

Perindopril starting dose errors in older adults in the Netherlands

A retrospective, cross-sectional, population-based study

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PREFACE

This thesis was written for my master's degree in pharmacy at Utrecht University. For the past 20 weeks, I have committed myself fully to conducting research at Erasmus Medical Center. The subject of my research is about perindopril starting dose errors in older adults in the Netherlands. This fascinating topic addresses the prescription patterns of healthcare providers in a very vulnerable group of our population, the older adults. The study strives to identify both the current state of perindopril starting dose prescriptions as well as past patterns and compares the in-clinical practice patterns to the recommendations of the guidelines. The purpose of this study is to contribute to improving healthcare for older adults by mapping the starting dose prescription patterns, with the intention to become a starting point for more research on this area of medication safety. This research has focused on antihypertensives as they have been very widely used among the older adults, and therefore have a great impact. Furthermore, in the antihypertensive field, there is still potential for optimizing the treatment in geriatric patients.

During my research, I have experienced numerous aspects of conducting research, such as writing research proposals, inclusion of general practitioners and working with Castor, which was very educative and contributed towards broadening my knowledge. In addition, collaborating with fellow researchers and visiting patients, has provided me with new insights and ideas, and strengthened my social skills likewise. Moreover, parallel to this project, I have also conducted a systematic review, in collaboration with BSc [REDACTED] about the sex differences in adverse drug events of antihypertensives. The preliminary outcomes were very interesting and conducting this study has added to my insights and experience on how to conduct systematic reviews in an adequate and professional way.

At the same time, I have encountered a lot of hardships as well, especially on the direction of the research topic and the setting of this study. Initially, our plan was to investigate the differences in starting doses between younger and older patients using subjects from the DECISION study, a study which is conducted by my supervisors MSc [REDACTED] and MSc [REDACTED]. However, the low sample size in this setting was not desirable to support clinically relevant outcomes. Consequently, we moved on to utilizing the Erasmus Rotterdam Gezondheid Onderzoek (ERGO) database. A research protocol had been made with our initial aims, plans and ideas (see Appendix A for details on our research protocol). However, this database contained data on insufficient younger perindopril users. Therefore, a switch to focus only on older perindopril users was necessary. In addition, due to some complications in our study group, it was not possible to include a lot of data that we had initially

wanted. Consequently, we were limited in both research objectives that we would have liked to investigate, and possible relationships between (in)dependent variables and outcomes. As for the latter, we can only speculate. However, this does not imply that we did not find very interesting and relevant outcomes as you will discover when you read further through this report.

In drawing the preface to a close, I would like to express my thanks to my daily supervisor MSc [REDACTED] giving me the opportunity to conduct my research on this very intriguing topic, and for providing me guidance and feedback during my research. I am also very thankful for his dedication towards showing me the aspects of conducting research which helped me expand my knowledge. Furthermore, I would like to thank MSc [REDACTED] for sharing her expertise with me and providing me insightful opinions and evaluations, so that I could develop my writing and research skills. I am also grateful for the time and effort Dr. [REDACTED] [REDACTED] has put into this project to make it possible for us to use the data from de Rotterdam study. I would also like to thank all other contributors who have given me feedback on the research protocol or ideas in general. Lastly, I would like to mention that I am grateful to my examiner Dr. [REDACTED] for offering me a sympathetic ear when discussing the rollercoaster of events during my research project, and for providing me practical information.

Thank you all and enjoy your reading.

BSc [REDACTED]
Rotterdam, October 10th, 2021

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE-I	<u>A</u>ngiotensin <u>C</u>onverting <u>E</u>nzyme <u>I</u>nhibitor
ADE(s)	<u>A</u>dverse <u>D</u>rug <u>E</u>vent(s)
CI	<u>C</u>onfidence <u>I</u>nterval
ERGO	Erasmus Rotterdam health study (also known as: the Rotterdam Study) (in Dutch: <u>E</u>rasmus <u>R</u>otterdam <u>G</u>ezondheid <u>O</u>nderzoek))
GSD	Mean Starting dose (in Dutch) (in Dutch: <u>G</u>emiddelde <u>S</u>tart <u>D</u>osering)
HYVET	The <u>H</u>Y pertension in the <u>V</u>ery <u>E</u>lderly <u>T</u>rial
IBM	<u>I</u>nternational <u>B</u>usiness <u>M</u>achines
MSD(s)	<u>M</u>ean <u>S</u>tarting <u>D</u>ose(s)
mg	<u>M</u>illigram(s)
NHG	Dutch general practitioners' community (in Dutch: <u>N</u>ederlands <u>H</u>uisartsen <u>G</u>enootschap)
NYHA	<u>N</u>ew <u>Y</u>ork <u>H</u>ealth <u>A</u>ssociation
PP	<u>P</u>erindopril <u>P</u>rescription
SD	<u>S</u>tandard <u>D</u>eviation
SEM	<u>S</u>tandard <u>E</u>rror of the <u>M</u>ean
SPRINT	<u>S</u>ystolic blood <u>P</u>ressure <u>I</u>ntervention <u>T</u>rial

ABSTRACT (ENGLISH)

BACKGROUND: To abate the risk of adverse drug events and improve therapy compliance in older patients, the Dutch general practitioners' community introduced the "start-low-go-slow"-principle for older adults in the Cardiovascular Risk Management guidelines in 2011. This advice implies that older patients should start an antihypertensive drug at the lowest available dose. It is unknown whether healthcare providers adhere to these guidelines and whether older patients genuinely start with the lowest dose in clinical practice. We aimed to investigate the difference between in-clinical practice prescribed and guideline recommended starting doses in older adults, using the antihypertensive drug perindopril as a proof of concept.

METHODS: We conducted a retrospective, cross-sectional, population-based study, using data from the Rotterdam Study. All patients aged 70 years and older with a recorded first perindopril prescription in the database between January 1, 1991, and February 8, 2021, were included. The mean starting dose (MSD) was calculated and compared to the guideline recommendation of 2 mg perindopril, using a one-sample t-test. A sub analysis was done to analyze the MSDs before and after 2011.

RESULTS: There were 1019 eligible patients. The overall mean starting dose of perindopril was 3.34 mg (SD \pm 1.623 mg). The mean starting dose prescribed to older adults in clinical practice was significantly higher than the recommended 2 mg perindopril. The MSD between 1991 and 2010 was 3.44 mg (SD \pm 1.506 mg). Between 2011 and 2020 a MSD of 3.23 mg (SD \pm 1.749 mg) was found. Both mean starting doses differed significantly from the guideline recommendations. A significant difference in MSDs pre- and post-2011 was found as well ($p = 0.0397$).

CONCLUSION: A small decrease in mean starting dose of perindopril in older adults has occurred after the introduction of the start-low-go-slow-principle in 2011. However, healthcare providers do not adhere to the guidelines as they still prescribe higher starting doses of perindopril in older patients than recommended by the national cardiovascular risk management guidelines. More research should be conducted to find out whether this is justified.

KEYWORDS: starting dose; adverse drug events; perindopril; prescribing; start-low-go-slow; older adults.

ABSTRACT (NEDERLANDS)

ACHTERGROND: Om het risico op bijwerkingen van medicijnen te verminderen en tevens de therapietrouw te bevorderen, introduceerde het Nederlandse Huisartsen Genootschap het 'start-laag-ga-langzaam'-principe voor ouderen in de Cardiovasculaire risicomanagement richtlijnen in 2011. Dit advies impliceert dat ouderen met de laagste dosering antihypertensivum zouden moeten starten. Echter is onduidelijk of zorgverleners deze richtlijn opvolgen en dus of ouderen daadwerkelijk starten met de laagste dosering in de klinische praktijk. In deze studie werd onderzocht of er een verschil was tussen de voorgeschreven startdoseringen in de praktijk en de aanbevolen startdosering in de richtlijnen, gebruikmakend van het antihypertensivum perindopril als bewijs van concept.

METHODE: Wij hebben een retrospectief, cross-sectioneel, bevolkingsonderzoek uitgevoerd, gebruikmakend van data afkomstig uit de Rotterdam Studie. Alle patiënten, welke 70 jaar of ouder waren en waarvan het eerste perindopril voorschrift is opgenomen in de database tussen 1 januari 1991 en 8 februari 2021, werden geïnccludeerd. De gemiddelde startdosering (GSD) van perindopril werd berekend en dit werd vergeleken met het advies van de richtlijn, 2 mg perindopril, met behulp van een one-sample t-toets. Een sub analyse was uitgevoerd om de GSD voor en na 2011 te analyseren.

