CHAPTER 11

Discussion
The objectives of this thesis were: to study the methods of orthostatic hypotension (OH) measurement itself; to study the clinical implications of OH in elderly patients; and to study factors (including OH) that are related to mortality and successful rehabilitation in nursing home residents.

In this chapter, the most important findings and the possible implications of findings will be presented and limitations and strengths in general and of the specific studies will be discussed. The discussion is structured in three parts: first the epidemiology, diagnostic strategies and definition of OH will be discussed; second the relationship between OH and different endpoints; and finally risk prediction capabilities of various supposed risk factors in a nursing home population will be discussed.

MAIN FINDINGS AND IMPLICATIONS FOR DAILY PRACTICE

Epidemiology

OH is a clinical sign commonly seen in elderly subjects. Population aging is associated with an increasing prevalence of OH. In chapter 6, a prevalence of OH of 37% in a nursing home population was found. The prevalence ranged from 29% on the somatic department, to 37% and 41% on the rehabilitation and the psychogeriatric department, respectively [1]. The prevalence of OH is also high in patients with a history of hypertension [2], cardiovascular diseases [3, 4], diabetes [5], and during acute hospitalization [6, 7]. The latter is described in chapter 7 of this thesis; a prevalence of OH of 34% was reported in hospitalized elderly patients with a hip fracture.

Despite the fact that OH frequently occurs in older subjects and seems to represent physical vulnerability and may lead to adverse outcomes [8, 9], OH is also described in comparatively healthy younger individuals [2, 10]. In chapter 2, a prevalence of OH of 66% was seen in adults >50 years old visiting an outpatient clinic of internal medicine, measured with a continuous blood pressure (BP) device. Even a higher prevalence of OH (94.1%) was seen in the study of Romero-Ortuno within community-dwelling participants aged 60 years and older, measured with a continuous BP device [11].

Patients with OH can experience orthostatic complaints like light-headedness, dizziness, or syncope. In our studies, the prevalence of orthostatic complaints ranged from 19% in elderly admitted to the hospital, to 22% in community-dwelling elderly, and to 25% in nursing home patients [1].
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Diagnostic strategies and definition of Orthostatic hypotension

In 1996, a consensus committee of the American Autonomic Society and the American Academy of Neurology defined OH as a drop in systolic blood pressure (SBP) of $\geq 20$ mmHg and/or diastolic blood pressure (DBP) of $\geq 10$ mmHg after postural change [12, 13]. This definition was based on clinical judgment, as epidemiologic data were unavailable at that time. In response to the study of Fedorowski et al. in 2011 [2], an updated consensus statement was published [14], and a higher cut-off point ($\Delta$SBP $>30$ mmHg) was advised for patients with supine hypertension (SBP $>160$ mmHg).

The impact of OH, as defined according to the consensus definition, on different clinical endpoints is questionable. The unclear association of OH with endpoints such as falling, rehabilitation and mortality, might partly be due to a poorly chosen definition of OH. In chapter 9 it was shown that OH, defined according to the 1996 and 2011 consensus definitions, is not related to orthostatic complaints or previous fall incidents in community-dwelling participants aged 65 years and older. Only a decrease of $\geq 25\%$ in SBP was related to complaints, whereas a decrease of $\geq 25\%$ in DBP was related to previous fall incidents. We performed a post-hoc analysis within a nursing home population, described in chapter 5, to assess whether a $\geq 25\%$ decrease in DBP and SBP were indeed related to previous fall incidents and orthostatic complaints. Neither the standard 1996 definition nor a $\geq 25\%$ decrease in DBP and SBP were found to be associated with previous fall accidents or orthostatic complaints. As the latter results were examined in a much smaller study population, it is quite evident that larger studies are necessary to replicate the present study. Besides, more research is necessary to either develop useful cut-off points for OH, or refute the notion that such measurements do have any value at all for clinical decision-making or prediction of incidents.

Although the studies presented in this thesis do not provide sufficient evidence to favour one particular definition, it can be suggested that it is worthwhile to at least include a relative decrease instead of an absolute fixed value in the definition. This approach is supported by a previous study of Fedorowski et al. [2], although they chose fixed cut-off points because this seemed more feasible for clinical practice. A decrease of $\geq 25\%$ in DBP and SBP seems a reasonable approach, although more prospective studies are needed to investigate this suggested relative decrease of BP as definition for OH.

