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Päivi Tuikkala

# *Cardiovascular medicines use in elderly population*

*Emphasis on blood pressure and serum lipids*

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EASTERN FINLAND

**PÄIVI TUIKKALA**

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## *Emphasis on blood pressure and serum lipids*

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## ABSTRACT

Cardiovascular diseases are responsible for one-third of global deaths and during recent years cardiovascular medicines have been the most commonly used medication among elderly persons. Today there are no age-specific guidelines on how to treat cardiovascular diseases in the elderly population. The target levels of blood pressure and blood lipids as well as the values at which treatments is started have become lower and lower over the years also among elderly persons. The present series of studies were designated to examine the use of cardiovascular medicines use with a special emphasis on blood pressure and serum lipids. According to the study, the use of cardiovascular medicines was common among elderly persons and the proportion of users increases with age and over time. In addition, the trend in current statin use seems to be moving towards more extensive use. The result shows that low serum total cholesterol level was associated with an increased risk of all-cause mortality among elderly who did not use serum lipid modifying medication. In studies concentrating on blood pressures, the orthostatic hypotension and drops in blood pressure seem to be more common than has previously been reported. The more medicines are in regular use, the more common is orthostatic hypotension. Since the increased and concomitant use of several cardiovascular medicines among elderly persons makes them sensitive to partly unknown adverse effects, it is important to assess the patient's physical function and outcomes of treatment. As well the medication monitoring focused on elderly patients and cardiovascular medication might optimise treatment and improve the quality of care for a large proportion of elderly persons.

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## TIIVISTELMÄ

Sydänsairaudet ovat osana kolmasosassa kuolemia ja sydänsairauksien lääkkeet ovat olleet vuosia eniten käytetty lääkeryhmä ikääntyneillä. Tällä hetkellä ei ole käytössä ikäspesifisiä hoitosuosituksia sydänsairauksien hoitoon, vaan hoito pohjautuu koko väestön kattaviin hoitosuosituksiin. Tutkimuksessa selvitettiin suomalaisten iäkkäiden (≥ 75 vuotta) sydän- ja verenpainelääkkeiden käyttöä ja kulutusta tutkimusvuosina 1998–2006. Tutkimuksessa keskityttiin erityisesti kolesteroli- ja verenpainelääkityksen erityispiirteisiin iäkkäillä. Työ perustuu neljään osatyöhön, joissa on käytetty Kuopio 75+ sekä Hyvän Hoidon Strategia (HHS) tutkimuksista saatuja terveys- ja lääkedatoja. Tutkimuksen mukaan sydänsairauksien lääkkeiden käyttö oli yleistä ja käyttäjien osuus kasvoi ikääntymisen ja ajan myötä. Vuonna 2003 jopa 87 %:lla tutkittavista oli yksi tai useampi sydänsairauksien lääke. Erityisesti kohonneen kolesterolin hoitoon käytettävien statiinien käyttö lisääntyi tutkimusaikana. Tulosten mukaan matala kolesteroli oli yhteydessä lisääntyneeseen kuolleisuuteen tutkittavilla, jotka eivät käyttäneet kolesterolilääkitystä. Tutkittaessa verenpaineita saatiin selville, että ortostaattinen hypotonia ja verenpaineen lasku näyttää olevan yleisempää kuin aiemmin on raportoitu. Mitä enemmän tutkittavilla oli säännöllisiä lääkkeitä käytössä, sitä yleisempää oli ortostaattinen hypotonia. Koska lisääntynyt ja usein yhtäaikainen lääkkeiden käyttö iäkkäillä saattaa altistaa tuntemattomille haittavaikutuksille, on tärkeää arvioida säännöllisesti potilaan fyysinen kunto ja hoidon tulokset. Myös lääkityksen säännöllinen arviointi iäkkäillä sydänsairailla auttanee parantamaan hoidon laatua ja parantaa iäkkäiden elämänlaatua.

Yleinen suomalainen asiasanasto: HDL-kolesteroli; ikääntyminen; ikääntyneet; LDL-kolesteroli; lääkehoito; lääkkeet - - käyttö; kolesteroli; verenpaine; lipidit - - veri; sydän- ja verisuonitaudit

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Oulainen, February 2011

Päivi Tuikkala

# *List of original publications*

This dissertation is based on the following articles which are referred to in the text by their Roman numerals:

I Hiitola PK, Enlund H, Sulkava RO, Hartikainen SA: Changes in the use of cardiovascular medicines in the elderly aged 75 years or older – a population-based Kuopio 75+ study. Journal of Clinical Pharmacy and Therapeutics 2007; 32: 253–259.

II Tuikkala P, Enlund H, Sulkava R, Hartikainen S: Characteristics of users of serum lipid modifying agents and outcomes of treatment among a cohort of elderly Finns aged 75 years or more (submitted).

III Tuikkala P, Hartikainen S, Korhonen MJ, Lavikainen P, Kettunen R, Sulkava R, Enlund H: Serum total cholesterol levels and all-cause mortality in a home – dwelling elderly population: a six year follow-up. Scandinavian Journal of Primary Health Care 2010; 28: 121–127.

IV Hiitola P, Enlund H, Kettunen R, Sulkava R, Hartikainen S: Postural changes in blood pressures and prevalence of orthostatic hypotension among the home-dwelling elderly aged 75 years or older. Journal of Human Hypertension 2009; 23: 33–39.

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# *Abbreviations*

| | |
|---|---|
| ACE-inhibitors | angiotensin-converting enzyme inhibitors (C09) |
| AT 1 | Angiotensin II receptor antagonist, type 1 (C09CA) |
| ATC | Anatomic Therapeutic Chemical classification system |
| BP | Blood pressure |
| CAD | Coronary artery disease |
| CARE | the Cholesterol and Recurrent Events (CARE) trial |
| CGA | Comprehensive Geriatric Assessment |
| CHD | Cardiac heart disease |
| CK | Creatine kinase |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| GeMS | Geriatric Multidisciplinary Strategy for the Good Care of the Elderly |
| HMGCoA | reductase inhibitors = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, statins (C10A) |
| HR | Hazard ratio |
| IHF | Ischeamic heart failure |
| JUPITER | Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial |
| LIPID | the Long-Term Intervention with Pravastatin in Ischaemic Disease |
| MI | Myocardial infarction |
| NHANES | National Health and Nutrition Examination Survey |
| NS | Not significant |
| OH | Orthostatic hypotension |
| OTC | Over –the-counter medicines |
| PROSPER | the Prospective Study of Pravastatin in the Elderly at Risk |
| PS | Propensity score |
| SBP | Systolic blood pressure |

| | |
|---|---|
| SCORE | Systemic Coronary Risk Evaluation |
| SD | Standard deviation |
| S-TC | Serum total cholesterol |
| S-HDLC | Serum high density lipoprotein |
| S-LDLC | Serum low density lipoprotein |
| SPSS | Statistical Package for Social Sciences |
| TG | Triglycerides |
| WHO | World Health Organization |
| 4S | The Scandinavian Simvastatin Survival Study |

# 1 Introduction

Cardiovascular diseases are responsible for one-third of global deaths and they are a leading and increasing contributor to the global disease burden (WHO 2002, Kesteloot et al. 2002). The prevalence of cardiovascular diseases increases with advancing age, leading to concomitant use of several medications.

In addition, the proportion of elderly persons is increasing in Finland and other western countries and, in general, elderly populations are often treated more actively than before. Many studies have reported an overall increase in the use of medicines among the elderly (Lernfelt et al. 2003). In Finland, the amount of drugs used has increased among both men and women, especially among persons aged 85 years and over (Linjakumpu et al. 2002b, Jyrkkä et al. 2006). During recent years cardiovascular medicines have been the most commonly used medications among elderly persons (Barat et al. 2000, Linjakumpu et al. 2002b, Kaufman et al. 2002).

Today there are no age-specific guidelines on how to treat cardiovascular diseases in the elderly population, but the goals are mainly the same as in the middle-aged population (Käypä hoito: Kohonnut verenpaine 2009, Käypä hoito: Dyslipidemiat 2009). The target levels of blood pressure and blood lipids as well as the values at which treatments are started have become lower and lower over the years also among elderly persons (Salomaa et al. 1994, Chobanian et al. 2003, Graham et al. 2007). For middle-aged patients with vascular disease, high serum total cholesterol as well as high blood pressure are associated with greater all-cause and cardiovascular mortality, and the benefits of treatments are well documented (Stamler et al. 1999, Stamler et al. 2000). However, the number of elderly participants in trials has been rather limited. In addition, some observational studies

of persons aged 65 years or older suggest that traditional risk factors like elevated cholesterol and blood pressure might be inversely associated with total mortality (Mattila et al. 1988, Schatz et al. 2001, Rastas et al. 2006).

Increased and concomitant use of several cardiovascular medicines among elderly persons makes them sensitive to partly unknown adverse effects. In the study by Tipping et al., cardiovascular drugs accounted for more than one-third of the total amount of adverse drug events among patients aged 65 years and older (Tipping et al. 2006). Also the use of serum lipid modifying agents together with other medications and changes in body composition and body function that occur with age may increase the risk of clinically important adverse reactions (Routledge et al. 2004).

There is not much population-based information available on cardiovascular drug use and age-related changes in elderly populations aged 75 years or more (Wills et al. 1996, Barat et al. 2000, Strandberg et al. 2001). Knowledge concentrating on these aspects is needed in order to guarantee safe and appropriate drug treatment.

# 2 Review of the literature

## 2.1 DEFINING AGEING

Ageing is defined mostly as a biological, psychological and social phenomenon. In the simplest definition, age is a chronological count of calendar years; in western countries ageing is usually measured in years (Stuart-Hamilton 2000). Biological ageing is associated with changes in the human organism and biological aging processes. The term describes the general state of a person's body. Social age refers to the societal expectations of how people should behave at a particular chronological age (Jyrkämä 1995). Chronological age is simply a measure of how many years old a person is. However, age alone is often a poor indicator. The chronological age at which old age begins is often between 60–70 years; at around these years psychological and physical changes tend to manifest themselves. In addition, older persons are often divided into young elderly (i.e. 60–75 years), old elderly (i.e. 75+ years) and old-old (i.e. 85+ years) (Stuart-Hamilton 2000, Arinzon et al 2005). In this study age refers to chronological age. In the literature part the target population is limited to 65 years or older and in the study part the limit is 75 years or older.

## 2.2 BLOOD PRESSURE, BLOOD LIPIDS AND AGEING

Cardiovascular changes are common in aging persons (Table 1). Age-related changes are most likely to be seen in the oldest old who have escaped cardiovascular outcomes earlier in their life (Lye & Donnellan 2000). It is often difficult to differentiate normal ageing from age-related pathology that is preventable or treatable.

*Table 1. Changes in cardiac function with age*

| | |
|---|---|
| Heart | Maximal heart rate ↓<br>Maximal aerobic capacity ↓<br>Calcification of the valvular system ↑<br>Rigidity of the myocardium ↑ |
| Blood vessels | Vascular stiffness, aortic and large artery thickness ↑<br>Systolic blood pressure ↑<br>Susceptibility to blood pressure lowering during postural changes (= orthostatic hypotension) ↑ |
| Fluid balance | Fluid in the blood vessels ↓<br>Circulation in the kidneys ↓ |
| Regulation systems | Function of nervous reflex regulating heart and blood vessels ↓<br>• Susceptibility to blood pressure changes ↑<br>Changes in hormonal regulation systems<br>• Heart response to adrenaline ↓<br>• Attenuation of the renin-angiotensin-aldosterone system of the kidneys |

*(Lye & Donnellan 2000, Tilvis & Aantaa 2001, Kostrzewski 2002)*

### 2.2.1 Blood pressure

#### 2.2.1.1 Hypertension

Systolic blood pressure (SBP) increases linearly with age, but diastolic blood pressure (DBP) increases until about the age of 60 and decreases thereafter (Franklin et al. 1997). Thus, isolated systolic hypertension becomes the predominant type of hypertension in older persons. DBP is a more potent cardiovascular risk factor than SBP until the age 50, but thereafter SBP seems to be more important (Franklin et al. 2001).

Many age-related changes in physiology increase blood pressure and make the essence of hypertension in elderly persons different compared with the young or middle-aged (Table 2). An increase in peripheral vascular resistance is a typical feature of hypertension in the elderly (Vanhanen 2001). An increase in arterial vascular stiffness, alterations in vessel structure and a decrease in elastin content may also

increase blood pressure. Thus, stroke volume does not change significantly with age, but arterial compliance declines, which contributes to an increase in systolic blood pressure (Supiano 2003).

*Table 2. Special characteristics of hypertension in the elderly*

| |
|---|
| Cardiac output ↓ |
| Arterial compliance ↓ |
| Renal blood flow ↓ |
| Peripheral vascular resistance ↑ |
| Renin concentration ↓ |
| Bradycardia ↑ |
| Orthostatic hypotension ↑ |
| Tolerance of medications ↓ |
| Underlying diseases ↑ |

*(Vanhanen 2001, Kostrzewski 2002)*

The definition of high blood pressure has undergone many changes towards lower values during the last few decades. The European guideline classifies blood pressure in three stages (Table 3) (Graham et al. 2007). The Finnish guideline classifies blood pressure as elevated when SBP is ≥ 140 mmHg or DBP is ≥ 90 mmHg. The newest guideline recommends lowering the target values: SBP < 140 mmHg and DBP < 85 mmHg (Käypä hoito: Kohonnut verenpaine 2009). The recommendations for antihypertensive medication are based not only on blood pressure levels, but also on the presence of other risk factors and diseases, like the presence of established CVD, diabetes, renal disease or other target organ damage (Graham et al. 2007, Mancia et al. 2009).

