes in the GFR after the statin prescription.**

Keywords statin; glomerular filtration rate; HMG-CoA reductase inhibitor; chronic kidney disease

Introduction

A 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (HMG-CoA reductase inhibitor) or statin is the first-line drug for a person with hyperlipidemia because this substance continuously inhibits the biosynthesis of cholesterol [1,2]. The 2011 European Society of Cardiology and the European Atherosclerosis Society guidelines [3] referred to cases of hyperlipidemia, which is common in patients with chronic kidney disease (CKD) [4–6]. The levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) commonly increase in many patients with nephrotic syndrome [7]. Therefore, patients with CKD should be prescribed aggressive statins to decrease their LDL-C level [8].

Many studies reported that statins enhance the glomerular filtration rate (GFR) and prevent reduction in renal function [9–12]. By contrast, some studies reported that statins do not affect and cannot reduce renal function [13,14]. Most studies on statins and renal function have a short study period. Different in other countries, only a few long-term follow-up studies comparing changes in renal function according to the type of statin used have been performed in Korea. One 6.5-year study reported that the use of statins is associated with a high risk of loss of kidney function [15]. Some studies insisted that a high-dose statin negatively affects renal function compared with a low-dose statin [16,17], and no examples of comparative studies are available for each statin type or dose.

The main function of a statin is to decrease the LDL-C

Received October 2, 2017; accepted June 15, 2018
Correspondence: Hun-Sung Kim, 01cadiz@hanmail.net

*Seo Yeon Baik and Hyunah Kim are co-first authors that contributed equally to this manuscript.

level and reduce the risk of cardiovascular disease (CVD). According to the 2013 American College of Cardiology (ACC)/American Heart Association (AHC) guideline [18], statins are divided into three groups based on intensity. The kind of statin prescribed is of minor importance as long as it belongs to the same intensity group as specified in the 2013 ACC/AHC guideline [18]. However, if differences are observed in the GFR between statins belonging to the same intensity group, then the statin should be selected carefully. In Korea, the safety of statins in terms of renal function must be further studied. Therefore, our study aimed to observe changes in GFR 4 years after statin was prescribed according to data from electronic medical records (EMR). In addition, we compared the changes in the GFR according to the statin intensity and type among statins in the same intensity group according to the 2013 ACC/AHC guideline [18].

Materials and methods

Study population

We included patients who visited the outpatient clinic of Seoul St. Mary's Hospital in Korea from January 2009 to December 2011 and took a statin for the first time (baseline). Three months after baseline and an average of 4 years after, we performed a retrospective cohort analysis. Over the 4-year observation the exclusion were as follows: the dose of the patient's statin was changed, the patient's statin was changed to a different type of statin, the patient was transferred to another hospital or follow-up with the patient was impossible, and the patient was excluded from the study.

Study design

The data of the following statins prescribed at Seoul St. Mary's Hospital were extracted: atorvastatin (10, 20, and 40 mg), fluvastatin (40 and 80 mg), pitavastatin (2 mg), pravastatin (10, 20, and 40 mg), rosuvastatin (10 and 20 mg), simvastatin (20 and 40 mg) and simvastatin + ezetimibe (10 mg). Patients who took an angiotensin II receptor blocker plus a statin were excluded from this study. According to the ACC/AHA guideline [18], statins are divided into three groups according to the LDL-C reduction rate: high intensity, moderate intensity, or low intensity. However, moderate-intensity statins are divided into two groups in Korea, namely, moderate high and moderate low [19]. Therefore, in the present study, we divided statins into the following four groups: high, moderate high, moderate low, and low intensity.

Baseline demographic characteristics, such as age, sex, and body mass index (BMI), were extracted from those who took statin for the first time. The fasting blood glucose, hemoglobin A1c, blood urea nitrogen (BUN), creatinine, TC, TG, high-density lipoprotein cholesterol (HDL-C), LDL-C, aspartate aminotransferase, alanine aminotransaminase, alkaline phosphatase, sodium, potassium, and creatine phosphokinase levels were extracted for each statin at baseline and after an average of 3 months and 4 years. To measure GFR, this study used the modification of diet in renal disease (MDRD)-GFR standard formula. The MDRD-GFR was calculated using the following standard formulas [20].

MDRD-GFR (mL/min/1.73m^2) =

$186 \times \text{Pcr (mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female),

MDRD-GFR reduction rate (%) = mean percent change (%) = $100 \times (\text{MDRD-GFR}_{\text{Baseline}} - \text{MDRD-GFR}_{4\ \text{years later}})/\text{MDRD-GFR}_{\text{Baseline}}$.

Depending on the degree of renal impairment and renal function, we classified the degree of renal function as follows [21]: normal GFR ($\geqslant$ 90 mL/min), mild decreased GFR (60–89 mL/min), moderately decreased GFR (30–59 mL/min), severely decreased GFR (15–29 mL/min), and renal failure GFR ($<$ 15 mL/min). Those with a GFR $<$ 30 mL/min were excluded. Our study data were divided and analyzed by GFRs $<$ 60 mL/min, 60–89 mL/min, and $\geqslant$ 90 mL/min.

Protection of privacy

All data extracted from the EMR was encrypted, and to identify a patient was not possible because identifying data, such as the patients' phone number and name, were removed. Therefore, our study did not access any private patient information and could not cause any physical risk to the patients. Given that the data were anonymous, the need for informed consent was not required. This study was approved by the institutional review board of the Catholic University of Korea.

