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RESEARCH ARTICLE

AGE CONSIDERATION WHEN PRESCRIBING FOR THE ELDERLY

[1]Howraa Abed, [2,*]Hana Morrissey and [3]Patrick A. Ball

[1]Home Medication Review Pharmacist Sydney, NSW, Australia
[2]Reader in Clinical Pharmacy, School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, United Kingdom
[3]Professor of pharmacy Practice, School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, United Kingdom

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ABSTRACT

Since the year 2000, the world elderly population increased by 48%. Medical problems become more predominant with aging leading to polypharmacy. Biological changes can occur with aging resulting in increased susceptibility of older people to medications and their side effects. These changes may have greater effect in a frail person or person with number or long-term or chronic diseases and conditions. Atorvastatin, rosuvastatin, perindopril, amlodipine and paracetamol are commonly used medications among elderly. This paper has reviewed clinical trials and publications on these medications among elderly. It has been found that the safety and effectiveness of these medications among elderly had been evaluated with the main focus on the effectiveness of these medications on different medical conditions and less focus on the effects of the elderly pharmacokinetics and pharmacodynamic changes on these medications. Thus, more clinical trials are required to test elderly biological changes' effects on these medications.

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INTRODUCTION

Since the year 2000, the world elderly population increased by 48% reaching 901, 000,000 in 2015. Considering the disparity of the definition of 'elderly' between developed (65 years old) and developing countries (60 years old) this statistics were based on persons aged 60 years of age and over (1, 2). In most people, medical problems become more predominant with aging leading to polypharmacy (1-3). In 2004, medication use by the elderly risen by 3-5 fold from the previous year and the authors expected that this trend will continue (4). Older persons are 2 fold likely to experience increase in medications effects and side effects than younger adults (5, 6). In many cases the severity of the side effects will reduce adherence to therapy and quality of life and may lead to increased doctors' visits and hospital admissions (6). For instance blood pressure medications decrease older people blood pressure more dramatically than younger adults (7). The high reduction in blood pressure can result in side effects including light-headedness, dizziness and falls which can further affect the older person quality of life or life if resulted in fractures or head injuries (7).

Corresponding author: **Hana Morrissey,**
Reader in Clinical Pharmacy, School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, United Kingdom.

Biological changes can occur with aging resulting in increased susceptibility of older people to medications and their side effects (5). The function of different organ systems is decreased with aging at different rates. These changes are not enough to alter daily function in the case of healthy old person, but may have greater effect in a frail person or person with number or long-term or chronic diseases and conditions (5). Older people account for the most of coronary heart disease deaths sedentary lifestyle and dietary indiscretion to compensate for required effort and unaffordable food cost have led to high metabolic syndrome prevalence in older people such as obesity, high lipid levels and insulin resistance (8). Different large-scale studies demonstrated the association between high total cholesterol levels and coronary heart disease among older people (9, 10). However, others studies disagreed with this conclusion and suggested that the link between coronary artery disease and total cholesterol is diminished with aging (11, 12). Ninety percent of people aged >= 65 years take >=1 medication every week and more than 40% takes >= 5 medications (13). Moreover, 12% of people aged >= 65 years take >= 10 medications (13). Typically, female takes more medications than male (6). Those who are frequently hospitalised, living in a nursing home or the frail receive the most medications (6). Older people who live in nursing homes take a mean of 7-8 regular medications in addition to over the counter medications (6).

The 2015 report of the Australian Bauru of Statistics on medicines highlighted the usage of medications among Australian population based on Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) information (14). The Australian Bauru of Statistics 2015 report divided the medications usage into different category including daily dose, prescription count and total cost (Table 1) (14). This paper will focus on the usage of five medications including atorvastatin, rosuvastatin, perindopril, amlodipine, paracetamol among elderly population.

MATERIALS AND METHODS

A search of the literature was conducted through Google™ Scholar, Medline™ and PubMed databases to identify studies in English language. The following keywords andterms were used:<Aging and drugs>, <medication usage among elderly>,<elderly elderly physiological changes>, <atorvastatin clinical trials AND elderly>, <rosuvastatin clinical trials AND elderly>, <perindopril clinical trials AND elderly>, <amlodipine clinical trials AND elderly>,<paracetamol clinical trials AND elderly>.Letters, commercial websites and commentaries were excluded, only informational websites and peer reviewed articles were included (Appendix 1).

RESULTS AND DISCUSSION

Statins: Several prospective randomized clinical trials demonstrated statins effectiveness in reducing major coronary incidents (15-18).

Table 1. Top 10 medications based on different category, based on the Australian Bauru of Statistics report, 2015 (14)

1.Top 10 drugs by defined daily dose 2015	
Drug	Total
ATORVASTATIN	69.99
PERINDOPRIL	48.95
ROSUVASTATIN	47.36
AMLODIPINE	41.35
PARACETAMOL	38.80
IRBESARTAN	37.63
CANDESARTAN	33.93
RAMIPRIL	30.48
TELMISARTAN	29.58
COLCHICINE	29.03
2.Top 10 drugs by prescription counts 2015	
Drug	Total
ATORVASTATIN	10,557,512
ROSUVASTATIN	9,432,332
ESOMEPRAZOLE	8,868,265
PARACETAMOL	7,365,631
PANTOPRAZOLE	6,356,909
PERINDOPRIL	6,119,841
AMOXYCILLIN	5,864,658
CEFALEXIN	5,604,590
METFORMIN HYDROCHLORIDE	5,155,883
AMOXYCILLIN with CLAVULANIC ACID	5,067,228
3.Top 10 drugs by total cost 2015	
Drug	Total Cost
ADALIMUMAB	329,711,021
ESOMEPRAZOLE	229,567,718
RANIBIZUMAB	213,608,450
AFLIBERCEPT	208,351,224
SALMETEROL and FLUTICASONE	204,998,295
ROSUVASTATIN	202,920,536
ETANERCEPT	168,593,840
PREGABALIN	161,937,157
INSULIN GLARGINE	150,832,113
RITUXIMAB	147,655,378

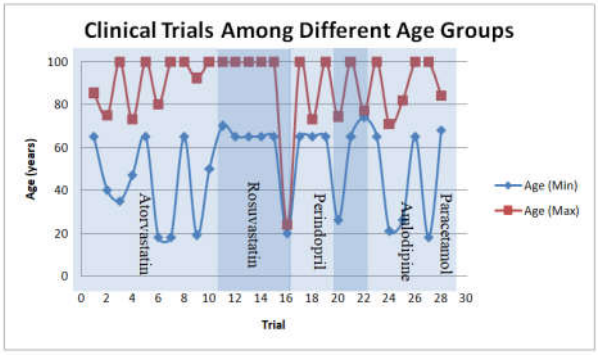

Figure 1. Atorvastatin, rosuvastatin, perindopril, amlodipine and paracetamol clinical trials among different age groups.

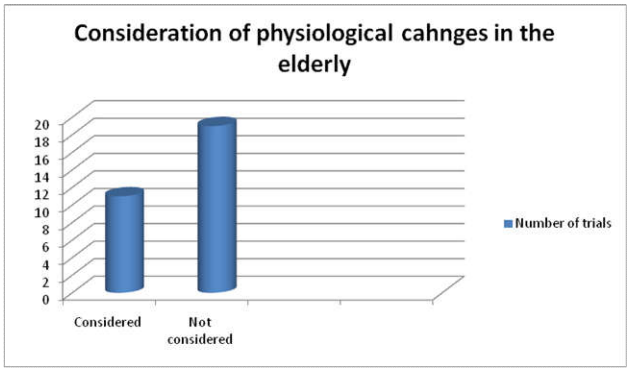

Figure 2. Clinical trials consideration of elderly physiological changes

However, the early trials lack adequate representation of the elderly patients (19) as a result the American Heart Association (AHA) has urged doctors to provide further evidence for statin treatment among the elderly (20). Adverse events have been a concern in the elderly patients (21) due to seriousness of side-effects versus the possible immediate or short-term benefit (21-24). Many studies propose that statins underutilized among elderly patients in cardiovascular disease primary and secondary preventions, have its established benefits (25, 26). This has been ascertained in the data from the Global Registry of Acute Coronary Events (GRACE) and the National Registry of Myocardial Infarction (12, 27, 28). Heart Protection Study (HPS), which recruited 9839 participants under the age of 65 years, 4891 participants aged between 65and70 years, and 5806 participants aged 70 years and over, indicated that that the relative reduction was similar in incident rates across different age groups (29).