RESULTATEN: 1.019 personen waren geschikt voor dit onderzoek. De algehele gemiddelde startdosering van perindopril was 3,34 mg (SD ± 1,623 mg). Dit was statistisch significant hoger dan de 2 mg perindopril welke werd aanbevolen door de richtlijnen. De GSD tussen 1991 en 2010 was 3,44 (SD ± 1,506 mg). Tussen 2011 en 2020 werd een GSD van 3,23 mg (SD ± 1,749 mg) gevonden. Beide doseringen verschilden significant van de richtlijnen. Een significant verschil werd ook gevonden in de GSD tussen pre- en post 2011 ($p = 0.0397$).

CONCLUSIE: De startdosering van perindopril bij ouderen is enigszins verlaagd na de introductie van het "start-laag-ga-langzaam"-principe in 2011. Echter, is tot dusver, het voorschrijfpatroon van artsen nog niet in overeenstemming met de richtlijnen. In de praktijk schreven artsen hogere startdoseringen perindopril aan ouderen voor dan wordt aanbevolen door de nationale cardiovasculaire risicomanagement richtlijnen. Er zou meer onderzoek moeten worden gedaan naar of dit gerechtvaardigd is.

SLEUTELWOORDEN: startdosering; bijwerkingen; perindopril; voorschrijven; start-laag-ga-langzaam; ouderen.

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1. INTRODUCTION

Hypertension is the most important risk factor for cardiovascular diseases. It is associated with a higher prevalence of cardiovascular complications and mortality, particularly in the geriatric population. Therefore, it is important to control blood pressure, especially in the vulnerable group like the older adults(1). To manage hypertension, antihypertensive drugs are being prescribed.

For decades, it has been acknowledged that antihypertensives are effective in reducing blood pressure in relatively young patients(2–4). In 2008, the HYVET study demonstrated the effectiveness and benefits of antihypertensives in decreasing blood pressure and thereby decreasing cardiovascular risk in older adults as well(5). A more recent conducted study, the SPRINT study, displays the benefits from intensive blood pressure control for both young and older adults(6). Even in hypertensive patients aged 75 years and older, intensive blood pressure control decreases the rate of cardiovascular complications compared to standard therapy(7).

On the other hand, antihypertensive drugs are known to cause adverse drug events (ADEs), especially when the treatment is more intensive(6). ADEs that frequently occur, depending on their respective classes, are (orthostatic) hypotension and syncope, which can lead to a fall in older adults who are already vulnerable, and therefore prone to bone fractures. Furthermore, renal impairment and electrolyte disturbances has been observed that can lead to hospitalization(8,9). Several studies have shown that older patients are, in general, two to three times more likely to be hospitalized as a result of a drug-related problem, compared to younger patients (10,11). About 16% of all hospitalizations of older patients are due to one or more ADEs (12). The occurrence of these ADEs can lead to therapy non-adherence and is also the primary cause for withdrawing from antihypertensive medication (13,14).

To abate the risk of ADEs, and improve therapy compliance in older patients, international and national guidelines recommend healthcare providers to prescribe according to the “start-low-go-slow”-principle in older adults. This principle, which was introduced in the Dutch cardiovascular risk management guidelines in 2011, implies that older patients should start at a lowest available dose, and slowly up-titrate to their individual attainable maintenance dose. This method allows for a more careful and cautious prescribing approach in the older adults, which may avoid the development of unnecessary ADEs as generally more than 75% of all ADEs are related to the dose(13,15–17). However, it is unknown whether these guidelines

have been adhered to by healthcare providers, and whether older patients genuinely start with the lowest starting dose in clinical practice.

This study will use the antihypertensive drug perindopril as a means to bring the healthcare providers' prescription patterns regarding the starting doses into perspective. Perindopril is a commonly prescribed antihypertensive drug in the Netherlands, and unlike other antihypertensive drugs, the guidelines provide specific dosing recommendations for this drug. This makes it reasonable to use this as the drug for a proof of concept. Perindopril is an angiotensin-converting enzyme inhibitor (ACE-I). It inhibits ACE which will eventually execute its vasodilating by reducing breakdown of bradykinin and decreasing aldosterone secretion. Common ADEs for this type of drug are hypotension and dry cough, which can be traced back to its mechanism of effect. There are 3 types of perindopril available on the Dutch market: perindopril arginine, tert-butylamine, and tosylate, in the dose units 2, 4, and 8 mg or 2.5, 5, and 10 mg, depending on the salt form. Guidelines recommend starting at the lowest available dose. Hence adherence to the guidelines would be represented adequately by prescribing 2 mg perindopril arginine or tert-butylamine, or 2.5 mg perindopril tosylate (18–20).

To elucidate the prescription patterns with regard to the starting doses in clinical practice, this study will investigate whether there is a difference between the prescribed starting doses of perindopril in older adults in clinical setting, and the guidelines' recommended starting dose, in the Netherlands. Since the start-low-go-slow principle was introduced in 2011, the mean starting doses of pre- and post 2011 will be compared as well. Furthermore, this research will shed light on the prescribed starting doses over the years and its distribution over the older population.

2. METHODS

2.1 Study design and setting

A retrospective, cross-sectional, population-based study was conducted using data from the Rotterdam study (RS).

The Rotterdam Study, also known as Erasmus Rotterdam Health Study (in Dutch: ERGO) is an ongoing, prospective, long-term, population-based study. It started in 1990 in Rotterdam Ommoord, a municipality in the city of Rotterdam, The Netherlands. ERGO was designed as a response to global demographic changes, especially the increase in incidence of chronic diseases in elderly people. Its aim is to discover the causes of these diseases and determine potential targets that might prevent the disease from developing(21,22).

Rotterdam Ommoord was chosen as the study area in 1990. A lot of families and elderly people lived there relatively long. Healthcare was well-organized and there was a strong collaboration between different healthcare professions. This allowed for a more complete overview of patient data in this area, which made Ommoord a very suitable residential area for the ERGO-study(21,22).

The ERGO-database currently consists of data from 4 cohorts. The study initially started with 7983 subjects, all 55 years or older, living in Rotterdam Ommoord. The response rate was 78% (of 10,215 invitees). In 2000, the second cohort consisted of 3011 subjects who were aged 55 years or older when they were invited. The response rate was 67% (out of 4472 invitees). In 2006, the study population was once more extended. 3932 subjects (65% of 6057 invitees) were included to the study. Unlike the previous two cohorts, the third cohort comprised of subjects aged 45-54 years. The overall response rate for all three cohorts was 72.0% (14,926 out of 20,744). In 2016, the fourth and latest cohort was recruited. This recruitment targeted subjects aged 40 years and older. It is expected that this extended phase will be completed in early 2020. The expected number of new subjects is 3000. By August 2021, the Rotterdam Study has included almost 18,000 participants. The exact inclusion rates for the fourth cohort have not been published yet and are expected to be announced in the next update of the Rotterdam Study(22).

All participants were extensively examined at the beginning of the study. Examination consisted of a 2-hour interview at home and 5-hours of physical examinations which took place in a specially built research facility in the district of Ommoord. The participants would have a

subsequent follow-up visits every 3-6 years. Medical records of patients were collected from Dutch general practitioners and were linked to the ERGO-database. The medication records which were collected from pharmacies were available as of January 1st, 1991. The records consisted of details on the product- and international non-proprietary name, strength of the drug, prescribed daily dose, duration of use, number of prescriptions and number of filled tablets or capsules(21,22).

2.2 Study population

The study population consisted of all patients recorded in the ERGO-database, between January 1, 1991, and February 8, 2021, and who were aged 70 years and older at the time of their first perindopril prescription. Patients without a recorded first prescription of perindopril were excluded.

2.3 Outcomes

The main outcome of the study was the difference between in-clinical prescribed starting doses of perindopril, represented by mean starting dose in mg, and the guideline recommended starting dose in older patients, defined as 2 mg perindopril. Subsequently the outcomes were analyzed to compare the mean starting doses for pre- and post-2011, and they were stratified for age subgroups. The secondary outcomes were (1) the percentage of patients that got the recommended starting dose, 2 mg for elderly, and (2) the trend of mean starting doses over the years between 1991 and 2021.

2.4 Co-variables

Covariates that were considered were age and sex. For stratification based on age groups, patients were sorted according to their age at the time of their first perindopril prescription in one of the following subgroups: 70 – 74, 75 – 79, 80 – 84, 85 – 89, and >90 years old.