*Table 3. Classification of blood pressure levels*

| Category | Systolic, mmHg | | Diastolic, mmHg |
|---|---|---|---|
| Optimal | < 120 | and | < 80 |
| Normal | < 130 | and/or | < 85 |
| High normal | 130–139 | and/or | 85–89 |
| | | | |
| Hypertension | | | |
| Grade 1 (mild) hypertension | 140–159 | and/or | 90–99 |
| Grade 2 (moderate) hypertension | 160–179 | and/or | 100–109 |
| Grade 3 (severe) hypertension | ≥ 180 | and/or | ≥ 110 |
| | | | |
| Isolated systolic hypertension | ≥ 140 | and | < 90 |

*(Graham et al. 2007, Käypä hoito: Kohonnut verenpaine 2009)*

The target levels of blood pressure in elderly persons are the same today as in younger persons, but the recommendation is to prescribe antihypertensive medication to elderly persons (80+ years) with a SBP value > 160 mmHg, with the goal of lowering it < 150 mmHg (Käypä hoito: Kohonnut verenpaine 2009, Mancia et al. 2009). According to the guidelines and studies, orthostatic measurement should be done to all elderly persons before treatment is started due to the decreased reactivity of baroreflex during postural changes (Graham et al. 2007, Beckett et al. 2008, Käypä hoito: Kohonnut verenpaine 2009).

Average blood pressure levels have decreased since the 1970s in Finland in all age groups, also among elderly persons (Vartiainen et al. 2000, Kattainen et al. 2002, Vartiainen et al. 2010). In the Framingham Heart Study, the prevalence of hypertension (≥ 140/90 mmHg or treated) was 63% in those aged 60–79 years, and 74% in those aged 80 years or older (Lloyd-Jones et al. 2005). In the NHANES 1999–2004 study, 62% of the elderly aged ≥ 80 years were treated with antihypertensives (Ostchega et al. 2007). Among non-institutionalised individuals aged 65+, 62% were hypertensive (Brindel et al. 2006). In Finland, 41% of men and 49% of women aged 65 year or more reported high blood

pressure or hypertension in 2007 (Aromaa & Koskinen 2002). In another Finnish population-based study, 76% of men aged ≥ 80 years had SBP higher than 140 mmHg, and correspondingly, 84% of women. In those aged 85 years the percentages were 60% and 78%, respectively (Lehtonen et al. 1995).

#### 2.2.1.2 Orthostatic hypotension

Orthostatic hypotension (OH) is a physical finding defined by the American Autonomic Society and the American Academy of Neurology as a systolic blood pressure decrease of at least 20 mm Hg (systolic OH) or a diastolic blood pressure decrease of at least 10 mm Hg (diastolic OH) or both within three minutes of standing up form a supine position or during head up-tilting (the American Autonomic Society and the American Academy of Neurology 1996). In some patients a significant fall in blood pressure may not be noted until they stand for at least 10 minutes (delayed orthostatic hypotension) (Gibbons & Freeman 2006).

Orthostatic hypotension has been observed in all age groups (Rose 2006), but its prevalence increases with age and it occurs more frequently in persons who are sick and frail (Lipsitz 1989, Tilvis et al. 1996, Shibao et al. 2007, Robertson 2008). Hospitalisation, prolonged bed rest and diseases such as Parkinson's disease are associated with OH (Mets 1995, Ooi et al. 1997, Gupta & Lipsitz 2007), as are haemodynamic conditions, such as hypovolemia and cardiac insufficiency and neurogenic causes such as multiple system atrophy and, for example, diabetic autonomic neuropathy (Bradley & Davis 2003). Other predisposing factors of OH are dehydration, poor nutrition and the bodily changes that occur with ageing (Robertson 2008). OH is negatively associated with body weight (Rutan et al. 1992, Ooi et al. 1997). From 6% to 30% of home-dwelling elderly persons had OH (Rutan et al. 1992, Räihä et al. 1995, Masaki et al. 1998, Luukinen et al. 1999, Atli & Keven 2006), and it is even more prevalent in residential care (Ooi et al. 1997, Ooi et al. 2000,

Weiss et al. 2002, Poon & Braun 2005, Vloet et al. 2005, Weiss et al. 2006) (Table 4). The frequency of OH in cohorts of patients recruited through hospital Parkinson's disease clinics ranges even up to 58% (Senard et al. 1997). The difference in prevalences varies due to factors like the definition of OH, the segment of the population (age, healthiness) and use of medications.

*Table 4. Prevalence (%) of orthostatic hypotension (OH) among elderly persons according to living status*

| Study | Population | Age (mean age) | N | Women % | Prevalence of OH % |
|---|---|---|---|---|---|
| Institution | | | | | |
| Weiss et al. 2002 | Acute geriatric ward | 62–99 (82) | 502 | 52 | 68 |
| Poon et al. 2005 | Geriatric clinic for veterans | (82) | 342 | 4 | 55 |
| Wloet et al. 2005 | Patients from two geriatric wards | 60–98 (80) | 85 | 48 | 52 |
| Ooi et al. 1997 | Long-stay residents from a nursing home | ≥ 60 | 911 | - | 52 |
| Ooi et al. 2000 | Long-stay residents from a nursing home | ≥ 60 | 844 | 80 | 50 |
| Boddaert et al. 2004 | Acute and intermediate-care geriatric ward | (84) | 57 | 81 | 32 |
| Home-dwelling | | | | | |
| Luukinen et al. 1999 | Home-dwelling elderly | ≥ 70 | 833 | 62 | 30 |
| Fisher et al. 2005 | Semi-independent residents from long-term healthcare facilities | ≥ 65 (83) | 179 | 80 | 23 |
| Verwoert et al. 2008 | Community-dwelling | ≥ 55 (68) | 5064 | 62 | 18 |
| Rutan et al. 1992 | Community-dwelling, non-institutionalised | ≥ 65 | 5201 | 54 | 18[1] |
| Atli et al. 2006 | Outpatient clinic[2] | > 65 | 61 | 43 | 15 |
| Masaki et al. 1998 | Population-based | 71–93 | 3522 | - | 7 |

[1]*includes also participants in whom the blood pressure procedure was aborted due to dizziness upon standing*

[2]*the patients without antihypertensive treatment, diabetes mellitus, history of myocardial infarction or heart failure*

Orthostatic hypotension may be symptomatic or asymptomatic. Because the blood pressure criteria for diagnosing OH are arbitrary, it often correlates poorly with symptoms (Weiss et al. 2004). Symptoms of postural hypotension and OH may include dizziness, lightheadedness and cognitive impairment, and these symptoms can be risk factors for syncope and falls, which can lead to functional impairment (Rutan et al. 1992, Ooi, et al. 2000, Kario et al. 2001, Heitterachi et al. 2002, Vloet et al. 2005).

OH can be caused by many different factors. The causes of orthostatic hypotension can be broadly divided into acute and chronic. Acute OH is usually secondary to medication or blood or fluid loss and chronic orthostatic hypotension is frequently due to altered blood pressure regulatory mechanisms and autonomic dysfunction. The ability to maintain haemodynamic homeostasis during position changes becomes less effective with age. OH is frequently a consequence of an altered blood pressure regulatory mechanism and autonomic dysfunction like loss of buffering reflexes (Gupta & Lipsitz 2007). In healthy persons, muscle contraction increases venous return of blood to the heart through one-way valves that prevent blood from pooling in dependent parts of the body. If this compensatory mechanism remains insufficient, the baroreceptor reflex is the body's rapid response system for dealing with changes in blood pressure. The baroreceptor reflex is the body's rapid response system for dealing with changes in blood pressure. Baroreceptor sensitivity decreases with age and a larger change in blood pressure is needed to activate the baroreceptor system and produce the compensatory response (Supiano 2003). Attenuated baroreceptor sensitivity might be one reason for blood pressure variation in older persons. If blood pressure falls, such as in rising from a supine to a standing position, the baroreceptor firing rate decreases. Failure of the baroreceptor system to produce an adequate response to a sudden fall in blood pressure causes orthostatic hypotension. Acute hypotension results in a disinhibition of

sympathetic activity within the medulla, so that sympathetic activity increases. These autonomic changes cause vasoconstriction, tachycardia and positive inotropy. The latter two changes increase cardiac output and lead to a partial restoration of arterial pressure (Sparks & Rooke 1987).

OH can also be caused by several medicines administered for other conditions, such as antihypertensives (Poon & Braun 2005), antidepressants (Liu et al. 1995, Poon & Braun 2005), alpha-adrenergic blocking agents (Mets 1995, Souverein et al. 2003, Poon & Braun 2005), vasodilators like nitroglycerin, and medication for Parkinson's disease (Ooi et al. 1997). In addition, arterial stiffness plays an important role in OH (Boddaert et al. 2004, Gupta & Lipsitz 2007). Medicines are major non-neurogenic causes of orthostatic hypotension. OH may be more prevalent in elderly persons due to increased use of vasoactive medications. In the study by Poon & Braun, there was a significant relationship between the number of medicines used and the presence of OH (Poon & Braun 2005). Withdrawal of fall-risk-increasing medicines like psychotropics, i.e. antidepressants and sedatives, and cardiovascular medications i.e. diuretics and digoxin showed a significant reduction in OH in older people (van der Velde et al. 2007).

The impact of OH on mortality is still under research. Some studies have concluded that it has no impact on vascular or nonvascular mortality (Tilvis et al. 1996, Weiss et al. 2006). In contrast, in some studies it has been associated with cardiovascular and all-cause mortality (Masaki et al. 1998, Luukinen et al. 1999, Luukinen et al. 2004, Verwoert et al. 2008). The presence of OH has been a significant, independent predictor of five-year all-cause mortality. The degree of blood pressure drop corresponds linearly to the increase in mortality (Masaki et al. 1998). An association with mortality and morbidity has been reported even for blood pressure drops lower than those fulfilling the OH criteria (Masaki et al. 1998, Luukinen et al. 2004). The risk of cardiovascular disease and mortality was especially strong

among very old subjects with OH (Verwoert et al. 2008). A Finnish study reported a link between diastolic OH, but not systolic OH, and the prevalence of myocardial infarction (Luukinen et al. 2004). Hypotension with OH may be an early comorbid marker of primary incipient dementia (Yap et al. 2008). In addition, OH seems to reflect a decline in overall health (Masaki et al. 1998).

About 50% of elderly persons occasionally meet the criteria of orthostatic hypotension, and evaluation and therapy are primarily driven by symptoms (Robertson 2008). Because OH itself is not a disease, the first step in treating OH is to diagnose and manage the underlying cause. Patients with symptoms or without a specific cure often benefit from non-pharmacologic treatment like slow, careful changes in position and increases in salt and fluid intake (Lipsitz 1989, Shannon et al. 2002, Lahrmann et al. 2006). The mineral corticoid fludrocortisone is used by some patients to expand intravascular volume (Lipsitz 1989).

### 2.2.2 Blood lipids

Women's cholesterol levels increase up to age 70 and decline thereafter. Men's serum total cholesterol levels usually increase up to age 60 (Abbott et al. 1998, Primatesta & Poulter 2000). Men's triglyceride level increases up to age 60 and declines thereafter; in women it declines after 70 years. This effect is more prominent in women than in men, thus hypercholesterolemia is more common in elderly women than in elderly men (Kannel 1996, Tresch & Aronow 1999, Aromaa & Koskinen 2002). In the study by Abbott et al (1998) the levels of serum total cholesterol (S-TC) and serum low-density lipoprotein cholesterol (S-LDLC) declined and the level of serum high-density lipoprotein cholesterol (S-HDLC) increased. The alterations in S-TC and S-HDLC levels may be expected to occur with advancing age regardless of risk factor status (Abbott et al. 1998). S-HDLC seems to protect elderly persons of all ages and both genders against cardiovascular disease (Cooney et al. 2009).

About half of all the elderly aged 75 years have atherosclerotic disease (Wenger 2007). The average S-TC level of men in the UK aged 75 years or more was 5.5 mmol/l and the S-HDLC level was 1.3 mmol/l. In women the values were 6.3 mmo/l and 1.6 mmol/l, respectively (Primatesta & Poulter 2000). In Finland, among the elderly aged 65 years or older, women have higher levels of S-TC and S-LDLC than men. Of woman aged 65 years or more, 39% had a S-TC level higher than 6.5 mmol/l. In men the respective proportion was 25%. Of women, 87% had a S-LDLC level ≥ 3.0 mmol/l and of men, 82%. Eighteen percent of women and 37% of men had a S-HDLC level < 1 mmol/l and 29% of the elderly had a triglyceride level ≥ 2.0 mmol/l (Aromaa & Koskinen 2002). In the population aged 75 years or more, S-LDLC values were higher among women than in men (average 3.4 to 3.5 mmol/l vs. 3.0 to 3.3 mmol/l), whereas S-HDLC levels among men were significantly lower (average 1.3 to 1.4 mmol/l vs. 1.6 mmol/l) (Strandberg et al. 2003).

### 2.2.3 Treatment guidelines for hyperlipidemia

In Finland, like in other European countries, the recommended blood lipid level in the adult population is < 5 mmol/l for S-TC, < 3 mmol/l for S-LDLC and > 1 mmol/l for S-HDLC. In the latest guidelines, cholesterol levels should be lower in patients with risk factors (i.e. diabetes): < 4.5 mmol/l for S-TC and < 2.5 mmol/l for S-LDLC level (S-TC < 4.0 mmol/l and S-LDLC < 2.0 mmol/l, if possible). In very-high-risk patients (arterial disease with symptoms and diabetes), the S-LDLC level should be lower than 1.8 mmol/l (Graham et al. 2007, Käypä hoito: Dyslipidemiat 2009). In the American guidelines, the most important factor is S-LDLC, and it is the primary target of therapy. The updated version of the Adult Treatment Panel (ATP III guideline of the American Heart Association and the National Education Panel) points out that the LDL cholesterol level in high-risk patients (persons with CHD or CHD risk equivalents (non-coronary forms of clinical atherosclerotic disease, diabetes or

multiple risk factors)) should be < 1.81 mmol/l (70 mg/dl) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001, Grundy et al. 2004). Today there are no specific guidelines for the care of elderly persons. The guidelines accentuate that the first line of treatment is to change the way of life through a healthier diet and physical exercise before starting medication. In elderly persons, diet changes must be made carefully. No benefits of weight loss have been shown in elderly aged 65 years or more, and the risk of malnutrition is high (Käypä hoito: Aikuisten lihavuuden hoito 2006, Käypä hoito: Dyslipidemiat 2009). ATP III points out that there is no age restriction when selecting persons with established coronary heart disease for LDL-lowering therapy. Older persons in the ATP III guideline include male persons aged 65 years or more and female persons aged 75 years or more. In contrast to the Finnish guidelines, the first line of therapy for older persons in the American guidelines is primary prevention and therapeutic lifestyle changes (incl. weight reduction and physical activity). In addition, LDL-lowering drugs can also be considered when older persons are at higher cardiovascular risk because of multiple risk factors (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001).