Atorvastatin: Atorvastatin has been extensively studied among the elderly and shown to have positive effects on CHD clinical outcomes (12). The 'Assessing Goals in the Elderly' (SAGE) study examined intensified statin treatment in 893CHD elderly patients aged between 65–85 years (17) who were diagnosed with stable CHD (LDL-C between 100-250 mg/dL, had ≥ 1 ischaemic event at baseline). Participants were monitored using 48-hours ambulatory ST segment ECG monitoring (17). Pravastatin 40 mg/day or atorvastatin 80 mg/day were assigned randomly to the participants who were followed-up for 12 months. The results showed that patients who were treated with pravastatin - had a significant reduction in LDL-C when compared with those treated with atorvastatin, (32% vs55% at 12 months), total cholesterol, apolipoprotein B and triglycerides at both3 and 12 months ($p < 0.001$ for all).

Both medications demonstrated a significant and equal reduction in the number and duration of episodes of chest pain (where an event marker button is pressed at the onset of symptoms on ambulatory ECG monitor) compared to baseline (17). It had been noted that all-cause mortality was reduced by 77% (1.3 vs 4%, hazard ratio [HR] 0.33, 95% confidence interval [CI] 0.13–0.83, p = 0.014) and acute cardiovascular cases trend were fewer (8.1 vs 11.2%, HR 0.71, 95% CI 0.46–1.09, p = 0.114) with atorvastatin compared to pravastatin at 12 months. A secondary investigation of the 'Treating to New Targets' (TNT) trial showed a 19% relative risk reduction in major cardiovascular cases in participants aged 65 years and over (3809patients) who receivedhigh-dose atorvastatin (30). Patients received intensified atorvastatin treatment (all ages) showed similar absolute risk decline by2.3%. Moreover, elderly participants who received atorvastatin 80 mg daily had lower CHD death, nonfatal or fatal strokes and nonfatal non-procedure-associated MI rates however, this reduction was not deemed to be of statistical significance (30). Also, this study suggested that high-risk older participants with existing CHD could benefit from the treatment as it could offer clinical advantage (12, 30).

Another study "The Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) " recruited 8888 participants aged less or equal to 80 years who suffered acute MI, showed participants who received atorvastatin experienced considerably lower mean levels of total triglycerides and cholesterol and LDL-C, after 4.8 years average follow-up when compared with participants who received simvastatin (31). The primary outcome (defined as time to first occurrence of a major coronary event) was not considerably decreased with atorvastatin treatment (31). However, there were considerable rates decrease of major cardiovascular cases and acute nonfatal MI. the study did not publish separate data regarding elderly participants in the trial, but the authors' preliminary analysis did not show any statistically considerable treatment group interference by age (12, 31). In another study, the effects of pravastatin 40 mg daily (standard dose) and atorvastatin 80 mg daily (intensified dose), in 4162 participants was evaluated (32).

The results revealed that atorvastatin group showed greater reduction in their average LDL-C than pravastatin group and median LDL-C was led for atorvastatin than with pravastatin. The main end point (defined as the death from any reason including unstable angina which required rehospitalisation e.g., MI, stroke and revascularization) was decreased by 16% in the atorvastatin group compared to pravastatin group. The benefit from atorvastatin was evidentas early as 30 days after treatment commencement and was steady over time (32). Ray *et al.,* (2007) in a post-hoc analysis of patients aged 70 years old data, showed a higher percentage of participants reached the LDL-C targets at thirty days in the atorvastatin 80 mg daily group compared to participants of the same age in the pravastatin 40 mg daily group (p < 0.001,74.6% versus 27.7%,) (33). The achievement of LDL-C target of <70 mg/dL and maintenance for two years, resulted ina 40% lower death risk and unstable angina or MI events when compared to participants who did not reach the target or maintained it. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, (n=3086 participants, 1672 >65 years), participants were assigned randomly to either placebo or atorvastatin 80 mg daily for 16 weeks, 24-96 hours after hospital admissiondue to ACS (34).

Olsson *et al.,* (2007) defined primary end point as (nonfatal acute myocardial infarction, resuscitated cardiac arrest, recurrent symptomatic myocardial ischemia with objective evidence requiring rehospitalization)) Secondary end points were the occurrence of individual components of the primary end point and the occurrence of nonfatal stroke, new or worsening congestive heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia, coronary revascularization, time to occurrence of any of the secondary end points, and percent changes in lipid levels from baseline to end of study. Olsson *et al.,* (2007) (concluded that the primary end pointrelative reductions in LDL-C were similar in older and younger patients who were treated with atorvastatin (14% versus 22%, p = 0.62). Additionally, 34 of the elderly participants were needed to be treated compared to 40 younger participants (35). In the 80 years old group, received atorvastatin, 34% reduction in the LDL-C was achieved compared to participants in placebo group (35). The treatment effects were the same between older and younger groups of each primary and secondary end point components (35).

Age and gender effects on atorvastatin pharmacokinetics followed one 20mg tablets dosing were examined in 16 elderly (66–92 years old) and 16 young (19–35 years old) participants (36). Both groups composed of 50% women and 50% men. A validated enzyme inhibition bioassay was used to quantify atorvastatin plasma equivalent concentrations (36). All participants tolerated atorvastatin well (36). Elderly participants showed 42.5% higher equivalent maximum concentration (C_{max}) than young participants (36). C_{max} was 17.6% lower in men than in women. Additionally, the half life ($t_{1/2}$) and the mean area under the concentrationtime curve ($AUC_{0-\infty}$) were 36.2% longer and 27.3% greater, respectively, in elderly participants than in young participants and 11.3% higher and 19.9% longer, respectively, in men than in women (36). The study stated that it is unclear whether gender- and age related changes in atorvastatin pharmacokinetics will be clinically important and whether they would affect atorvastatin extensive first pass hepatic metabolism. Thus, more trials are required to ensure atorvastatin efficacy and safety among different age and gender groups (36).

Summary of findings: Based on the reviewed studies, atorvastatin shown that while the reduction in LDL-C is better than pravastatin it is less effective in reducing total cholesterol, apo-lipoprotein B and triglycerides. Moreover, atorvastatin showed significant reduction in the number and duration of episodes of chest pain, all-cause mortality and acute cardiovascular cases trend. High-dose atorvastatin showed to lower relative risk in major cardiovascular cases, CHD death, nonfatal or fatal strokes and nonfatal non-procedure-associated MI. The benefit from atorvastatin was evident as early as 30 days after treatment commencement and was steady over time. Elderly participants showed 42.5% higher equivalent maximum concentration (C_{max}) than young participants, the half□life ($t_{1/2}$) was longer and the mean $AUC_{0-\infty}$was greater.

Rosuvastatin: The a placebo-controlled, double-blind, randomized multi-centre Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin JUPITER study, (n=17,802 participants aged ≥50 years for men and ≥60 years for women), participants were randomly assigned to receive either placebo or rosuvastatin 20 mg/day (37). JUPITER study was stopped after 1.9 years

average follow-up because of the reduction in the arterial revascularization, stroke, myocardial infarction, unstable angina hospitalization, or death due to cardiovascular reasons were evident. Primary endpoint was statistically significant in rosuvastatin participants compared to participants in the placebo group (37). The subgroups' results in rosuvastatin participants with similar noted reduction in relative hazard showed lack of evidence for heterogeneity based on gender, age (>65 and ≤65 years), ethnic or race group, place of origin, status regarding traditional risk and Framingham Risk Score (FRS) (37). Glynn *et al.,* (2010) evaluated the safety and efficacy of rosuvastatin in 5695 participants aged >70 at baseline (38). The elderly group (23% of total participants) accounted for 49% of the total 393 who reached the primary endpoints (The primary end point was the occurrence of a first cardiovascular event (myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes). However, it was noted that the elderly participants had different other cardio-vascular risk factors profile to the younger subjects. The older subjects had higher percentages of participants with hypertension and women, and lower percentages of cigarette smoking and obesity than the younger participants (38). Also, the study results illustrated that in the rosuvastatin participants theHigh Sensitivity C-Reactive Protein (hsCRP) levels and lipid levels were reduced similarly in both the younger and the elderly groups (38).

