



Sex/Gender Differences in the Effect of Lipid-Lowering Agents on Dementia Risk

Mi-Young Kim, Hyejin Jee, Sooyoung Shin, Sukhyang Lee and Yi-Sook Jung

College of Pharmacy, Ajou University, Suwon, Korea

Introduction

Dementia, one of the major causes of cognitive decline among older people, is becoming a considerable burden on families and society due to the increasing life expectancy worldwide. Several studies have revealed that IHD was associated with an increased risk of dementia. Therefore, the development of an effective method for reducing the risk of dementia in the IHD population is clinically important. Recently, a number of reports have supported the notion that statins are associated with a reduced risk of dementia. However, studies on the association between statin therapy and dementia risk are currently controversial. Moreover, a previous observational study demonstrated that the risk reduction of Alzheimer's disease induced by statin use varied across sex and race/ethnicity. A better understanding of sex-related differences in drug efficacy is essential for providing potential therapeutic strategies for men and women individually. Therefore, given the lack of research focusing on patients with IHD, the aim of this study was to investigate the association between statin use and dementia risk in elderly Korean patients with IHD across seven commonly prescribed statins in view of sex, age, and exposure duration differences.

Methods

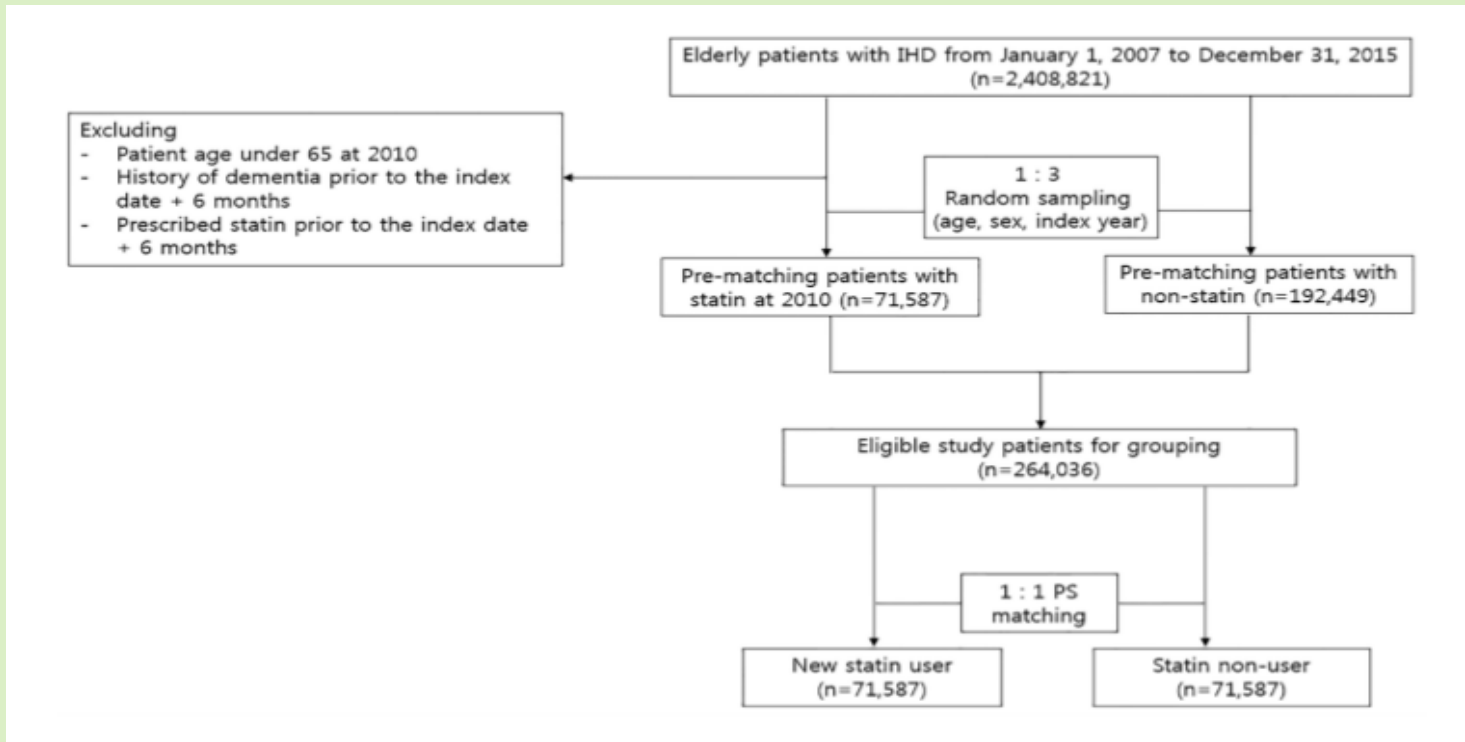


Fig. 1. Flowchart of criteria used to select participants for the study

Results

1. Baseline Characteristics

	Total (n = 143,174)		Male (n = 57,737)		Female (n = 85,437)	
	Non-Statins (n = 71,587)	Statin (n = 71,587)	Non-Statins (n = 28,725)	Statin (n = 29,012)	Non-Statins (n = 42,862)	Statin (n = 42,575)
Age						
