Comparison of serum lipid management between elderly and non-elderly patients with and without coronary heart disease (CHD)

Rumiko Shimizu a, Haruki Torii a, Daisuke Yasuda a, Yoshinori Hiraoka a, Yutaka Furukawa b, Akihiro Yoshimoto c, Toshio Iwakura d, Naoki Matsuoka d, Keisuke Tomii e, Nobuo Kohara f, Tohru Hashida g, Noriaki Kuma a,⁎

a Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, 1-1-3 Minatojima, Chuo-ku, Kobe 650-8586, Japan
b Department of Cardiology, Kobe City Medical Center General Hospital, 2-2-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Japan
c Department of Nephrology, Kobe City Medical Center General Hospital, 2-2-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Japan
d Department of Respiratory Medicine, Kobe City Medical Center General Hospital, 2-2-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Japan
e Department of Diabetes and Endocrinology, Kobe City Medical Center General Hospital, 2-2-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Japan
f Department of Cardiology, Kobe City Medical Center General Hospital, 2-2-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Japan
g Department of Pharmacy, Kobe City Medical Center General Hospital, 2-2-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Japan

A R T I C L E   I N F O
Article history:
Received 15 February 2016
Received in revised form 1 June 2016
Accepted 5 June 2016
Available online 08 June 2016

Keywords:
Coronary heart disease (CHD)
Elderly
LDL-cholesterol
Lipid-lowering medication
Non-HDL-cholesterol

A B S T R A C T
Serum lipid management in patients aged ≥75 has not been precisely explored. We, therefore, compared the serum lipid management between the two age groups with and without coronary heart disease (CHD).

We, therefore, retrospectively reviewed medical charts of patients who were hospitalized in the departments of internal medicine during a period of 14 months. Serum lipid goal attainment was explored by applying the lipid goals for patients aged <75 to those aged ≥75. In 1988 enrolled patients, 717 subjects (30.1%) were aged ≥75. Among them, 43.1% and 32.4% of the patients had CHD, 44.2% and 41.0% were primary prevention at high-risk, and 14.5% and 14.6% were primary prevention at moderate-risk in patients aged ≥75 and aged <75, respectively. Serum LDL-C goal achievement rates in CHD were 66.9% and 65.0% in patients aged ≥75 and <75 respectively (p = 0.334). In the primary prevention at high-risk, these rates were 73.5% and 63.3%, in patients aged ≥75 and <75, respectively (p = 0.001). They were 77.9% and 58.1% in primary prevention at moderate-risk aged ≥75 and <75, respectively (p < 0.001). In CHD, lipid-lowering medication subscription rates were significantly lower in patients aged ≥75 (60.1%) than those aged <75 (73.8%, p < 0.001).

In conclusion, in CHD, serum lipid goal attainment was comparable between the two age groups although the lipid-lowering drugs were less frequently prescribed in patients aged ≥75. Without CHD, it was significantly better in patients aged ≥75 than those aged <75 although the lipid-lowering drug subscription rates were comparable between the two age groups.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

The incidence and prevalence of atherosclerotic cardiovascular disease (ACVD) increase with age (de Ruijter et al., 2009; Berthold and Gouni-Berthold, 2011; Phan and Bittner, 2014; McDermott, 2007; Petersen et al., 2005; Rosamond et al., 2007), and the majority of ACVD events occur after age 70 years (Stone et al., 2014). In 2009, the annual mortalities from acute myocardial infarction per 100,000 Japanese population were 12.4 and 18.4 in people aged 50 to 54 years and 55 to 59 years, respectively. These rates were 127.8 and 215.0 in the older people aged ≥65 years and ≥75 years, respectively. Thus, more than 10-fold higher ACVD mortality was observed in the elderly (≥75) age group when compared to the middle (50 to 59) age group (Japan Atherosclerosis Society, 2014). Because demographic aging is proceeding at an unprecedented speed in Japan, the incidence for ACVD is also predicted to be increasing. Dyslipidemia, especially the high LDL cholesterol (LDL-C) level, is one of the most important risk factors for ACVD; therefore, management of LDL-C is extremely important for preventing ACVD in the older population. However, the importance of dyslipidemia as an ACVD risk factor in older adults appeared controversial (Ettinger et al., 1992). Several studies have suggested that the association between cholesterol levels and ACVD weakens with age and that there may be little potential benefit from screening and treating older patients with dyslipidemia (Gordon and Rifkind, 1989; Mariotti et al., 1986; Garber et al., 1991). Conversely, some investigators have
shown that cholesterol concentrations retain a significant risk factor for ACVD in the elderly (Benfante and Reed, 1990; Barrett-Connor et al., 1984; Rubin et al., 1990), and lowering serum cholesterol in the elderly may have a greater impact on ACVD than in the middle age people because the absolute attributable risk of ACVD from dyslipidemia is greater in the older age group than in the middle age group, although the relative risk of ACVD derived from dyslipidemia is smaller in the older age group than in the middle age group.