The international consensus definition recommends continuous beat-to-beat BP measurement to diagnose OH, and it is advised to compare BP measurements after 5 minutes of rest in supine position to BP measurement within 3 minutes in standing position [12]. A previous study suggested a lack of specificity for diagnosing OH by using the continuous beat-to-beat BP that could lead to incorrect diagnosis [11]. However, in daily practice automated sphygmomanometers are commonly used for this purpose, but due to the inability to
register BP at each heartbeat, this results in a quite significant risk of underreporting with regard to the lowest BP readings compared to continuous measurement of BP [15, 16]. Finally, as many elderly patients are not able to stand for several minutes, orthostatic BP measurements in standing position after 5 minutes supine rest cannot always be performed. In chapter 2 a difference was seen in BP response between standing and sitting postural change. Although no significant difference in prevalence of OH was observed, the positive and negative proportion of agreement of the prevalence of OH were at most moderate which indicates relevant differences in diagnosing OH on an individual level depending on the method used. In addition, in chapter 3 no difference in prevalence of OH was observed between OH measurements using the continuous or the interval BP measurement device but the positive and negative proportion of agreement were low. Therefore, the continuous BP measurement cannot be replaced by and compared to an interval BP measurement to diagnose OH.

Taken all together, postural change to a standing position cannot be substituted by allowing a sitting position and a continuous BP measurement cannot be replaced by an interval BP measurement to diagnose OH in elderly patients, since these methods will result in the identification of partially different populations to have OH.

Orthostatic hypotension and clinical implications in elderly

In previous literature, OH has been found to be associated with different clinical endpoints like falling, cardiovascular diseases, and mortality. Although such assumptions were made, those supposed associations have become questionable given the lack of evidence in the current literature. In the section below, the relationship between OH and the possible clinical implications in the elderly population will be discussed.

Orthostatic hypotension and falling

In chapters 4, 5, and 6 the previously poorly characterized relationship between OH and falling was described. In the prospective cohort study in chapter 4, no relationship between OH and falling or recurrent falling was found in a nursing home population.

However, the individual patient data (IPD) meta-analysis presented in chapter 5 showed a significant relationship between OH and time to first fall incident; the hazard ratio (HR) in the one-stage cox proportional hazard model was 1.52 (95% Confidence Interval (CI) 1.23-1.88). No significant relationship between OH and falling was found in the one-stage logistic regression analysis (Odds Ratio (OR) 1.21 (95% CI 0.87-1.68) and the two-stage logistic and cox regression analyses. Since the number of eligible studies was limited, only a small number of prospective studies were included in this meta-analysis. Within the scope of this small number of studies, this meta-analysis is the only study that used the consensus definition of OH, included a representative group of elderly, and adjusted for important confounders within individual patient data.
In chapter 6, the relation between OH, orthostatic complaints, and previous falling was investigated in a nursing home population; no significant relationships were found.

Several reviews described a theoretical relationship [17, 18], but did not perform a meta-analysis with the available data due to the small number of studies [19]. Besides, important limitations were seen in previous studies that described the relationship between OH and falling. The lack of prospective fall data [11, 20, 21], the lack of adjustment for important confounders [22, 23], and the lack of using the international consensus definition of OH [23-25] are examples of limitations in previous studies. In the previous studies OH was mentioned as an independent risk factor for recurrent falls [26, 27], a decrease in SBP was reported to be related to falling [22, 25], and symptomatic OH or orthostatic complaints were described as a predictor for falling [5, 28]. In our prospective studies, orthostatic complaints and symptomatic OH were investigated; no significant relationships were seen with (recurrent) falling or previous fall incidents (chapters 4 and 6) [1].

Because of the small number of studies included in the meta-analysis (chapter 5), we performed a post-hoc analysis in which we included the results of our prospective study into the meta-analysis (table 2). Patients with OH had a HR of 1.26 (95%CI 1.04-1.52) on a first fall incident in the study periods assessed. Although a significant relationship was seen in the post-hoc analysis, the HR decreased considerably compared to the HR in the original meta-analysis presented in chapter 5 (HR 1.52 (95%CI 1.23-1.88).