2.5 Study size

A preliminary search has been conducted in the ERGO-database which resulted in more than 1000 patients who were eligible for inclusion based on age and perindopril prescription. The sample size is fixed in a retrospective study; therefore, a sample size calculation was not required.

2.6 Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 24 (IBM Corporation, Armonk, New York, United States).

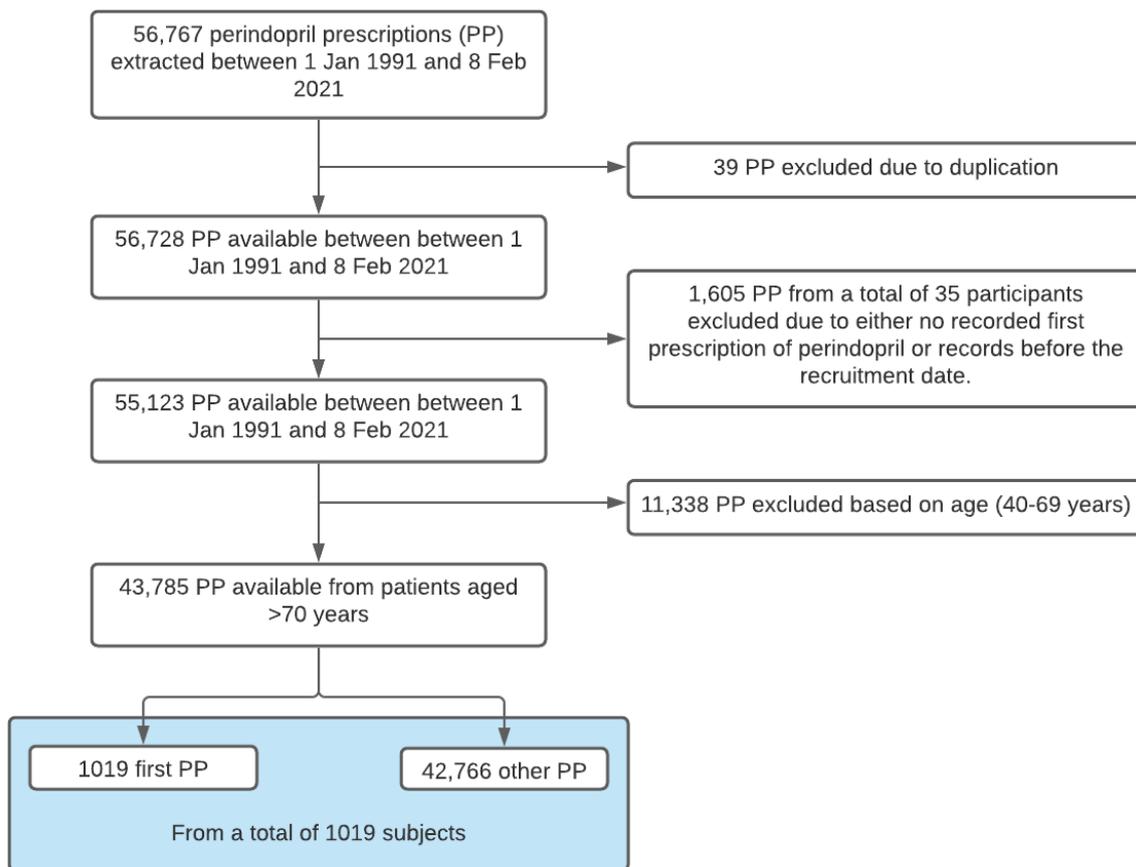
The mean starting doses of older patients was calculated. Using a one-sample t-test, we compared the mean starting dose of perindopril of all years between 1991 – 2021 to the guidelines (2 mg). Thereafter, we conducted a power analysis as well. Subsequently, we applied age-specific stratification for comparison of the mean starting doses to the guidelines. In addition, the mean starting doses between 1991 – 2010 and 2011 – 2020 were compared, both to the guidelines as well as in-between the defined periods. In the latter case, an unpaired t test was performed.

Descriptive statistics were used to analyze the frequency distribution of starting doses per year from 1991 to 2021. Furthermore, the distribution of starting doses (1 to 8 mg perindopril) in the population was analyzed.

3. RESULTS

The ERGO-database contained a total of 55,123 perindopril prescriptions between January 1, 1991, and February 8, 2021. Exclusion based on age left us 43,785 perindopril prescriptions of all patients aged >70 years. These prescriptions belonged to a total of 1,019 patients. Figure 1 displays the search results of the in- and exclusion procedure.

Figure 1 Search results on inclusion and exclusion of subjects



Abbreviation: PP = perindopril prescriptions

3.1 Demographic characteristics

The mean age in the older adult population is 78.84 years. This group consisted mostly of patients between 75 – 79 years old (31.0%), followed by people aged 70 – 74 (26.8%), 80 – 84 (25.0%), 85 – 90 (12.3%) and people aged 90 years and older (4.9%) (see Appendix B Table 1 for the frequencies). There were notably more females than males (respectively 53.6% and 46.4%). In table 1 the demographic characteristics of the patients are shown at baseline.

Table 1: Demographic characteristics at baseline

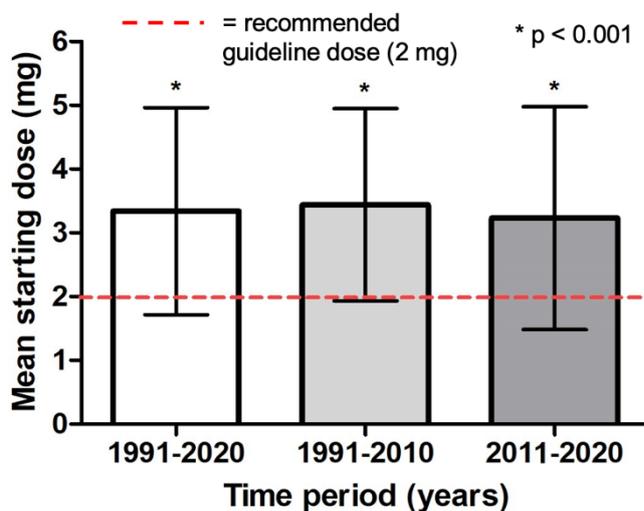
Characteristics	Older patients (N=1019)
Age (years), mean (SD)	78.84 (5.799)
Age categories, n (%)	
- 70 – 74	273 (26.8)
- 75 – 79	316 (31.0)
- 80 – 84	255 (25.0)
- 85 – 90	125 (12.3)
- > 90	50 (4.9)
Sex, n (%)	
- Male	473 (46.4)
- Female	546 (53.6)

Abbreviation: SD = standard deviation.

3.2 Outcomes on in-clinical practice starting dose

Between 1991 and 2020, the overall mean starting dose of perindopril, which was prescribed to 1,019 older adults, was 3.34 mg. The in-clinical practice starting dose differed significantly from the guidelines which recommends starting at 2 mg. In 2011 the start-low-go-slow principle was introduced into the Dutch guidelines. If divided into the pre and post introductions to the guidelines, a mean starting dose of 3.44 mg can be found between 1991 and 2010 in 557 older subjects. The prescribed mean starting dose after 2011 has decreased to 3.23 mg, found in 462 subjects. Both starting doses, before and after 2011, are significantly different from the recommended dose. The decrease in mean starting dose from pre- to post-2011 was significant as well ($p = 0.0397$). Figure 2 shows an overview of the mean starting doses compared to the guidelines (see Appendix B Table 2 for the absolute numbers).