mean ± SD	72.3 ± 5.3	72.1 ± 5.4	71.7 ± 5.1	71.6 ± 5.2	72.6 ± 5.4	72.4 ± 5.5
65–75 years	54,292 (75.8)	54,281 (75.8)	22,685 (78.8)	22,913 (79.2)	31,368 (73.8)	31,368 (73.8)
75–85 years	16,014 (22.4)	15,959 (22.3)	5,607 (19.5)	5,660 (19.5)	10,299 (24.2)	10,299 (24.2)
>85 years	1,281 (1.8)	1,347 (1.9)	433 (1.5)	439 (1.5)	908 (2.1)	908 (2.1)
Comorbidities						
Hypertension	53,606 (74.9)	53,541 (74.8)	21,233 (74.8)	21,464 (74.7)	32,373 (76.2)	32,077 (76.2)
Diabetes	25,682 (35.9)	25,951 (36.3)	10,895 (37.9)	11,210 (38.6)	14,787 (34.6)	14,741 (34.6)
Ischemic stroke	8,639 (12.1)	8,935 (12.5)	4,029 (14.0)	4,334 (14.9)	4,610 (10.8)	4,601 (10.8)
Depression	6,013 (8.4)	5,720 (8.0)	1,087 (3.8)	1,783 (6.1)	4,206 (9.8)	3,937 (9.2)
Parkinson	767 (1.1)	712 (1.0)	287 (1.0)	263 (0.9)	480 (1.1)	449 (1.0)
Schizophrenia	262 (0.4)	137 (0.2)	130 (0.4)	62 (0.2)	132 (0.3)	75 (0.2)
CCI score						
≤1	30,328 (42.4)	30,319 (42.4)	11,600 (40.4)	11,607 (40.0)	18,728 (43.7)	18,712 (43.7)
2	15,887 (22.2)	15,816 (22.1)	6,276 (21.9)	6,296 (21.7)	9,611 (22.4)	9,520 (22.4)
≥3	25,372 (35.4)	25,452 (35.6)	10,849 (37.7)	11,109 (38.3)	14,523 (33.9)	14,343 (33.9)
Concurrent medication						
Antiplatelet agents	47,713 (66.7)	61,540 (86.0)	19,609 (68.1)	26,364 (91.2)	28,104 (65.6)	35,176 (82.9)
ACEIs or ARBs	43,101 (60.2)	52,675 (73.6)	17,200 (60.0)	21,614 (74.5)	25,901 (60.4)	31,061 (73.1)
Beta Blockers	25,479 (35.6)	36,279 (50.7)	9,822 (34.2)	15,377 (53.0)	15,657 (36.5)	20,902 (48.9)
CCBs	42,245 (59.0)	43,666 (61.0)	16,367 (57.7)	16,673 (57.5)	25,878 (60.4)	26,993 (63.4)
Antidiabetic agents	21,770 (30.4)	26,268 (36.7)	9,220 (32.1)	11,093 (38.2)	12,550 (29.3)	15,175 (35.7)
PPis	30,867 (43.1)	37,237 (52.0)	12,043 (42.2)	14,423 (50.0)	18,824 (43.9)	22,814 (53.6)
Follow-up duration (year)						
mean ± SD	5.2 ± 1.7	5.0 ± 1.4	5.2 ± 1.8	5.0 ± 1.3	5.1 ± 1.7	4.9 ± 1.5