Treatment with lipid modifying agents can also be divided into primary and secondary prevention based on concomitant diseases and the total risk for cardiovascular outcomes. Primary prevention includes healthy individuals, i.e. persons with adverse lifestyles without atherosclerotic disease or its symptoms (Käypä hoito: Dyslipidemiat 2009). The objective of coronary heart disease prevention in healthy high-risk persons is to reduce the risk of manifesting coronary heart disease (Wood et al. 1998). The objective of secondary prevention is to reduce the progression of atherosclerotic disease, the risk of disability and mortality, and to prolong survival in patients with coronary heart disease or other atherosclerotic disease (Wood et al. 1998).

The guidelines point out that the treatment decisions should always be based on the total risk. In Europe, one of the most commonly used risk assessments is the SCORE (Systematic Coronary Risk Evaluation) system, based on total cardiovascular risk. In SCORE the following risk factors are integrated: gender, age, smoking, SBP and S-TC or the S-TC/S-HDLC ratio. SCORE shows the ten-year risk of fatal cardiovascular disease in high-risk regions of Europe, but it should be noted that the SCORE system is not applicable among patients aged 65 years or more (De Backer et al. 2003). In the United States and Canada the start of treatment is also based on total cardiovascular risk: the Framingham Cardiac Risk Score. It can be used to estimate the 10-year risk of developing hard cardiac heart disease (myocardial infarction and coronary death). The following risk factors are integrated into it: gender, age, smoking, SBP, S-TC, S-HDLC and if the person is currently on any medication to treat high BP (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). The Framingham Risk Score also provides tools for estimating the 10-year risk of developing general cardiovascular disease. It contains the following predictors: age, diabetes, smoking, treated and untreated SBP, S-TC and S-HDLC (BMI can be used to replace lipids in a simpler model) (D'Agostino et al. 2008). The Framingham Risk Score is not applicable among patients aged more than 79 years.

The most-used criteria for starting treatment are patients with established cardiac heart failure, peripheral artery disease or cerebrovascular atherosclerotic diseases. Treatment can be started for asymptomatic individuals who are at high risk of developing cardiovascular diseases because of multiple risk factors for developing a cardiovascular event or markedly raised levels of single risk factors like cholesterol or blood pressure, or diabetes mellitus with microalbuminuria. One reason to start therapy is if an individual has close relatives with early-onset atherosclerotic cardiovascular disease or asymptomatic individuals at

particularly high risk (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001, Käypä hoito: Dyslipidemiat 2009, Mancia et al. 2009).

### 2.2.4 Trials on serum lipid modifying agents

The proportion of elderly participants and their mean age in clinical trials has been low (Table 5). In most cases subpopulation analyses of the oldest old participants are not done due to the small number of old-old participants. Today the age range in clinical trials of elderly persons is between 65 and 82 years. Similarly, the proportion of women is often underrepresented; in real life patients in the elderly population are more than twice as likely to be women than in clinical trials. High blood cholesterol levels among elderly persons have been studied mainly in studies concentrating on secondary prevention (Miettinen et al. 1997, Lewis et al. 1998, Hunt et al. 2001, Heart Protection Study Collaborative Group 2002, Shepherd et al. 2002, Kjekshus et al. 2007). The impact of primary prevention on cardiac heart disease in older adults (> 75 years) without a history of cardiovascular events is insufficient (Shepherd et al. 2002, Ridker et al. 2008).

*Table 5. Secondary and primary prevention studies of statin use among elderly persons*

| Study | Age range, yrs (mean age) | N | Wo-men | Inclusion criteria % | Study drug | RR (95% CI) |
|---|---|---|---|---|---|---|
| Secondary prevention | | | | | | |
| 4 S<br>Miettinen et al. 1997 | 65–70 (67) | 1021 | 24 | MI > 6 months or stable angina pectoris. S-TC 5.5–8.0 mmol/l. TG ≤ 2.5 mmol/l | Simvastatin 20 mg vs. placebo | Total mortality 0.66 (0.48–0.90)<br>CHD mortality 0.57 (0.39–0.83) |
| CARE<br>Lewis et al. 1998 | 65–75 (69) | 1283 | 19 | MI 3–20 months, S-TC < 6.2 mmol/l, S-LDLC 3.0–4.5 mmol/l, TG < 4.0 mmol/l | Pravastatin 40 mg vs. Placebo | CHD mortality 0.55 (0.37–0.82) |
| LIPID<br>Hunt et al. 2001 | 65–75 (69) | 3514 | 20 | MI or unstable angina pect., S-TC 4.0–7.0 mmol/l | Pravastatin 40 mg vs. Placebo | Total mortality 0.79 (0.68–0.93) CHD mortality 0.76 (0.62–0.93) |
| HPS<br>HPS Group 2002 | 65–80 (n/a) | 10697 | 25[a] | Vascular disease or diabetes | Simvastatin 40 mg vs. Placebo | First major vascular event rate 23.1 vs 32.2 |
| CORONA<br>Kjekshus et al. 2007 | ≥ 60 (73), 41% ≥ 75 | 5011 | 4 | IHF (NYHA II–IV, LVEF < 40%) | Rosuvastatin 10 mg vs. plasebo | Total mortality 0.95 (0.86–1.05) CV-death, nonfatal MI and nonfatal stroke 0.92 (0.83–1.02). Any coronary event 0.92 (0.82–1.12) |
| Primary- and secondary prevention | | | | | | |
| PROSPER<br>Shepherd et al. 2002 | 70–82 (75) | 5804 | 52 | Pre-existing vascular disease or raised risk (smoking, hypertension or diabetes) | Pravastatin 40 mg vs. placebo | Total mortality 0.97 (0.83–1.14). CHD death or non-fatal MI or fatal or non-fatal stroke 0.85 (0.74–0.97) |
| Primary prevention | | | | | | |
| JUPITER<br>Ridker et al. 2008 | 60–71 (Md 66) | 17802 | 38 | Apparently healthy with high hs-CRP | Rosuvastatin 20 mg vs. plasebo | Total mortality 0.80 (0.67–0.97)<br>Occurrence of a first major cardiovascular event; nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure or confirmed death from CV causes 0.53 (0.40–0.69) |

*MI= myocardial infarction, CHD= coronary heart disease, S-TC=serum total cholesterol, S-LDLC= serum total lo- density lipoprotein cholesterol, TG= triglycerides, IHF= Ischaemic heart failure, [a]data contain a cohort of young and elderly patients*

#### 2.2.4.1 Primary prevention studies on the use of statins

The PROSPER trial addressed the high-risk elderly population (age 70–82 years) with existing vascular disease (secondary prevention) or at high risk of developing vascular disease (primary prevention). Primary prevention was part of the study and there was no statistical difference between the placebo and statin groups and cardiovascular outcomes (Shepherd et al. 2002). In contrast, in the JUPITER trial, apparently healthy people on rosuvastatin (median age 66) with CRP concentrations > 2.0 mg/l had significant reductions in ischemic vascular events as well as total mortality (Ridker et al. 2008). Unfortunately the follow-up period was only 1.9 years. Due to the short follow-up, coincidence might have had an influence on the results of the JUPITER study.

#### 2.2.4.2 Secondary prevention trials on the use of statins

Many studies have shown that using of statins reduces all-cause mortality among patients with risk factors for vascular disease (Afilalo et al. 2008). The Scandinavian Simvastatin Survival Study (4S) was the first clinical trial to show significant reductions in total as well as coronary mortality among elderly persons using statins (Miettinen et al. 1997). The CARE and LIPID studies showed that elderly persons treated with statins had a lower risk for coronary events and of dying from coronary events. In the CARE study patients with myocardial infarction and a S-TC level < 6.2 mmol/l and a S-LDLC level of 3.0–4.5 mmol/l who were on pravastatin were associated with a lower risk for major coronary events and stroke (Lewis et al. 1998). In the LIPID study, patients with coronary heart disease and a S-TC level of 4.0–7.0 mmol/l, pravastatin reduced the risk for all major cardiovascular events and all-cause mortality (Hunt et al. 2001). The PROSPER trial addressed the high-risk elderly population (age 70–82 years) with existing vascular disease (secondary prevention) or at high risk of developing vascular disease (primary prevention). There was no difference in all-

cause mortality between the pravastatin and placebo groups, but in secondary prevention the risk for coronary disease mortality or non-fatal MI was lower in elderly persons on pravastatin (Shepherd et al. 2002). A new study on the use of rosuvastin in older patients with ischaemic heart failure showed that use did not reduce the primary outcome or the number of deaths from any cause despite having favorable effects on lipid levels, but it reduced the number of cardiovascular hospitalisations (Kjekshus et al. 2007). Comparable results were also observed in the GISSI-HF study on patients with heart failure treated with rosuvastatin (GISSI-HF Investigators 2008).

### 2.2.5 High blood pressure and high cholesterol levels as risk factors

For middle-aged patients with vascular disease, traditional cardiovascular disease risk factors like high serum cholesterol and high blood pressure are associated with greater all-cause and cardiovascular mortality (MacMahon et al. 1990, Stamler et al. 1999, Stamler et al. 2000). Also the benefits of cholesterol-lowering/blood pressure-lowering treatments are well documented in middle-aged populations (LaRosa et al. 1999, Ogden et al. 2000). There are several difficulties in interpreting mortality predictors in old age, and there are only a few population-based studies among elderly persons aged 75 years or more. Some studies have shown that, for example hypertension or hypercholesterolemia are associated with better prognosis in older persons and the association between lipid levels/blood pressure and total mortality are different in the elderly compared with the younger population (Mattila et al. 1998, Stamler et al. 1999, Stamler et al. 2000, Schatz et al. 2001). Some observational studies of persons aged 65 years or older suggest that not only cholesterol (Weverling-Rijnsburger et al. 1997, Song, Sung & Kim 2000, Schatz et al. 2001, Casiglia et al. 2003, Schupf et al. 2005, Tikhonoff et al. 2005, Spada et al. 2007) but also blood pressure might be inversely associated

with total mortality (Mattila et al. 1988, Kronmal et al. 1993, Hakala et al. 1997, Rastas et al. 2006, van Bemmel et al. 2006, Oates et al. 2007, Molander et al. 2008). With ageing the predictive power of these traditional risk factors seems to disappear or at least lose some of its predictive potency (Menotti et al. 2004). This is partly due to the selective survival (individuals with risk factors are likely to die at a younger age than those without) and survivor effect (leading to a surviving population with fewer risk factors) (Tresch & Aronow 1999). Based on a large meta-analysis, it seems that the relative effect of total cholesterol and systolic blood pressure above 145 mmHg on ischaemic heart disease mortality attenuates in all age groups and the association between total cholesterol and total stroke mortality is inverse in the age group of 70–89 years and among those with systolic blood pressure above 145 mmHg (Prospective Studies Collaboration et al. 2007).

Sometimes the inverse association between blood pressure or serum total cholesterol and mortality has been interpreted to be due to confounding by chronic diseases such as dementia (Manolio et al. 1993, Guo et al. 1998). Still, some epidemiological studies have shown that an inverse association remains among the oldest old even when adjusted for co-morbid diseases (Kronmal et al. 1993, Weverling-Rijnsburger et al. 1997, Hakala et al. 1997, Schatz et al. 2001, Schupf et al. 2005, Rastas et al. 2006, van Bemmel et al. 2006, Oates et al. 2007, Molander et al. 2008).

## 2.3 USE OF CARDIOVASCULAR MEDICATION

Wholesale sales of cardiovascular drugs in Finland totaled 230 million euro in 2007, which makes them the third largest group in terms of sales. The consumption of cardiovascular drugs increased by 8% from the year 2006 (Suomen lääketilasto 2008). In general, the use of diuretics decreased (1%). In contrast, the use of beta blocking agents (1%) and

calcium channel blockers (7%) increased in 2007. The biggest increase was in the newest group of cardiovascular medicines; the use of agents acting on the renin angiotensin system increased by 10%.

### 2.3.1 Use of cardiovascular medication among elderly populations

The amount of drugs in use has increased among both men and women, especially among persons aged 85 years and over (Jylhä 1994, Linjakumpu et al. 2002a, Linjakumpu et al. 2002b, Jyrkkä et al. 2006). In Finland, cardiovascular medicines like antihypertensives have for decades been the most-used medication among elderly persons, reflecting the high prevalence of cardiovascular diseases (Nissinen et al. 1989, Korhonen et al. 2008a). Overall, over half of the elderly population in Finland used cardiovascular medicines (Linjakumpu et al. 2002b). Similarly, cardiovascular drugs followed by central nervous system drugs are the most commonly used prescription drugs among the Danish and Swedish elderly (Barat et al. 2000, Rosholm et al. 1998, Jörgensen et al. 2001) and similar results have been reported in other European countries (Nobili et al. 1997) and the United States (Kaufman et al. 2002) (Table 6).

*Table 6. Use of cardiovascular (CV) medicines among home-dwelling elderly persons*

| Reference | | Setting | Subjects | N | Use of cv medicines |
|---|---|---|---|---|---|
| Nobili et al. 1997 | Italy 1990–1993 | Cross-sectional study with randomly selected patients from 34 practice records | ≥ 75 years | 261 | 62% of men, 79% of women |
| Jörgensen et al. 2001 | Sweden 1994 | Retrospective cohort study | ≥ 65 years | 4642 | 47% of the study group |
| Barat et al. 2000 | Denmark 1997–1999 | Cross-sectional study with a random sample | ≥ 75 years | 492 | 46% of the study group |
| Strandberg et al. 2001 | Finland 1998–1999 | A population-based, cross-sectional postal survey | Subpopulation ≥ 75 years with CHD | 717 | 76% of men, 80% of women (regular medication) |
| Linjakumpu et al. 2002 | Finland 1990–1991 and 1998–1999 | Two cross-sectional studies | ≥ 65 years | -90–91: 1131<br>-98–99: 1197 | 75–84 yr 57% (men), 63% (women)<br>> 84 yr 60% (men), 76% (women)<br>75–84 yr 57% (men), 65% (women)<br>> 84 yr 56% (men), 85% (women) |
| Brekke et al. 2006 | Norway 1997–1999 | A population-based postal survey | 70–74 years | 3341 | Antihypertensive medicine (C02, C03, C07, C08, C09): 35% of men, 33% of women |
| Lernfelt et al. 2003 | Sweden (1971–) 2000 | Cohort study | 70 years<br>79–80 years | 506<br>212 | 70 years: 40% of study group<br>79–80 years: 47% of men and 45% of women |
| Jyrkkä et al. 2006 | Finland 1998–2003 | Prospective follow-up study | ≥ 75 years | 339 | 1998: 79% of all home-dwelling, 54% of all in institutions<br>2003: 86% of all home-dwelling, 80% of all in institutions |

In the study by Fishkind et al. the most-used cardiovascular medicines among elderly persons were diuretics, beta blockers and calcium channel blockers (Fishkind et al. 1997). The use of acetylsalicylic acid (68.3% of men, 61.0% of women) and long-acting nitrates (54.7% and 52.9%, respectively) and beta blockers (52.4% and 54.7%, respectively) is high among elderly persons with coronary disease (Strandberg et al. 2001). In the USA, the medicines most used by the elderly aged 75+ were acetylsalicylic acid (53.8%), statins (25.3%) and beta blockers (19.6%) (Nahin et al. 2009). In Finland, the most-used cardiovascular medicines among centenaries were diuretics (59% of all users) (Korhonen et al. 2008a).