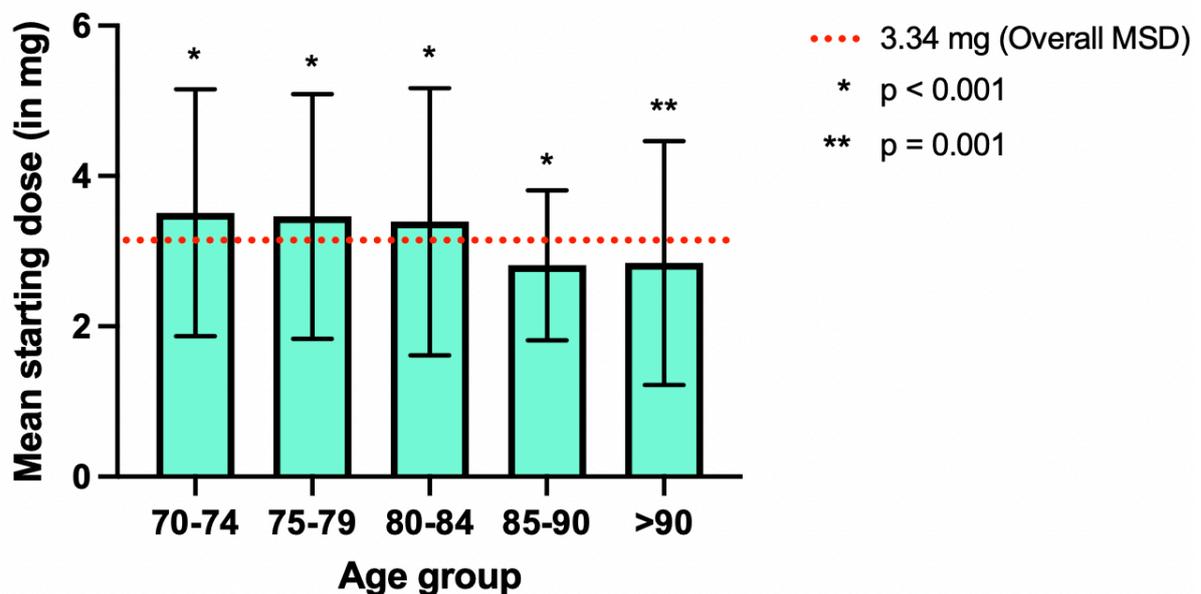
Figure 2 Mean starting dose in older patients compared to the guidelines



3.3 Outcomes on mean starting doses in age subgroups

Figure 3 displays the comparison between in-practice starting doses and guideline recommended starting doses stratified for age. Results demonstrate that there is a statistically significant difference between in-clinical practice mean starting doses compared to the guidelines for all age subgroups. The highest mean starting dose (3.51 mg +/- 1.643 mg) was prescribed to patients aged 70 to 74 years old. The lowest prescribed starting dose was 2.81 mg (+/- 0.998 mg) in the age subgroup 80-84 years. There was a steady decline in mean starting dose between the age groups 70-74 and 85-90 years old, after which the mean starting dose rose in subjects aged 90 and older (see Appendix B Table 3 for the absolute numbers).

Figure 3 Comparison between in-practice starting dose and guidelines for age subgroups

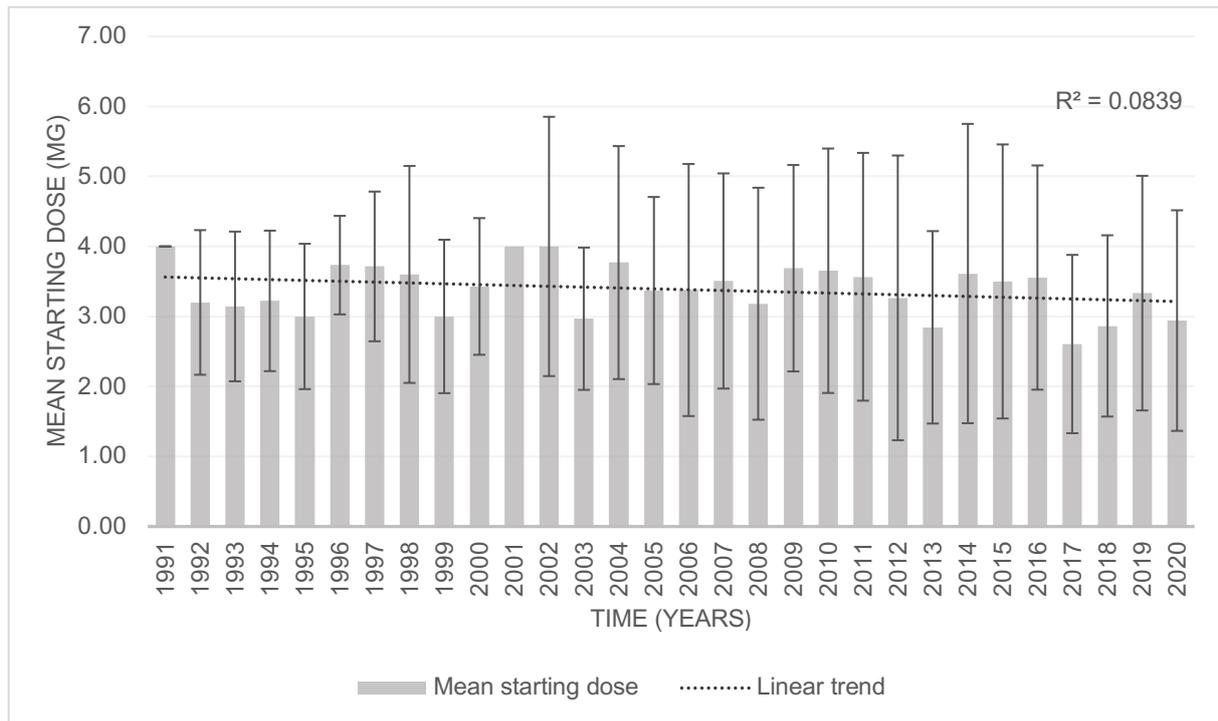


Abbreviation: MSD = mean starting dose

3.4 Trends of starting doses over the years

In figure 4 the mean starting doses in older patients between 1991 and 2020 is displayed (see Appendix B Table 4 for the frequencies). The mean starting doses in clinical practice were fluctuating throughout the years. There was no clear upward or downward trend over the years. The lowest mean starting dose of perindopril was 2.82 mg (+/-1.359) in 2013, and the highest was 4.00 mg, which was found in 1991, 2001 and 2002. Comparing the mean starting doses between pre- and post-2011, there was no decreasing trend in mean starting doses after 2011.

Figure 4 Mean starting doses in older patients in the period 1991 – 2020

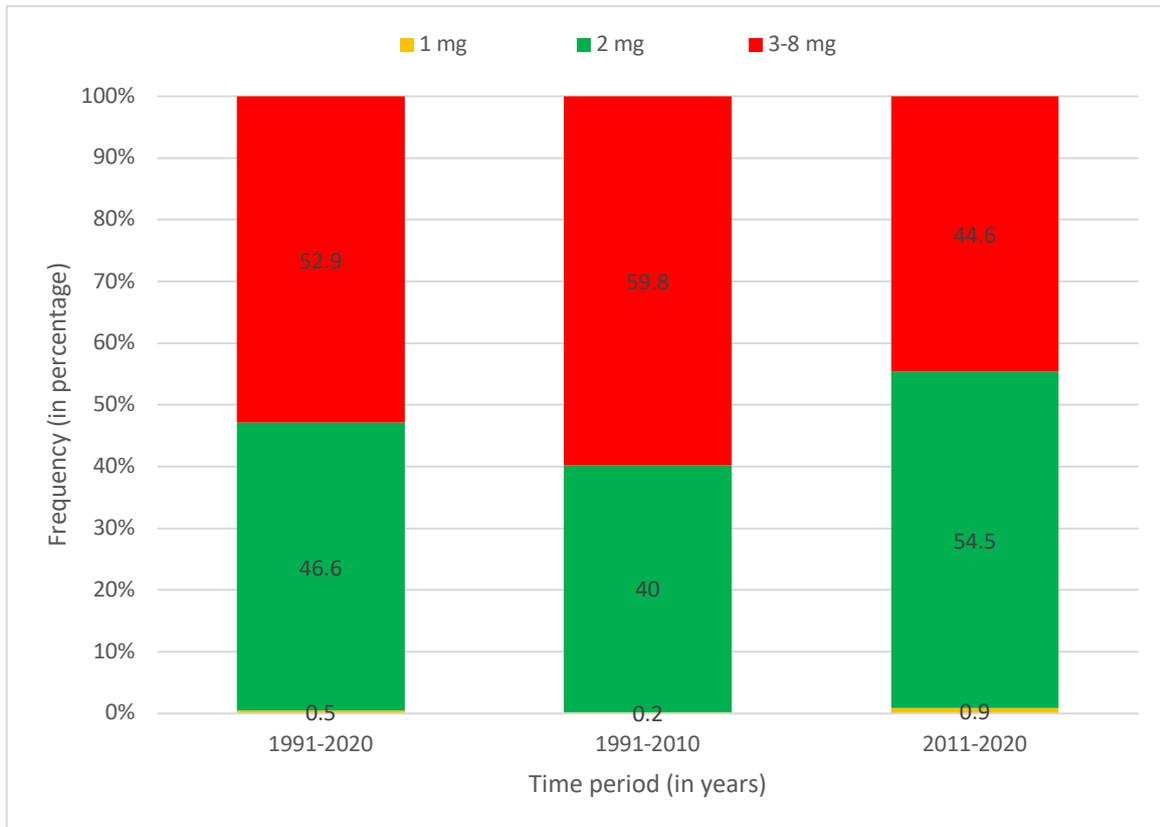


3.5 Distribution of prescribed starting doses

The distribution of prescribed starting doses of perindopril is shown in figure 5. The overall distribution of prescribed starting doses demonstrates that 46.6% (474 out of 1019) of the older adults were prescribed 2 mg according to the recommended guidelines. 52.9% (539 out of 1019) of the first perindopril prescriptions were prescribed in a higher dose ranging between 3 to 8 mg. Out of 539 that were prescribed a higher dose, 45.5% received 4 mg, 0.2% received 6 mg and 7.2% received 8 mg. In 0.5% (5 subjects) of the cases, a starting dose lower (1 mg) than recommended was prescribed.