The rosuvastatin participants' averageLDL-C levels were half those in both age groups who received placebo. Also, It was noted in both age groups that the average hsCRP levels were about 36% less in the rosuvastatin participants compared to the placebo group (38). The JUPITER participants aged >70 years showed primary endpoint (The primary end point was the occurrence of a first cardiovascular event (myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes) rates of 1.99 and 1.22 per 100 person-years of follow-up in the placebo and rosuvastatin groups, respectively (38). The relative risk reduction (RRR) is slightly more uncertain among the elderly participants than younger participants aged between 50 and 69 years. Furthermore, the primary endpoint events absolute reduction was 48% greater among elderly participants than younger participants when combined with the fact that old people had more cardiovascular events rate JUPITER study illustrated that the adverse events rates were higher among the older participants than younger participants, however, rosuvastatin group did not show additional side effects than those presented in the placebo group. JUPITER study has been recognized to have several limitations of its overall design (39). This includes the possibility that benefits might be exaggerated due to the early trial termination (40). However, the USA Food and Drug Administration's independent review concluded that any the RR reduction potential over estimation because of early termination would be negligible and not alter the overall trial findings (41). It has been stated that the elderly aged >= 65years and young populations don't show different rosuvastatin plasma concentrations (42). Cytochrome P450 2C9 mainly metabolises rosuvastatin to N-desmethyl rosuvastatin, the main metabolite (42). The time to reach rosuvastatin peak plasma concentrations is between 3-5 hours after oral dosing and its elimination half-life (t1/2) is nearly 19 hours (42). 28% and 72% of rosuvastatin total body clearance is cleared renally and hepatically respectively after administering rosuvastatin intravenously (42).

Moreover, as rosuvastatin dose increases the area under the plasma concentration-time curve (AUC) and peak concentration (Cmax) increase in approximate amount (42, 43). Rosuvastatin absolute bioavailability is nearly 20% (42). 20% decrease in rate of rosuvastatin absorption was noted if it was administered with food based on Cmax value,but the extent of absorption was not affected based on AUC value (42). Additionally, morning or evening rosuvastatin administration showed same plasma concentrations (42). Eighty eight percent of rosuvastatin bounds to plasma proteins, mainly albumin which is independent and reversible of plasma concentrations (42).

Summary of findings: Based on the reviewed literature rosuvastatin had shown to reduce the arterial revascularization, stroke, myocardial infarction, unstable angina hospitalization, or death due to cardiovascular reasons. Also, rosuvastatin reduced the average LDL-C levels, the hsCRP levels and the occurrence of a first cardiovascular event had reduced more significantly among the elderly who received rosuvastatin than younger people. However, the adverse events rates were higher among the older than younger people but no differencein plasma concentrations.

Perindopril: Perindopril safetyand effectiveness among elderly had been evaluated in a large USA trial of 3010 participants aged 65 years and over (44). The study showed that treatment with perindopril as a monotherapy resulted in blood pressure reduction in both young and elderly participants diagnosed with hypertension. Only 51.9% and 41.4% of young and elderly participants respectively achieved target blood pressure of <130/80 mm Hg when taking perindopril as a monotherapy to control hypertension (44). The study indicated that hypertensive elderly participants did not respond to 4mg daily dose adequately. Increasing daily dose to 8mg improved blood pressure reduction in both elderly and young participants (44). At week-12, the 8mg daily dose improved blood pressure control by nearly 5-fold in both age groups (44). The blood pressure target of 130/80 mmHg (primary endpoint) achieved by 15.6% of patients diagnosed with both diabetes and hypertension when taking perindopril monotherapy (44). Moreover, the study found that perindopril was well tolerated, safe and effective in reducing blood pressure in all elderly participants', aged >75 years (44). Cough incidence was established in both elderly and young participants (7-10%) and postural hypotension incidence was low (less or equal to 0.2%). These results support the safety profile and tolerance of perindopril (44). A meta-analysis showed a significant reduction in the number of patients reaching primary endpoint when they administered perindopril compared with all other ACEIs (29). A randomized, double-blind, parallel-group, placebo-controlled, multi-centre study evaluated perindopril effects on heart remodelling as well as clinical outcome among elderly aged >=65 years cardiac patients (45). The study recruited 1252 participants (with >=40% ejection fraction of the left ventricle and current acute MI) who were assigned to either placebo or perindopril erbumine 8mg daily dose for 12 months (45). The study found that after one year of treatment with perindopril 8mg per day, progressive remodelling of the left ventricle was reduced but clinical outcomes did not change or improve (45). Another double-blind randomized study evaluated the usage of perindopril 4mg per day versus placebo in 850 participants aged >70 years who are diagnosed with heart failure and currently taking diuretics, found that hospitalisation due to heart failure complications (a

combination of unplanned heart failure associated with hospitalisation and all-cause mortality death) were reduced in perindopril group after one year treatment (31). Also, perindopril group showed improvement in the walking distance and functional class after one year (31).

A crossover, double□blind, acute study examined the effect of age on the pharmacodynamics and pharmacokinetics of angiotensin converting enzyme inhibitor "S□9780" and perindopril (which is S-9780 ester prodrug). One milligran S□9780 was administered intravenously and eight milligram perindopril was administered orally. The study conducted in 8 young (aged 29 ± 3 years) and 8 elderly (aged 71 ± 3 years) healthy participants. The younger participants suffered only from mild light□headedness and headache which are more common among them compared with the elderly participants who suffered from higher blood pressure fall rate (35% ± 17% vs 19% ± 7%; $p < 0.025$). S□9780 bioavailability was greater among elderly participants due to greater conversion rather than absorption. S□9780 renal clearance was greater in the young participants than in the elderly (110 ± 39 ml/ min vs 67 ±31 ml/min ; $p < 0.03$). Thus, the study suggested an approximate 50% dose reduction for elderly patients with consideration to any pre-existing reduced renal function which might require further adjustment (46).

Summary of findings: It has been found from the reviewed studies that perindopril was well tolerated, safe and effective in reducing blood pressure in all elderly people including those aged >75 years. Studies show that increasing daily dose to 8mg improved blood pressure reduction in both elderly and young people.Perindopril bioavailability was greater among elderly participants due to greater conversion rather than absorption. However, renal clearance was greater in the young than in the elderly people. Thus, it has been suggested an approximate 50% dose reduction for elderly patients with consideration to any pre-existing reduced renal function which might require further adjustment.

Amlodipine: A study conducted among elderly diagnosed with hypertension aged between 65 and73 years and youngerparticipants aged between 28 and 34 year who were given IV amlodipine followed by oral amlodipine once daily for two weeks, found that the elderly participants had a reduced amlodipine clearance compared with the young participants after the IV infusion. This prolongation of amlodipine half-life resulted in greater reduction in systolic and diastolic blood pressure compared to young participants. After fourteen weeks treatment, systolic blood pressurewas significantly reduced in the elderly group, while diastolic blood pressure was reduced at two and fourteen weeks treatment (47).

A USA large recent community-based trial showed that amlodipine was more effective among elderly participants when compared to younger than 65 years (48). Also, other studies found that majority of participants tolerated amlodipine at good or excellent levels (49, 50). Furthermore, it has been illustrated that amlodipine tendency to cause vasodilatory adverse-effects was reduced due to its slow absorption nature when it was given orally. Another study showed that the circadian rhythms of blood pressure were not altered among participants whose blood pressure was controlled by a 24 hours amlodipine dosage (51). Moreover, the heart dimension was decreased (51).

Furthermore, 75% of the participants (elderly) had normal blood pressure after treatment with amlodipine as a monotherapy (51). Another study concluded that low dose amlodipine per day were efficacious and well tolerated by elderly with hypertension (52). The study illustrated that diastolic and systolic blood pressure readings were decreased at weeks 8 (153 +/- 17, 90 +/- 9 mmHg) and 12 (152 +/- 16, 90 +/- 9 mmHg) when compared with week 0 (164 +/- 16, 99 +/- 6 mmHg) and 16 (162 +/- 19, 95 +/- 9 mmHg) (52). It has been documented that amlodipine pharmacokinetics are not altered significantly in elderly or patients with renal impairment (53). However, hepatically impaired patients showed reduced clearance rates (53). Amlodipine absorption is slow when administered orally (53). The peak plasma concentration reached 6-12 h after dose and the absolute bioavailability is 60-80% (53, 54). Amlodipine has an extended elimination half-life (t1/2) (40-60 h) (54) due its great volume of distribution and low clearance rate (53). Additionally, amlodipine once daily dosing is sufficient to maintain mean effective plasma concentrations (53). Amlodipine steady state is reached after 7^{th}-9^{th} dose when administered once daily (53). The sharp fluctuations in plasma concentration (that are resulted from vasodilatation-induced adverse effects such as flushing, tachycardia and headache) were not seen in amlodipine pharmacokinetic properties compared with other calcium antagonists (53). Blood pressure is reduced slowly over 4h to 8h followed single doses and may gradually reaches baseline again over 24h to 72 h (54). It has been noted that the heart rate has not been changed followed the dose due to the gradual onset hence physiological reflexes are not stimulated (54). Additionally, baseline blood pressure is returned gradually over 7 to10 days followed amlodipine treatment discontinuation with no 'rebound' effect indication (54).