By performing an IPD meta-analysis including prospective studies it can be concluded that OH could still be a predictor for a first fall incident. The lower boundary of the 95% confidence interval, after including the results of chapter 5, does not exclude the possibility of the association being irrelevant. Furthermore, the odds ratios of falling were not significantly different between patients with and without OH. Therefore, more prospective studies are needed for a precise estimate of the relationship between OH and falling.

Table 1. Adjusted odds ratios and Hazard ratios for the effect of orthostatic hypotension on the risk of falling with individual patient data (one-stage method). The odds ratios can be interpreted as a measure of the association of OH to falling (the dependent variables). Hazard ratios refer to time to first fall incident.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI) (4 studies)</th>
<th>Hazard ratio (95% CI) (3 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH (model 1)</td>
<td>0.84 (0.66-1.07) (n=1271)</td>
<td>1.09 (0.92-1.30) (n=1199)</td>
</tr>
<tr>
<td>OH (model 2)</td>
<td>0.83 (0.65-1.06) (n=1271)</td>
<td>1.08 (0.91-1.28) (n=1199)</td>
</tr>
<tr>
<td>OH (model 3)</td>
<td>1.05 (0.80-1.38) (n=1203)</td>
<td>1.26 (1.04-1.52) (n=1131)</td>
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**Orthostatic hypotension and successful rehabilitation**

Nursing homes in the Netherlands provide care and long-stay facilities for elderly with chronic mental or physical diseases and the majority also provides rehabilitation services. Since the prevalence of OH in elderly staying in nursing homes is high and OH considered to be related to falling, we hypothesized that OH could be an important prognostic factor for chances of rehabilitation in a nursing home population.

In chapters 6 and 7 the relationship between OH and successful rehabilitation was described in a nursing home population and in hospitalized elderly with a hip fracture, respectively. In nursing home residents, patients with OH were found to have a higher chance of successful rehabilitation compared to patients without OH (chapter 6) [1]. A possible explanation for this rather counterintuitive relationship could be that either patients with OH are more adapted to their disabilities (including having already adjusted their home environment to their disabilities) or may be used to a less active life, allowing a quicker discharge to their own home. The results could also be a matter of coincidence.

Conflicting results, as presented in chapter 6, were seen in hospitalized patients with a hip fracture; OH measured during the first days of hospitalization was not related to rehabilitation (chapter 7). When comparing both study populations, patients included in the study with hospitalized hip fracture patients seemed to have less multi-morbidity, used less medication, and baseline blood pressure was lower. The high prevalence of OH in the hospitalized patients could be partially caused by the hip fracture itself and hospital admission-related factors like bed rest, surgery, inadequate water intake, and blood loss. In these circumstances, OH may very well be a temporary phenomenon and therefore not a predictor for an endpoint like successful rehabilitation [7]. In the study of Weiss et al., the impact of OH in hospitalized patients on mortality was described, and they advised to divide patients in 2 groups; patients with episodic OH, as is seen during hospitalization, and established OH (repeated measurements) [6]. Analogous to the association with mortality, one may hypothesize that episodic and sustained OH have different associations with rehabilitation. Episodic OH may have no consequences for chances of rehabilitation, whereas sustained OH may be much more relevant. Measuring OH in the first week of rehabilitation within a nursing home might possibly be a more accurate predictor for successful rehabilitation.