The Japan Atherosclerosis Society guidelines for prevention of atherosclerotic cardiovascular diseases 2012 (JAS2012-GL) suggest the following: Subjects with dyslipidemia whose ages are between 65 and 74 should be treated in the same way as those aged below 65 to achieve their serum lipid goals. In cases of subjects with dyslipidemia whose ages are no less than 75 (≥75), patients with primary prevention for coronary heart disease (CHD) can be treated individually by the specific decision of the attending physician, although dyslipidemic patients with secondary prevention for CHD should be treated equally to those whose ages are below 65 to achieve their serum lipid goals (Japan Atherosclerosis Society, 2014). We, therefore, anticipated that the lipid goal attainment in CHD (secondary prevention) may be similar between patients aged ≥75 and <75 and that it may be better in patients aged <75 than in those aged ≥75 whose serum lipid control may not be mandatory in some cases.

Thus, to examine whether patients with dyslipidemia aged ≥75 (the elderly group) are treated differently from those aged <75 (the non-elderly group), serum lipid goal achievement rates were compared by applying the lipid goal for the patients aged <75 to those aged ≥75 by use of the JAS-GL2012. In addition, those rates were further compared between the two age groups in different risk category subgroups, such as high-risk and moderate-risk patients with primary prevention for CHD and those with secondary prevention for CHD. Furthermore, contents of lipid-lowering medication were compared between the elderly and non-elderly groups.

2. Methods

2.1. Study population

Medical charts of all the patients who were hospitalized in the Departments of Nephrology, Diabetes, Neurology, Respiratory Medicine and Cardiology, at Kobe City Medical Center General Hospital, Kobe, Japan, from April 1st, 2012 to May 31st, 2013 were retrospectively reviewed. Sixteen hundred and sixty (1660) subjects without lipid data, as well as 137 patients who underwent regular dialysis because of chronic renal failure, were excluded. As a result, a total of 1988 patients were enrolled. The numbers of patients who were enrolled from Departments of Nephrology, Diabetes, Neurology, Respiratory Medicine and Cardiology were 180, 176, 41, 277 and 1314, respectively.

2.2. Statistical analysis

Continuous variables are presented as mean ± standard error of mean (SEM), and categorical variables are shown as percentages and numbers. Continuous variables were compared using the Student’s t-test and Welch’s t-test, if the Levene test showed the equal and unequal variance, respectively. The significance in the differences for categorical variables was determined by the χ² test. Moreover, supplementary residual analysis was performed for comparisons of more than two categories. All statistical analyses were carried out using IBM SPSS Statistics 23 (SPSS Inc.). P values below 0.05 (p < 0.05) were considered as statistically significant.

3. Results

3.1. Patient enrollment

Medical charts of all the 3785 patients who were hospitalized in the Departments of Nephrology, Diabetes, Neurology, Respiratory Medicine and Cardiology at Kobe City Medical Center General Hospital, from April 1st, 2012 to May, 31st, 2013 were retrospectively reviewed. Sixteen hundred and sixty (1660) subjects without lipid data, as well as 137 patients who underwent regular dialysis because of chronic renal failure, were excluded. As a result, a total of 1988 patients were enrolled. The numbers of patients who were enrolled from Departments of Nephrology, Diabetes, Neurology, Respiratory Medicine and Cardiology were 180, 176, 41, 277 and 1314, respectively.