The distribution before 2011 was more unfavorable to the guidelines compared to the distribution after 2011. Between 1991 and 2010, 333 out of 557 subjects (59.8%) of the perindopril users were prescribed a higher dose than recommended. Most non-recommended doses that were being prescribed were 4 mg (53.5%), followed by 8 mg (5.9%), and 6 mg (0.4%). 1 subject (0.2%) received 1 mg. 40% had received the recommended dose of 2 mg. In 2011 to 2020 the percentage of right recommended starting dose prescription had increased to 54.5% (252 out of 462 subjects), whereas the percentage of wrong recommended doses decreased to 44.6% (206 out of 462 subjects). In this period, 166 patients (35.9%) received 4 mg as the initial dose, and 40 subjects (8.7%) received 8 mg. 4 patients (0.9%) received 1 mg as their starting dose (see Appendix B Table 5a to 5c for absolute numbers).

Figure 5 Distribution of prescribed starting doses of perindopril



4. DISCUSSION

This study demonstrates that healthcare providers are prescribing starting doses of perindopril in older patients which are not in accordance with the start-low-go-slow principle advocated in the national CVRM guidelines, therefore, showing non-adherence to the national guidelines. While there has been a decrease in mean starting doses of perindopril when comparing the period before and after the introduction of the start-low-go-slow-principle, indicating that the (new) guidelines may have had an influence on the prescription pattern, the Dutch general practitioners continue to consistently prescribe significant higher initial doses of perindopril than the recommended lowest available dose of the respective drug.

The result is unexpected as older adults are usually frailer and more prone towards adverse drug events. Therefore, they should be treated carefully. Furthermore, polypharmacy is common in the older age group. Studies have displayed that older adults take 2-9 drugs per day on average(23). It is associated with more interactions between several drugs and a higher risk of adverse drug events, which may lead to hospitalization(24,25). By starting with a lower dose in older adults with polypharmacy, the risk of ADEs may be decreased.

An explanation for higher starting doses in clinical practice may involve the SPRINT study. The SPRINT study is an important study that has demonstrated that intensive treatment reduces the risk of cardiovascular complications even more than the standard therapy, even in the older population. This study is very well-known in the healthcare setting. Based on the outcomes of this study, healthcare providers may be more inclined to start treatment more intensively to strive for a decrease of cardiovascular risks, rather than reducing the risk of adverse drug events. Furthermore, it is generally accepted that blood pressure rises with age. Therefore, it is not rare that older adults are often diagnosed with a higher blood pressure. A higher blood pressure may trigger the healthcare providers to prescribe a higher dose as older adults are more prone to the risks of cardiovascular complications. However, this does not clarify the declining, yet doses higher than recommended, mean starting doses between age subgroups from 70 to 90 years old. It is presumed that the decline may be due to the increased awareness of frailty with these high ages, therefore, healthcare providers may be more careful in their treatment in this particular population. Especially, in the frailer group, quality of life can be more important. These explanations are only speculations as we did not obtain numerous variables, and therefore we cannot draw a final conclusion with certainty about our assumption. Nevertheless, the fact remains that all starting doses in the different age subgroups are significantly higher than recommended.

There were several strengths to this study. First, this study contributes to a very actual topic of research in the Netherlands. At present, research is focusing more and more on medication safety. This study imparts new insights to this particular theme as it investigates potential medication dispensing errors due to non-adherence of healthcare providers to the guidelines. To our knowledge, this is the first study that has investigated the starting dose prescription patterns in clinical practice, thereby filling the knowledge gap and elucidate the starting dose prescription patterns of perindopril in older adults. In addition, this study uses real-world data from the ERGO study, which is more favorable towards the representation of the general population. The use of real-world data, consequently, resulted in a larger sample size as well. The sample size, which was normally distributed, was sufficiently large as was the study power.

On the other hand, this study contained various limitations as well. The main limitation was that several covariables from the data source could not be provided to us. Covariates that we wished for were length, weight, body mass index, systolic blood pressure, diastolic blood pressure, cholesterol levels, kidney function, smoking status, alcohol use, comorbidities and (type of) antihypertensive drugs in use. As a result of these missing variables, we were not able to associate which patient-related characteristics would influence the prescription pattern of healthcare providers and consequently could not discuss the results without making assumptions and speculations on these influences.

Furthermore, the absence of information on numerous covariates, resulted in the inability to exclude subjects based on our predefined exclusion criteria, which were subjects without a known 90-days history prior to their first perindopril prescription, and subjects with heart failure of NYHA class II and higher. However, the latter's influence on the clinical meaning of the found outcome is minimal. The hypertensive population differs physiologically from the population who are suffering from heart failure as well. Dutch guidelines mention equal starting dose regimens for both indications, however, the Dutch heart failure guidelines, are emphasizing the low starting doses even more(26). Therefore, inclusion of heart failure patients would lower the starting dose naturally. However, the outcome still indicates that older adults are being prescribed a significant higher dose than recommended. This suggests that either the number of patients with heart failure is very small in the studied population or that despite suffering from heart failure, patients still get prescribed an initial higher starting dose. The latter adds to another point of interest.

The criterion regarding the 90-days history adds to the restraint of missing values, however, if solely investigating the question regarding the mean starting dose, would not have an influence on this specific outcome.

Another constraint concerns the lack of information on clinical effects, which restricts the relevance of this study. It is suggested that lower starting doses will decrease the risk of

adverse drug events, however, this could not be proven with our data. Furthermore, it would be interesting to investigate the relationship between the starting dose and the effectiveness. Especially, whether the lower starting doses will have the desired blood pressure lowering effect or, if not, what the additional benefit is of starting with a higher initial dose. In the end, the clinical outcomes and the effects that will be experienced by the patient, is what is most relevant.

Lastly, it must be noted that when stratifying on mean starting doses per year, the number of subjects before 2003 were too small to provide a clear and strong conclusion on the prescription pattern trend over the years. However, when combining all MSDs before and after 2011, a significant difference could be evinced.

All in all, based on these results, our study suggests that there is a lot to do on catching up with the guidelines to avoid medication errors due to adverse events and non-adherence of the same guidelines. However, healthcare providers are directly into contact with the patients and are more aware of the clinical setting, so they may be able to better judge the optimal treatment for their patients, or inadequately may think so. The question remains whether we should adhere to the guidelines, or whether we should change them.

More research is needed, especially research taking the clinical effects like effectivity on blood pressure lowering and safety concerning adverse drug events and hospitalization, into consideration. These outcomes are more crucial and meaningful for the target group, the older patients. We also suggest investigating the relation between starting dose and therapy adherence since therapy adherence is crucial in the treatment of hypertension. Starting doses theoretically may have a substantial impact on this. In addition, patient-related characteristics should be taken into account as well to be able to study which factors may be influencing the prescription patterns of healthcare providers, and whether this is justifiable or not. The identification of factors for which prescribing a different dose is justifiable, will contribute to a better individualized therapy. Furthermore, we suggest investigating this similar concept for other antihypertensive drugs as well, particularly for antihypertensive drugs with less specific dosing advice, as it is interesting to investigate how healthcare providers have interpreted and implemented the guidelines in clinical practice. Besides, studying the dose units of the starting doses, we advise to investigate the up-titration time as this may be important in the avoidance of ADEs as well. All in all, the main point is to conduct meaningful research by uncovering the unknown aspects of antihypertensives in older adults to optimize treatment and improve quality of life.