The use of digitalis in the treatment of heart failure has decreased over the years. In 1992 and 2000 it had almost disappeared as an alternative in the treatment of heart failure (men aged 70 years 4%, women aged 70 years 0%) (Lernfelt et al. 2003). In Finland, 10% of the elderly aged 100 years or older used digitalis (Korhonen et al. 2008a). In the USA 17% of the study subjects used digitalis (Fishkind et al 1997). In Canada, 32% of long-term residents with heart failure used digitalis (Misiaszek et al. 2005).

In the study by Putnam et al. (2004) there was a difference in the use of beta blockers between genders (men used more) (Putnam et al. 2004). In a Finnish study women more often used ACE inhibitors, diuretics and digitalis (Strandberg et al. 2001). In comparison, in 1989 women used more diuretics, but beta blockers were more common among men in Finland (Nissinen et al. 1989). In the Framingham study, the use of thiazide diuretics increased in patients older than age 60 years, with women using them more often than men (Lloyd-Jones et al. 2005). In many studies there were no significant differences between genders in the use of blood pressure and cholesterol lowering medicines (Chen et al. 2001, Brekke et al. 2006).

### 2.3.2 Use of serum lipid modifying agents

The use of serum lipid modifying agents, especially statins (HMG CoA reductase inhibitors), has increased rapidly among elderly persons in Finland and other western countries, and the trend in current statin use seems to be moving towards more extensive use among elderly persons (Walley et al. 2005) (Table 7). In 1971–1972 only 1% of men aged 70 years or more and 3% of women aged 70 years or more used serum lipid modifying agents (Lernfelt et al. 2003). Since the 1990s the use of serum lipid modifying agents has increased rapidly and mostly among the oldest old, peaking in the age group of 70–79 years in both sexes (Hartz et al. 2007). In 2000 more than 10% of elderly persons used cholesterol-lowering medication. The use of serum lipid modifying agents increased tenfold during these years among men and threefold among women (Lernfelt et al. 2003, Carroll et al. 2005, Raymond et al. 2007).

*Table 7. Use of lipid modifying agents among home-dwelling elderly persons*

| Reference | | Setting | Subjects | N | Outcome |
|---|---|---|---|---|---|
| Lemaitre et al. 1998 | United States of America | Cohort study | ≥ 65 years | 5201 | 1989–1990: 5% (men), 6% (women)<br>1995–1996: 8% (men), 10% (women) |
| Majeed et al. 2000 | England and Wales | 288 general practices database | Subpopulation 75–84 years | 112829 | 1996: 0.6%. Of those with IHD: 2.4% (men) and 2.5% (women) |
| Primatesta et al. 2000 | England 1998 | Cross-sectional survey | Subpopulation ≥ 65 years | 2195 | Of all, 4% |
| Primatesta et al. 2004 | England and Scotland 1998 | Cross-sectional survey | Subpopulation 65–74 years | | Of all, 7% |
| Brekke et al. 2006 | Norway 1997–1999 | A population-based postal survey | 70–74 years | 3341 | Of all, 13% |
| Strandberg et al. 2001 | Finland 1998–1999 | A population-based, cross-sectional postal survey | Subpopulation ≥ 75 years with CHD | 717 | 14% of women<br>19% of men |
| Whincup et al. 2002 | Britain 1998–2000 | Cross-sectional survey in 24 general practice | Men 60–75 years | 3689 | Of all, 8%; those with MI, 36%; with angina pectoris, 23% |
| Lernfelt et al. 2003 | Sweden 1971-2000 | Cohort study | 70-80 years | 973 | 1971–1972: 1% (men) and 3% (women)<br>2000: 10% (men) and 9% (women) |

*Table 7. Continued*

| Reference | | Setting | Subjects | N | Outcome |
|---|---|---|---|---|---|
| DeWilde et al. 2003 | England, Wales 1994–2001 | Database of about 300 general practitioner with IHD patients | Subpopulations 75–84 years and ≥ 85 years | 75–84: 9901<br>85+: not reported | In 1998: 75–84 years 10%; 85+, 1% |
| Hartz et al. 2004 | Norway 2001 | Cross sectional population-based study | Subpopulation > 70 years | Subpopulation not reported<br>Total: 7973 | 19% of men and 14.5% of women |
| Bartholomeeusen et al. 2008 | Flanders 1994–2003 | Database of 47 general practices | Subpopulation ≥ 75 years | 925 | 1994: 11% in the group with cholesterol test<br>2003: 35% in the group with cholesterol test |
| Raymond et al. 2007 | British Columbia 1996–2004 | Person-specific data set | Subpopulation 65–84 years and ≥85 years | Not reported | 1996: 65–84 yr 4%, ≥ 85 yr 0.5%<br>2004: 65–84 yr 21%, ≥ 85 yr 8% |
| Nahin et al. 2009 | United States of America 2000–2002 | Cross-sectional analysis | ≥75 years | 3070 | Of all, 25% |
| Korhonen et al. 2008 | Finland 2000–2005 | Prescription register | ≥ 65 years in 2005 | 2310 | 2000, 19%<br>2003, 31%, 2005: 40% |
| Ruokoniemi et al. 2008 | Finland 1995–2005 | Prescription register | Subpopulation ≥ 75 years | Not reported | Men in 1995, 0.7%, and 28% in 2005. In women, respectively, 0.7% and 26%. |

The use of serum lipid modifying agents has increased also in Finland (Martikainen et al. 1997, Ruokoniemi et al. 2008). In 2007 lipid modifying agents were used 20% more than in 2006 (Suomen lääketilasto 2008). One-year prevalence increased forty-fold from 1995 to 2005, from 7.0 per 1000 to 283.3 per 1000 in males and from 6.7 per 1000 to 264.4 per 1000 in females among persons aged at least 75 years (Ruokoniemi et al. 2008). One out of three elderly persons aged 65 years or more used serum lipid modifying agents (Aromaa & Koskinen 2002, Savolainen 2007).

## 2.4 ADVERSE DRUG EVENTS ASSOCIATED WITH THE USE OF CARDIOVASCULAR MEDICATIONS

Treatment of cardiovascular diseases with multiple, concomitant medications to achieve cardiovascular benefits must be balanced against potential harm among elderly persons. With ageing, all aspects of pharmacokinetics and pharmacodynamics (absorption, distribution, metabolism, excretion and target organ sensitivity) may be affected and the possibility of adverse drug events may increase (Ewing 2002, Cassel 2003) (Table 8).

*Table 8. Adverse effects of cardiovascular medicines in elderly populations*

| Medicine group | Adverse effect |
|---|---|
| Cardiac glycosides | Cardiac arrhythmias<br>States of confusion, nausea, vomiting, blurred vision (halos around objects; yellow, green, white) |
| ACE inhibitors | Cough, dry mouth, dizziness, rash<br>Hyperkalemia, hypoglycaemia |
| Angiotensin II antagonists | Dizziness<br>Hypotonia, weakness |
| Beta blocking agents | Heart failure, bradycardia, dizziness<br>Intermittent claudication |
| Calcium channel blockers | Constipation, oedema, weakness |
| Vasodilatators | Hypotonia |
| Diuretics | Disorders of salt balance, hypokalemia, hypomagnesemia<br>Dehydration<br>Fatigue, dizziness, orthostatic symptoms<br>Impaired glucose tolerance |
| Nitrates | Headache, orthostatic symptoms |
| HMG-CoA reductase inhibitors (statins) | Constipation, nausea, diarrhoea<br>Myalgia (muscle pain, aching, weakness)<br>Myositis (myalgia + elevated serum levels of creatine kinase)<br>Rhabdomyolysis |

*(Tilvis & Aantaa 2001, Ewing 2002, Tomlinson & Mangione 2005, Aronow & Frishman 2007, Pharmaca Fennica 2009)*

It has been shown that medicines used mainly for hypertension are associated with adverse events apart from their cardiovascular outcomes. The current guidelines suggest the use of several medications, if needed, to control hypertension (Chobanian et al. 2003, Käypä hoito: Kohonnut verenpaine 2009). Every tenth hypertensive patient reported symptoms related to antihypertensive medication spontaneously, and 20% did so when asked for symptoms (mean age of patients, 64 years) (Kumpusalo et al. 1997). In the same study, 80% of hypertensive patients reported at

least one symptom and an average of four symptoms. Dizziness, headache, muscular cramps, cough and faintness are adverse drug events perceived by patients and that are associated with antihypertensive medications. With increasing age, symptoms like dry mouth, dizziness during postural changes, other dizziness, urinary incontinence and constipation increased (Kumpusalo et al. 1997).

Higher cumulative exposure to antihypertensive medications has been associated with adverse events on physical performance, but not on cognition or depression (Agostini et al. 2007). In the study by Euser SM et al., for persons aged 65 to 74, higher baseline systolic and diastolic blood pressure were related to worse cognitive function 11 years later, but at older ages (75+) higher SBP and DBP were related to better cognitive function 11 years later. The effect of blood pressure on cognition was strongest in the highest age group (aged 85) (Euser et al. 2009). In the study by Tipping et al., cardiovascular drugs accounted for 36% of total adverse drug events among patients aged 65 years and older (Tipping et al. 2006).

The use of serum lipid modifying agents together with polypharmacy and impaired renal and hepatic function and certain concomitant medications may increase the risk of clinically important adverse events (Routledge et al. 2004). The most common side event is skeletal myopathy, with symptoms ranging from pain and fatigue to serious rhabdomyolysis. All statins are associated with the adverse effects of myopathy (Pasternak et al 2002), and symptoms of myopathy may occur at any time after initiation of statin therapy. Factors that may increase the risk of myopathy are, for example, age > 80 years, being female and frailty (Fig 1). In general populations, patients who may benefit most from statin therapy often are patients with comorbidities and multiple medications. Due to this, they also are at high risk for myopathies and other adverse effects (Ballantyne et al. 2003). Myositis refers to muscle symptoms, as myositis with increased levels of creatine kinase (CK) and muscle-related

pathologies is most often confirmed by serum CK levels (Tomlinson and Mangione 2005). However, muscle weakness or muscle pain has also been reported without CK elevation suggesting that the CK level may not be an adequate test for muscle pathology (Phillips et al 2002). In clinical trials with strict inclusion criteria and frequent monitoring, the incidence of muscle problems is reported to be low. The incidence of severe myopathy is low, occurring in less than 0.1% of patients receiving statin monotherapy (Staffa et al. 2002). But, it has been indicated that less serious adverse effects, like muscle pain and weakness, are underreported, and their incidence increases among patients taking multiple medications and among those with multiple risk factors, and it may be up to 10.5% in the general population (Bruckert et al. 2005). In addition, the incidence of less severe muscle complaints is not well defined among the elderly population (Thompson et al. 2003). In the study by Buettner et al., in adults aged ≥ 40 years, statin users were significantly more likely to report musculoskeletal pain than were non-users (Buettner et al. 2008).

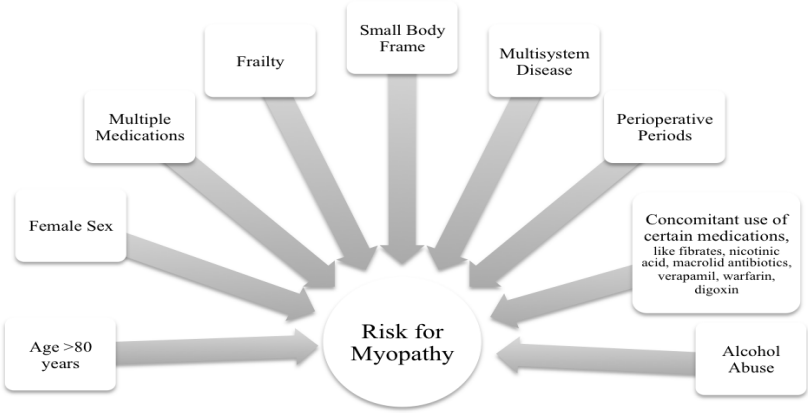



*Figure 1. Factors that may increase the risk of myopathy in statin users (Tomlinson S & Mangione K 2005)*

# *3 Aims of the study*

The general aim of this study was to investigate the use of cardiovascular medicines and outcomes of treatment among elderly persons aged 75 years or more.

The specific aims of this study were:

1. To analyse the use of cardiovascular medication among elderly persons according to age and sex and other socio-demographic background variables.
2. To analyse the use of serum lipid modifying agents with special reference to concomitant cardiovascular risk factors and the effects of treatment on lipid levels.
3. To examine the relationship between serum total cholesterol and six-year all- cause mortality in elderly persons when adjusted for concomitant diseases
4. To study postural changes in blood pressure and prevalence of orthostatic hypotension. In addition, to find associations between the use of medications and orthostatic hypotension.

# *4 Material and methods*

The present thesis is comprised of two prospective, longitudinal, population-based studies focusing on the clinical epidemiology of diseases, functional capacity and use of medicines in a population of elderly persons aged 75 years or older.