3.2. Patient characteristics

Characteristics of enrolled patients are summarized in Table 1. There was a significant difference in the proportion of patients aged ≥75 (overall: p < 0.001), due to the higher prevalence of patients aged ≥75 in Department of Respiratory Medicine (p < 0.01) and the lower prevalence of those in Departments of Nephrology (p < 0.05) and Diabetes (p < 0.01). BMI (p < 0.001), all lipid levels (p < 0.001) and eGFR (p < 0.001) were significantly lower in patients aged ≥75 than those aged <75. In addition, the prevalence of female (p < 0.001), HT (p = 0.001), CKD (p < 0.001) and CHD (p < 0.001) was significantly higher in patients aged ≥75 than those aged <75.

3.3. Comparison of LDL-C and non-HDL-C levels and their target level achievement rates between male and female

To explore whether the gender imbalance between patients aged ≥75 and <75 can be the cause for the differences in lipid levels between the two age groups, lipid profiles were compared between male and female. As shown in Table 2, LDL-C (p < 0.001), HDL-C (p < 0.001) and non-HDL-C (p < 0.001) levels were significantly higher in female than in male. However, TG (p < 0.001) level was significantly lower in female than in male. LDL-C target level achievement rates were 68.4% and 66.8%, in male and in female, respectively (p = 0.255). These rates for non-HDL-C were 70.8% and 70.3%, respectively (p = 0.427). Thus, lipid target level achievement rates were comparable between male and female, although there were significant differences in lipid levels.

3.4. Comparison of risk stratification profiles between the elderly and the non-elderly age groups

Prevalence of CHD was 41.3% and 32.4% in patients aged ≥75 and <75, respectively. (Fig. 1). In addition, none of the patients in patients aged ≥75 was stratified into low-risk, even though 12.0% of the patients were stratified into low-risk in patients aged <75 (Fig. 1). Prevalence of
primary prevention at high-risk patients was 44.2% and 41.0% in patients aged ≥75 and <75, respectively, (Fig. 1).

3.5 Comparison of LDL-C and non-HDL-C target level achieving rates between the elderly and the non-elderly age groups

LDL-C and non-HDL-C target level achievement rates were 71.4% and 75.6% in patients aged ≥75, and these rates were 65.8% and 67.7%, respectively, in patients aged <75. Thus, to our surprise, LDL-C and non-HDL-C target level achievement rates were significantly higher in patients aged ≥75 than those aged <75 (p = 0.006 and p = 0.001, respectively).

Lipid target attainment was further evaluated in the different risk category subgroups. In CHD, LDL-C and non-HDL-C target level achievement rates were 66.9% and 74.7%, respectively, in patients aged ≥75, and they were 65.0% and 69.8%, respectively, in patients aged <75. Thus, in CHD, LDL-C and non-HDL-C target level achievement rates were significantly higher in patients aged ≥75 than those aged <75 (p = 0.334 and p = 0.092, respectively, Fig. 2A and B). In the primary prevention at high-risk subgroup, however, LDL-C and non-HDL-C target level achievement rates were higher in patients aged ≥75 (73.5% and 75.1%, respectively) than those aged <75 (63.3% and 64.3%, respectively). These differences were statistically significant (p = 0.001 and p = 0.001, respectively, Fig. 2C and D). In the primary prevention at moderate-risk subgroup, LDL-C and non-HDL-C target level attainment also was better in patients aged ≥75 (77.9% and 79.8%, respectively) than those aged <75 (58.1% and 59.1%, respectively). These differences also were statistically significant (p < 0.001, Fig. 2E and F). In CKD-G, LDL-C and non-HDL-C target level attainment rates were higher in patients aged ≥75 (70.2% and 69.5%, respectively) than those aged <75 (58.1% and 59.1%, respectively), which were statistically significant differences (p = 0.018 and p = 0.036, respectively). In DM-G, in addition, they were 78.0% and 80.5%, respectively, in patients aged ≥75, and 69.3% and 71.5%, respectively, in those aged <75, which were also significantly higher in patients aged ≥75 than those aged <75 (p = 0.044 and p = 0.036 for LDL-C and non-HDL-C, respectively).

3.6 Comparison of lipid-lowering medication prescription rates between the elderly and the non-elderly age groups

The prescription rates of lipid-lowering drugs were compared between patients aged ≥75 and those aged <75. Lipid-lowering medication prescription rates were 41.6% and 39.9% in patients aged ≥75 and <75, respectively. Thus, lipid-lowering medication prescription rates appeared to be comparable (p = 0.248) between the two age groups.