Table 1. Characteristics of study patients.

► Female patients accounted for 60% (85,437) of all patients, and the total average age was 72 years. The central follow-up period is 5.2 years for non-users and 5.0 years for statin users.

2. The Impact of Statin Use on Dementia Risk in Men and Women with IHD

Dementia Incidence, n (%)					
Total (n = 143,174)					
	n	case, n	(%)	HR (95% CI)	p-value
Non-user	71,587	14,122	19.7	reference	
Statin user	71,587	14,249	19.9	0.95 (0.92–0.97)	<0.001
Atorvastatin	45,753	9,312	20.4	0.96 (0.93–0.99)	0.003
Simvastatin	10,888	2,282	21.0	1.02 (0.98–1.07)	0.320
Rosuvastatin	8,231	1,428	17.3	0.82 (0.78–0.87)	<0.001
Pitavastatin	2,676	498	18.6	0.89 (0.82–0.98)	0.013
Pravastatin	2,538	468	18.4	0.86 (0.78–0.94)	0.001
Fluvastatin	934	162	17.3	0.84 (0.72–0.98)	0.032
Lovastatin	567	99	17.5	0.87 (0.71–1.06)	0.164
Male (n = 57,737)					
	n	case, n	(%)	HR (95% CI)	p-value
Non-user	28,725	4,619	16.1	reference	
Statin user	29,012	4,644	16.0	0.92 (0.88–0.96)	<0.001
Atorvastatin	17,970	2,919	16.2	0.92 (0.88–0.97)	0.001
Simvastatin	4,075	675	16.6	0.98 (0.90–1.06)	0.582
Rosuvastatin	4,038	603	14.9	0.87 (0.80–0.95)	0.002
Pitavastatin	1,153	178	15.4	0.90 (0.78–1.04)	0.157
Pravastatin	1,130	170	15.0	0.83 (0.71–0.97)	0.016
Fluvastatin	448	62	13.8	0.85 (0.66–1.08)	0.188
Lovastatin	198	37	18.7	1.15 (0.84–1.60)	0.385
Female (n = 85,437)					
	n	case, n	(%)	HR (95% CI)	p-value
Non-user	42,862	9,503	22.2	reference	
Statin user	42,575	9,605	22.6	0.96 (0.93–0.99)	0.003
Atorvastatin	27,783	6,393	23.0	0.97 (0.94–1.00)	0.075
Simvastatin	6,813	1,607	23.6	1.03 (0.98–1.09)	0.275
Rosuvastatin	4,193	825	19.7	0.82 (0.76–0.88)	<0.001
Pitavastatin	1,310	320	24.5	0.90 (0.80–1.01)	0.063
Pravastatin	1,408	298	21.2	0.89 (0.79–0.99)	0.048
Fluvastatin	486	100	20.6	0.87 (0.71–1.06)	0.164
Lovastatin	369	62	16.8	0.74 (0.58–0.95)	0.018

HR, hazard ratio; CI, confidence interval.

Table 2. Impact of statin use on the dementia risk in patients with IHD

► Among statins, rosuvastatin was associated with the greatest (18%) protective effect on dementia incidence. In the male group, atorvastatin, rosuvastatin, and pravastatin users showed significantly decreased HRs for dementia. In the female group, rosuvastatin, pravastatin, and lovastatin users showed remarkable effects on decreasing the risk of dementia.