*Table 9. Design, population and main outcome of publications I–IV presented in this doctoral thesis*

| **Publications (I–IV refers to original publication)** | **Design** | **Data** | **Time** | **Main outcomes measured** |
|---|---|---|---|---|
| Work I | Cohort | Kuopio 75+ | 1998–2003 | 1) Use of cardiovascular medications<br>2) Changes in the use of cardiovascular medication |
| Work II | Cross-sectional analysis with a two-year follow-up of a cohort study | GeMS | 2002–2004 | 1) Use of serum lipid modifying agents<br>2) Changes in cholesterol levels |
| Work III | Prospective cohort study | Kuopio 75+ | 1998–2003 | 1) Six-year all-cause mortality |
| Work IV | Cross-sectional analysis of a population-based cohort | GeMS | 2004 | 1) Prevalence of orthostatic hypotension, and the associations with the use of medicines<br>2) Changes in blood and pulse pressures following postural change |

## 4.1 STUDY POPULATION

The study population consists of two different study populations: Kuopio 75+ (work I & III) and the GeMS study (work II & IV), both carried out in the City of Kuopio, Finland.

### 4.1.1 Kuopio 75+ study (Work I, III)

The Kuopio 75+ study is a prospective, population-based, multidisciplinary health study focusing on the clinical epidemiology of diseases, medication and functional capacity in elderly persons aged 75 years or older. All subjects aged 75 years or more living in the City of Kuopio on January 1, 1998 (N = 4518), were eligible. From this population a random sample of 700 persons was drawn. The final cohort included 601 participants (86%): 79 declined to participate, 15 died before the examination and five could not be contacted. The final cohort attended a structured clinical examination and an interview conducted by a geriatrician and a trained nurse. Of these 601 clinically examined subjects 74% were females. At the baseline 87% (n = 523) were home-dwelling and 13% (n = 78) lived in institutional care. The follow-up survey was conducted in 2003 with 339 participants (females 75%) in the same way as in 1998, except that there was no clinical examination by a physician. The loss of participants due to death (n = 233) during the follow-up period was significant, and in addition 29 participants declined to participate or could not be reached. Of the surviving persons, 85% (n = 289) were home-dwelling and 15% (n = 50) lived in institutional care.

In work III, out of 523 home-dwelling participants, 30 who used lipid modifying agents and three persons with missing data on cholesterol and blood pressure measurement were excluded. Thus the final sample consisted of 490 home-

dwelling elderly who were examined in 1998. The mean age of the participants was 81 years and 72% were females.

### 4.1.2 GeMS study (II, IV)

The GeMS study (Geriatric Multidisciplinary Strategy for Good Care of the Elderly) consisted of all the inhabitants, whether living in an institution or at home, in the city of Kuopio in eastern Finland who were aged 75 years or older on November 1, 2003. From this population, a random sample of 1000 persons was drawn.

In the GeMS study the subjects were randomised into intervention (n = 500) and comparison (n = 500) groups. Of the randomised subjects, 162 persons declined to take part in the survey, 55 died before the examination and two moved away. The participation rate was 78% (n = 781) in the entire population, 81% (n = 404) in the intervention group and 75% (n = 377) in the comparison group.

The final study population attended a structured clinical examination and an interview conducted by a trained nurse in 2004. Physiotherapists tested their functional capacity, strength and balance. In 2006, 116 participants had died before the examination, one had moved away, and seven persons declined to take part in the survey. The remaining 657 participants attended a similar examination as in 2004.

In work IV, of all the examined elderly persons in 2004 (n = 781), we excluded those in institutional care (n = 82) and the home-dwelling elderly without an orthostatic test (n = 46). Work IV is based on information from the 653 home-dwelling elderly with an orthostatic test. Of the participants, 70% were females and the mean age of our participants was 81 years.

Work II is based on information from all the elderly persons examined in 2004 and 2006 with cholesterol measurements (n = 622). Of all the elderly persons examined in 2004 and 2006 (n = 657), seven did not have a cholesterol measurement in 2004, 18 did not have a cholesterol measurement in 2006 and ten did not have a cholesterol

measurement in neither 2004 nor 2006. The mean age of the participants was 80 years and 71% were females.

## 4.2 METHODS

### 4.2.1 Methods in the Kuopio 75+ Study (I, III)

The data for the Kuopio 75+ study were collected by means of interviews, clinical examinations and clinical tests. A trained nurse at the outpatient clinic of a municipal hospital interviewed the participants about their use of medicines and recorded the medicines they were currently taking. The participants were also asked to bring their prescriptions and medicine containers with them to the examination. In addition, a geriatrician reviewed the medication and examined the subjects' overall physical and mental health. A close relative or a caregiver gave the required information if the participant could not answer the questions. If a participant was unable to visit the municipal hospital, a nurse and a geriatrician visited the home to perform the interview and examination and to check the use of medication.

To collect the data, medical records from the municipal health centre, home nursing service, local hospitals and the Kuopio University Hospital were also available. Mortality data were obtained from Statistics Finland, which is the National Health Register Authority in Finland. Life span was calculated from the date of examination in 1998 to 31.12.2003. There was no loss to follow-up.

### 4.2.2 Methods in the GeMS Study (II, IV)

The basic demographic and clinical data were collected by means of interviews and measures (i.e. cholesterol). A trained nurse interviewed all the study participants about their health and health behaviour. The use of medicines was asked from the participants and the medicines they were currently taking were recorded. The participants were also asked to bring their prescription forms and medicine containers with

them to the interview. A Comprehensive Geriatric Assessment (CGA) of the subjects randomised into the intervention group was done yearly. In the GeMS study, physicians who were trainees in geriatrics, trained nurses and physiotherapists did the CGA. The CGA was not specifically aimed at cardiovascular risk factors or serum lipids. There were no differences in the use of serum lipid modifying agents or cholesterol levels between the intervention and comparison groups during the years 2004–2006. As there were no differences, we combined the study groups in work III. If the person him/herself could not answer the questions, a relative or a caregiver gave the required information. If the participant was unable to visit the clinic, a trained nurse made a home visit. Medical records from the municipal health centre, home nursing service, local hospitals and Kuopio University Hospital were also available. To define concomitant diseases, we used the National Insurance Institution Special Refund Registers for 2003 and 2005.

### 4.3 VARIABLE DEFINITIONS

**Use of medicines**

Both regularly and irregularly taken prescribed and non-prescribed medicines were recorded. If a medicine was taken daily or at regular intervals, it was recorded as being in regular use. If it was taken only when needed, it was recorded as being in irregular use. The medicines were classified according to the Anatomic Therapeutic Chemical (ATC) classification system, version 2004, recommended by the World Health Organization (WHO) for drug utilisation studies. (I–IV)

**Self-rated health**

In assessing self-rated health, the participants were asked to grade their health as good, fairly good, moderate, fairly poor

or poor. For the analyses, the participants with good or fairly good health were combined as having good health and the participants with fairly poor or poor health were combined as having poor health and thus the final classification was good, moderate and poor. (III)

**Cardiovascular medicines**

According to the ATC classification cardiovascular medicines (C) include cardiac therapy and medicines used mainly for hypertension, diuretics, beta blocking agents, calcium channel blockers and agents acting on the renin-angiotensin system. Preventive medication for cardiovascular diseases includes lipid modifying agents, low-dose aspirin and warfarin. In counting the number of cardiovascular medicines in use, fixed combinations of two different agents were counted as one medicine. (I)

**Orthostatic hypotension**

The criteria for orthostatic hypotension (OH) were those defined by the American Autonomic Society and the American Academy of Neurology: a systolic blood pressure decrease of at least 20 mm Hg (systolic OH) or a diastolic blood pressure decrease of at least 10 mm Hg (diastolic OH) within three minutes of standing up (American Autonomic Society and the American Academy of Neurology 1996). (IV)

**Serum lipid modifying agents**

According to the ATC classification, serum lipid modifying agents (C10) included cholesterol and triglyceride reducers HMG CoA reductase inhibitors (statins, C10AA). In addition, it included fibrates (C10AB), bezafibrate (C10AB02), bile acid sequestrants (C10AC), cholestyramine (C10AC01) and other lipid modifying agents (C10AX) and ezemibid (C10AX09). (II)

**Serum total cholesterol**

Serum total cholesterol was measured once by the laboratorian in the Kuopio University Hospital after 12-hour fasting. All serum total cholesterol assays were analyzed in the Kuopio University Hospital laboratory using standard enzymatic techniques (II, III) (Käypä hoito: Dyslipidemiat 2009). To determine if cholesterol levels had changed during the study period, the difference between levels had to be greater than +/- 0.2 mmol/l for total and LDL cholesterol levels and greater than +/- 0.1mmol/l for HDL cholesterol level. (II)

**Concomitant diseases**

The Social Insurance Institution Special Refund Register was used in 2003 and 2005 to define concomitant diseases. The participants were classified as having coronary artery disease/diabetes mellitus/hypertension if they were entitled to special refunds for coronary artery disease/diabetes mellitus/hypertension before the examination. The subgroup with no risk for cardiovascular outcomes included non-smoking elderly persons without special refunds for diabetes mellitus, coronary artery disease and hypertension or any diagnosis of these diseases. (III)

### 4.4 DATA ANALYSIS

Statistical analyses in this doctoral thesis were performed with SPSS 11.5 and 14.0 (Statistical Package for Social Sciences). The statistical tests were two-sided and the criterion of statistical significance was $p < 0.05$.

The results in work I are presented as proportions of medicine users and mean numbers (± 95% CI) of medicines used. McNemar's test was used to analyse the statistical significance of changes in medicine use between the surveys in 1998 and 2003. The statistical significance of differences in categorical variables was analysed using the chi-square test.

In addition, in work III the statistical significances of differences between exposures groups were tested using the Kruskal-Wallis test, and in work II continuous variable differences were analysed using the non-parametric Mann-Whitney U-test. The T-test was used to analyse the differences in pulse pressures between the OH groups in work IV. In work II, data for total, HDL and LDL cholesterol levels are presented as the mean ± SD for the baseline examination in 2004 and the follow-up examination in 2006. The two-sided non-parametric Wilcoxon test was used to assess the statistical significance of changes in cholesterol levels during the study period.

The Kaplan-Meier method was used to estimate survival and compared using the log-rank test. The association between S-TC and mortality was analysed using the Cox proportional hazards model. A supplementary analysis a propensity score (PS) for each participant in the Cox model was included. The PS was estimated with a multinomial logistic regression model that included the following variables: age (continuous variable), atrial fibrillation, dementia, NYHA classification, systolic blood pressure (continuous variable), use of loop diuretics, Mini-Mental state examination score, sex, self-reported health, diabetes mellitus, history of cancer, valvular insufficiency, history of hypertension, myocardial infarction, bypass operation, use of long-acting nitrates, use of blood pressure-lowering medication, obstructive pulmonary disease, Parkinson's disease, heart failure (Boston criteria). In the PS-adjusted model, coronary disease variables were included individually.

### 4.5 ETHICAL CONSIDERATIONS

Written informed consent was obtained from the study participants or their caregivers and relatives. The Kuopio 75+ study and the GeMS study were approved by the Ethics Committee of the Hospital District of Northern Savo and the University Hospital of Kuopio.

# 5 Results

## 5.1 PREVALENCE OF CARDIOVASCULAR MEDICINES USE (I)

Regular use of cardiovascular medicines increased during the years 1998–2003 from 80% to 87% ($p < .001$) among the study population ($n = 339$). The number of medicines used ranged from 0 to 8. The mean number of regularly used cardiovascular medicines increased from 2.1 (95% CI 1.9–2.3) to 2.7 (95% CI 2.5–2.9, $p < .001$) during the follow-up period. The use of three or more cardiovascular medicines increased especially with advanced age (Table 10).

*Table 10. Number and mean number of regularly used cardiovascular (CV) medicines* and proportions of users (%) in all the survivors aged 75 years or more by age groups in 1998 and 2003*

| | Age at baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 75–79 (n = 171) | | 80–84 (n = 116) | | 85 + (n = 52) | | Total (n = 339) | |
| | 1998 | 2003 | 1998 | 2003 | 1998 | 2003 | 1998 | 2003 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Number of CV medicines** | | | | | | | | |
| 0 | 35 (20) | 27 (16) | 24 (21) | 13 (11) | 9 (17) | 5 (10) | 68 (20) | 45 (13) |
| 1–2 | 77 (45) | 64 (3) | 39 (33) | 34 (29) | 23 (44) | 12 (23) | 139 (41) | 110 (33) |
| ≥3 | 59 (35) | 80 (47) | 53 (46) | 69 (60) | 20 (39) | 35 (67) | 132 (39) | 184 (54) |
| **Mean number of CV medicines in regular use** | | | | | | | | |
| | 1.9 | 2.4 | 2.2 | 2.9 | 2.1 | 3.1 | 2.1 | 2.7 |
| (95 % CI) | (1.7–2.2) | (2.1–2.7) | (1.9–2.6) | (2.6–3.2) | (1.8–2.6) | (2.6–3.5) | (1.9–2.3) | (2.5–2.9) |

** including preventive medication: low-dose aspirin, lipid modifying agents and warfarin*

### 5.1.1 Use of cardiovascular medicines

The most-used cardiovascular medicines in both years were beta-blocking agents. In 2003 every other participant used at least one beta-blocking agent. The use of low-dose aspirin was also high (Table 11). Among the medicines used mainly for hypertension, the use of diuretics, beta blockers and ACE inhibitors and AT 1 receptor antagonists increased significantly during the follow-up period ($p < .001$). The most-used group of cardiac therapies was long-acting nitrates. The use of cardiovascular medicines increased among both men and women. In 1998, 32% of women and 14% of men used diuretics. In contrast, the use of low-dose aspirin was more common among men (49% vs. 36%) in 1998. In 2003 there was no significant differences between genders.

According to age, the proportion of ACE inhibitor and AT 1 receptor antagonist users increased significantly (from 20% to 28%, $p < .001$) among the youngest age group. Among the oldest old (85+), the proportion of diuretic users doubled during the study period (from 31% to 62 %, $p < .001$).