5. CONCLUSION

This study concluded that healthcare providers in the Netherlands do not adhere to the start-low-go-slow principle, which is recommended by the Dutch guidelines, when prescribing perindopril. Healthcare providers prescribe, on average, higher starting doses of perindopril than recommended to older patients in clinical practice. About half of the older patients are prescribed a dose not in accordance with the guideline's recommendations. In addition, there has been no convincing downtrend in mean starting doses over the years. However, when comparing the mean starting doses before and after the introduction of the start-low-go-slow-principle, a small decrease in starting dose was shown after 2011. Yet the mean starting dose of perindopril was still not in accordance with the guidelines.

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APPENDIX

APPENDIX A: STUDY PROTOCOL

In appendix A, the study protocol for the study we initially would have liked to conduct is shown. This study protocol was written in collaboration with my daily supervisor MSc. D. Hassan, and contains the input, mainly through feedback, from Dr. L.E. Visser, MSc. L.E.J. Peeters-Kalicharan, Dr. J. Versmissen, Dr. K. Hek, Prof. Dr. Ir. L. van Dijk, Prof. Dr. P.M.L.A. van den Bemt, and Prof. Dr. B.H. Stricker.

**The Association of age with the starting Dose of Perindopril
(ADaPt)
(2021)**

PROTOCOL TITLE:

Protocol ID	-
Short title	-
Version	1
Date	29-06-2021
Coordinating investigator/project leader	<i>MSc</i> [REDACTED] <i>BSc</i> [REDACTED]
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	[REDACTED]
Subinvestigator(s)	<i>MSc</i> [REDACTED] <i>Dr.</i> [REDACTED] <i>Dr.</i> [REDACTED] <i>Prof.</i> [REDACTED] <i>Prof.</i> [REDACTED] <i>Prof.</i> [REDACTED]
Sponsor (in Dutch: verrichter/opdrachtgever)	<i>Erasmus MC</i>
Subsidising party	<i>Not applicable</i>
Independent expert (s)	<i>Not applicable</i>
Pharmacy	<i>Not applicable</i>

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ADE(s)	Adverse Drug Event(s)
AE(s)	Adverse Event(s)
BP	Blood Pressure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVA	Cerebro Vascular Accident
CVD	Cardiovascular Disease
eGFR	estimated Glomerular Filtration Rate
GP	General Practitioner
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MI	Myocardial Infarction
NHG	The Dutch College of General Practitioners; in Dutch: Nederlands huisartsen genootschap
NYHA	New York Heart Association (classification)
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: To mitigate Adverse Drug Events (ADE), national and international guidelines recommend caution when prescribing antihypertensive medication in older patients; “start-low-go-slow”. As ADEs caused by antihypertensive medication is an important cause of medication related hospital admissions, it would be interesting to see if and how these recommendations have been followed over the years. Furthermore, the association between adherence to the recommendations and ADEs needs to be determined, in order to assess the added clinical value of these recommendations.

For this study, the prescribed starting doses and up-titration time of perindopril or patients aged >70 years will be compared to those aged between 40 and 55 years.

Objective(s): Our primary objective is:

- To determine the difference in starting dose of perindopril in hypertensive patients aged >70 and aged 40 to 55 years.

Secondary objectives are:

- To determine the difference in up-titration time of the perindopril dose between patients aged >70 and aged 40 to 55 years.
- To determine the effect of the starting dose on the occurrence of ADEs in patients aged >70 and aged 40 to 55 years.
- To determine if there is a difference to what maintenance doses patients aged 40 to 55 years will reach compared to patients aged >70.
- Can a difference in adherence (or non-adherence) be observed between patients aged >70 and patients aged 40 to 55 years?

Study design: Retrospective database study

Study population: Patients aged 70 or older using perindopril for the first time will be included and compared to patients aged 40 to 55, who also use perindopril for the first time. All patients will be included from the ERGO-database.

Intervention: Not applicable

Main study endpoint(s): The primary study endpoint is:

- Difference in starting dose of perindopril in **mg** between patients aged >70 and patients aged 40 to 55 years.

Secondary study endpoints are:

- Time between first dose and the maintenance dose of perindopril in **days** in both age groups, i.e. the up-titration time;
 - o Maintenance dose is defined as two to three consecutive prescriptions, without change in dosage or discontinuation of perindopril
- **Proportion** of patients with adverse drug events associated with perindopril use, within two months after their first prescription, in both group of patients. These Adverse events will be derived using the following proxies.
 - o Sudden dose-reduction, without the start of any other antihypertensive drug
 - o Discontinuation of perindopril, without the start of another antihypertensive drug
- The maintenance dose in mg in both age groups
- The (non-)adherence rate in both age groups

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness: Patients will experience no burden or any increased risks.

1. INTRODUCTION AND RATIONALE

Over the years, proof of effectiveness of hypertension control has been undisputed [1]. Even in vulnerable groups of patients, like the elderly, hypertension control seems to be effective in decreasing cardiovascular endpoints, like mortality, Myocardial Infarction (MI) and stroke [1-3]. However, it is also well known that elderly patients are at risk for Adverse Drug Events (ADEs) potentially leading to hospitalization [4-5].

To mitigate ADEs in the management of hypertension, national and international guidelines warn healthcare providers to be cautious when prescribing antihypertensive drugs for these elderly patients: “start-low-go-slow” [6-9]. Beside a lower starting dose, the up-titration of the drug-dose should be done under regular monitoring of Blood Pressure (BP) and should be done over a longer period of time in the elderly compared to younger patients [6].

In this study, we want to focus on perindopril. Perindopril was the study-drug in a previous study by our group (DECISION) and thus more (real-live experience and) information about the use and about patients using it is available. Furthermore, in contrast to some other antihypertensive drugs, specific dosing advice of perindopril, both for older and younger patients, are given by various Dutch guidelines. This makes comparing the differences of perindopril starting doses in different age groups justifiable.

For example, for over a decade, the NHG CVRM guideline recommends to older patients (>70 years) 2 mg perindopril per day and younger patients 4 mg perindopril per day when prescribed for the first time. This is in accordance with the dosing information in the summary of product characteristics (SmPC) of the pharmaceutical producers [8]. Both sources recommend to increase dosage after a period of 30 days, when the therapy is well tolerated.

Although The Dutch center of expertise for geriatric pharmacology (Ephor) states that perindopril does not need to be dosed by age, they do recommend to initiate therapy with a dose of 2 mg a day in older patients, which is in accordance with both the NHG guidelines and the SmPC.

The following questions remain unanswered; do the recommendations to “start-low and go-slow” with perindopril have any effect? Have these recommendations been followed by caretakers over the years, and if so, how have they been followed? To answer these questions, we want to know if there is a difference in starting dose and up-titration time of perindopril between elderly patients (>70 years) and younger patients (40-55 years old). Thereafter, we will analyze if the following (or the lack) of recommendations has led to more or less adverse (drug) events related to perindopril and possible non-adherence.

For this study, the database of Erasmus Rotterdam Gezondheid Onderzoek (ERGO) will be used. The ERGO study is a big prospective cohort study, which follows the population of Ommoord, a suburban of Rotterdam. Initially, patients 55 years and older were included in the ERGO study. However, since 2006 and 2016, respectively patients over 45 and 40 years were also included. Patients' healthcare data are collected over a very long period (since 1991) and stored in this database, making this database ideal to demonstrate over time if and how recommendations have been followed by healthcare professionals, and what the effects of these recommendations are on AEs.

2. OBJECTIVES

Primary objective(s):

Our primary objective is to find out if guideline recommendations, concerning the starting dose of 2 mg perindopril, for older patients (> 70 years) have been followed by healthcare providers.

Secondary objective(s):

- To determine the effect of the starting dose on the occurrence of ADEs in hypertensive patients aged > 70 years and aged 40 to 55 years. The occurrence of ADEs will be derived from the following proxies.
 - o Sudden dose-reduction, without the start of any other antihypertensive drug
 - o Discontinuation of perindopril, without the start of another antihypertensive drug
- To determine if there is a difference in the time of up-titration of the starting dose to maintenance dose between patients aged >70 and aged 40 to 55 years.
- To determine if there is a difference to what maintenance doses patients aged 40 to 55 years will reach compared to patients aged >70 years.
- Can a difference in adherence (or non-adherence) be observed between patients aged > 70 and patients aged 40 to 55 years?

3. STUDY DESIGN

A retrospective, cross-sectional, population-based-study, using patients from the ERGO-study from Rotterdam, will be conducted.