Also, relationships between different clinically relevant factors and successful rehabilitation were described in chapter 7. The factors diabetes mellitus (DM), SBP, handgrip strength and fear of falling (FOF) were significantly related to successful rehabilitation. The hazard of successful rehabilitation in patients with DM was lower than patients without DM (HR 0.47 (95%CI 0.26-0.85)), which was also reported in the previous study (chapter 6). It is known that coexisting disease negatively influences the outcome of rehabilitation [29]. Several studies described a clear relationship between DM and poor rehabilitation outcome [30, 31].
The chances of successful rehabilitation increased by 15% (95%CI 3-28%) for every 10-mmHg increase in SBP. In a previous study, higher blood pressure in frail patients was related to lower all-cause mortality while the opposite relationship was seen in non-frail patients [32]. Therefore, it was not unexpected that higher SBP is associated with a higher chance of successful rehabilitation. Handgrip strength (HR 1.05 (95%CI 1.01-1.08)) was positively and FOF (HR 0.87 (95%CI 0.79-0.97)) was negatively associated with time to successful rehabilitation. Poor muscle strength and FOF are frequently seen in elderly patients, and these factors are also related with the level of frailty [33-35] and functional outcome [36-39]. Although no relation was found regarding handgrip strength and successful rehabilitation, in the analysis with handgrip strength as a confounder in the analysis of OH in relation to successful rehabilitation, handgrip strength turned out to be a significant confounder (chapter 7). Despite the fact that no evidence was provided for a relationship between handgrip strength and time to successful rehabilitation in chapter 7, previous studies described that measuring handgrip strength preoperatively reflects the baseline condition of a patient and is a predictor of complications or length of hospital stay [40, 41]. Handgrip strength measurement can be used to identify those patients who are frailer and might need a different approach during hospital stay [40]. Normative values of handgrip strength are available due to the large study of Dodds et al [42]. In elderly aged ≥65 years a handgrip strength <26 kg in men and <16 kg in women is considered as weak [43]. In the study described in chapter 7, 31% of the patients met these cut-off points of weak handgrip strength.

FOF is common, being present in up to 50% of elderly patients who are rehabilitating, and is related to outcome [37, 44]. Previous studies described that FOF may restrict physical activity, which causes immobility and further loss of functional independence and falling [45, 46].

Orthostatic hypotension and mortality in elderly

In chapter 8 it was concluded that OH was related to increased all-cause mortality, but only in patients at the psychogeriatric department [47]. In previous studies it was shown that the presence of OH is associated with an increase in the risk of cardiovascular disease, cardiovascular mortality or all-cause mortality in elderly people [19, 48-55]. Although several explanations of the pathophysiological link between OH and mortality are described, it is questionable whether OH is the independent causal factor or the result of one or more other components within the pathophysiological process [3, 4]. Diseases like DM, atrial fibrillation, hypertension, and Parkinson disease are all related to both OH and mortality. Furthermore, baroreflex dysfunction and impaired hemodynamic homeostasis play an important role in mediating cardiovascular disease and mortality, but are also mentioned in the pathogenesis of OH [3].
In chapter 8 only in patients at the psychogeriatric department a relationship was seen between OH and all-cause mortality [47]. Apparently, a decrease in blood pressure upon standing is related to increased mortality within a cognitive impaired population. Although a recent retrospective study showed no associations between dementia and OH [56], dementia and its (cardiovascular) causes may explain the observations in chapter 8. Arterial stiffness and lower blood pressure will cause hypoperfusion of the brain, and are associated with accelerated cognitive decline [57, 58]. Also, autonomic dysfunction caused by neurodegenerative diseases like dementia could lead to OH [57]. In spite of the fact that OH was related to mortality within this specific population, both Harrell’s C and $R^2$ showed only small improvements when adding OH to the multivariate models, thus the additional value of OH in risk prediction is limited.

Two recent meta-analyses of observational studies described a significant relationship between OH and mortality. In both analyses, OH was related to an increased risk of all-cause mortality [3, 53]. In the most recent meta-analysis, the presence of OH, compared to the absence of OH, was associated with all-cause mortality with a relative risk (RR) of 1.50 (95%CI 1.24-1.81) in the total study population followed by a RR of 1.26 (95%CI 0.99-1.62) in patients aged 65 years or older [3]. These meta-analyses are limited by the lack of sufficient appropriate studies. Both meta-analyses described that the overall effect of OH on mortality is possibly mediated by classic risk factors instead of an independent causal mechanism [3, 53]. Taken this all together, a relationship between OH and mortality was seen, but the additional value of OH with respect to mortality in elderly patients is limited.