Lipid-lowering medication prescription rates were further compared between these two age groups in the different risk category subgroups. In CHD, lipid-lowering medication subscription rates were significantly lower in patients aged ≥75 (60.1%) than in those aged <75 (73.8%, p < 0.001, Fig. 3A). In the primary prevention at high-risk subgroup, these rates were comparable between the two age groups (31.2% and 30.7%, respectively, p = 0.467, Fig. 3B). In the primary prevention at moderate-risk subgroup, lipid-lowering medication

Table 1
Characteristics of enrolled patients.

| Department                  | Enrolled patients | Aged ≥75 years | Aged <75 years | p    |
|-----------------------------|-------------------|----------------|----------------|------|
| Nephrology                  | 100 (180)         | 27.8 (50)      | 72.2 (130)     | <0.001 |
| Diabetes                    | 100 (176)         | 21.0 (37)      | 79.0 (139)     | <0.001 |
| Neurology                   | 100 (41)          | 39.0 (16)      | 61.0 (25)      | <0.001 |
| Respiratory Medicine        | 100 (277)         | 44.8 (124)     | 55.2 (153)     | <0.001 |
| Cardiology                  | 100 (1314)        | 37.3 (400)     | 62.7 (824)     | <0.001 |
| Total                       | 100 (1988)        | 36.1 (717)     | 63.9 (1271)    | <0.001 |
| Age, y                      | 67.7 ± 0.3 (1988) | 81.2 ± 0.2 (717) | 60.0 ± 0.4 (1271) | <0.001 |
| Mean body mass index (kg/m²)| 23.1 ± 0.1 (1939/1988) | 22.1 ± 0.1 (695/717) | 23.7 ± 0.2 (1244/1271) | <0.001 |
| Gender                      |                   |                |                |      |
| Male                        | 64.4 (1280)       | 58.6 (420)     | 67.7 (860)     | <0.001 |
| Female                      | 35.6 (708)        | 41.4 (297)     | 32.3 (411)     |      |
| Lipid profiles              |                   |                |                |      |
| LDL-C (mg/dL)               | 100.3 ± 0.7 (1981/1988) | 94.3 ± 1.1 (715/717) | 103.7 ± 0.9 (1266/1271) | <0.001 |
| TG (mg/dL)                  | 132.7 ± 1.8 (1896/1988) | 118.4 ± 2.5 (716/717) | 140.7 ± 2.5 (1270/1271) | <0.001 |
| HDL-C (mg/dL)               | 51.3 ± 0.4 (1988) | 49.6 ± 0.6 (717) | 52.3 ± 0.5 (1273/1271) | <0.001 |
| Non-HDL-C (mg/dL)           | 124.9 ± 0.9 (1986/1988) | 116.8 ± 1.3 (679/717) | 129.7 ± 1.1 (1152/1271) | <0.001 |
| eGFR (mL/min/1.73 m²)       | 64.9 ± 1.0 (1974/1988) | 55.4 ± 0.9 (715/717) | 70.3 ± 1.4 (1259/1271) | <0.001 |
| Values are expressed as percent (n) or mean ± SEM (n). | | | | |

Table 2
Comparison of lipid profiles between male and female.

| Lipid profile | Male            | Female          | p    |
|---------------|-----------------|-----------------|------|
| LDL-C (mg/dL) | 97.2 ± 0.9 (1273/1280) | 106.0 ± 1.3 (708) | <0.001 |
| TG (mg/dL)    | 137.8 ± 2.4 (1279/1280) | 123.4 ± 2.6 (707/708) | <0.001 |
| HDL-C (mg/dL) | 48.7 ± 0.4 (1280) | 56.2 ± 0.6 (708) | <0.001 |
| Non-HDL-C (mg/dL) | 122.0 ± 1.0 (1165/1280) | 130.1 ± 1.6 (686/708) | <0.001 |

Values are expressed as mean ± SEM (n).

Fig. 1. Comparison of risk stratification in patients between patients aged ≥75 (panel A) and <75 (panel B).
subscription rates were also comparable between the two age groups (20.2% and 14.0% for patients aged ≥75 and <75, respectively, \( p = 0.114, \) Fig. 3C). In CKD-G, they were 31.9% and 26.2% in patients aged ≥75 and <75, respectively (\( p = 0.160 \)). In DM-G, they were comparable between the two age groups (35.8% and 36.7%, respectively, \( p = 0.471 \)).