Summary of findings: It had been found in the reviewed literature that the elderly had a reduced amlodipine clearance resulting in the prolongation of the half-life and greater reduction in systolic and diastolic blood pressure compared to young people. Also, amlodipine was found to cause reduced vasodilatory adverse-effects due to its slow absorption nature when it was given orally. It has been documented that amlodipine pharmacokinetics were not altered significantly in elderly.

Paracetamol: Paracetamol oral bioavailability (F) has been investigated in number of studies. One study found that F in older participants was similar to F of young participants (55). More than one study showed that young participants tended to have a higher F of both elixir and tablets than older participants (56, 57). However, clinical relevance was not significant (56). Furthermore, F remained the same in all other age groups (57). Three studies found that there was no significant difference in half-life and lag time ($\mathbf{t}_{lag}$) between different age groups (56, 58, 59). Older participants showed longer absorption time when taken paracetamol elixir with food than younger participants. Caution should be considered when applying these results in clinical practicedue to the great inter-individual differences regardless of age (57). The difference of the extent and the rate of absorption between different age groups were not clinically significant. Moreover, theabsence of older frail participants from these studies makes their results not conclusive to all age group. Volume of distribution ($\mathbf{V}_d$) might be influenced by age. It has been shown that older participants had relatively lower $\mathbf{V}_d$ than younger participants (60). The decreased $\mathbf{V}_d$ with age is

potentially due to the paracetamol relative hydrophilic nature and the high fat portion among older persons compared to younger persons, consequently increasing plasma concentration of paracetamol among older persons (61).

Another study illustrated that health condition can potentially affect pharmacokinetics. Frail older participants showed lower $\mathbf{V}_d$ than young and robust older participants (60). This result has been supported in Ellmers *et al.,* (1991) study which showed lower $\mathbf{V}_d$ among frail older participants than robust older persons. More than one study demonstrated that robust older women had smaller $\mathbf{V}_d$ than older robust men which is potentially due the fact that women's total body weight composed of larger amount of fat than men (62-64). More than one study (63-66) investigated sex-related differences in pharmacokinetic parameters between robust male and female older adults, of which four studies reported a smaller Vd in women compared with men ($p < 0.05$), ranging from 8.5 to 17.5% (62-64). This is probably caused by the larger proportion of fat in a woman's total body weight.It is reasonable to state that Vd decreases with increasing age, most pronouncedly in frail older people. Changes in Vd determine the influence of the loading dose, and the elimination half-life. Both statistical and clinical significance are still unknown.It has been shown in more than one trial that paracetamol clearance is reduced among robust older participants compared to younger participants (1).

However, Triggs *et al.,* (1975) and Miners *et al.,* (1988) showed no substantial differences between different aged group (67, 68). Another study, comparing paracetamol CL on days 1 and 7 during repeated administration, reported no paracetamol accumulation. However, this does not imply anything regarding possible accumulation of the (toxic) metabolites.Additional factors besides age, such as disease, concomitant medication or general physical status (e.g. frailty), may influence paracetamol metabolism. One study showed a 26.4% decrease in the clearance (calculated using body weight) of paracetamol among frail participants compared with older robust older participants (1). However, the results differ when clearance was calculated using liver unit volume. Frail participants' clearance rate reduced significantly by 32.9 and 37.5 % when compared with robust older and young cases, respectively, but there is no significant difference between robust older and young participants (60). When CL was expressed per unit volume of liver, no significant differences were found between young and robust older participants, but it was significantly reduced in the frail participants. These results demonstrate that disease state and/or frailty can play a role in reducing clearance (60).

Hepatotoxicity, gastrointestinal toxicity and nephrotoxicity have reported as possible side effects associated with paracetamol usage among elderly in seven studies (69-75). Mitchell *et al.,* (2011) study indicated that the concentrations of alanine aminotransferase (ALAT) were the highest among younger participants when compared with robust older and frail older participants who were slightly above and within reference range, respectively (69). Another study conducted by Jahr *et al.,* (2012) found that the liver enzyme did not differ significantly between participants65years old or more in placebo and paracetamol groups (70). Two studies stated that paracetamol usage showed no significant differences in between controls and hospitalised participants with duodenal ulcer or gastrointestinal bleeding (71, 73).

However, Rahme *et al.,* (2002) reported that participants who administered lower paracetamol dose were less likely to suffer gastrointestinal event when compared with participants who administered higher paracetamol dose (75). Creatinine clearance showed no significant reduction in the placebo and paracetamol groups in Koppert *et al.,* (2006) study (72). Additionally, α-1-microglobulin, urine albumin, potassium and sodium showed a slight not significant increase (72).

Summary of findings: Studies reviewed showed different opinion on the bioavailability of paracetamol changes in older people. The elderly showed longer absorption time when taken paracetamol elixir than younger people and relatively lower $\mathbf{V}_d$ than younger participants. It had been noted that disease state and/or frailty can play a role in reducing clearance.Hepatotoxicity, gastrointestinal toxicity and nephrotoxicity have reported as possible side effects associated with paracetamol usage among elderly in several studies.

Statistical summary: Out of the 29 studies reviewed older people had been the main focus of 16 (55%) studiesonly but they were included in12 studies (Figure 1).

The effect of age-related biologic and physiological (pharmacokinetic and pharmacodynamics) changes among elderly on drug dosageand selection had been either studied or not in different studies. As shown in figure 2, ninteen studies did not discuss the effects of elderly physiological changes on medications. Most of these papers included elderly with different medical conditions and studied the effectiveness of different drugs (atorvastatin, rosuvastatin, perindopril, amlodipine and paracetamol) on specific medical conditions (19 papers out 30, 63%). However, only eleven studies discussed elderly physiological (pharmacokinetic and pharmacodynamics) changes directly on medication usage.

Conclusion

It is apparent that the main focus of the most clinical trial was testing medications' (atorvastatin, rosuvastatin, perindopril, amlodipine and paracetamol) effectiveness on different medical conditions with less focus on the effect of the elderly pharmacokinetic and pharmacodynamics changes on these medications and in many cases just predict the age effect rather than the actual effect. Thus, more clinical trials should focuson the effects of the age-related biological changes on medications which potentially can play a role in reducing medications' side effects among elderly.

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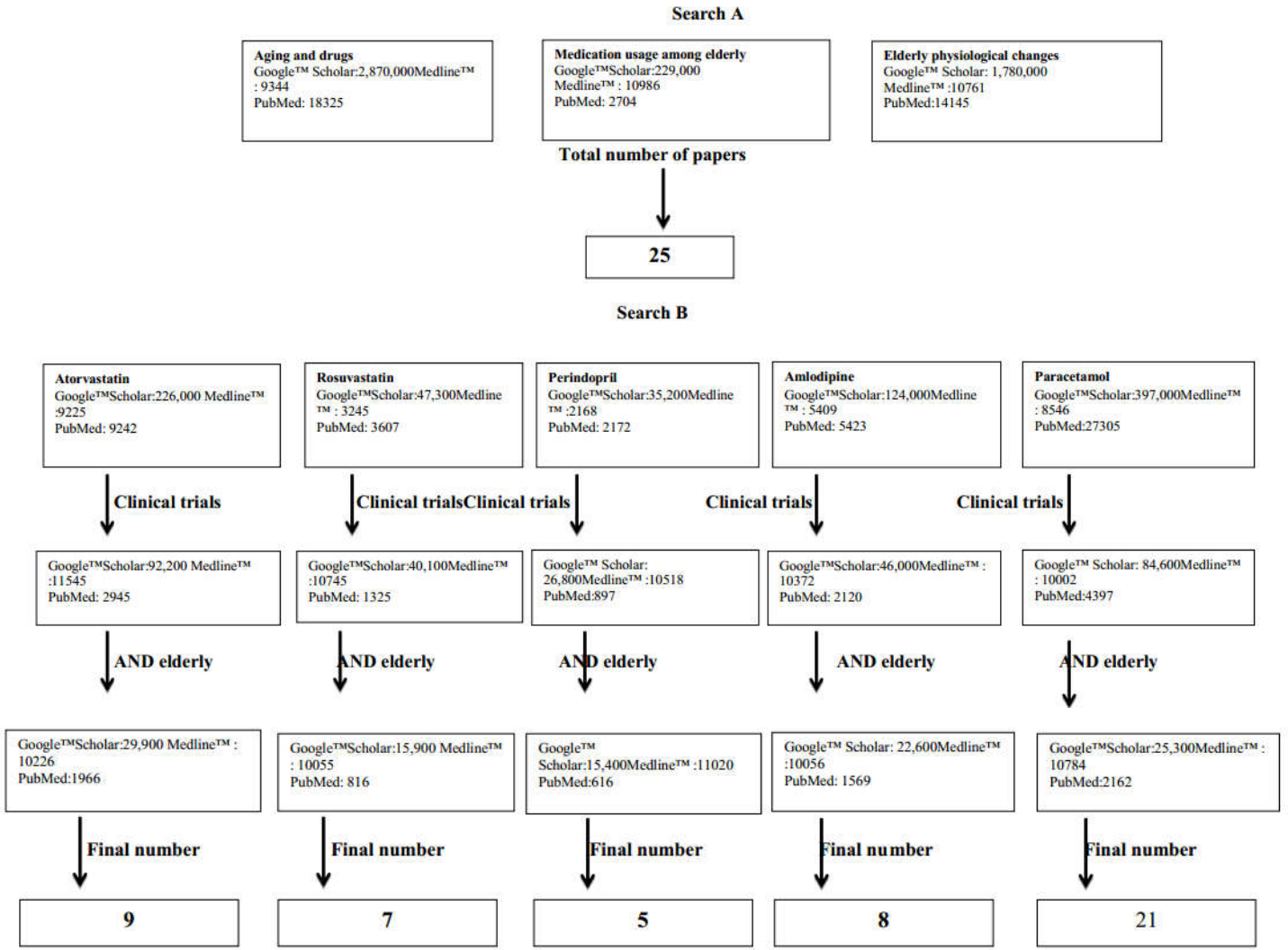
Appendix I: Search method