Statistical analysis

Descriptive statistics are presented as a mean and standard deviation or a percentage of participants. To determine whether a different statin and statin intensity affected the MDRD-GFR rate change at 3 months and 4 years, respectively, analysis of variance tests were conducted, followed by post-hoc analysis by using the Bonferroni correction. The association between a statin and a poor MDRD-GFR outcome ($<$ 60 mL/min/1.73 m^2) was analyzed using logistic regression with confounders. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), and a two-sided $P < 0.05$ was considered statistically significant.

Results

The data of 13 268 patients prescribed a statin at a hospital for the first time from January 2009 to December 2011

were extracted (Fig. 1). Among these patients, those whose baseline MDRD-GFR values (6484 patients) or MDRD-GFR values at 3 months and 4 years (2256 patients) were not available were excluded from the study. Additionally, 792 patients who changed to another type of statin over the 4-year follow-up period and 58 patients whose MDRD-GFR values were < 30 mL/min/1.73 m^2 were excluded from the study. Ultimately, 3678 patients were observed and analyzed in this study.

Baseline characteristics

Regarding the baseline characteristics of patients prescribed a statin for the first time (Table 1), 26.3% were prescribed atorvastatin (966/3678 patients), 21.7% rosuvastatin (797/3678), 19.4% simvastatin (713/3678), and 13.6% pitavastatin (500/3678). Patients' average age was 65.7 ± 11.3 years, and 2086 patients were aged $\geqslant 65$ years old (56.7%). The average BUN level was 16.0 ± 5.3 mg/dL, and the average creatinine level was 0.9 ± 0.2 mg/dL. The average MDRD-GFR level was 83.5 ± 22.2 mL/min/1.73 m^2, with 33.8% of patients (1245/3678 patients) with an MDRD-GFR level $\geqslant 90$ mL/min/1.73 m^2, 54.5% (2005/3678) with an MDRD-GFR level of 60–90 mL/min/1.73 m^2, and 11.6% (428/3678) with an MDRD-GFR level 30–60 mL/min/1.73 m^2.

Changes in the MDR-GFR according to the statin intensity

When comparing the changes in the MDRD-GFR after classifying statins based on their LDL-C-lowering potencies (Table 2), the MDRD-GFR increased by $3.2\% \pm 0.2\%$ on average 3 months after the first statin prescription, indicating statistically significant improvement (from 83.5 ± 0.4 mL/min/1.73 m^2 to 85.4 ± 0.4 mL/min/1.73 m^2, $P < 0.001$). However, after 4 years of follow-up after the first statin prescription, the MDRD-GFR decreased by $3.2\% \pm 0.4\%$, indicating statistically significant deterioration (from 83.5 ± 0.4 mL/min/1.73 m^2 to 79.9 ± 0.4 mL/min/1.73 m^2, $P < 0.001$). Regarding the difference between baseline MDRD-GFR values and those 3 months after, significant differences were observed between the moderate to high intensity statin groups (from 82.3 ± 0.7 mL/min/1.73 m^2 to 85.1 ± 0.9 mL/min/1.73 m^2, $P < 0.001$) and moderate to low-intensity statin groups (from 83.7 ± 0.5 mL/min/1.73 m^2 to 85.6 ± 0.6 mL/min/1.73 m^2, $P < 0.001$). A comparison of baseline MDRD-GFR values and those 4 years after showed that the MDRD-GFR values decreased significantly in all groups. However, no significant differences were observed among the four groups in terms of changes in MDRD-GFR values after 3 months ($P < 0.204$) and 4 years ($P < 0.441$).

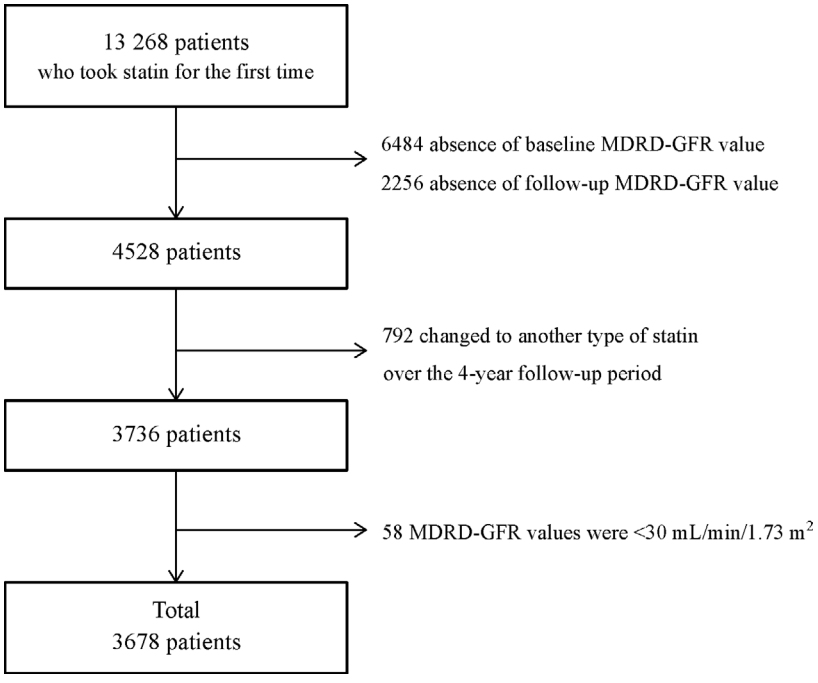

Fig. 1 Study flow diagram. GFR, glomerular filtration rate. MDRD, modification of diet in renal disease.