3. Association between Statin Use and Dementia Risk According to the Exposure Duration of Statin

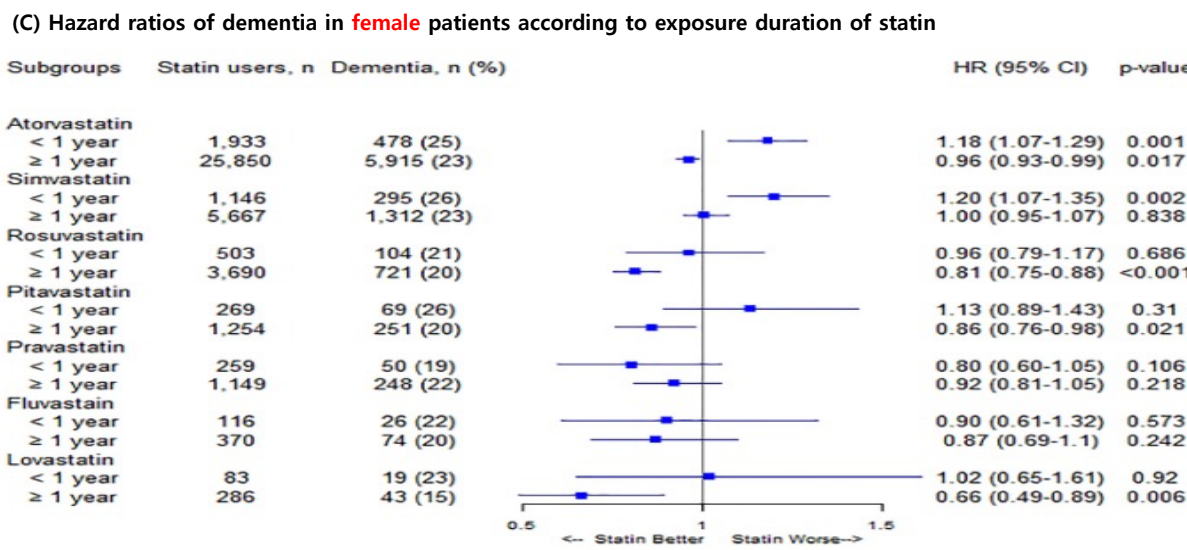
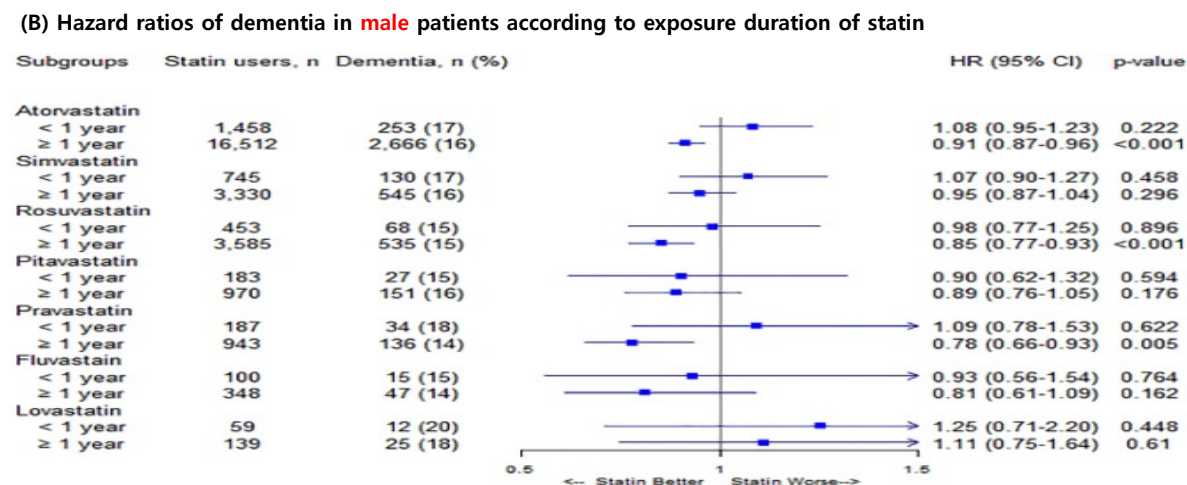
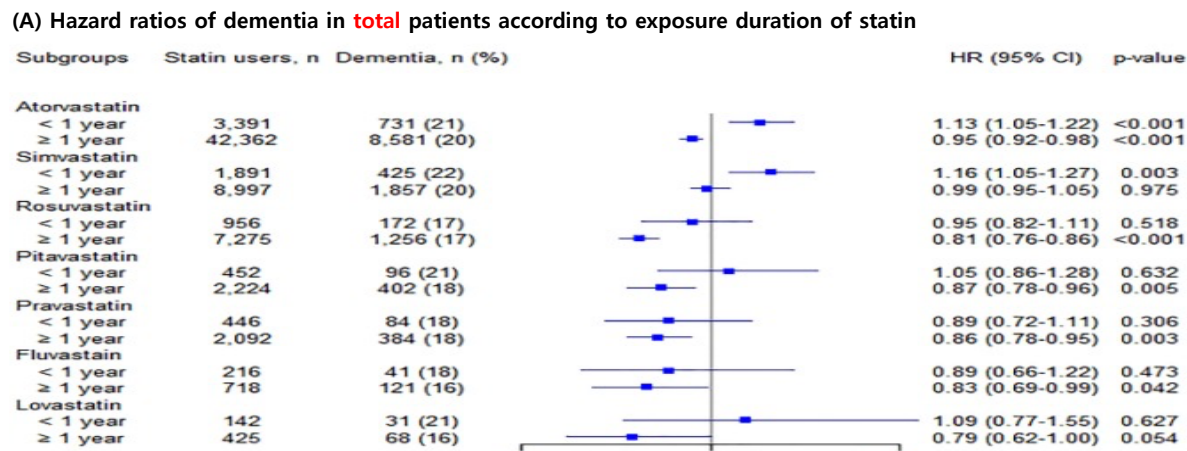