Aging and drugs, medication usage among elderly, elderly physiological changes, atorvastatin, atorvastatin clinical trials, atorvastatin clinical trials AND elderly, rosuvastatin, rosuvastatin clinical trials, rosuvastatin clinical trials AND elderly, perindopril, perindopril clinical trials, perindopril clinical trials AND elderly,amlodipine, amlodipine clinical trials, amlodipine clinical trials AND elderly, paracetamol, paracetamol clinical trials, paracetamol clinical trials AND elderly. Letters, commercial websites and commentaries were excluded, only informational websites and peer reviewed articles were included.


Search A
Aging and drugs
Google™ Scholar:2,870,000Medline™ : 9344
PubMed: 18325
Medication usage among elderly
Google™Scholar:229,000
Medline™ : 10986
PubMed: 2704
Elderly physiological changes
Google™ Scholar: 1,780,000
Medline™ :10761
PubMed:14145
Total number of papers
25
Search B
Atorvastatin
Google™Scholar:226,000 Medline™ :9225
PubMed: 9242
Rosuvastatin
Google™Scholar:47,300Medline™ : 3245
PubMed: 3607
Perindopril
Google™Scholar:35,200Medline™ :2168
PubMed: 2172
Amlodipine
Google™Scholar:124,000Medline™ : 5409
PubMed: 5423
Paracetamol
Google™Scholar:397,000Medline™ : 8546
PubMed:27305
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Google™Scholar:92,200 Medline™ :11545
PubMed: 2945
Google™Scholar:40,100Medline™ :10745
PubMed: 1325
Google™ Scholar: 26,800Medline™ :10518
PubMed:897
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Google™ Scholar:15,400Medline™ :11020
PubMed:616
Google™ Scholar: 22,600Medline™ :10056
PubMed: 1569
Google™Scholar:25,300Medline™ : 10784
PubMed:2162
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Appendix II: articles used in the paper (Derived from papers' abstract)

Age Consideration When Prescribing for the Elderly						
Reference	**Type of study**	**Sample size**	**Result**	**Physiological changes among elderly considered**	**Clinical trial among elderly considered**	**Conclusion drawn from the study**
Atorvastatin						
Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation. 2007 Feb 13;115(6):700-7. PubMed PMID: 17283260. Epub 2007/02/07. eng.	Subjects were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d and followed up for 12 months.	893	Compared with moderate pravastatin therapy, intensive atorvastatin therapy was associated with reductions in cholesterol, major acute cardiovascular events, and death in addition to the reductions in ischemia observed with both therapies.	No	Yes	The contrast between the therapies' differing efficacy for major acute cardiovascular events and death and their nonsignificant difference in efficacy for reduction of ischemia suggests that low-density lipoprotein cholesterol-lowering thresholds for ischemia and major acute cardiovascular events may differ. The Study Assessing Goals in the Elderly (SAGE) demonstrates that older men and women with coronary artery disease benefit from intensive statin therapy.
Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet (London, England). 2004 Aug 21-27;364(9435):685-96. PubMed PMID: 15325833. Epub 2004/08/25. eng.	Patients were randomised to placebo (n=1410) or atorvastatin 10 mg daily (n=1428).	2838	Atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol. No justification is available for having a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins.	No	Yes	The debate about whether all people with this disorder warrant statin treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld. benefits of statin therapy far outweigh any safety concerns, especially among older CHD patients who may be otherwise healthy. By reducing morbidity related to acute coronary events, statins can enhance the quality of life and lead to a more productive old age. While extra caution is warranted with high-dose statin therapy, particularly in those with concomitant medical conditions such as chronic kidney or liver disease, increased chronological age alone should not exclude any patient from receiving the benefits of such treatment. Atorvastatin has been proven to improve clinical outcomes, even when compared to other statins in large randomized clinical trials, and is generally well tolerated in the elderly population. It is therefore a suitable choice when considering statin therapy in this group of patients

Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet (London, England). 2004 Aug 21-27;364(9435):685-96. PubMed PMID: 15325833. Epub 2004/08/25. eng.	Patients were randomised to placebo (n=1410) or atorvastatin 10 mg daily (n=1428).	2838	Atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol. No justification is available for having a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins.	No	Yes	The debate about whether all people with this disorder warrant statin treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld. benefits of statin therapy far outweigh any safety concerns, especially among older CHD patients who may be otherwise healthy. By reducing morbidity related to acute coronary events, statins can enhance the quality of life and lead to a more productive old age. While extra caution is warranted with high-dose statin therapy, particularly in those with concomitant medical conditions such as chronic kidney or liver disease, increased chronological age alone should not exclude any patient from receiving the benefits of such treatment. Atorvastatin has been proven to improve clinical outcomes, even when compared to other statins in large randomized clinical trials, and is generally well tolerated in the elderly population. It is therefore a suitable choice when considering statin therapy in this group of patients
Cournot M, Cambou JP, Quentzel S, Danchin N. Key factors associated with the under-prescription of statins in elderly coronary heart disease patients: Results from the ELIAGE and ELICOEUR surveys. International journal of cardiology. 2006 Jul 28;111(1):12-8. PubMed PMID: 16046011. Epub 2005/07/28. eng.	. Two cross-sectional pharmaco-epidemiological surveys were carried out among French cardiologists. Patients' risk factors, medical history, treatments, lipid values and the physicians' various motives for the non-prescription of statins were recorded. Patients not treated with statins reached 37% in the age-group > or =70 years and 14% in the age-group 35-69 years. The main reason given for statin non-prescription was the lack of a medical indication (2.5% of the age-group 35-69 years and 14% of the age-group > or =70 years). Among patients > or =70 years, the lack of indication was more often cited in the following conditions: 1) in very old patients (36% of lack of indication in the age-group >85 years vs. 10% in 70-75 years), 2) when lipid values were not available (20% when data were not available vs. 9%) and 3) when the patient had no prior history of myocardial infarction (MI) (20% when no history of MI vs. 7%). These factors were not associated with lack of indication among patients <70 years. History of intolerance or side effect was given for 1.3% and 14% of patients for each of the groups (35-69 and > or =70) and poor overall patient adherence was cited in 1% and 2%, respectively. The primary reason for the under-prescription of statins in elderly coronary patients is the perceived lack of indication, which stresses the need of extensive guidelines for prescription in elderly patients. Several factors associated with this perception seem to be specific to the elderly.	1148 coronary patients aged 35 to 69 years and 1489 patients aged > or =70 years.	Patients not treated with statins reached 37% in the age-group > or =70 years and 14% in the age-group 35-69 years. The main reason given for statin non-prescription was the lack of a medical indication (2.5% of the age-group 35-69 years and 14% of the age-group > or =70 years). Among patients > or =70 years, the lack of indication was more often cited in the following conditions: 1) in very old patients (36% of lack of indication in the age-group >85 years vs. 10% in 70-75 years), 2) when lipid values were not available (20% when data were not available vs. 9%) and 3) when the patient had no prior history of myocardial infarction (MI) (20% when no history of MI vs. 7%). These factors were not associated with lack of indication among patients <70 years. History of intolerance or side effect was given for 1.3% and 14% of patients for each of the groups (35-69 and > or =70) and poor overall patient adherence was cited in 1% and 2%, respectively.	No	Yes	The primary reason for the under-prescription of statins in elderly coronary patients is the perceived lack of indication, which stresses the need of extensive guidelines for prescription in elderly patients. Several factors associated with this perception seem to be specific to the elderly