Risk prediction capabilities of blood pressure and HRQOL in nursing home patients

Blood pressure in elderly

International guidelines regarding blood pressure targets and treatment in elderly are inconsistent due to limited outcome data in this population [59]. In chapter 8, we described the relationship between blood pressure and mortality in a nursing home population. A significant relationship was only observed between DBP and all-cause mortality. The overall mortality risk increased by 17% (95%CI 2-34%) for every 10-mmHg increase in DBP [47]. Previous studies showed that a low DBP was associated with an increased all-cause mortality risk, especially in the oldest and frailest individuals [60, 61].

In the study by Odden et al. stratified analyses according to frailty were performed; in non-frail patients a positive relationship was described and in frail patients blood pressure was not related to mortality [62]. Van Hateren et al. described that in elderly patients with diabetes, higher blood pressure was related to increased cardiovascular mortality in non-frail patients, while an inverse relationship was seen in frail patients [32]. Taken this all together, a relationship between blood pressure and mortality in the elderly apparently exists, but this seems to be affected by the level of frailty.
Although the study described in chapter 8 showed that DBP is an independent risk factor for mortality, its practical implications still remain to be determined. Based on the lack of increase in Harrell’s C values when adding DBP to the adjusted models, one may conclude that the additional value of DBP in mortality prediction is very limited. It is important to realize that this study group is a frail group of patients with multi-morbidity, probably much more determinative for mortality than DBP itself. Only the authors of the observational PARTAGE study and the study of Askari et al. had specifically investigated this relationship in a nursing home population before [63, 64]. The authors of the PARTAGE study described that lower DBP was associated with higher mortality (RR 0.84 (95%CI 0.72-0.99)) [65]. No association between blood pressure and cardiovascular outcome was reported in the study of Askari et al. [64].

The predictive value of BP in nursing home patients is not only limited, but the need for intensive treatment of hypertension in elderly remains questionable as well. The results from both the HYVET and the SPRINT studies suggest intensive treatment of hypertension in elderly to be beneficial [66, 67]. Both studies showed a reduction of cardiovascular events and deaths from any cause after antihypertensive therapy. However, the generalizability of both studies appeared to be limited because mostly healthy elderly patients were included. In the HYVET study, patients with heart failure, dementia and/or requiring nursing care were excluded [66]. In the SPRINT study, patients with a history of DM, stroke, symptomatic heart failure or left ventricular ejection fraction <35%, a clinical diagnosis of dementia, living in a nursing home, an expected survival of less than 3 years, and a SBP of less than 110 mmHg following 1 minute of standing were excluded [67]. By excluding large groups of elderly subjects, the patients in these studies do not adequately represent the general elderly population. This selection bias is illustrated by the low mortality rates in both treatment groups in the SPRINT trial. We compared the mortality rates in the SPRINT trial to the mortality rates of the age and gender-matched general populations in the Netherlands in 2012 [68] and the United States (US) in 2010 [69] (figure 1). Remarkably, both the standard and the intensive treatment groups in the SPRINT trial had a two-fold better life expectancy than the life expectancy of the age and gender-matched general populations in the Netherlands and the US. Therefore, the results of the SPRINT trial will only have implications for a very select group of vital elderly patients.

At this moment, the Dutch guideline ‘Cardiovascular risk management’ advises antihypertensive treatment in case of SBP >140 mmHg or SBP >160 mmHg within patients above 70 or 80 years old, respectively [70]. Treatment goals described in the Dutch guideline are mainly based on studies like the HYVET trial and do not represent the frail elderly patient like the patients living in a nursing home. The US guideline recommends a SBP treatment target of 150 mmHg for adults >60 years of age [71].
Discussion

Since the predictive value of BP in nursing home patients is limited and hypertension trials within this population are lacking, a higher SBP target value (also even higher than 160 mmHg) can be considered as acceptable in specific subjects and antihypertensive treatment might be minimized. Beside BP, one should take into account quality of life in this specific population compared to younger (and more vital) patients since side effects of antihypertensive treatment could have serious consequences. Large trials investigating antihypertensive treatment in elderly, without excluding large groups of elderly, are needed.

Figure 1. All-cause mortality rates of the SPRINT trial, and the age- and gender matched general populations in the Netherlands and United States of America.