Table 1 Baseline characteristics of patients prescribed a statin for the first time

	Atorvastatin			Fluvastatin		Pitavastatin	Pravastatin			Rosuvastatin		Simvastatin		Simvastatin + Ezetimibe	
	10 mg	20 mg	40 mg	40 mg	80 mg	2 mg	10 mg	20 mg	40 mg	10 mg	20 mg	20 mg	40 mg	10 mg	20 mg
n	767	166	33	42	78	500	85	127	129	741	56	680	33	145	96
Sex (male), *n* (%)	376 (49.0)	85 (51.2)	19 (57.6)	25 (59.5)	32 (41.0)	212 (42.4)	34 (40.0)	44 (34.7)	57 (44.2)	350 (47.2)	26 (46.4)	288 (42.4)	20 (60.6)	65 (44.8)	37 (38.5)
Age, year	66±11	65±12	70±12	59±12	67±8	66±11	68±10	64±10	65±10	65±12	62±12	67±12	68±8	65±10	62±12
Age (>65 years), *n* (%)	441 (57.5)	88 (53.0)	22 (66.7)	17 (40.5)	48 (61.5)	253 (50.6)	48 (56.5)	56 (44.1)	68 (52.7)	375 (50.6)	22 (39.3)	404 (59.4)	22 (66.7)	72 (49.7)	36 (37.5)
Diabetes mellitus, *n* (%)	361 (47.1)	65 (39.2)	15 (45.5)	7 (16.7)	34 (43.6)	209 (41.8)	28 (32.9)	42 (33.1)	37 (28.7)	353 (47.6)	24 (42.9)	300 (44.1)	15 (45.5)	68 (46.9)	35 (36.5)
Fasting blood glucose, mg/dL	135±65	137±60	155±90	120±35	118±32	126±44	122±41	121±39	125±42	137±72	150±98	124±39	124±28	135±50	137±81
HbAlc, %	7.2±1.6	7.1±1.6	7.2±1.5	6.6±0.9	6.8±0.9	6.9±1.4	6.78±1.2	7.1±1.7	6.7±1.2	7.4±1.8	7.7±2.4	6.9±1.2	6.7±0.8	7.1±1.4	7.0±2.0
BUN, mg/dL	16±5	17±7	17.1±4.0	16±6	17±4	16±5	16±6	15±5	16±5	16±5	16±7	16±5	15±5	16±6	16±5
Creatinine, mg/dL	0.9±0.3	0.9±0.3	0.9±0.2	1.0±0.3	0.9±0.3	0.9±0.2	0.9±0.3	0.8±0.2	0.9±0.3	0.9±0.2	0.9±0.3	0.9±0.2	0.9±0.2	0.9±0.3	0.8±0.2
MDRD-GFR, mL/min/1.73m^2	83.4±22.2	82.2±21.8	81.3±20.6	83.6±19.7	77.0±18.0	85.1±21.4	79.1±18.9	86.0±19.5	85.2±19.8	82.4±20.0	85.3±27.6	83.6±26.4	81.7±14.2	85.5±22.8	88.6±19.6
MDRD-GFR category															
⩾90 mL/min/1.73 m^2, *n* (%)	263 (34.3)	58 (34.9)	9 (27.3)	12 (28.6)	17 (21.8)	183 (36.6)	22 (25.9)	50 (39.4)	55 (42.6)	237 (32.0)	16 (28.6)	208 (30.6)	6 (18.2)	57 (39.3)	52 (54.2)
60–89 mL/min/1.73m^2, *n* (%)	409 (53.3)	82 (49.4)	21 (63.6)	26 (61.9)	48 (61.5)	274 (54.8)	50 (58.8)	66 (52.0)	65 (50.4)	410 (55.3)	34 (60.7)	389 (57.2)	24 (72.7)	70 (48.3)	37 (38.5)
<60 mL/min/1.73 m^2, *n* (%)	95 (12.4)	26 (15.7)	3 (9.1)	4 (9.5)	13 (16.7)	43 (8.6)	13 (15.3)	11 (8.7)	9 (7.0)	94 (12.7)	6 (10.7)	83 (12.2)	3 (9.1)	18 (12.4)	7 (7.3)
Total cholesterol, mg/dL	183±43	198±54	208±82	223±45	178±36	203±47	197±37	215±43	215±47	196±56	228±71	180±43	177±57	195±45	234±51
Triglyceride, mg/dL	154±82	172±116	267±454	192±144	136±71	160±87	167±87	160±78	144±72	169±125	184±97	152±100	181±75	163±98	178±122
HDL-C, mg/dL	50±13	48±11	43±12	44±10	52±13	51±13	50±13	50±16	52±12	52±14	49±13	53±14	51±13	52±15	51±12
LDL-C, mg/dL	110±35	126±47	121±45	140±42	103±32	128±39	127±31	143±34	131±45	125±45	157±62	104±37	108±48	117±36	145±46
AST, IU/L	26±17	25±13	24±11	40±30	23±7	27±14	24±9	26±19	27±15	25±13	28±17	25±11	24±10	27±16	28±21
ALT, IU/L	28±24	29±22	25±15	59±57	25±12	31±27	25±13	28±20	30±25	28±19	30±16	28±21	26±13	29±19	33±26
ALP, IU/L	67±47	64±20	59±18	77±50	60±18	65±26	68±23	63±22	71±22	67±45	65±20	66±24	70±22	64±20	63±20
Sodium, mEq/L	141±3	140±3	140±3	141±2	141±2	141±2	141±3	141±2	141±3	141±3	141±3	141±3	141±2	140±2	141±3
Potassium, mEq/L	4.4±0.4	4.3±0.4	4.2±0.4	4.3±0.5	4.4±0.3	4.3±0.4	4.3±0.4	4.3±0.4	4.3±0.4	4.3±0.4	4.4±0.5	4.4±0.4	4.3±0.4	4.4±0.4	4.3±0.4
CPK, IU/L	111±140	98±71	113±65	101±74	107±65	108±124	99±79	127±180	127±160	104±72	143±167	105±127	100±44	116±98	95±65