Figure 2. Hazard ratios of dementia risk in according to statin therapy duration

► In male patients, those with long-term use for ≥ 1 year of atorvastatin, rosuvastatin, or pravastatin were less likely to develop dementia. For female patients, the long-term use of atorvastatin, rosuvastatin, pitavastatin, or lovastatin appeared to reduce the risk of dementia incidence. On the other hand, short-term therapy with either atorvastatin or simvastatin was associated with an increased risk of dementia in female patients.

4. Association between Statin Use and Dementia Risk According to Age

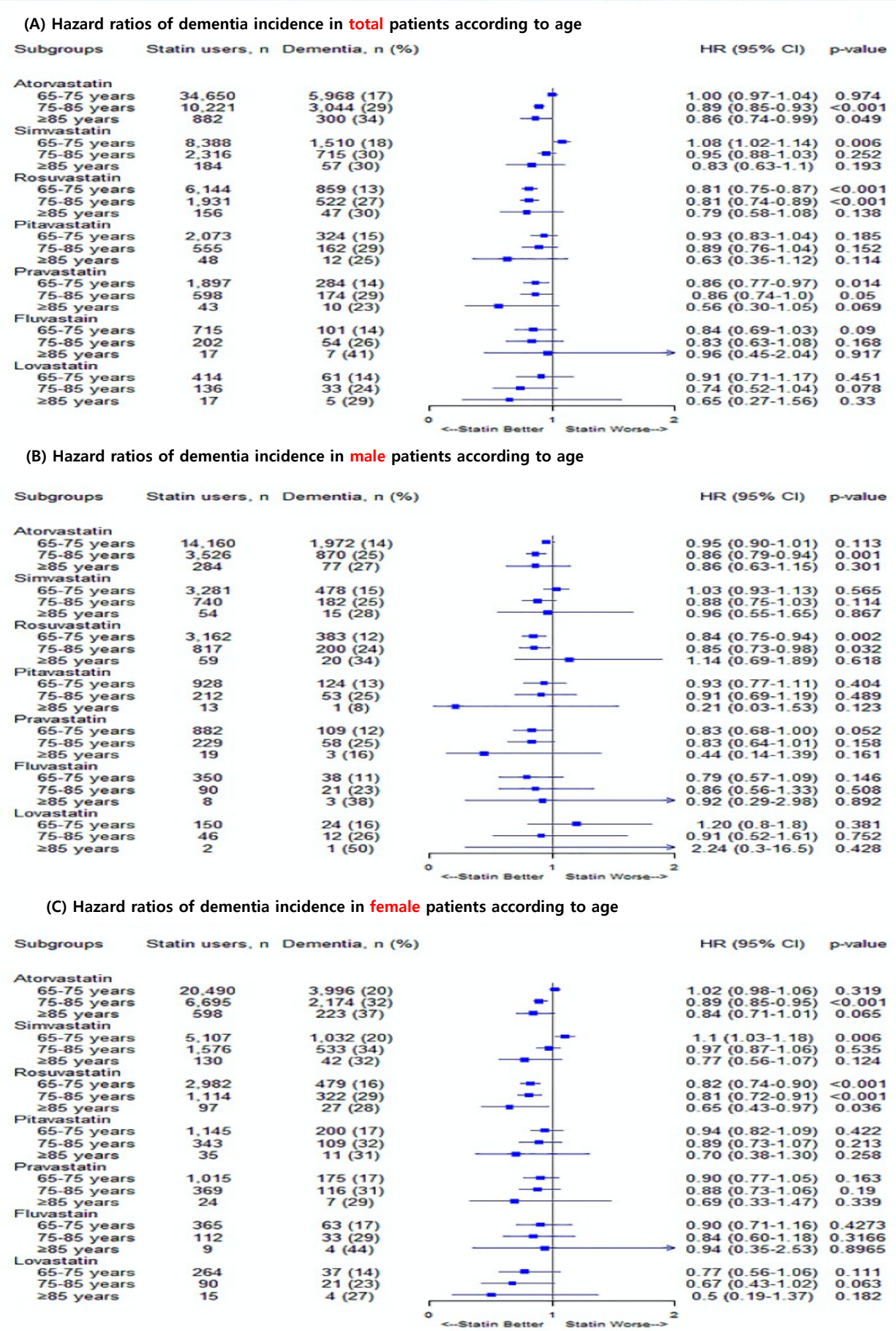


Figure 3. Hazard ratios of dementia risk in according to age

► Atorvastatin users were less likely to develop dementia in the 75–85 years old and >85 years old subgroup compared to non-users. Rosuvastatin users had a dementia protective effect in all three subgroups (65–75 years old, 75–85 years old and >85) in female patients. However, for male patients, the risk of dementia was lower in two subgroups aged 65–75 and 75–85 years. Pravastatin use has been shown to reduce the overall risk of dementia in patients aged 65 to 75 and 75 to 85 years old.

Conclusion

Our study demonstrated that statin therapy was associated with a reduction in dementia risk in Korean patients with IHD. The beneficial effects of statins were varied according to sex differences. This suggests that patients with IHD can reduce their risk of dementia using a particular statin. Clinician should consider the apparent differences in statin efficacy between sexes, as well as types of statins. The use of appropriate statin types with regard to sex differences may provide a relatively inexpensive way to reduce the burden of dementia. It is related to the **third goal of the Sustainable Development Goals (SDGs), “Ensuring healthy lives and promote well-being for all at all ages”**. In addition, the effects of statins are known to have racial differences, but there are few studies on Asians. Therefore, the results of this study are considered to be helpful in **“SDG 10: reduced inequalities”**.