Health related quality of life in a nursing home population
Health related quality of life (HRQOL) is considered to be an important outcome in the evaluation of interventions or treatment in different diseases [72]. Low HRQOL corresponds to substantial limitations in physical, emotional and social well-being and will to a varying degree be due to the presence of a specific medical condition or its treatment [73]. HRQOL in individual patients can be used to measure disease-related distress and overall perception of health. Next to the evaluation of HRQOL as a separate outcome measure, HRQOL also has a prognostic value in non-nursing home settings [74-76]; a lower HRQOL score has been associated with an increased mortality risk, also in elderly patients. In summary, deviations in
HRQOL could have a variety of implications in decision-making processes regarding patients and medical interventions, especially in elderly patients. In chapter 10, we discussed the relationship between HRQOL, rehabilitation, and mortality in nursing home patients. HRQOL as assessed by the RAND-36 was significantly associated with mortality in three dimensions, but partly in opposite directions. Higher scores on the dimensions vitality (HR 0.88 (95%CI 0.77-0.99)) and mental health (HR 0.86 (95%CI 0.75-0.98)) were related to a lower mortality risk, whereas a higher score on the dimension role functioning-physical (HR 1.08 (95%CI 1.02-1.15)) was related to a higher mortality risk. However, based on the minimal increase in Harrell’s C values when adding role functioning-physical, vitality or mental health to the adjusted models, the additional value of these dimensions in mortality prediction is limited. HRQOL represents a person’s perspective about his or her physical and emotional wellbeing and changes in health. Knowledge of a person’s perspective could have implications for decision-making by nursing home caregivers [77]. Although the predictive value of HRQOL on mortality seems limited, it can still be advised to assess HRQOL for information about the degree of wellbeing experienced by a patient as such. For example, the AgeCoDe study showed that management of chronic diseases in elderly benefits from focusing on factors like HRQOL. Improvement in HRQOL was seen when the number of physical activities increased. Besides, HRQOL declined with increasing age, walking disability, and hearing impairment [78]. By using a HRQOL questionnaire regularly during nursing home admission, changes in HRQOL can be monitored and relatively simple approaches, like commencing physical activities, could improve HRQOL. Despite the minimal predictive value of HRQOL in nursing home residents, there are sufficient reasons, as mentioned above, to be informed about patients’ HRQOL in a nursing home population.

STRENGTHS AND LIMITATIONS

Several strengths and limitations need to be addressed. The main strengths of the studies presented in this thesis were the well-defined study populations, the prospective nature, and the number of clinically relevant variables adjusted for in multivariate analyses. The main limitations are the observational design and the small study samples. Because of the observational design, establishing a causal relation was not possible, only relationships were described. The small study sample decreases the precision and generalizability of the observed findings.

In 1996, OH was defined as a drop in systolic blood pressure (SBP) of >20 mmHg or diastolic blood pressure (DBP) of >10 mmHg after postural change [12, 13]. This definition was based on clinical judgment, as epidemiologic data were unavailable at that time. In response to
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the study of Fedorowski et al. in 2011 [2], an updated consensus statement was published [14], and a higher cut-off point (ΔSBP >30 mmHg) was advised for patients with supine hypertension (SBP >160 mmHg). In all studies described in this thesis the 1996 definition of OH was used. Although chapter 9 showed no relationship between OH defined by the update consensus statement and previous fall incidents or orthostatic complaints, it cannot be excluded that some results would be slightly different when using OH results as defined by the updated consensus statement.

In addition to these general strengths and limitations, specific strengths and limitations were present in the specific study designs. This thesis is based on different studies in three different populations; nursing home patients, hospitalized elderly, and community-dwelling elderly. The strengths and limitations of studies form each of these populations will be discussed separately below.

Nursing home patients
A large part of this thesis was based on a representative Dutch nursing home population. This specific population is often excluded in studies in the elderly. The statement on representativeness is based on the fact that admission to a Dutch nursing home requires approval of a central indication committee, which implies that all patients are assessed using the same admission criteria. Besides, the nursing home facility in the present study was a general nursing home, with somatic, psychogeriatric and rehabilitation departments, comparable to most other Dutch nursing homes. No groups of patients were excluded in the present nursing home population.