Categorical variables are reported as frequencies (%), and continuous variables are reported as mean±SD.
AST, aspartate aminotransferase; ALT, alanine aminotransaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDRD, modification of diet in renal disease.

Table 2 Comparison of changes in the MDRD-GFR rate at 3 months and 4 years after a statin was prescribed

	n	Baseline	3 months later	% (SE)	*P* value	4 years later	% (SE)	*P* value
High intensity statin	89	83.8±2.7	86.3±4.3	2.6±2.2		78.6±3.3	−6.5±2.5*	
Moderate to high intensity statin	940	82.3±0.7	85.1±0.9	3.9±0.4**	0.204	79.5±0.7	−2.6±0.7**	0.441
Moderate to low intensity statin	2154	83.7±0.5	85.6±0.6	3.1±0.3**		79.9±0.5	−3.2±0.5**	
Low intensity statin	254	83.3±1.2	86.6±1.8	2.1±0.8*		80.0±1.4	−3.13±1.3*	

Data are expressed as mean±SE. GFR, glomerular filtration rate; MDRD, modification of diet in renal disease. *P <0.05 versus baseline. **P <0.001 versus baseline.

Changes in the MDR-GFR according to each type of statin

Regarding changes in the MDRD-GFR for each statin (Table 3), the MDRD-GFR was improved statistically significant with all statins, except pravastatin, for the first 3 months. Especially for rosuvastatin and fluvastatin, MDRD-GFR values increased by 4.3% ± 0.5% (from 82.6 ± 0.7 mL/min/1.73 m^2 to 86.0 ± 0.8 mL/min/1.73 m^2, $P < 0.001$) and 4.0% ± 1.2% (from 79.3 ± 1.7 mL/min/1.73 m^2 to 82.3 ± 1.9 mL/min/1.73 m^2, $P < 0.001$), respectively. A comparison of baseline MDRD-GFR values and those after 4 years showed that the MDRD-GFR values decreased significantly for all statins, except fluvastatin and simvastatin. When comparing MDRD-GFR values between each statin, significant differences were observed between atorvastatin and fluvastatin (−5.3% ± 0.7% vs. 1.2% ± 2.2%, $P < 0.05$) and between atorvastatin and simvastatin (−5.3% ± 0.7% vs. −0.7% ± 0.8%, $P < 0.05$). No statistically significant differences were observed between the MDRD-GFR reduction rates of the other pairs of statins.

The results of the logistic regression analysis of the proportion of MDRD-GFR values that decreased < 60 mL/min/1.73 m^2 compared with the differences between changes in MDRD-GFR values between each statin are shown in Table 4. After adjusting for sex and age, the rate of MDRD-GFR values that decreased < 60 mL/min/1.73 m^2 was significantly low only in pitavastatin (odds ratio [OR]= 0.64, 95% confidence interval [CI]= 0.46–0.87, $P < 0.005$) and simvastatin (OR = 0.69, 95% CI = 0.53–0.91, $P < 0.008$) compared with atorvastatin.

Changes in the MDRD-GFR according to each statin within the same intensity group

According to the 2013 ACC/AHC guidelines, we classified statins based on intensity and compared the changes in MDRD-GFR values between each statin (Table 5). In atorvastatin (40 mg), MDRD-GFR values significantly decreased after 4 years in the high-intensity group (from 81.3 ± 3.6 mL/min/1.73 m^2 to 72.1 ± 3.7 mL/min/1.73 m^2, $P < 0.001$), and no significant change was observed in rosuvastatin (20 mg) (from 85.3 ± 3.7 mL/min/1.73 m^2 to 82.4 ± 4.7 mL/min/1.73 m^2, $P = 0.308$). The rate of change in MDRD-GFR values after 4 years was smaller for rosuvastatin (20 mg) than that for atorvastatin (40 mg). However, no statistically significant difference was found between the two statins (−11.4% ± 3.1% vs. −3.53% ± 3.4%, $P = 0.094$). In the moderate to high-intensity groups, no statistically meaningful differences were also noted among atorvastatin (20 mg), rosuvastatin (10 mg), and simvastatin (40 mg) (−3.5% ± 2.0% vs. −2.7% ± 0.8% vs. 3.5% ± 3.2%, respectively; $P = 0.234$). In the moderate to low-intensity groups, for all statins, except fluvastatin (80 mg) and simvastatin (20 mg), the MDRD-GFR values decreased meaningfully after 4 years. When comparing MDRD-GFR values after 4 years between each statin, only a significant difference was observed between atorvastatin (10 mg) and simvastatin (20 mg) (−5.5% ±