*Table 11. Percentages (%) and numbers of all survivors who regularly used cardiovascular medicines, by medicine group in 1998 and 2003*

| | Age at baseline | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 75–79 (n = 171) | | 80–84 (n = 116) | | 85 + (n = 52) | | Total (n = 339) | | P-value |
| | 1998 | 2003 | 1998 | 2003 | 1998 | 2003 | 1998 | 2003 | |
| | n (%) | N (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | |
| **Cardiac therapy** | 45 (26) | 50 (32) | 48 (41) | 56 (48) | 24 (46) | 33 (64) | 117 (35) | 144 (43) | *** |
| Digoxin | 12 (7) | 16 (9) | 13 (11) | 14 (12) | 8 (15) | 6 (12) | 33 (10) | 36 (11) | NS |
| Long-acting nitrates | 37 (22) | 46 (27) | 42 (36) | 50 (43) | 21 (40) | 30 (58) | 100 (29) | 126 (37) | *** |
| **Medicines used mainly for hypertension** | | | | | | | | | |
| Diuretics | 39 (23) | 46 (27) | 37 (32) | 56 (48) | 16 (31) | 32 (62) | 92 (27) | 134 (40) | *** |
| Beta blockers | 75 (44) | 78 (46) | 57 (49) | 75 (61) | 21 (40) | 24 (46) | 153 (45) | 173 (51) | * |
| Calcium channel blockers | 34 (20) | 41 (24) | 17 (15) | 15 (13) | 9 (17) | 12 (23) | 60 (18) | 68 (20) | NS |
| ACE inhibitors and AT 1 receptor antagonists | 34 (20) | 48 (28) | 24 (21) | 38 (33) | 8 (15) | 15 (29) | 66 (20) | 101 (30) | *** |
| **Preventive medication** | | | | | | | | | |
| Lipid modifying agents | 18 (11) | 29 (17) | 6 (5) | 9 (8) | 1 (2) | 3 (6) | 25 (7) | 41 (12) | *** |
| Low-dose aspirin | 69 (40) | 82 (48) | 44 (38) | 49 (42) | 20 (39) | 28 (54) | 133 (39) | 159 (47) | * |
| Warfarin | 6 (4) | 18 (11) | 13 (11) | 23 (20) | 3 (6) | 5 (10) | 22 (7) | 46 (14) | *** |

*McNemar's test: *** $p \leq 0.001$, ** $p \leq 0.01$, * $p \leq 0.05$, NS= not significant*

## 5.2 CHOLESTEROL VALUES AND USE OF SERUM LIPID MODIFYING AGENTS (I, II, III)

### 5.2.1 Use of serum lipid modifying agents

In the Kuopio 75+ study, only 7% of all the elderly persons used serum lipid modifying agents. The corresponding proportion in 2003 was 12% (Table 12). There was no difference between genders in the use of serum lipid modifying agents. In the GeMS study, the use of serum lipid modifying agents increased during the study period from 30% to 34% among all the study participants. In 2004, 31% of men used serum lipid modifying agents and 29% of women. The use of serum lipid modifying agents was more common among men also in 2006 (38% vs. 33%).

*Table 12. Use (%) of serum lipid modifying agents among the study populations*

| Study | Study year | Age at study baseline | | | |
|---|---|---|---|---|---|
| | | 75–79 | 80–84 | 85+ | Total |
| | | % | % | % | % |
| Kuopio 75+ | 1998 | 11 | 5 | 2 | 7 |
| | 2003 | 17 | 8 | 6 | 12 |
| GeMS | 2004 | 36 | 30 | 12 | 30 |
| | 2006 | 41 | 36 | 13 | 34 |

The use of serum lipid modifying agents increased among high-risk patients. Still, among those with hypertension the prevalence of use was only 34% in 2006 (Table 13).

*Table 13. Use of serum lipid modifying agents in 2004 and 2006 according to demographics and concomitant cardiovascular risk factors*

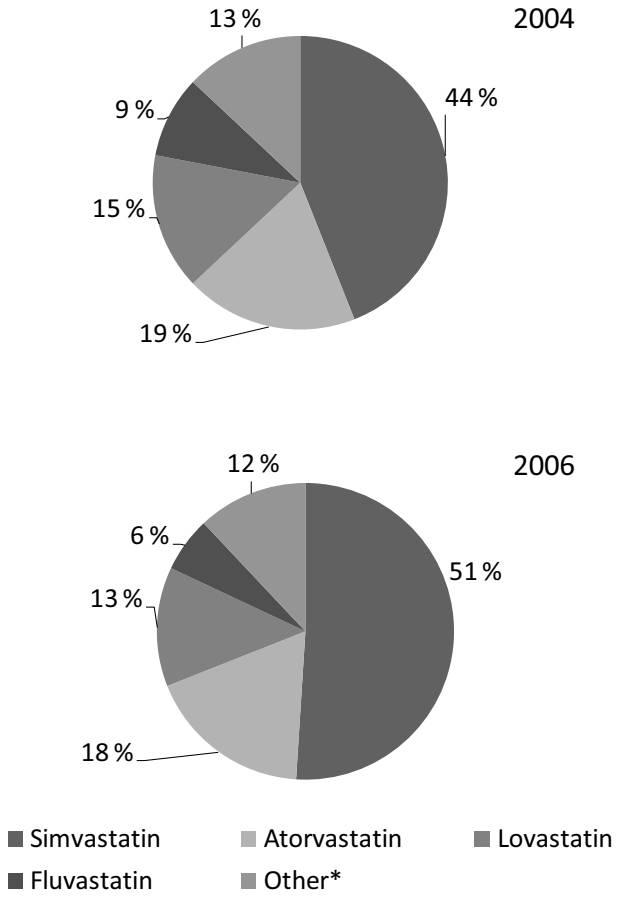
| | **User in 2004 n (%)** | | **User in 2006 n (%)** |
|---|---|---|---|
| Age at baseline | | Age at baseline | |
| 75–79 | 112 (36) | 75–79 | 130 (41) |
| 80-84 | 58 (30) | 80–84 | 68 (36) |
| 85+ | 14 (12) | 85+ | 15 (13) |
| Gender | | Gender | |
| Women | 128 (29) | Women | 143 (33) |
| Men | 56 (31) | Men | 70 (38) |
| Hypertension | | Hypertension | |
| No (n=375) | 109 (29) | No (n=365) | 125 (34) |
| Yes (n=247) | 75 (30) | Yes (n=257) | 88 (34) |
| CAD[a] | | CAD[a] | |
| No (n=431) | 82 (19) | No (n=414) | 99 (23) |
| Yes (n=189) | 101 (53) | Yes (n=206) | 117 (57) |
| Diabetes | | Diabetes | |
| No (n=584) | 168 (29) | No (n=579) | 191 (33) |
| Yes (n=36) | 15 (42) | Yes (n=41) | 21 (51) |
| Smoking* | | Smoking* | |
| Non-smoker (n=431) | 126 (29) | Non-smoker (n=441) | 142 (32) |
| Former smoker (n=164) | 48 (29) | Former smoker (n=158) | 60 (38) |
| Current smoker (n=21) | 9 (43) | Current smoker (n=18) | 10 (56) |
| CVD risk factors[b] | | CVD risk factors[b] | |
| 0 (n=125) | 21 (17) | 0 (n=100) | 14 (14) |
| 1 (n=301) | 98 (33) | 1 (n=311) | 114 (37) |
| 2 (n=77) | 39 (51) | 2 (n=85) | 46 (54) |
| 3 or more (n=13) | 8 (62) | 3 or more (n=14) | 10 (71) |

[a] *CAD= coronary artery disease*

[b] *risk factors for cardiovascular outcomes incl. diabetes, coronary artery disease, hypertension and current smoker*

** four missing values in 2004 and three in 2006*

The most-used statin in the GeMS study was simvastatin (Fig 2). There was no difference between genders in the use of serum lipid modifying agents.




** incl. Pravastatin, rosuvastatin bezafibrate, cholestyramine, research medicine*

*Figure 2. Use of different serum lipid modifying agents in 2004 and 2006 among the elderly persons using cholesterol-lowering medication*

### 5.2.2 Cholesterol levels in 2004 and 2006

The mean serum total cholesterol (S-TC) and serum low-density lipoprotein levels tended to decrease ($p < .001$), while the level of serum high-density lipoprotein increased ($p = .049$) among all the examined elderly during the follow-up (Fig 3).

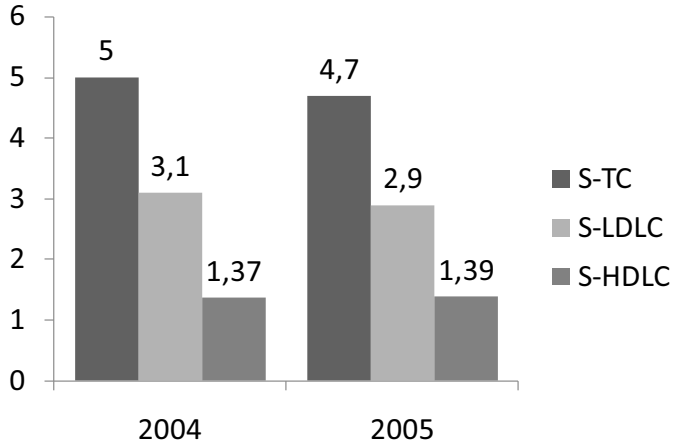



*Figure 3. Serum total (S-TC), low-density (S-LDLC) and high-density (S-HDLC) lipoprotein levels among all the examined elderly persons in 2004 and 2006*

Women had higher S-TC ($p < .001$), S-LDLC ($p < .05$) and S-HDLC ($p < .001$) levels than men in both years. In addition, the cholesterol levels varied during the study period according to concomitant diseases and the number of risk factors (Table 14).

*Table 14. Mean (SD) serum total (S-TC), high-density lipoprotein (S-HDLC) and low-density lipoprotein (S-LDLC) cholesterol levels (mmol/l) according to concomitant diseases in 2004 and 2006.*

| | S-TC | | S-HDLC | | S-LDLC | |
|---|---|---|---|---|---|---|
| | **2004** | **2006** | **2004** | **2006** | **2004** | **2006** |
| All | 5.0 (±0.99) | 4.7 (±0.97) | 1.37 (±0.38) | 1.39 (±0.40) | 3.1 (±0.86) | 2.9 (±0.84) |
| Women | 5.1 (±0.98) | 4.8 (±0.95) | 1.43 (±0.40) | 1.45 (±0.41) | 3.2 (±0.85) | 3.0 (±0.83) |
| Men | 4.7 (±0.94) | 4.4 (±0.96) | 1.22 (±0.33) | 1.23 (±0.33) | 3.0 (±0.87) | 2.8 (±0.86) |
| Hypertension | 4.9 (±0.92) | 4.7 (±0.95) | 1.32 (±0.36) | 1.36 (±0.38) | 3.1 (±0.80) | 3.0 (±0.82) |
| CAD[a] | 4.6 (±0.86) | 4.3 (±0.83) | 1.31 (±0.36) | 1.31 (±0.38) | 2.8 (±0.78) | 2.6 (±0.73) |
| Diabetes | 4.7 (±1.09) | 4.6 (±1.28) | 1.21 (±0.49) | 1.23 (±0.41) | 2.9 (±0.83) | 2.8 (±0.97) |
| Smoking | | | | | | |
| No | 5.1 (±0.98) | 4.8 (±0.93) | 1.41 (±0.40) | 1.44 (±0.41) | 3.2 (±0.85) | 3.0 (±0.81) |
| Former | 4.7 (±0.97) | 4.5 (±1.02) | 1.29 (±0.36) | 1.26 (±0.34) | 3.0 (±0.85) | 2.8 (±0.90) |
| Yes | 4.7 (±1.13) | 4.3 (±1.13) | 1.31 (±0.45) | 1.33 (±0.44) | 3.0 (±0.91) | 2.6 (±0.92) |
| CVD risk factors[b] | | | | | | |
| 0 | 5.3 (±0.98) | 5.0 (±0.97) | 1.46 (±0.40) | 1.47 (±0.39) | 3.4 (±0.87) | 3.1 (±0.85) |
| 1 | 4.8 (±0.92) | 4.7 (±0.92) | 1.35 (±0.37) | 1.38 (±0.40) | 3.1 (±0.81) | 2.9 (±0.82) |
| 2 | 4.7 (±0.98) | 4.4 (±1.05) | 1.27 (±0.40) | 1.28 (±0.35) | 2.9 (±0.85) | 2.7 (±0.84) |
| 3+ | 4.4 (±0.60) | 4.0 (±0.67) | 1.14 (±0.28) | 1.17 (±0.57) | 2.7 (±0.44) | 2.4 (±0.57) |

[a] *coronary artery disease*

[b] *incl. hypertension, coronary artery disease, diabetes and current smoking*

The decrease in cholesterol levels was most obvious among new serum lipid modifying agents users (non-user in 2004, user in 2006). Among those who stopped using them (user in 2004, non-user in 2006), cholesterol levels increased.

### 5.2.3 Cholesterol levels and all-cause mortality

The study participants were divided into thirds based on serum total cholesterol (S-TC) levels. The participants with S-TC levels < 5 mmol/l tended to be older, male, had lower systolic blood pressure and more commonly used loop diuretics and more commonly suffered from diseases such as dementia, diabetes mellitus, asthma/COPD and heart diseases (Table 15). The participants in the lowest third (< 5 mmol/l) had the highest risk of death (Fig 4).