Several limitations need to be addressed. Firstly, OH measurements in elderly can be difficult due to mobility problems. Therefore, the postural change was performed from lying to standing in 36% of the somatic patients, 87% of the rehabilitation patients, and 66% of the psychogeriatric patients. The remaining patients performed the postural change from lying to sitting. Post-hoc analyses stratified according to postural position were performed, which did not relevantly change results. Based on chapter 2, where it was stated that postural change to standing position cannot be substituted by allowing a sitting position, it can not be excluded that differences in postural position has influenced the results.

Secondly, recall problems regarding previous and prospective fall incidents need to be mentioned. Information regarding previous falls was based on questioning patients or participants and prospective fall incidents were registered by the medical staff. In patients with cognitive problems, recall bias could play a more important role than in a younger population. It is very likely that the actual number of patients with fall incidents was higher. Thirdly, although a validation study had been performed, the adequacy of using the RAND-36 questionnaire within a nursing home population has been questioned [79, 80]. An
important issue is that the RAND-36 entails several potential inappropriate questions for this population [79, 80]. Due to the high heterogeneity in the nursing home population in general, the use of the RAND-36 could be more suitable for subgroups of rehabilitation patients, like e.g. those with higher cognitive and physical functioning [80]. Finally, the impact of multi-morbidity in a frail group of elderly is considerable, influencing different endpoints like falling, successful rehabilitation, HRQOL, and mortality. Although we have adjusted for an important set of relevant variables in the multivariate model, multi-morbidity could still have relevantly influenced the results as presented in this thesis.

Hospitalized elderly patients
The main strength of the study within hospitalized elderly patients was the setting in a general hospital, and only a few exclusion criteria were used, whereby this group can be seen as a representative group of elderly hip fracture patients. There were also important limitations. Firstly, although recruitment and testing took place preferably on the day of admission, 18% of the handgrip strength measurements were not measured preoperatively. However, stratified analyses according to timing of handgrip strength measurement did not alter the results. Secondly, as expected, the proportion of immobile patients was high in this study group. In 98% of the patients an OH measurement could not be performed from lying to standing. Like discussed before, the two postural changes identify different patients having OH. Finally, OH was only measured once during the follow-up period, which only detected episodic OH. By using repeated OH measurements sustained OH could also have been established. Future studies are needed to evaluate the clinical implications of sustained OH on rehabilitation.

Community-dwelling elderly
The studies including community-dwelling elderly were performed in a general hospital on an outpatient clinic of internal medicine, and in elderly aged >60 years participating in a fall risk screening and prevention program. The strengths of the studies within the outpatient clinic were the randomization of the measurements (non-blinded randomization for both the sequence of the postural changes and the side of the BP measurements) and the fact that all measurements were performed and evaluated by the same individual to overcome inter-observer bias. The generalizability is limited to elderly patients visiting the internal medicine outpatient clinic. Limitations of these studies were the relatively small study sample. Due to the fact that the patients included in this study had to be able to stand for five minutes without assistance, the study group was slightly biased compared to the general population and the results are, of course, only useful in patients who are able to stand.
The strength of the study, including elderly subjects participating in the fall risk screening and prevention program, was that this study not only focused on elderly patients but also on older people without specific medical problems. Several limitations need to be addressed. Firstly, blood pressure measurement in the supine position was only performed once, namely at 3 minutes. This probably has led to an underestimation of the actual prevalence of OH, because OH is defined as a decrease of SBP or DBP within 3 minutes. Second, two types of bias could have occurred: recall and selection bias. Previous fall incidents were based on participants’ report, which could have resulted in recall bias. Selection bias may have occurred as patients participated in this study, were the selection of participants willing to participate and who actively made the effort to join this program. This could have led to registration of participants who had complaints more often or had gone through a previous fall incident. This might limit generalization to the general population of community-dwelling elderly.