Benner JS, Pollack MF, Smith TW, Bullano MF, Willey VJ, Williams SA. Association between short-term effectiveness of statins and long-term adherence to lipid-lowering therapy. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2005 Jul 15;62(14):1468-75. PubMed PMID: 15998926. Epub 2005/07/07. eng.	A retrospective cohort study was conducted among enrollees in a Southeastern managed care plan who started therapy with atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin between October 1999 and August 2001, were enrolled for > or =12 months before and > or =6 months after treatment initiation, and had at least one LDL cholesterol measurement in the year before and 4-12 weeks after the start of therapy. Patients were followed up via electronic pharmacy and medical records for up to 33 more months. The follow-up period was divided into 3-month intervals; patients were considered adherent if statin therapy was available > or =80% of the time. A generalized linear model for repeated measures quantified the association between change in LDL cholesterol at 4-12 weeks and medication adherence in subsequent intervals, adjusting for demographic, clinical, and health-service-use variables.	9,510	The final sample consisted of 9510 patients. Medication adherence decreased significantly over time: 59%, 40%, 34%, and 21% of patients were adherent at 3, 6, 12, and 36 months, respectively. Mean +/- S.D. LDL cholesterol reduction at 12 weeks was 28.9% +/- 19.9%. The relative LDL cholesterol reduction at 12 weeks was significantly and independently associated with subsequent medication adherence: Compared with subjects in the first quartile of LDL cholesterol reduction, those in quartiles 2, 3, and 4 were more likely to be adherent in any subsequent interval (adjusted odds ratio [95% confidence interval], 1.26 [1.12-1.42], 1.25 [1.11-1.40], and 1.15 [1.02-1.29], respectively). Other independent predictors of adherence in months 4-36 included adherence during the initial three months of therapy, age, and recent history of coronary revascularization.	No	Yes	Greater reduction in LDL cholesterol levels during the first three months of statin therapy was associated with greater adherence to lipid-lowering drug therapy.
Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Annals of internal medicine. 2007 Jul 3;147(1):1-9. PubMed PMID: 17606955. Epub 2007/07/04. eng.	A prespecified secondary analysis of the Treating to New Targets study, a randomized, double-blind clinical trial.	10,001 patients (256 sites in 14 countries participating in the Treating to New Targets study.)	The analysis suggests that additional clinical benefit can be achieved by treating older patients with CHD more aggressively to reduce low-density lipoprotein cholesterol levels to less than 2.6 mmol/L (<100 mg/dL). The findings support the use of intensive low-density lipoprotein cholesterol-lowering therapy in high-risk older persons with established cardiovascular disease. Click here for related information on atorvastatin	No	yes	
Pedersen TR, Faergeman O, Kastelein JJP, Olsson AG, Tikkanen MJ, Holme I, et al. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial InfarctionThe IDEAL Study: A Randomized Controlled Trial. JAMA. 2005;294(19):2437-45.	A prospective, randomized, open-label, blinded end-point evaluation trial.	8888	In this study of patients with previous MI, intensive lowering of LDL-C did not result in a significant reduction in the primary outcome of major coronary events, but did reduce the risk of other composite secondary end points and nonfatal acute MI. There were no differences in cardiovascular or all-cause mortality.	No	Yes	Patients with MI may benefit from intensive lowering of LDL-C without an increase in noncardiovascular mortality or other serious adverse reactions.

Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. The New England journal of medicine. 2004 Apr 8;350(15):1495-504. PubMed PMID: 15007110. Epub 2004/03/10. eng.	A comparison study between 40 mg of pravastatin daily dosing (standard therapy) and 80 mg of atorvastatin daily dosing (intensive therapy). The primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event. Follow-up lasted 18 to 36 months (mean, 24).	4162	The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group (P<0.001). Kaplan–Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin (P=0.005; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.	No	Yes	Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.
Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001 Apr 4;285(13):1711-8. PubMed PMID: 11277825. Epub 2001/04/13. eng.	A randomized, double-blind trial conducted from May 1997 to September 1999, with follow-up through 16 weeks at 122 clinical centers in Europe, North America, South Africa, and Australasia.	3086 adults.	For patients with acute coronary syndrome, lipid-lowering therapy with atorvastatin, 80 mg/d, reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization	No	Yes	
Olsson AG, Schwartz GG, Szarek M, Luo D, Jamieson MJ. Effects of high-dose atorvastatin in patients > or =65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study). The American journal of cardiology. 2007 Mar 1;99(5):632-5. PubMed PMID: 17317362. Epub 2007/02/24. eng.	The MIRACL study randomized patients to 16 weeks of 80 mg/day of atorvastatin or placebo 24 to 96 hours after ACS. This post hoc analysis compared benefits of 80 mg of atorvastatin in older (> or =65 years) versus younger (<65 years) patients.	3,086 patients(MIRACL)	Event rates were approximately two- to threefold higher in older than in younger patients. Treatment-by-age heterogeneity testing indicated no difference in treatment effect by age for any of the primary or secondary end points, and relative risk decreases in the primary end point with atorvastatin versus placebo were similar in younger and older patients (22% vs 14%, respectively). The safety profile of atorvastatin was similar between the 2 age groups.	No	Yes	These results and a greater immediate cardiovascular risk in older patients argue for early, intensive atorvastatin therapy as routine practice after ACS.

Gibson DM, Bron NJ, Richens MA, Hounslow NJ, Sedman AJ, Whitfield LR. Effect of Age and Gender on Pharmacokinetics of Atorvastatin in Humans. The Journal of Clinical Pharmacology. 1996;36(3):242-6.	The effects of age and gender on the pharmacokinetics of atorvastatin after administration of single 20-mg tablets of atorvastatin were studied	32	The equivalent maximum concentration of atorvastatin was 42.5% higher in elderly participants than in young participants and 17.6% higher in women than in men. The mean area under the concentration-time curve and half-life were 27.3% greater and 36.2% longer, respectively, in elderly adults than in young adults and 11.3% lower and 19.9% shorter, respectively, in women than in men.	Yes	Yes	Results of subsequent safety and efficacy trials should help clarify the clinical significance of these pharmacokinetic differences.
Rosuvastatin						
Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. The New England journal of medicine. 2008 Nov 20;359(21):2195-207. PubMed PMID: 18997196. Epub 2008/11/11. eng.	a randomized, double-blind, placebo-controlled, multicenter trial Subjects were randomly assigned to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.	17,802	In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.	No	Yes	
Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Annals of internal medicine. 2010 Apr 20;152(8):488-96, W174. PubMed PMID: 20404379. Pubmed Central PMCID: PMC2946369. Epub 2010/04/21. eng.	a randomized, double-blind, placebo-controlled trial. , Participants were randomly assigned in a 1:1 ratio to receive 20 mg of rosuvastatin daily or placebo.	5695 were 70 years or older.	In apparently healthy older persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin reduces the incidence of major cardiovascular events.	No	Yes	

Mora S, Ridker PM. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)--can C-reactive protein be used to target statin therapy in primary prevention? The American journal of cardiology. 2006 Jan 16;97(2A):33A-41A. PubMed PMID: 16442935. Epub 2006/01/31. eng.	Review article		The most important action of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is their ability to lower levels of low-density lipoprotein (LDL) cholesterol. Statins have proved highly effective in reducing the risk of cardiovascular events in both primary and secondary prevention studies. However, the magnitude of risk reduction associated with statins is greater than that predicted on the basis of LDL cholesterol lowering alone. A likely explanation for this effect is the anti-inflammatory action of statins. Following the observation that high-sensitivity C-reactive protein (hs-CRP) is a powerful predictor of cardiovascular events, investigators in the Cholesterol and Recurrent Events (CARE) and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trials demonstrated that the magnitude of risk reduction associated with statin therapy was higher among those with elevated hs-CRP levels. In addition, there is accumulating evidence that statins lower plasma levels of hs-CRP in a manner largely independent of LDL cholesterol lowering. In contrast, little benefit has been demonstrated for statin therapy in the absence of both hyperlipidemia and inflammation. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is a large multinational, long-term, double-blind, placebo-controlled, randomized clinical trial designed to assess directly whether statin therapy (rosuvastatin 20 mg/day) should be given to apparently healthy individuals with low LDL cholesterol levels but elevated hs-CRP levels--a critical issue for the prevention of cardiovascular disease. Support for the concept behind the JUPITER trial is also now available from several recent trials comparing different intensities of statin therapy on disease progression as well as clinical end points. These studies indicate that the hs-CRP level achieved after initiation of statin therapy may be as important as the LDL cholesterol level achieved. All of these data raise the possibility that hs-CRP could be used to target high-risk patients who may benefit from early statin use. Ongoing work will determine whether hs-CRP reduction, independent of LDL cholesterol reduction, results in a net clinical benefit	-	Yes	
Narla V, Blaha MJ, Blumenthal RS, Michos ED. The JUPITER and AURORA clinical trials for rosuvastatin in special primary prevention populations: perspectives, outcomes, and consequences. Vascular health and risk management. 2009;5:1033-42. PubMed PMID: 20057896. Pubmed Central PMCID: PMC2801627. Epub 2010/01/09. eng.	This review outlines the JUPITER and AURORA trials, interprets the data and significance of the results, analyses the drawbacks and impact of both trials and delineates the potential for further clinical trials.			No	Yes	
Ridker PM, Glynn RJ. The JUPITER Trial: responding to the critics. The American journal of cardiology. 2010 Nov 1;106(9):1351-6. PubMed PMID: 21029837. Epub 2010/10/30. eng.	Responding to the critics of the JUPITER Trial			No	Yes	