*Table 15. Baseline characteristics of 490 home-dwelling participants aged 75 years or more by serum total cholesterol level*

| **Characteristic** | **< 5mmol/l n = 159** | **5-5.9 mmol/l n = 157** | **≥ 6 mmol/l n = 174** | **Total n = 490** | **P-value** |
|---|---|---|---|---|---|
| Age, years (SD) | 82 (± 4.8) | 81 (± 4.5) | 80 (± 3.7) | 81.4 (± 4.4) | < .001 |
| Sex | | | | | |
| Male (%) | 61 (38) | 47 (30) | 27 (16) | 135 (28) | < .001 |
| Mean SBP, mmHg (SD) | 142 (± 24.6) | 152 (± 23.2) | 156 (± 23.4) | 150 (± 24.4) | < .001 |
| Mean S-TC, mmol/l (SD) | 4.33 (± 0.5) | 5.48 (± 0.3) | 6.94 (± 0.8) | 5.6 (± 1.2) | < .001 |
| S-HDLC | 1.24 (± 0.3) | 1.48 (± 0.4) | 1.63 (± 0.4) | 1.5 (± 0.4) | |
| S-LDLC | 1.86 (± 0.5) | 2.64 (± 0.5) | 3.62 (± 0.8) | 2.7 (± 0.9) | |
| Self-reported health* (%) | | | | | |
| Good | 42 (28) | 57 (37) | 73 (42) | 172 (36) | .089 |
| Moderate | 78 (50) | 69 (45) | 75 (43) | 222 (46) | |
| Poor | 33 (22) | 29 (19) | 26 (15) | 88 (18) | |
| MMSE, mean (SD) | 23.3 (± 7) | 25.3 (± 5) | 25.4 (± 4) | 24.7 (± 5) | .017 |
| Use of medications (%) | | | | | |
| Blood pressure lowering medication† | 101 (64) | 104 (66) | 118 (68) | 323 (66) | .707 |
| Long-acting nitrates | 56 (35) | 44 (28) | 54 (31) | 154 (31) | .383 |
| Loop diuretics | 40 (25) | 11 (7) | 15 (9) | 66 (14) | < .001 |

*Table 15. Continued*

| Characteristic | < 5mmol/l n = 159 | 5-5.9 mmol/l n = 157 | ≥ 6 mmol/l n = 174 | Total n = 490 | P-value |
|---|---|---|---|---|---|
| Diseases (%) | | | | | |
| Dementia | 35 (22) | 21 (13) | 19 (11) | 75 (15) | .014 |
| Diabetes mellitus | 41 (26) | 32 (20) | 23 (13) | 96 (20) | .015 |
| Cancer | 39 (25) | 30 (19) | 33 (19) | 102 (21) | .363 |
| Atrial fibrillation* | 43 (27) | 24 (15) | 13 (8) | 80 (17) | < .001 |
| Valvular insufficiency* | 48 (32) | 40 (28) | 51 (31) | 139 (30) | .673 |
| Coronary disease‡* | 58 (37) | 43 (28) | 62 (36) | 163 (34) | .189 |
| Stroke | 21 (13) | 17 (11) | 15 (9) | 53 (11) | .404 |
| NYHA‖ classification* | | | | | < .001 |
| 1 | 41 (30) | 60 (39) | 50 (30) | 151 (33) | |
| 2 | 46 (33) | 64 (42) | 81 (49) | 191 (42) | |
| 3 or 4 | 52 (37) | 30 (20) | 34 (21) | 116 (25) | |
| Obstructive pulmonary disease | 28 (18) | 17 (11) | 16 (9) | 61 (13) | .048 |
| Parkinson's disease | 6 (4) | 2 (1) | 2(1) | 10 (2) | .167 |

** variables with some missing values*

*† including: diuretics except loop-diuretics, beta blocking agents, calcium channel blockers or agents acting on the renin-angiotensin system*

*‡ including: myocardial infarction, bypass operation or coronary angioplasty*

*‖ New York Heart Association functional classification*

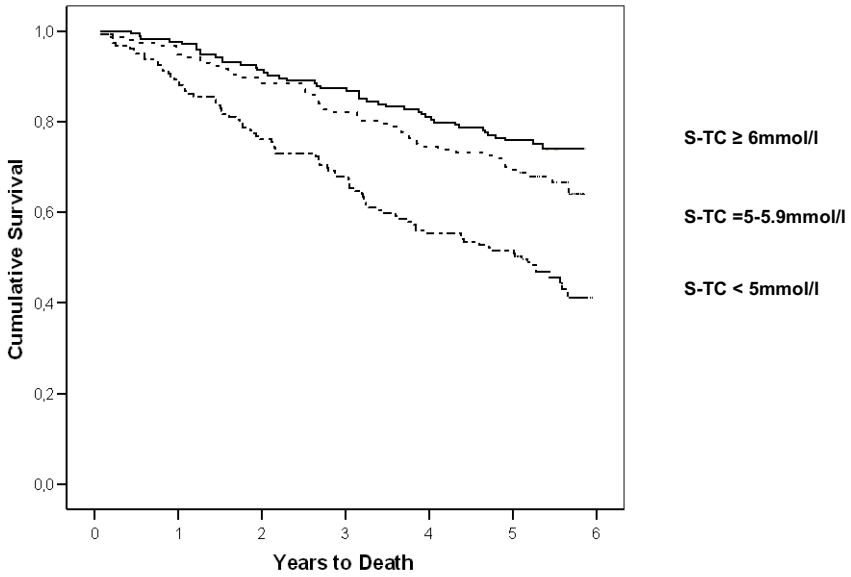



*Figure 4. Serum total cholesterol (S-TC) and mortality using Kaplan-Meier survival analysis (Log rank p < 0.001)*

When S-TC treated as a continuous variable, the age- and sex-adjusted HR of death for each 1 mmol increase in S-TC was 0.78 (95% CI 0.68–0.89). In the multivariable analysis, the HR of death for a 1 mmol increase in S-TC was 0.82 (95% CI 0.70–0.95). In addition, age, dementia, use of loop diuretics and atrial fibrillation were significantly associated with the risk of death (Table 16).

*Table 16. Significantly associated hazard Ratios (HR) of death among the participants (n = 490) calculated from Multivariate Cox Proportional Hazards Models*

| **Risk Factor** | **HR** | **95 % CI** | **P-value** |
|---|---|---|---|
| Serum total cholesterol | 0.82 | 0.70–0.95 | .008 |
| Age | 1.12 | 1.08–1.16 | < .001 |
| Dementia | 2.71 | 1.84–3.98 | < .001 |
| Use of loop diuretics | 1.98 | 1.34–2.94 | < .001 |
| Atrial fibrillation | 1.60 | 1.09–2.37 | .018 |

When S-TC < 5 mmol/l was used as the reference value, an inverse association between S-TC and mortality was seen in the age- and sex-adjusted, multivariable analysis and propensity score-adjusted model (Table 17). When adjusted for sex and age, an inverse association between S-TC and mortality was seen in the participants without concomitant diseases, i.e. dementia, stroke, obstructive pulmonary disease and no history of hypertension or cancer. High serum total cholesterol (≥ 6 mmol/l) was associated with decreased mortality in the participants with systolic blood pressure < 140 mmHg. In the participants with systolic blood pressure ≥ 140 mmHg, the association was attenuated but significant (age- and sex-adjusted HR = 0.59, 95% CI=0.36–0.98).

*Table 17. Hazard ratios (HR) of death among the participants according to serum total cholesterol (S-TC) thirds calculated from Multivariate Cox Proportional Hazards Models*

| S-TC | HR Model 1* | HR Model 2† | HR Model 3‡ |
|---|---|---|---|
| < 5 mmol/l | 1 (ref) | 1 (ref) | 1 (ref) |
| 5–5.9 mmol/l | 0.57 (95 % CI 0.40–0.80) | 0.62 (95 % CI 0.42–0.93) | 0.57 (95 % CI 0.38–0.84) |
| ≥ 6 mmol/l | 0.48 (95 % CI 0.33–0.70) | 0.59 (95 % CI 0.39–0.89) | 0.42 (95 % CI 0.28–0.62) |

*Cox proportional hazard model*

** adjusted for age and sex*

*† adjusted for age, atrial fibrillation, dementia, use of loop diuretics, stroke. Variables in the initial model: systolic blood pressure (continuous variable), sex, self-reported health, diabetes mellitus, history of cancer, valvular insufficiency, coronary disease (incl. myocardial infarction, bypass operation or coronary angioplasty), use of long-acting nitrates, use of blood pressure-lowering medication, obstructive pulmonary disease, NYHA classification (New York Heart Association functional classification)*

*‡ propensity-score-adjusted model. Variables in the model: age (continuous variable), atrial fibrillation, dementia, NYHA classification, systolic blood pressure (continuous variable), use of loop diuretics, Mini-Mental state examination score, sex, self-reported health, diabetes mellitus, history of cancer, valvular insufficiency, history of hypertension, myocardial infarction, bypass operation, use of long-acting nitrates, use of blood pressure-lowering medication, obstructive pulmonary disease, Parkinson's disease, heart failure (Boston criteria)*

## 5.3 ORTHOSTATIC HYPOTENSION (IV)

### 5.3.1 Postural changes in blood pressures

In work II, almost 70% of all the examined elderly experienced a systolic blood pressure drop in the orthostatic test after one minute standing, and 60% did so after three minute standing. Diastolic blood pressure dropped in 39% of the elderly persons after one minute of standing and in 32% after three minute of standing.

### 5.3.2 Prevalence of orthostatic hypotension

Orthostatic hypotension (OH) was recorded in as much as 34% of the study population (Fig 5). The prevalence of OH was 31% among those aged 75–79, 35% among those aged 80–84 and 40% among the oldest old (85+). Only the combination of systolic and diastolic OH increased significantly with age ($p < .05$). There was no difference between genders in the prevalence of OH.

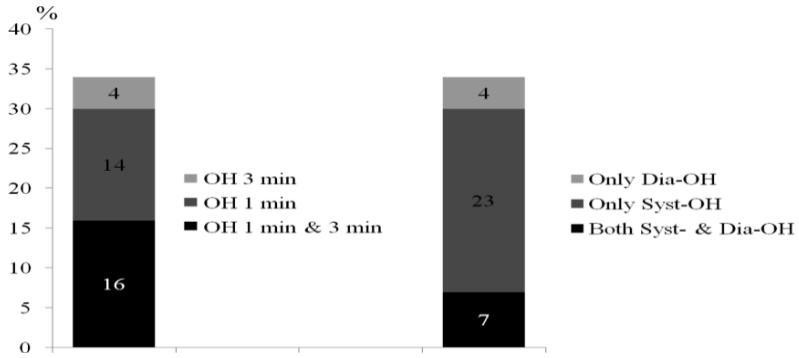



*Figure 5. Prevalence of different types of OH among all the elderly persons*

### 5.3.3 Orthostatic hypotension and the use of medicines

The association between the number of medicines in regular use and the prevalence of OH was statistically significant. ($p < .05$, Table 18). The more medicines in regular use, the more common was OH. There was no association between any particular medicine and OH. There was no association between the number of irregularly used medicines or total medication and OH.

*Table 18. Use of medications and mean numbers (95% CI) of medicines used according to the presence of OH (n = 653)*

| **Medical groups (ATC code)** | **OH +**<br>**n = 220 (%)** | **OH –**<br>**n = 433 (%)** | **Total**<br>**653 (%)** | **P-value** |
|---|---|---|---|---|
| Diuretics (C03) | 69 (31) | 107 (25) | 176 (27) | .077 |
| Beta blocking agents (C07) | 114 (52) | 218 (50) | 332 (51) | .741 |
| Calcium channel blockers (C08) | 57 (26) | 112 (26) | 169 (26) | 1.000 |
| Agents acting on renin-angiotensin system (C09) | 69 (31) | 159 (37) | 228 (35) | .193 |
| Organic nitrates (C01DA) | 59 (27) | 116 (27) | 175 (27) | 1.000 |
| Alpha blockers (G04CA) | 13 (6) | 16 (4) | 29 (4) | .228 |
| Drugs for Parkinson's disease (N04B) | 7 (3) | 5 (1) | 12 (2) | .118 |
| Antipsychotics (N05A) | 11 (5) | 23 (5) | 34 (5) | 1.000 |
| Tricyclic antidepressants (N06AA) | 6 (3) | 3 (1) | 9 (1) | .068 |
| Causative medication | | | | |
| 1 | 70 (44) | 123 (44) | 193 (44) | |
| 2 | 62 (39) | 104 (37) | 166 (37) | |
| 3 or more medicines | 29 (18) | 56 (20) | 85 (19) | |
| Mean (95% CI) | 1.31 (1.2–1.5) | 1.17 (1.1–1.3) | 1.22 (1.1–1.3) | .106 |
| Antihypertensives | | | | |
| 1 | 71 (32) | 143 (33) | 214 (33) | |
| 2 | 62 (28) | 121 (28) | 183 (28) | |
| 3 or more medicines | 36 (17) | 70 (16) | 106 (16) | |
| Mean (95% CI) | 1.43 (1.3–1.6) | 1.39 (1.3–1.5) | 1.41 (1.3–1.5) | .900 |
| Regularly used medicines | | | | |
| Mean (95% CI) | 5.03 (4.6–5.4) | 4.59 (4.3–4.9) | 4.74 (4.5–5.0) | .049 |
| Irregularly used medication | | | | |
| Mean (95% CI) | 1.27 (1.1–1.5) | 1.27 (1.2–1.4) | 1.27 (1.2–1.4) | .624 |
| Total medication | | | | |
| Mean (95% CI) | 6.30 (5.8–6.7) | 5.86 (5.5–6.2) | 6.01 (5.7–6.3) | .074 |

### 5.3.4 Orthostatic hypotension and pulse pressures

Pulse pressure was significantly higher in the OH+ participants than in the OH– participants in a supine position, after one minute of standing and after three minutes of standing. After rising to a standing position, the decrease in pulse pressures was more pronounced in the OH+ participants than in the OH– participants.

# 6 Discussion

## 6.1 STUDY POPULATION

The Kuopio 75+ study and the GeMS study were both population-based studies with a random sample of elderly Finns aged 75 years or more, with wide inclusion criteria. More than 2 out of 3 of the participants were women. Previously, cardiovascular mortality has been higher in the area of East Finland, but during the past decades the differences in risk factors such as blood pressure levels have decreased, and serum cholesterol levels have become similar to those in West Finland (Nissinen et al. 1993). Therefore, the generalisability of the study results to the general elderly population in Finland is presumably good. Usually old patients differ from trial patients of any age due to their other comorbidities and multiple drug usage, which are often without exception exclusion criteria for entering clinical trials (Lye & Donnellan 2000).

The participants in institutional care tended to be older and had poorer health status than the home-dwelling elderly. Due to missing data, the participants in institutions were excluded from work III and IV. In work II the intervention and control group were combined for the analysis. A Comprehensive Geriatric Assessment (CGA) of the subjects randomised into the intervention group was done yearly. The CGA was not specifically aimed at cardiovascular risk factors or serum lipids. There were no differences in the use of serum lipid modifying agents or cholesterol levels between the intervention and control groups during the study period, but there is a possibility to a different treatment between the intervention and control groups in 2006.