CONCLUSION

The general aim of this thesis was to study the OH measurements itself, to study the clinical implications of OH in elderly patients, and to study factors (including OH) that are related to mortality and successful rehabilitation in nursing home residents. This thesis shows that the approach and interpretation of the finding of OH in elderly patients needs to be adjusted. OH measurements do not add much to clinical decision-making or predicting outcomes in the majority of elderly patients, in both outpatient and nursing home settings. OH defined by the current International consensus definition is not related to important clinical endpoints, at least not in the populations studied for this thesis. Moreover, it can be questioned whether an OH measurement is necessary in any circumstance in elderly patients, or that instead potential actions (e.g. de-prescribing antihypertensive treatment) should be based on the presence of orthostatic complaints. Furthermore, the mortality prediction capabilities of BP and HRQOL are very limited in a nursing home population. Since the predictive value of BP in nursing home patients is limited and hypertension trials within this population are lacking, the need for antihypertensive treatment should be individually assessed, taking into account factors like the degree of frailty, the estimated survival time, and the chances or presence of side effects of medication. Although the mortality prediction capability of HRQOL is limited in a nursing home population, measuring HRQOL in this patient category could lead to increased understanding of factors that negatively impact HRQOL. Since morbidity is already very high and life expectancy is short in nursing home patients, quality of life is probably the most important variable to evaluate.
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Based on the results of this thesis it can be concluded that:

1. Deviation from the current consensus on OH measurement will result in the identification of a partially different population to be diagnosed with OH.
   a. Postural change during OH measurements in supine followed by a standing position cannot be substituted by allowing a sitting position in the elderly population, since this will result in the identification of a partially different population (supposed) to have OH.
   b. A continuous BP measurement cannot be replaced by and compared to an interval BP measurement to diagnose OH in elderly patients.

2. The clinical relevance of OH in elderly patients, using the consensus definition, is limited.
   a. OH, defined according to the consensus, is not related to orthostatic complaints or previous fall incidents.
   b. The relationship between OH and clinical endpoints like falling, rehabilitation, and mortality is minimal.

3. The mortality prediction capabilities of blood pressure and HRQOL are very limited in a nursing home population.

Finally, I have formulated the following recommendations for daily practice and future research.

1. The approach of OH in elderly patients needs to be changed:
   a. OH measurement should not be part of usual care in clinical decision-making regarding OH. OH measurements in elderly patients do not have additional value in clinical decision-making or predicting outcomes in the majority of elderly patients.
   b. Inquiring after orthostatic complaints instead of measuring OH. It can be questioned whether an OH measurement is necessary in any circumstance in elderly patients, or that instead potential actions (e.g. de-prescribing antihypertensive treatment) should be based on the presence of orthostatic complaints.
   c. In the exceptional situation that an OH measurement is performed, it should be performed according to the current consensus definition. Despite that I recommend that OH measurements should not be part of usual care, most health care providers will not change the approach (in order to follow current guideline recommendations). In those cases, the clinician must take into account the facts that postural change to standing position cannot be replaced by postural change to sitting position and a continuous BP measurement cannot be replaced by and compared to an interval BP measurement in elderly patients.
Discussion

2. **Further research is needed to allow the identification of possible clinically relevant cut-off points for orthostatic hypotension.** Since the current consensus definition is not related to important endpoints, its clinical relevance seems very limited, at least for the population studied in this thesis. More prospective studies are needed to investigate different definitions, including relative decreases, and its clinical relevance.

3. **The role of orthostatic hypotension on falling needs to be refuted or confirmed.** By performing an individual patient data meta-analysis with prospective studies it can be concluded that OH plays a role to experience a first fall incident. Since the results of this meta-analysis are imprecise, more prospective studies are needed.

4. **Antihypertensive treatment in elderly patients requires an individual approach.** Since the predictive value of BP in nursing home patients is limited and hypertension trials within this population are lacking, the need for antihypertensive treatment should be individually assessed, taking into account factors like the degree of frailty, the estimated survival time, and the chances or presence of side effects of medication. Furthermore, large trials investigating antihypertensive treatment in elderly, without excluding large groups of frail elderly and nursing home patients, are needed to develop tailor-made treatment.

5. **Studies on HRQOL in a nursing home are needed.** Knowledge of HRQOL in a nursing home could have implications for nursing home care givers. Especially, the influence of de-medicalizing, e.g. de-prescribing medicine, on HRQOL is of interest. Therefore prospective studies are needed to evaluate the use of HRQOL questionnaires as a helpful tool supporting clinical decision-making in nursing homes.
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