Perindopril						
Neutel JM, Weber MA, Julius S, Cohn JN, Turlapaty P, Shen Y, et al. Clinical experience with perindopril in elderly hypertensive patients: a subgroup analysis of a large community trial. American journal of cardiovascular drugs : drugs, devices, and other interventions. 2004;4(5):335-41. PubMed PMID: 15449975. Epub 2004/09/29. eng.	participantsreceived open-label perindopril 4 mg once a day for 6 weeks. After 6 weeks the dosage was either maintained (group I) or increased to 8 mg/day (group II) based on the physician's assessment of blood pressure (BP) response. Patients were then followed for another 6 weeks for a total study duration of 12 weeks.	3010	Demographic and baseline clinical characteristics revealed a higher proportion of women, longer duration of hypertension and higher baseline systolic BP (SBP) among elderly than young (<65 years, n = 7332) hypertensive patients. A clinically relevant BP reduction of similar magnitude was obtained in elderly and young patients with perindopril monotherapy. At week 12, the mean reduction in BP from baseline was 18.4/8.7 mm Hg in the elderly and 17.5/11.3 mm Hg in the young. Elderly patients with hypertension not responding adequately to the 4 mg/day dosage at week 6 had a BP reduction of 6.3/3.6 mm Hg (group II). Up-titration to an 8 mg/day dosage for another 6 weeks gave an additional 8.9/3.5 mm Hg reduction resulting in a total reduction of 15.2/7.1 mm Hg from baseline. A similar magnitude of increase in response to up-titration of perindopril was seen in young patients. BP control (<140/90 mm Hg) on perindopril monotherapy was achieved in 41.4% of elderly and 51.9% of young patients. In both age groups, up-titration to an 8.0 mg/day dosage in group II patients increased BP control by approximately 5-fold at week 12 (28.2% in the elderly and 36.4% in the young). A similar increased response on BP reduction and BP control (<140/90 mm Hg) with up-titration was seen in elderly subgroups of African American and diabetic patients. The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommended target goal of <130/80 mm Hg was achieved with perindopril monotherapy in 15.6% of hypertensive diabetic patients. Perindopril reduced BP effectively and safely in very elderly (> or =75 years) hypertensive patients. Perindopril was well tolerated in elderly patients including high-risk groups. The incidence of cough (7-10%), the most common symptom, was similar in all age groups. The low incidence of postural hypotension (< or =0.2%) observed in the elderly and very elderly further supports the good tolerance and safety profile of the drug. Data analysis from this study suggests that community physicians, in general, are less aggressive in controlling BP in the elderly and more inclined to treat or control diastolic BP than SBP.	No	yes	Perindopril treatment is effective and well tolerated in elderly patients with hypertension.

Ferrari R. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. Archives of internal medicine. 2006 Mar 27;166(6):659-66. PubMed PMID: 16567606. Epub 2006/03/29. eng.	Double-blind, randomized, parallel-group, multicenter, placebo-controlled study. Participants were randomized to receive perindopril erbumine or placebo (8 mg/d) for 12 months.	1252	The primary end point (death, hospitalization for heart failure, or left ventricular remodeling) occurred in 181 patients (35%) taking perindopril and 290 patients (57%) taking placebo, with a significant absolute risk reduction of 0.22 (95% confidence interval, 0.16 to 0.28; P<.001). A total of 126 patients (28%) and 226 patients (51%) in the perindopril and placebo groups, respectively, experienced remodeling. The mean increase in left ventricle end-diastolic volume was 0.7 mL with perindopril compared with 4.0 mL with placebo (P<.001). In the perindopril group, 40 deaths (6%) and 22 hospitalizations (4%) for heart failure occurred, whereas 37 deaths (6%) and 30 hospitalizations (5%) occurred in the placebo group. Treatment did not affect death, whereas the hospitalization rate for heart failure was slightly reduced (absolute risk reduction, 0.01; 95% confidence interval, -0.01 to 0.02). No treatment effect on other secondary end points (cardiovascular death, hospitalization for reinfarction or angina, and revascularization) was detected.	No	Yes	One year treatment with 8 mg/d of perindopril reduces progressive left ventricular remodeling that can occur even in the presence of small infarct size, but it was not associated with better clinical outcomes.
Lees KR, Green ST, Reid JL. Influence of age on the pharmacokinetics and pharmacodynamics of perindopril. Clinical Pharmacology & Therapeutics. 1988;44(4):418-25.	double-blind, crossover, acute study	16	Mild headache and light-headedness were the only adverse effects and were more common in the younger subjects. Blood pressure fall was greater in the elderly even after correction for starting blood pressure. Bioavailability of S-9780 was increased in the mainly because of increased conversion rather than absorption. Renal clearance of S-9780 was lower in the elderly	Yes	Yes	Dose reduction of approximately 50% is suggested for elderly patients with further adjustment proportional to any preexisting diminished renal function.

Amlodipine						
Abernethy DR, Gutkowska J, Lambert MD. Amlodipine in elderly hypertensive patients: pharmacokinetics and pharmacodynamics. Journal of cardiovascular pharmacology. 1988;12 Suppl 7:S67-71. PubMed PMID: 2467133. Epub 1988/01/01. eng.	Participantsreceived amlodipine by i.v. infusion (2.5, 5.0, or 10.0 mg). Patients were then started on oral amlodipine 2.5 mg daily for 2 weeks, at the end of which amlodipine disposition and effect were evaluated over one 24-h dose interval. Patients were treated subsequently with amlodipine in an escalating dose protocol (maximum 10.0 mg once daily) for 12 weeks to control blood pressure.	14	After i.v. amlodipine, clearance tended to be decreased in elderly as compared with young patients with resulting prolongation in elimination half-life (64± 20 vs. 48 ± 8 h; mean ± SD). Maximum decrease in systolic blood pressure (SBP) after i.v. doses tended to be greater in the elderly (-34 ± 15 vs. -23 ± 15 mm Hg) and maximum decrease in diastolic blood pressure (DBP) was similar in the two groups (− 21 ± 10 vs. - 18 ± 7 mm Hg). SBP was significantly decreased after 14 weeks' therapy in the elderly at doses ranging from 2.5 to 10.0 mg per day (171 ± 17 to 149 ± 22 mm Hg; $p < 0.01$). DPB was decreased both at 2 and 14 weeks' therapy in the elderly(baseline 100 ± 7, 2 weeks 93 ± 5, 14 weeks 90 ± 5 mm Hg; $p < 0.01$ vs. baseline). Similar decreases in DBP were noted in young patients (baseline 96 ± 6, 2 weeks 81 ± 15, 14 weeks 84 ± 15 mm Hg). Humoral measures at baseline (pretreatment), 2 weeks' therapy, and 14 weeks' therapy were as follows: norepinephrine (640, 498, 454 pg/ml; NS), epinephrine (70, 59, 60 pg/ml; NS), plasma renin activity (1.5, 1.8, 2.0 ng ml−1h−1; NS), urinary aldosterone excretion rate (11.4, 13.4, 11.0 µg/24 h; NS), and plasma atrial natriuretic factor (71.1, 80.4, 68.3 pg/ml; NS). Amlodipine clearance tends to be decreased in elderly patients, suggesting increased drug accumulation during chronic dosing. No obvious drug-related side effects were noted in any patient.	No	Yes	Amlodipine is effective as single-drug therapy in the treatment of both systolic and diastolic hypertension in the elderly and diastolic hypertension in younger patients.
Pascual J. Hypertension control in the elderly with amlodipine. Current medical research and opinion. 2000;16(1):33-6. PubMed PMID: 16422032. Epub 2006/01/21. eng.	Research article		Treatment of hypertension in the elderly reduces the incidence of cardiovascular events. Some classes of antihypertensive drugs, including long-acting dihydropyridine calcium channel blockers such as amlodipine, can be prescribed in the presence of comorbid conditions. The results of clinical trials support the use of long-acting dihydropyridine calcium channel blockers in the elderly;	-	Yes	Amlodipine has been shown to be effective and well tolerated in the elderly population.
Abernethy DR. Amlodipine: pharmacokinetic profile of a low-clearance calcium antagonist. Journal of cardiovascular pharmacology. 1991 1991;17 Suppl 1:S4-7. PubMed PMID: 16296697. eng.			Amlodipine is absorbed gradually after oral administration (peak plasma levels 6-12 h postdose) and has an absolute bioavailability of 64%. Low clearance and a high volume of distribution give amlodipine a long elimination half-life, and mean effective plasma levels are maintained with once-daily doses. With repeated once-daily dosing, the steady state is achieved after the seventh to ninth dose. The pharmacokinetic properties of amlodipine avoid the sharp fluctuations in plasma level seen with other calcium antagonists that are associated with vasodilatation-induced side effects such as tachycardia, headache, and flushing.	Yes	Yes	The pharmacokinetics of amlodipine are not significantly altered in elderly or renally impaired patients, but there is reduced clearance in patients with hepatic impairment. There are no pharmacokinetic interactions between amlodipine and cimetidine or digoxin.