Table 3 Comparison of changes in the MDRD-GFR rate at four years after a statin was prescribed

	n	Baseline	3 months later	% (SE)	*P* value	4 years later	% (SE)	*P* value
Atorvastatin	966	83.2±0.7	84.1±0.7	2.2±0.4**		77.7±0.8	−5.3±0.7**	
Fluvastatin	120	79.3±1.7	82.3±1.9	4.0±1.2**		79.5±2.0	1.2±2.2	
Pitavastatin	500	85.1±1.0	87.4±1.0	3.5±0.6**		82.0±1.0	−2.9±0.8**	
Pravastatin	341	84.0±1.1	84.3±1.1	0.9±0.7	<0.001	79.1±1.2	−4.7±1.2**	<0.001
Rosuvastatin	797	82.6±0.7	86.0±0.8	4.3±0.5**		79.8±0.8	−2.8±0.8**	
Simvastatin	713	83.5±1.0	85.5±0.9	0.2±0.5**		81.2±0.8	−0.7±0.8	
Simvastatin + Ezetimibe	241	86.7±1.4	88.2±1.4	2.6±0.9*		81.6±1.5	−4.6±1.4**	
Total	3678	83.5±0.4	85.4±0.4	3.2±0.2	<0.001	79.9±0.4	−3.2±0.4	<0.001

Data are expressed as mean±SE. GFR, glomerular filtration rate; MDRD, modification of diet in renal disease. *P <0.05 versus baseline. **P <0.001 versus baseline.

Table 4 Association between a specific statin and change in the MDRD-GFR

	Univariable		Multivariable*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.08 (1.07 – 1.09)	<0.001	1.08 (1.07 – 1.09)	<0.001
Sex (male)	1.06 (0.89 – 1.26)	0.536	1.29 (1.07 – 1.55)	0.008
Statin		0.018		0.045
Atorvastatin	Reference		Reference	
Fluvastatin	0.85 (0.52 – 1.40)	0.520	1.01 (0.61 – 1.70)	0.959
Pitavastatin	0.61 (0.45 – 0.83)	0.001	0.64 (0.46 – 0.87)	0.005
Pravastatin	0.70 (0.50 – 0.99)	0.041	0.79 (0.56 – 1.13)	0.195
Rosuvastatin	0.81 (0.63 – 1.03)	0.089	0.89 (0.69 – 1.14)	0.353
Simvastatin	0.74 (0.57 – 0.95)	0.021	0.69 (0.53 – 0.91)	0.008
Simvastatin + Ezetimibe	0.61 (0.41 – 0.92)	0.018	0.75 (0.49 – 1.14)	0.173

*Adjusted for age and sex. GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; OR, odds ratio; CI, confidence interval.

Table 5 Comparison of changes in the MDRD-GFR rate at 4 years after a statin was prescribed among the subgroups

	MDRD-GFR			MDRD-GFR reduction	*P* value
	N	Baseline	Visit 2 (4 years)	% (SE)	
High intensity statin					
Atorvastatin (40 mg)	33	81.3±3.6	72.1±3.7	−11.4±3.1**	0.094
Rosuvastatin (20 mg)	56	85.3±3.7	82.4±4.7	−3.5±3.4	
Moderate to high intensity statin					
Atorvastatin (20 mg)	166	82.2±1.7	77.8±1.8	−3.5±2.0	
Rosuvastatin (10 mg)	741	82.4±0.7	79.7±0.8	−2.7±0.8**	0.234
Simvastatin (40 mg)	33	81.7±2.5	83.9±3.2	3.5±3.2	
Moderate to low intensity statin					
Atorvastatin (10 mg)	767	83.4±0.8	77.9±0.9	−5.5±0.8**	
Fluvastatin (80 mg)	78	77.0±2.0	76.2±2.3	0.4±3.1	
Pitavastatin (2 mg)	500	85.1±1.0	82.0±1.0	−2.9±0.8**	<.001
Pravastatin (40 mg)	129	85.2±1.8	79.4±1.8	−5.2±1.9**	
Simvastatin (20 mg)	680	83.6±1.0	81.0±0.8	−0.9±0.8	
Low intensity statin					
Fluvastatin (40 mg)	42	83.6±3.0	85.6±3.6	2.8±2.7	
Pravastatin (20 mg)	127	86.1±1.7	82.2±2.1	−4.0±1.9*	0.117
Pravastatin (10 mg)	85	79.1±2.1	73.9±2.2	−4.8±2.2*	
Others					
Simvastatin (20mg) + Ezetimibe (20 mg)	96	88.6±2.0	85.1±2.1	−2.2±2.3	0.135
Simvastatin (20mg) + Ezetimibe (10 mg)	145	85.5±1.9	79.3±1.9	−6.3±1.7**	

Data are expressed as mean±SE. GFR, glomerular filtration rate; MDRD, modification of diet in renal disease. *P <0.05 versus baseline, **P <0.01 versus baseline.

0.8% vs. −0.9% ± 0.8%, $P < 0.001$). Not much difference was found between the remaining statins.

Discussion

With the rise of the aging population, the number of patients with chronic diseases, such as CVD, is also increasing [22,23]. An increased risk of renal disease is found in patients with CVDs, and dyslipidemia is common in patients with CKD [24,25]. Therefore, the kidney function should be carefully considered before prescribing statins. The 2011 EAS/ESC guidelines [3] emphasized that CKD is the sole risk factor of coronary artery disease, and worsening of GFR in patients with CKD is directly related to the worsening of LDL-C, TC, and TG levels. Accordingly, to prescribe statins to patients with hyperlipidemia in CKD is necessary. This work is the first study

conducted in Korea that analyzed changes in the GFR for statins within the same intensity groups, as specified by the 2013 ACC/AHC guidelines [18].