High response rates are needed to ensure generalisability to a wider population. Compared with the other population-

based studies among elderly persons, the response rates of 86% (Kuopio 75+) and 78% (GeMS) can be considered rather good. The response rates of other studies among elderly persons have ranged between 78% and 96% (average 89%). A response rate of less than 70% has traditionally been considered poor and needs to be interpreted with caution (Jesson 2001).

## 6.2 DESIGN OF THE STUDIES

Both studies were prospective, population-based cohort studies. Work I, II and III were studies with a follow-up which allowed explanation of causes or consequences between variables. On the other hand, work IV was a cross-sectional analysis, and this limits the present study results to proportions and associations. The main problem was in determining whether drug use preceded or followed the occurrence of the outcome (orthostatic hypotension) (Rothman & Greenland 1998, Rothman 2002).

## 6.3 DEFINITIONS AND MEASUREMENTS OF THE STUDY VARIABLES

The data were collected using different methods: clinical examinations, interviews and registry data were used. Drug use was measured both from databases and as a self-reported drug use. The use of a geriatrician to examine the participants' overall physical and mental health increased the quality of the data collection and thus decreased misclassification of the study variables. Also, the study nurses were instructed and trained in data collection.

**Use of medicines**

Regularly and irregularly taken prescribed and non-prescribed medicines were recorded. Compared with many

other studies, we also have data for OTC drugs. To ensure the reliability of the medication data, the medical records from the municipal health centre, home nursing service, local hospitals and the Kuopio University Hospital were also available. The reliability of the collection of medication data was also improved by asking the participants to bring their medicine containers and prescription forms with them to the interview, and medication information was also checked from the medical records and caregivers or family members, if needed. Cardiovascular medicines are typically used daily for a long period. Especially in cross-sectional studies regularly used medications are likely to be recorded more reliably than irregularly used (Ryynänen 1993).

**Blood pressure**

The main sources of systematic error in blood pressure measurement in hypertension are differences in the devices and differences in the measurement techniques of the observers (nurse/physicians). To avoid errors like inaccuracy of the device and the circumstances of measurement, blood pressure was measured twice after ten minutes of rest in a sitting position by a trained nurse using a calibrated mercury column sphygmomanometer according to the national guidelines (Käypä hoito: Kohonnut verenpaine 2009, Beevers et al. 2001).

**Orthostatic hypotension**

The prevalence of orthostatic hypotension was based on one measurement. Therefore, the observed results may be weakened by misclassification of the main exposure variables. In clinical practice, the skills and knowledge of nurses are often inadequate for diagnosing OH in elderly patients (Vloet et al. 2002). In our study, the study nurses were instructed and trained to measure blood pressures accurately. The blood pressure recordings were made after 10 minutes' rest, but the time of day for measuring blood

pressure, meals and daily activities differed between persons, which may have influenced our results.

**Cholesterol levels**

All the serum total cholesterol assays were analysed in the Kuopio University Hospital laboratory using standard enzymatic techniques according to the national guidelines (Käypä hoito: Dyslipidemiat 2009). Cholesterol was measured only once each time, so the observed results may be weakened by misclassification of the main exposure variables. Serum total cholesterol was measured once after 12 hours of fasting and analysed in the Kuopio University Hospital to guarantee the accuracy of the analysis. The technique employed had to detect small changes and differences in cholesterol levels. In work II, the persons were categorised as having changes in their cholesterol levels during the study period only if the difference between levels was greater than +/- 0.2 mmol/l for total cholesterol and LDL cholesterol and +/- 0.1 mmol/l for HDL cholesterol.

**Concomitant diseases**

We used the National Social Insurance Institution Special Refund Registers for 2003 and 2005 to define concomitant diseases in work II to ensure equality between the intervention and control groups. We classified a participant as having a disease if the participant was entitled to special refunds for the medication costs of that disease before the respective examination. The non-risk subgroup with cardiovascular outcomes included non-smoking elderly persons without special refunds for diabetes, coronary artery disease and hypertension medication costs. To increase the reliability of the classification into the non-risk subgroup, the patient records were reviewed from the hospital and health centre for any diagnosis of coronary artery disease, diabetes or hypertension (current/past).

## 6.4 Discussion of the results

### 6.4.1 Use of cardiovascular medicines

In the Kuopio 75+ study the proportion of elderly persons regularly using cardiovascular medicines increased from 80% to 87%, and their common use was comparable to the findings of other studies (Wills et al. 1996, Barat et al. 2000, Strandberg et al. 2001). Still, their use in our study was more common than in some earlier studies (Nissinen et al. 1989, Lloyd-Jones et al. 2005). Concomitant use of at least three cardiovascular medicines increased, so cardiovascular medicines might be one reason why total medication use increases with advancing age. Today elderly men and women are treated more actively than before, also for cardiovascular diseases. Elderly persons living in institutions used significantly more loop diuretics than home-dwelling elderly persons, and their use increased more than among the home-dwelling survivors. Loop diuretics are often necessary in the treatment of heart failure in elderly persons, but in addition to loop diuretics, the guidelines have also recommended using ACE inhibitors and beta blocking agents in the treatment of heart failure (Gambassi et al. 1998).

The increased use of cardiovascular medicines reflects the high prevalence of cardiovascular diseases in older age, because the proportion of users increased even though preventive medicines like low-dose aspirin, warfarin and lipid modifying agents were not counted. In Finland, cardiovascular medicines were the third biggest group in terms of sales, and consumption increased by 8% in 2008, so the study subjects do not differ from the total population (Suomen lääketilasto 2008). Medicine users treated for cardiovascular diseases had a more than four times higher risk for polypharmacy than drug users in general (Bjerrum et al. 1998, Jyrkkä et al. 2006). Use of cardiovascular medications together with polypharmacy and age-impaired renal and hepatic function may increase the risk of adverse events that are not well defined among the elderly population. An

additional problem is physicians' reluctance to discuss about possible adverse events with elderly patients. According to a recent study, physicians told about adverse events to less than half of men and one-third of women aged 75 year or older (Meriranta 2009).

### 6.4.2 Cholesterol values and use of serum lipid modifying agents

In 1998 only 7% of all elderly persons used serum lipid modifying agents, while in 2004 in the GeMS study, one-third of the study population used cholesterol-lowering medicines during the two-year follow-up period. Our results are consistent with some previous studies that have reported increased use of cholesterol-lowering medicines among elderly persons (Raymond et al. 2007, Korhonen et al. 2008b). In 2004–2006, the use of serum lipid modifying agents increased among those aged 75–84 years, but not among those aged 85 years or more. Among those with three or more risk factors, two-thirds used these drugs. It seems that treatment practices have changed towards more active secondary prevention in elderly persons. In our study, the prevalence of serum lipid modifying agent use in patients with established coronary heart disease was much higher than the estimates in a previous study (Primatesta & Poulter 2006). On the other hand, 14% of the elderly persons without traditional risk factors of cardiovascular outcomes used lipid modifying agents in 2006. Most of the data on drugs have been obtained from middle-aged persons, but it is estimated that the use of serum lipid modifying agents together with polypharmacy and impaired renal and hepatic function and certain concomitant medications may increase the risk of clinically important adverse events (Routledge et al. 2004). In addition, the incidence of muscle pain and other less severe adverse events is not well defined among the elderly population.

The cholesterol levels improved during the follow-up period, with men having better outcomes than women both

among those not using any medicines and those using cholesterol-lowering medicines. Also those with CAD and several risk factors had lower cholesterol levels. Although women had higher cholesterol levels in both years, the use of cholesterol-lowering medicines was higher among men, like in many other studies (Daly et al. 2006, Enriquez et al. 2008). This may indicate that symptoms of coronary artery disease in older female patients are not recognised.

A high S-TC level was not associated with an increased risk of all-cause mortality during the six-year follow-up. The inverse association remained clear and significant when adjusted for co-morbid diseases. In fact, high cholesterol levels in elderly persons do not seem to be a risk factor of mortality (Schatz et al. 2001, Schupf et al. 2005). The overall predictive power of cholesterol on mortality seems to decline with age (Menotti et al. 1998). Our results support previous reports on increased risk of death associated with low total cholesterol (Kronmal et al. 1993, Corti et al. 1997Weverling-Rijnsburger et al. 1997, Song, Sung & Kim 2000, Schatz et al. 2001, Brescianini et al. 2003, Casiglia et al. 2003, Schupf et al. 2005, Tikhonoff et al. 2005, Spada et al. 2007). One explanation might be that all our participants were 75 years or older, with a mean of over 81 years at the baseline, a value higher than in many other studies (Corti et al. 1997, Casiglia et al. 2003, Brescianini et al. 2003, Schupf et al. 2005). Therefore, it is possible that our participants were less susceptible to diseases associated with high cholesterol than were those who died before the age of 75, either as a result of a lack of additional risk factors (smoking, diabetes, hypertension) or due to some undefined protective factors. The difference between age groups was seen in a Finnish study on subjects without coronary heart disease, where an increase in total cholesterol increased all-cause mortality in men aged 55 to 64, but not in men aged 65 to 74 (Pekkala 1994). Unfortunately, only 30 elderly of those examined in 1998 used serum lipid modifying agents. Due to the small number, those elderly treated with statins were excluded

from the analysis. Therefore, it is not possible to make any conclusions about the benefits and harms of lipid lowering treatment of the elderly in this population. The effect of total cholesterol level on mortality may be different in those using lipid lowering medication. On the other hand, our study results are significant due to their wide generalisability. In most clinical trials elderly women are underrepresented compared with men (Lewis et al. 1998, Hunt et al. 2001, Ridker et al. 2008).

### 6.4.3 Orthostatic hypotension

Systolic blood pressure dropped in two-thirds of the home-dwelling elderly, and every third had orthostatic hypotension. This figure was higher than in many previous studies (Rutan et al. 1992, Masaki et al. 1998, Atli & Keven 2006). OH and low blood pressure have been found to be associated with dizziness and an increased risk of falling, and too little attention has been paid to a drop in blood pressure too small to fulfil the criteria of orthostatic reaction (Rutan et al. 1992, Kario et al. 2001, Vloet et al. 2005). In frail elderly persons with low blood pressure, even a small drop in blood pressure can be a risk factor for falling. Previous studies have reported an increase in the prevalence of orthostatic hypotension with advancing age (Rutan et al. 1992, Masaki et al. 1998). That trend was not very obvious in our study population aged 75 or older. However, our population was older (mean age 81 years) than many of those previously reported, and they had multiple co-morbidities and medications.

We found that a high number of regularly used medicines is associated with orthostatic hypotension. Poon et al found a relationship between OH and potentially causative medication (Poon & Braun 2005). In old individuals it is often impossible to determine whether OH is caused by medicines or the underlying diseases or both. In addition, our study was a cross-sectional study and this limits the conclusions.

The OH-positive participants showed an increase in heart rate slightly more often than the OH-negative persons, while a minority of the OH-negative persons maintained their blood pressure by increasing their heart rate. This might indicate that reflex tachycardia is secondary in preventing an orthostatic reaction even in elderly persons. In the present study, pulse pressure in a supine position was higher in the OH-positive than in the OH- negative subjects. This can be explained by the fact that an increased resting pulse pressure indicates stiffness of the major arteries. Still, after rising to a standing position the decrease in pulse pressure was also more pronounced in the OH-positive than in the OH-negative persons. Increased pulse pressure has been associated with a risk of major cardiovascular complications and mortality (Blacher et al. 2000). However, mean pressure is not the only factor resulting in a high cardiovascular risk in old patients.

OH in elderly persons was independent of blood pressure in the sitting position. In our study diastolic OH after one minute of standing was found to be more prevalent in persons with low blood pressure in a sitting position. In the study by Luukinen et al diastolic OH after one minute predicted cardiovascular mortality in old persons (Luukinen et al. 1999). In addition, a diastolic blood pressure drop after one minute of standing, even when it is small enough not to fulfil the criteria of orthostatic hypotension, identifies elderly persons with a high risk for myocardial infarction (Luukinen et al. 2004). This might be due to the load the heart is exposed to upon rising up, and it may provoke coronary insufficiency and a decrease in stroke volume in a frail elderly person.

# 7 Conclusions

This doctoral thesis examined the use of cardiovascular medications in an elderly population. In addition, a number of associations and outcomes with used medications and orthostatic hypotension and cholesterol levels were studied. The following conclusions can be drawn:

1. The use of cardiovascular medicines is common among elderly persons. The proportion of users increases with age and over time.

2. The trend in current statin use seems to be moving towards more extensive use among elderly persons. Use of serum lipid modifying agents is targeted more at secondary prevention.

3. A low serum total cholesterol level is associated with an increased risk of all-cause mortality among elderly who did not use serum lipid modifying medication. The inverse association remains clear and significant when adjusted for co-morbid diseases.

4. Orthostatic hypotension and drops in blood pressure seem to be more common among home-dwelling elderly persons than has previously been reported. The more medicines are in regular use, the more common is orthostatic hypotension among (frail) elderly persons.

# *8 Implications for research and practice*

Concomitant use of cardiovascular medicines is in accordance with recent treatment guidelines. However, the prevalence of using several cardiovascular drugs concomitantly suggests that there is a need to assess the outcomes of treatment more comprehensively than before. Today we do not have any special treatment guidelines for the care of elderly persons. Appropriate use of cardiovascular drugs in the elderly requires knowledge of age-related physiological changes, the effects of concomitant diseases that alter the pharmacokinetic and pharmacodynamic effects of cardiovascular drugs, and drug– drug interactions. In order to create specific guidelines for treatment among the elderly population, we need more clinical trials in the use of cardiovascular medications in the elderly population aged 75 years or more.

The study results also suggest the need to test orthostatic hypotension in patients aged 75 years or older regardless of their blood pressure levels in a sitting position. In addition, clinicians should assess medication in persons with orthostatic hypotension to prevent risks of falling and cardiovascular hazards. Medication monitoring focused on elderly patients and cardiovascular medication might optimise treatment and improve the quality of care for a large proportion of elderly persons.

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**Päivi Tuikkala**

# *Cardiovascular medicines use in elderly population*

## *Emphasis on blood pressure and serum lipids*

Cardiovascular diseases are responsible for one-third of global deaths and during recent years cardiovascular medicines have been the most commonly used medication among elderly persons. The present thesis was designated to examine the use of cardiovascular medicine use with a special emphasis on blood pressure and serum lipids and was based on Kuopio 75+ study and GeMS study.

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