Thus, lipid-lowering medication was less frequently prescribed in patients aged ≥75 than those aged <75 in the secondary prevention for CHD, and was almost equally prescribed in patients aged ≥75 and <75 in the primary prevention at high-risk and moderate-risk subgroups, including CKD-G and DM-G. These results were quite different from what we had anticipated before this study.

In addition, contents of the lipid-lowering medication were compared between patients aged ≥75 and <75. Prescription rates for drug combinations and monotherapies of lipid-lowering drugs were compared between two age groups in the total enrolled patients (Table 3) and in the patients with CHD (Table 4). The combination of statin plus EPA was more frequently prescribed in patients aged <75 than in those aged ≥75, in the total enrolled patients (Table 3) as well as in those with CHD (Table 4). These differences were statistically significant (\( p = 0.002 \) and \( p = 0.001 \), respectively). In CHD, furthermore, statin monotherapy was also significantly more prevalent in patients aged <75 than those aged ≥75 (\( p = 0.016 \), Table 4).

4. Discussion

Atherosclerosis is a continuous degenerative process, and its burden increases progressively with aging (Ulucam, 2012). Dyslipidemia is one of the most important risk factors in the development of atherosclerosis.
According to the JAS2012-GL, patients aged \( \geq 75 \) with dyslipidemia and primary prevention for CHD should be individually treated flexibly by the decisions of their attending physicians based upon the condition of each patient, such as accompanying other chronic diseases, frailty, drug tolerability, and social activities. On the other hand, patients aged 65–74 with dyslipidemia should be treated in the same way as those aged \(< 65\) to achieve their serum lipid goals (Japan Atherosclerosis Society, 2014).

The PROSPER trial showed that three-year statin treatment in patients aged 70 to 82 years, including secondary prevention patients, decreased the risk of death from CHD plus nonfatal myocardial infarction by 19%, clearly demonstrating that intervention with statins may be indicated for the elderly. A decreased incidence of CHD was more clearly observed in men than in women, and in secondary prevention patients compared to primary prevention patients; however, these differences were statistically insignificant (Shepherd et al., 2002). In addition, meta-analyses of the Cholesterol Treatment Trialists’ (CTT) collaboration revealed that patients aged \( \geq 75\) tended to be less effective in the CHD risk reductions by statins than those aged \(< 75\); however, they were not statistically significant differences (Baigent et al., 2010).

In the present study, the status of the serum lipid management in real-world clinical practice has been explored comparing the patients aged \( \geq 75\) to those aged \(< 75\). To the best of our knowledge, this is the first report that was directed to the elderly patients (aged \( \geq 75\)) comparing their serum lipid goal attainment rates to those in the non-elderly (aged \(< 75\)) patients. In fact, we had supposed that the LDL-C and non-HDL-C target level achievement rates in patients aged \( \geq 75\) may be lower than those aged \(< 75\) in the primary prevention, and that they may be comparable in the secondary prevention patients, according to the guideline. Contrary to our expectation, the LDL-C and non-HDL-C target level achievement rates tended to be higher in the elderly (aged \( \geq 75\)) patients than those aged \(< 75\) in the primary prevention, although they are comparable between patients aged \( \geq 75\) and those aged \(< 75\) in the secondary prevention. In patients aged \( \geq 75\) with CHD, lipid-lowering medication subscription rate was 60.1%, which was lower than that (73.8%) in patients aged \(< 75\). They may result from the fact that lipid levels in patients aged \( \geq 75\) were lower than those in patients aged \(< 75\) which appeared to be supported by previous studies (Ettinger et al., 1992; Schupf et al., 2005).

In the elderly, they more often have advanced presymptomatic atherosclerotic vascular lesions, which impose CHD events, than in the non-elderly subjects (Kannel, 2002). Elevated serum cholesterol is associated with greater number of CHD events (higher absolute risks) in the

![Fig. 3. Comparison of lipid-lowering medication prescription rates between patients aged \( \geq 75\) and \(< 75\) in various risk category subgroups Lipid-lowering medication prescription rates were compared between patients aged \( \geq 75\) and \(< 75\) in various risk category subgroups, such as CHD (panel A), primary prevention at high-risk (panel B) and moderate-risk (panel C) subgroups. Values are expressed as percent. The \( p \) values were derived from \( \chi^2 \) statistics.](image-url)
Values are expressed as percent (n).