In studies that observed changes in MDRD-GFR values for < 1 year after the first statin prescription, the MDRD-GFR values showed no change or increase, which contrasts with our study's finding. In one study [26], the GFR increased by 11.3% (from 42.3 ± 11.1 mL/min/1.73 m^2 to 47.1 ± 18.5 mL/min/1.73 m^2, $P < 0.05$) 20 weeks after the first rosuvastatin (10 mg) prescription. A significant difference was observed in patients who were not prescribed any statin. In another study [27], the creatinine clearance also increased after 48 weeks of taking fluvastatin (20 mg). An increase in GFR caused by statin use in the early stage seems to indicate a distinct anti-inflammatory effect of statins. In a study performed on rats [28], the ischemia–reperfusion injuries and GFR improved after 3 days of injecting statins. In a study conducted on mice [29], the ischemia–reperfusion injuries of the kidney improved with statin administration. The results of the study indicated that statins have a pleiotropic effect, such as enhancing endothelial cell dysfunction and activating endothelial nitric oxide synthase, and an anti-inflammatory effect. One study reported that stress kinase was activated and cell apoptosis was reduced with statins [30].

In a 6-year follow-up observation, the GFR value for atorvastatin (10 mg) increased significantly by 3.5–5.2 mL/min/1.73 m^2 [31]. In pravastatin prescribed for 5 years, the estimated GFR (eGFR) value increased significantly by 6.3% ($P < 0.03$) [32]. Among the patients with renal disease or CVD treated with percutaneous coronary intervention, those prescribed a statin had a higher eGFR than those who were not prescribed a statin (47.3 ± 12.6 mL/min/1.73 m^2 vs. 42.0 ± 17.7 mL/min/1.73 m^2, $P = 0.001$) [33]. Regarding treating to new targets-CKD [33] and GREACE-CKD [9], statins had positive effects on renal functions, such as improvement of the eGFR and proteinuria reduction. Research showed a reduction in the eGFR after 4 years of prescribing statins. This finding is difficult to clarify because of no controls. However, our study does not claim that statins improve or aggravate kidney function. We aimed to determine whether or not a difference exists between each statin. (Possibly, the eGFR has been decreased because of aging.)

Many contradictory results are observed regarding an increase or decrease in the GFR after patients have taken statins in the long-term. However, regardless of whether the GFR decreases, taking a statin is strongly encouraged before renal function severely worsens [34]. The reason is that statin does not work well in severe chronic renal failure. However, the purpose of statin in patients with CKD is to reduce the risks of a cardiovascular disorder rather than to prevent the worsening of renal functions. A statin prescription should be carefully considered because the effect of statin is decreased in end-stage renal failure [35]. Using a statin can decrease the worsening of GFR. This aspect seems essential. The contradictory results in terms of an increase or decrease in the GFR seem to be affected by different types of statins rather than by all statins in general. In the present study, for all statins, except fluvastatin and simvastatin, the MDRD-GFR values decreased significantly. For pitavastatin (OR = 0.64) and simvastatin (OR = 0.69), the relative rate of MDRD-GFR values < 60 mL/min/1.73 m^2 was significantly lower than that for atorvastatin. For elderly men, the MDRD-GFR value decreased significantly. In a study on different sex groups, among those with chronic renal disorder diseases, men's GFR values (3.3%, $P < 0.001$) decreased more than that of women's (0.3%, $P = 0.46$) [32].

According to the 2011 FDA adverse event reporting system [36], the frequency of renal failure associated with atorvastatin is lower than that associated with any other type of statin. In the Planet trial [37], atorvastatin had a greater renoprotective effect than rosuvastatin. According to the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [38], high statin doses have several negative effects on the kidneys because of the increased incidence rates of proteinuria and hematuria. Whether or not the negative effects on the kidneys differ according to the type or potency of statin used remain controversial. In this study, we did not observe changes in GFR according to different statin doses. The reason was that a low dose of statins or a less potent statin is sufficient to meet LDL-C targets as Koreans have a lower BMI than the people from Western countries [39]. Prescribing a large dose of statins or potent statins is not of great concern because high-intensity statin prescription is rare in Korea [39,40]. Thus, comparing statins belonging to the same intensity group seemed important. However, in the present study, no statistically significant differences were observed between statins in the same intensity group except for the moderate-to-low intensity group. In this particular group, significant differences were found only between atorvastatin (10 mg) and simvastatin (20 mg).

Given that this study was a retrospective cohort study of EMR data [41,42], several limitations exist. First, this study did not include a control group that was not prescribed statins. This work can neither be concluded nor generalized categorically because of the absence of the control group. In other words, we do not suggest that statins themselves exacerbate eGFR. Second, this study only assessed simple changes in the MDRD-GFR after the statin prescription. For a statin prescription to have the ultimate effect on patients with CKD, to compare the incidence rates of CVDs and acute renal failure is necessary. Therefore, a large-scale study should be conducted in the future based on the study results. Lastly, we could not consider other CVD risk factors. Identification of other CVD risk factors is not possible in an EMR-

based clinical research. A standardized study design is recommended to minimize any unknown factor because it is one of the limitations of an EMR-based retrospective cohort study.