Abernethy DR. Pharmacokinetics and Pharmacodynamics of Amlodipine. Cardiology. 1992;80(suppl 1)(Suppl. 1):31-6.	-	-	Amlodipine is a low-clearance, dihydropyridine calcium antagonist. The slow rate of elimination (elimination half-life of 40-60 h) confers several pharmacokinetic characteristics that are not seen with other calcium-antagonist drugs.It has high oral bioavailability (60-80%) and accumulates to a steady-state with once-daily administration over a period of 1-1 ½ weeks.	Yes	-	Amlodipine is a low-clearance, dihydropyridine calcium antagonist which is effective for the treatment of hypertension and angina pectoris with once-daily dosing.
Paracetamol						
Mian P, Allegaert K, Spriet I, Tibboel D, Petrovic M. Paracetamol in Older People: Towards Evidence-Based Dosing? Drugs & aging. 2018;35(7):603-24. PubMed PMID: 29916138. Epub 06/19. eng.	A search was performed to retrieve studies on paracetamol pharmacokinetics and safety in older people or studies that performed a sub-analysis of pharmacokinetics and safety in older people.	27 studies were included and studied	Differences in paracetamol CL and Vd between young and robust older people have been reported, with an even further decrease in those pharmacokinetics parameters in frail older people. Based on the—albeit limited—observations retrieved in our search, there is no evidence that supports a higher incidence of hepatotoxicity in paracetamol at normal dosages in older subjects. Overall, due to limited and heterogeneous evidence, it was difficult to drawn firm and meaningful conclusions on changed risk for paracetamol safety in older people.	Yes	Yes	Population pharmacokinetics modelling can be considered a valuable tool to develop more evidence-based dosing advice for older people. In addition, more clinical studies with enriched clinical characteristics (e.g. comorbidity, comedication, frailty) should be conducted to study both the pharmacokinetics of paracetamol (and its metabolites) and its safety parameters.
Fulton B, James O, Rawlins MD. The influence of age on the pharmacokinetics of paracetamol [proceedings]. British journal of clinical pharmacology. 1979 Apr;7(4):418P. PubMed PMID: 444368. Epub 1979/04/01. eng.	Each individual received both oral (500mg Panadol)and intravenous (500mg) paracetamol on separate occasion one week apart. None was receiving any drug known to induce hepatic microsomal oxidation and all had normal biochemical indices of hepatic and renal function. Venous blood was sampled over 6 h following drug administration and plasma concentration determined by gas chromatography. A two compartment open model was used in the analysis of the data.	23	In the elderly, Plasma paracetamol clearance and the volume of central compartment were significantly reduced as compared with the young. Bioavailability was similar in the two groups.	Yes	Yes	The results suggest that although bioavailability of paracetamol is normal in the elderly, paracetamol conjugation is impaired

Wynne HA, Cope LH, Herd B, Rawlins MD, James OF, Woodhouse KW. The association of age and frailty with paracetamol conjugation in man. Age and ageing. 1990 Nov;19(6):419-24. PubMed PMID: 2285011. Epub 1990/11/01. eng.	The association of age, physical frailty and liver size upon hepatic conjugation reactions was studied using paracetamol as a model drug.	47	Paracetamol clearance expressed in terms of body weight was significantly lower in the fit elderly than in the fit young subjects, and was lowest in the frail elderly subjects (p less than 0.01). There was no difference in paracetamol clearance expressed per unit volume of liver between the fit young and fit elderly subjects but it was significantly reduced in the frail subjects. Although the partial metabolic clearance to paracetamol sulphate was preserved per unit volume of liver with ageing and frailty, the partial metabolic clearance to paracetamol glucuronide per unit volume of liver was markedly reduced in the frail elderly (p less than 0.01) when compared with the fit subjects.	Yes	Yes	These results show that age-associated changes in paracetamol clearance are attributable to both changes in liver volume and in general health. The findings underline the important influences of the elderly person's physical state upon drug clearance.
Bedjaoui A, Demotes-Mainard F, Raynal F, Vincon G, Galley P, Albin H. [Effect of age and sex on the pharmacokinetics of paracetamol]. Therapie. 1984 Jul-Aug;39(4):353-9. PubMed PMID: 6484879. Epub 1984/07/01. Influence de l'age et du sexe sur la pharmacocinetique du paracetamol. fre.				Yes	Yes	
Mitchell SJ, Hilmer SN, Murnion BP, Matthews S. Hepatotoxicity of therapeutic short-course paracetamol in hospital inpatients: impact of ageing and frailty. Journal of clinical pharmacy and therapeutics. 2011 Jun;36(3):327-35. PubMed PMID: 21545612. Epub 2011/05/07. eng.	An observational cohort study. Treatment group participants commenced regular paracetamol (3-4 g/day) during their hospital admission, whereas the control group was not exposed to paracetamol. In both groups, plasma alanine aminotransferase (ALT) was measured at baseline and day 5, and risk factors for raised ALT were recorded. A random serum paracetamol concentration was measured at day 5 in the treatment group.		No older frail treatment participants had an abnormal day 5 ALT. Odds ratios for having a day 5 ALT above the upper limit of normal (ULN) with paracetamol use, compared with unexposed controls, were 3·7 [95% confidence intervals (CI): 0·32, 41·59] for older not frail participants and 2·5 (95% CI: 0·34, 18·3) for younger participants. Decreasing frailty score independently predicted a day 5 ALT above the ULN ($P < 0·05$). Day 5 serum paracetamol concentrations were highest in older frail participants ($P < 0·005$).	Yes	yes	Higher paracetamol concentrations observed in frail older patients after 5 days of therapeutic paracetamol do not necessarily indicate an increased risk of hepatotoxicity.

Koppert W, Frotsch K, Huzurudin N, Boswald W, Griessinger N, Weisbach V, et al. The effects of paracetamol and parecoxib on kidney function in elderly patients undergoing orthopedic surgery. Anesthesia and analgesia. 2006 Nov;103(5):1170-6. PubMed PMID: 17056950. Epub 2006/10/24. eng.	The study determine the effects of IV paracetamol or parecoxib on renal function in elderly patients undergoing orthopedic surgery. this is a randomized and placebo-controlled study. After their arrival in the postanesthesia care unit, patients received an initial dose of the study medication, paracetamol 1000 mg IV (n = 25), parecoxib 40 mg IV (n = 25), or saline IV (n = 25); subsequent doses were administered for the next 3 days. Opioids were provided as rescue medication. Blood and urine samples were collected before and after surgery, and markers of renal function were determined.	75	During the first 2 h after the initial dose of parecoxib, creatinine clearance was slightly diminished (125 +/- 83 to 86 +/- 45 mL/min, P < 0.05), whereas no significant decrease of creatinine clearance was observed in the placebo and paracetamol groups. After all treatments, sodium and potassium excretion as well as urine albumin and alpha-1-microglobulin were transiently increased (group differences: not signicifant). In conclusion, glomerular and tubular functions were transiently affected in all patients after orthopedic surgery; however, the differences between the treatment groups were small and not clinically relevant.	Yes	Yes	Further studies are warranted to determine adverse renal effects of longer-lasting therapy with these drugs, especially in patients with renal impairment or concomitant diseases.

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