4. STUDY POPULATION

4.1 Data sources

All data will be sourced from the ERGO-study database. Data about medication in the ERGO-database is sourced from patients' pharmacies.

4.2 Inclusion criteria

We will include patients over 70 years old and patients between 40 and 55 years old, who have hypertension and are prescribed perindopril for the first time. Patients aged 40 years or younger, can't be included, because they are not included in the ERGO-database.

4.3 Exclusion criteria

- Patients who don't have a medical history present in ERGO-database of at least 90 days before first intake of perindopril
- Patients with heart failure (NYHA classification II or higher)

4.4 Sample size calculation

A preliminary search in the ERGO-database gave us more than 1000 patients, who could be included. In case of non-significant differences in primary results, we will perform a retrospective power calculation of our sample size to disregard non-significance as a result of a too small sample size. For adjusting for every covariate, at least 10 patients per covariate must be included. As we expect to encounter over 1000 patients in this database, we foresee no problems with the sample size to correct for covariates.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Not applicable

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7 NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non-Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8 METHODS

8.1 Study endpoints

8.1.1 Main study endpoints

The main study endpoint is the difference in the mean starting dose of perindopril in **mg**, between both age-groups.

8.1.2 Secondary study endpoints

Secondary study endpoints are;

- Mean time in days/months from first dose to maintenance dose of perindopril:
 - o Maintenance dose is defined as two to three consecutive prescriptions, without change in dosage or discontinuation of perindopril
- Percentages of patients, in both age groups, possibly effected by adverse events due to the use of perindopril *.
- Percentage of patients getting the “recommended” starting dose in both age groups.
- Difference of mean maintenance doses of perindopril in mg between younger and elderly patients.
- Rate of discontinuation of perindopril in both age groups**.
- Rate of non-adherence in both age group calculated with the medication possession ratio.

* Possibility of adverse events occurrence will be derived from the following proxies:

- Sudden dose-reduction, without the start of any other antihypertensive drug
- Discontinuation of perindopril, without the start of another antihypertensive drug

** Stopping with perindopril use and starting with another ACE-inhibitor or an ARB is associated with respectively a shortage or availability problems of perindopril in the Netherlands and ACE-inhibitors caused cough.

8.1.3 Other study parameters

The following parameters will be collected from the database:

- Sex (male/female)
- Age (years)
- Body Mass Index (BMI) (kg/m²)
 - o Body weight (kg) (if present)
 - o Body length (m) (if present)
- Co-morbidities (categorized into headache/migraine, hyperlipidemia, hypercholesterolemia, diabetes, cardiovascular disease, COPD, impaired renal function (eGFR (CKD-EPI) < 50 ml/min/1.73m²) and other, at ERGO baseline inclusion)
- Smoker (never/former/current)
- Alcohol use (yes/no and if available alcohol consumption as grams per day)
- Cholesterol levels (mmol/L)
- If present, the latest known mean blood pressure value, within 30 days before first intake of perindopril (systolic and diastolic in mmHg)
- If present, the latest known mean blood pressure value, within 30 days after first intake of perindopril (Systolic and diastolic in mmHg)
- Total (active) number of drugs in use at time of perindopril start.
- Dose of antihypertensive drugs (other than perindopril) in use, categorized into; low, medium, or high
- Number and type of antihypertensive drugs (other than perindopril) in use (see appendix A for ATC-codes).
- If present, prescribing healthcare provider (general practitioner or specialist)

8.2 **Randomisation, blinding and treatment allocation**

Not applicable.

8.3 **Study procedures**

Inclusion

Data from the ERGO database between the years 2000 and 2021 will be used for this study. All patients in the study using perindopril for the first time will be included and the required covariates (described in section 8.1) will be extracted. Patients will be excluded when there is no history available 90 days prior to the first prescription of perindopril. Patients will also be considered ineligible if they have heart failure classified NYHA II or higher. These eligible patients will be divided into two age-groups: A) patients aged between 40 and 55 years and B) patients aged 70 years or older.

Main study endpoints

In each group, the first prescription of each patient will be assessed for investigation of the primary endpoint. The mean starting dose of each group will be calculated. The difference in mean starting dose between group A and group B, will represent the difference in starting doses between elderly and younger patients.

Secondary study endpoints

To determine the mean time in days from the first dose to the maintenance dose in each group, we will take the date of the first prescription of the starting dose as the start date, and the date of the first prescription of the maintenance dose as the end date. Maintenance dose is defined as two or more consequent prescription, without change in dosage or ceasing of perindopril. A mean difference in time can be calculated using these start and end dates.

To determine the percentage of patients getting the “recommended” dose, the frequency of the “recommended” dose will be determined in each group. The recommended dose is defined as a starting dose of 2 mg in older patients and 4 mg in younger patients.

To assess if there is a difference in reported AEs per age group, the frequency of AEs will be determined in both groups. AEs will be determined by means of the following proxies: sudden dose-reduction and discontinuation of perindopril, without the start of any other antihypertensive drug

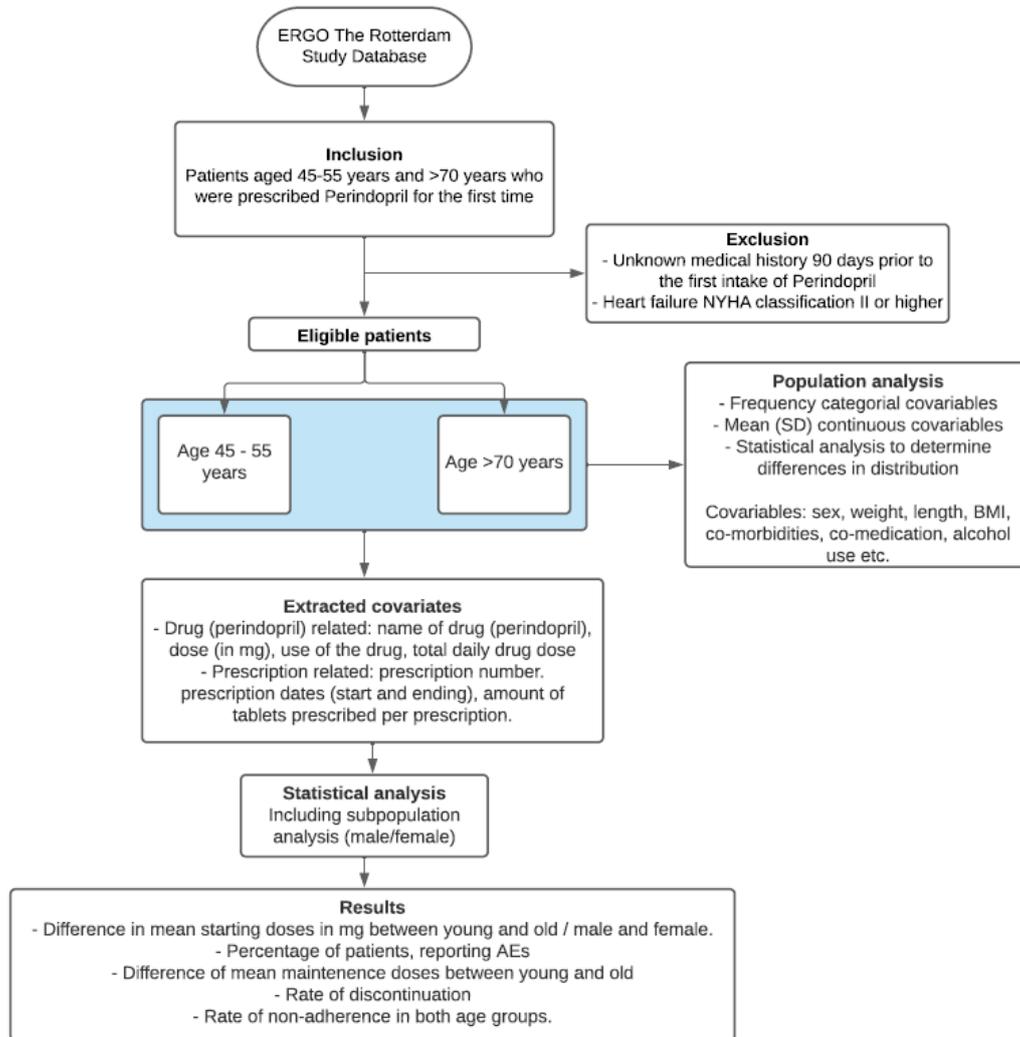
Furthermore, to prevent misclassification of the AE, patients taking another new antihypertensive drug at the same time as perindopril or within 60 days after the first intake of perindopril will be excluded. The difference in reported AE will be given as a percentage of only adverse events which are likely attributed to perindopril.