Conclusions

No clinical research has been conducted on the stability of the kidneys in those taking statin in Korea. The most import part for authors was first in selecting statin, "how much LDL-C should be lowered to reach the goal." Thus, the choice of statins is most critical, and the intensity group (high-, moderate- or low-intensity group) should be selected in accordance with LDL-C lowering effect based on the 2013 ACC/AHC guideline [18]. Moreover, statin should be selected and prescribed within the same intensity group, which is entirely up to the clinician. No guidelines are also available for it. Therefore, comparing based on the type and dose of statin to offer a minimal help with the selection is our aim.

When prescribing statins to hyperlipidemic patients with CKD, physicians should consider if their purpose is merely to decrease the LDL-C level or to reduce the risks of diverse side effects on renal functions. Depending on the purpose of treatment, different types of statins should be used. For example, if the purpose is to decrease the LDL-C level, physicians can classify statins into groups based on their intensity. Then, physicians should also select a proper statin from the same group while considering its diverse side effects, such as renal function degradation and an increase in the blood glucose level. Indiscreetly generalizing the results is difficult because this study is an EMR-based, retrospective cohort study. However, our findings may indicate the focus of a future randomized controlled trial. We hope that a detailed large-scale study will be conducted on statins and changes in the GFR.

Acknowledgements

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (No. HC15C1362).

Compliance with ethics guidelines

Seo Yeon Baik, Hyunah Kim, So Jung Yang, Tong Min Kim, Seung-Hwan Lee, Jae Hyoung Cho, Hyunyong Lee, Hyeon Woo Yim, Kun-Ho Yoon, and Hun-Sung Kim declare they have no conflicts of interests. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. This research was also approved by the International Review Board of Seoul St. Mary's Hospital (KIRB-00465-005). Written informed consent was obtained from all patients included in the study.

References

1. Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. N Engl J Med 1988; 319(1): 24–33
2. Lee MH, Kim HC, Ahn SV, Hur NW, Choi DP, Park CG, Suh I. Prevalence of dyslipidemia among Korean adults: Korea national health and nutrition survey 1998–2005. Diabetes Metab J 2012; 36 (1): 43–55
3. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 Committees. EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32 (14): 1769–1818
4. Ahn JH, Yu JH, Ko SH, Kwon HS, Kim DJ, Kim JH, Kim CS, Song KH, Won JC, Lim S, Choi SH, Han K, Cha BY, Kim NH; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence and determinants of diabetic nephropathy in Korea: Korea national health and nutrition examination survey. Diabetes Metab J 2014; 38(2): 109–119
5. Kang YH, Jeong DW, Son SM. Prevalence of reduced kidney function by estimated glomerular filtration rate using an equation based on creatinine and cystatin C in metabolic syndrome and its components in Korean adults. Endocrinol Metab (Seoul) 2016; 31 (3): 446–453
6. Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003; 41: I–IV, S1–91
7. Agarwal R. Effects of statins on renal function. Am J Cardiol 2006; 97(5): 748–755
8. Moon BS, Kim J, Kim JH, Hyun YY, Park SE, Oh HG, Park CY, Lee WY, Oh KW, Lee KB, Kim H, Park SW, Rhee EJ. Eligibility for statin treatment in Korean subjects with reduced renal function: an observational study. Endocrinol Metab (Seoul) 2016; 31(3): 402–409
9. Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Elisaf M. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004; 57(7): 728–734
10. Fried LF, Forrest KY, Ellis D, Chang Y, Silvers N, Orchard TJ. Lipid modulation in insulin-dependent diabetes mellitus: effect on microvascular outcomes. J Diabetes Complications 2001; 15(3): 113–119
11. Tonelli M, Isles C, Craven T, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, West M, Packard C, Curhan GC. Effect of pravastatin on rate of kidney function loss in

people with or at risk for coronary disease. Circulation 2005; 112(2): 171–178
12. Lee TM, Lin MS, Tsai CH, Chang NC. Add-on and withdrawal effect of pravastatin on proteinuria in hypertensive patients treated with AT receptor blockers. Kidney Int 2005; 68(2): 779–787
13. Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, Zhang H. Effect of statins on kidney disease outcomes: a systematic review and meta-analysis. Am J Kidney Dis 2016; 67(6): 881–892
14. Kendrick J, Shlipak MG, Targher G, Cook T, Lindenfeld J, Chonchol M. Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study. Am J Kidney Dis 2010; 55(1): 42–49
15. Acharya T, Huang J, Tringali S, Frei CR, Mortensen EM, Mansi IA. Statin use and the risk of kidney disease with long-term follow-up (8.4-year study). Am J Cardiol 2016; 117(4): 647–655
16. Garcia MM, Varela CG, Silva PF, Lima PR, Góes PM, Rodrigues MG, Silva MdeL, Ladeia AM, Guimarães AC, Correia LC. Endothelial effect of statin therapy at a high dose versus low dose associated with ezetimibe. Arq Bras Cardiol 2016; 106(4): 279–288
17. Clarke AT, Johnson PC, Hall GC, Ford I, Mills PR. High dose atorvastatin associated with increased risk of significant hepatotoxicity in comparison to simvastatin in UK GPRD cohort. PLoS One 2016; 11(3): e0151587
18. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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. J Am Coll Cardiol 2014; 63: 2889–2934
19. Kim HS, Lee H, Park B, Park S, Kim H, Lee SH, Cho JH, Yoon KH, Cha BY, Kim JH, Choi IY. Comparative analysis of the efficacy of low- and moderate-intensity statins in Korea. Int J Clin Pharmacol Ther 2016; 54(11): 864–871
20. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999; 130(6): 461–470
21. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1–S266
22. Centers for Disease Control and Prevention. Public health and aging: trends in aging—United States and worldwide. JAMA 2003; 289(11): 1371–1373
23. Chae HB, Lee SY, Kim NH, Han KJ, Lee TH, Jang CM, Yoo KM, Park HJ, Lee MK, Jeon WS, Park SE, Moon HS, Park CY, Lee WY, Oh KW, Park SW, Rhee EJ. Age is the strongest effector for the relationship between estimated glomerular filtration rate and coronary artery calcification in apparently healthy Korean adults. Endocrinol Metab (Seoul) 2014; 29(3): 312–319
24. Fang Q, Zou C, Zhong P, Lin F, Li W, Wang L, Zhang Y, Zheng C, Wang Y, Li X, Liang G. EGFR mediates hyperlipidemia-induced renal injury via regulating inflammation and oxidative stress: the detrimental role and mechanism of EGFR activation. Oncotarget 2016; 7(17): 24361–24373
25. Campese VM, Nadim MK, Epstein M. Are 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors renoprotective? J Am Soc Nephrol 2005; 16(Suppl 1): S11–S17
26. Verma A, Ranganna KM, Reddy RS, Verma M, Gordon NF. Effect of rosuvastatin on C-reactive protein and renal function in patients with chronic kidney disease. Am J Cardiol 2005; 96(9): 1290–1292
27. Yasuda G, Kuji T, Hasegawa K, Ogawa N, Shimura G, Ando D, Umemura S. Safety and efficacy of fluvastatin in hyperlipidemic patients with chronic renal disease. Ren Fail 2004; 26(4): 411–418
28. Gueler F, Rong S, Park JK, Fiebeler A, Menne J, Elger M, Mueller DN, Hampich F, Dechend R, Kunter U, Luft FC, Haller H. Postischemic acute renal failure is reduced by short-term statin treatment in a rat model. J Am Soc Nephrol 2002; 13(9): 2288–2298
29. Sharyo S, Yokota-Ikeda N, Mori M, Kumagai K, Uchida K, Ito K, Burne-Taney MJ, Rabb H, Ikeda M. Pravastatin improves renal ischemia-reperfusion injury by inhibiting the mevalonate pathway. Kidney Int 2008; 74(5): 577–584
30. Quintavalle C, Fiore D, De Micco F, Visconti G, Focaccio A, Golia B, Ricciardelli B, Donnarumma E, Bianco A, Zabatta MA, Troncone G, Colombo A, Briguori C, Condorelli G. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation 2012; 126(25): 3008–3016
31. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, Wilson DJ, Zuckerman A, Wenger NK; Treating to New Targets Investigators. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. Clin J Am Soc Nephrol 2007; 2(6): 1131–1139
32. Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y; MEGA Study Group. Pravastatin and cardiovascular risk in moderate chronic kidney disease. Atherosclerosis 2009; 206(2): 512–517
33. Kaneko H, Yajima J, Oikawa Y, Tanaka S, Fukamachi D, Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Kano H, Uejima T, Koike A, Nagashima K, Kirigaya H, Sawada H, Aizawa T, Yamashita T. Effects of statin treatment in patients with coronary artery disease and chronic kidney disease. Heart Vessels 2014; 29 (1): 21–28
34. Shah S, Paparello J, Danesh FR. Effects of statin therapy on the progression of chronic kidney disease. Adv Chronic Kidney Dis 2005; 12(2): 187–195
35. Seliger SL, Weiss NS, Gillen DL, Kestenbaum B, Ball A, Sherrard DJ, Stehman-Breen CO. HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. Kidney Int 2002; 61(1): 297–304
36. Sakaeda T, Kadoyama K, Okuno Y. Statin-associated muscular and renal adverse events: data mining of the public version of the FDA adverse event reporting system. PLoS One 2011; 6(12): e28124
37. de Zeeuw D, Anzalone DA, Cain VA, Cressman MD, Heerspink HJ, Molitoris BA, Monyak JT, Parving HH, Remuzzi G, Sowers JR, Vidt DG. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. Lancet Diabetes Endocrinol 2015; 3(3): 181–190

38. Albert MA, Glynn RJ, Fonseca FA, Lorenzatti AJ, Ferdinand KC, MacFadyen JG, Ridker PM. Race, ethnicity, and the efficacy of rosuvastatin in primary prevention: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Am Heart J 2011; 162(1): 106–14.e2
39. Kwon JE, Kim Y, Hyun S, Won H, Shin SY, Lee KJ, Kim SW, Kim TH, Kim CJ. Cholesterol lowering effects of low-dose statins in Korean patients. J Lipid Atheroscler 2014; 3(1): 21–28 (in Korean)
40. Kim M, Kim HK, Ahn Y, Park H, Jeong MH, Cho JG, Park JC, Kim YJ, Cho MC, Kim CJ. Comparing high-intensity versus low-to moderate-intensity statin therapy in Korean patients with acute myocardial infarction. J Lipid Atheroscler 2014; 3(2): 97–104 (in Korean)
41. Kim HS, Kim H, Jeong YJ, Kim TM, Yang SJ, Baik SJ, Lee SH, Cho JH, Choi IY, Yoon KH. Development of clinical data mart of HMG-CoA r(HMG-CoA) Reductase inhibitor for varied clinical research. Endocrinol Metab (Seoul) 2017; 32(1): 90–98
42. Cho KW, Kim SM, An CH, Chae YM. Diffusion of electronic medical record based public hospital information systems. Healthc Inform Res 2015; 21(3): 175–183