The rate of discontinuation of each group (A and B) will be assessed by the frequency of discontinuation of perindopril, without the start of any other ACE-inhibitor or ARBs. Discontinuation is defined as the absence of a repeat prescription, which is not due to patient death, availability problems and/or logistic problem*.

The rate of analyzed non-adherence in both age groups can be investigated with help of the medication possession ratio (MPR). MPR is defined as the sum of days' supply for all fills in period divided by the number of days in that period times 100. A MPR higher than 80% means that a subject is adherent. The following variables are needed: number of tablets dispensed per prescription, the dose unit per tablet, the dosage regimen, the start date of the prescription and the end date of the prescription. The frequency of non-adherence per age group will be considered to determine the rate of non-adherence.

* Stopping with perindopril use and starting with another ACE-inhibitor or an ARB is expected to be caused by respectively a shortage or availability problems of perindopril in the Netherlands and ACE-inhibitors caused cough.

Figure 1: study procedure



Abbreviations: AEs = Adverse Events, BMI = Body Mass Index, ERGO = Erasmus Rotterdam Gezondheid Onderzoek, mg = milligrams, NYHA = New York Heart Association (classification), SD = Standard Deviation

8.4 Withdrawal of individual subjects

Not applicable.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Not applicable.

8.6 Follow-up of subjects withdrawn from treatment

Not applicable.

8.7 Premature termination of the study

Not applicable.

9 SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

Not applicable.

9.2 AEs, SAEs and SUSARs

10.2.1 Adverse events (AEs)

Not applicable.

10.2.2 Serious adverse events (SAEs)

Not applicable.

10.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

Not applicable.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable.

10 STATISTICAL ANALYSIS

Statistical analysis will be performed using IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY, USA) and/or Stata version 15.

10.1 Primary study parameter(s)

Our primary endpoint is the mean starting dose of perindopril in **mg** in both older and younger patients. We will calculate the difference in mean starting dose between both age groups. Thereafter we will calculate the statistical significance using an unpaired, independent t-test for differences. To adjust for co-variables (referring to study parameters in section 8.3), we will use a linear regression model. The mean starting doses will be calculated for both groups of all years between 2000 – 2021.

We will also stratify on more specified age groups, 45-50; 50-55; 70-75; 75-80; 80+ for this end point.

Furthermore, descriptive data of both age groups will be analyzed and reported, i.e. the percentage of elderly patients starting with **2 mg** perindopril and younger patients starting with **4 mg**, as recommended by the NHG-guidelines.

An univariable analysis will be carried out on the covariables of group A and B. Patient baseline characteristics will be described by using frequency distribution (absolute number and a percentage) for categorical variables and calculating mean and standard deviation for continuous variables. The data distribution will be considered. To detect whether there is a difference between groups concerning the covariables (referring to study parameters in section 8.3) a chi-square test will be used for categorical variables and an independent t-test will be used for continuous variables. A p-value smaller than 0.05 will be considered significant.

10.2 Secondary study parameter(s)

One of our secondary study endpoints is the mean time in days/months from first dose to maintenance dose. We will calculate the difference in mean time from first dose to maintenance dose between both age groups. Thereafter we will calculate the statistical significance using an unpaired, independent t-test.

For the secondary endpoint related to difference in AEs, AEs will be processed as an absolute number of AE and a percentage. In the analysis of differences in AEs we will make use of the

Z-test. We will make use of the same process on recording our data, and statistical analyses to analyze rate of discontinuation and non-adherence.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis (if applicable)

Not applicable.

11 ETHICAL CONSIDERATIONS

11.1 Regulation statement

The use of anonymized healthcare data records for research purposes is allowed under certain conditions. When these conditions are fulfilled, neither obtaining informed consent from patients nor approval by a medical ethics committee is obligatory for this type of observational studies containing no directly identifiable data (art. 24 GDPR Implementation Act jo art. 9.2 sub j GDPR). Approval from the applicable governance bodies of the ERGO-study will be obtained before starting the study.

11.2 Recruitment and consent

Not applicable

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

Not applicable

11.5 Compensation for injury

Not applicable.

11.6 Incentives

Not applicable.

12 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The ERGO study database does not hold any directly identifying patient data. Data retrieved from the ERGO database for this study, will be stored anonymously for a period of 15 years. Data will be analyzed at Erasmus MC, or in times of COVID-19, with the approval of those in charge of the data, in the secure environment and secured online environment of Erasmus MC and are only accessible for members with permission. Members with permission are the intern

MSc-student, the PhD student conducting the research and other members of the research group. We will not publish at the level of individual patients.

12.2 Monitoring and Quality Assurance

We will work with the 4-eyes-principle. All syntaxes will be checked by a co-author.

12.3 Amendments

Not applicable.

12.4 Annual progress report

Not applicable.

12.5 End of study report

Not applicable.

12.6 Public disclosure and publication policy

Not applicable.

13 STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Not applicable.

13.2 Synthesis

Not applicable.

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Appendix A: Antihypertensive drugs and their ATC-codes

Groups of antihypertensive drugs	ATC-code
A1-Blocker	C02CA
Serotonine HT2 antagonist	C02KD
Renine-inhibitor	C09XA
Antiadrenergic agents, centrally acting	C02AB/C
ACE-inhibitors	C09A
ACE-inhibitors in combination with diuretics	C09BA
ACE-inhibitors in combination with calcium channel blockers	C09BB
ACE-inhibitors in combination with 'other'	C09BX
AT-II-inhibitor	C09CA
AT-II-inhibitor in combination with diuretics	C09DA
AT-II-inhibitor in combination with calcium channel blockers	C09DB
AT-II-inhibitor in combination with thiazide diuretics and with Calcium channel blockers	C09DX
Beta blockers	C07A
Beta blockers in combination with thiazide diuretics	C07B
Beta blockers in combination with other diuretics	C07C
Beta blockers in combination with thiazide diuretics and other diuretics	C07D
Beta blockers in combination with vasodilatation drugs	C07E
Beta blockers in combination with 'other'	C07F
Calcium channel blockers	C08
Calcium channel blockers in combination with diuretics	C08G
Calcium channel blockers in combination with	C09DX
Renine-inhibitor with Calcium channel blockers	C09XA53
Diuretics	C03
Calcium channel blockers in combination with AT-II-inhibitor and thiazide diuretics	C09DX01
Renine-inhibitor in combination with hydrochlorothiazide	C09XA52
Renine-inhibitor in combination with amlodipine and hydrochlorothiazide	C09XA54

APPENDIX B: ROUGH STUDY RESULTS

Table 1: Age (in years) the date of the first perindopril prescription

		Frequency	Percent	Valid Percent	Cumulative Percent
Age	70	48	4.7	4.7	4.7
	71	52	5.1	5.1	9.8
	72	50	4.9	4.9	14.7
	73	59	5.8	5.8	20.5
	74	64	6.3	6.3	26.8
	75	66	6.5	6.5	33.3
	76	61	6.0	6.0	39.3
	77	68	6.7	6.7	45.9
	78	64	6.3	6.3	52.2
	79	57	5.6	5.6	57.8
	80	50	4.9	4.9	62.7
	81	57	5.6	5.6	68.3
	82	50	4.9	4.9	73.2
	83	53	5.2	5.2	78.4
	84	45	4.4	4.4	82.8
	85	31	3.0	3.0	85.9
	86	27	2.6	2.6	88.5
	87	28	2.7	2.7	91.3
	88	23	2.3	2.3	93.5
	89	16	1.6	1.6	95.1
90	16	1.6	1.6	96.7	
91	14	1.4	1.4	98.0	
92	6	0.6	0.6	98.6	
93	4	0.4	0.4	99.0	
94	2	0.2	0.2	99.2	
95	5	0.5	0.5	99.7	
96	1	0.1	0.1	99.8	
98	1	0.1	0.1	99.9	
99	1	0.1	0.1	100.0	
	Total	1019	100.0	100.0	

Table 2: Mean starting doses compared to guidelines (2 mg)

	N	Mean (mg)	SD	Mean difference (mg)	95% CI	p
1991-2020	1019	3.34	1.623	1.343	[1.24, 1.44]	<0.001
1991-2010	557	3.44	1.506	1.438	[1.31, 1.56]	<0.001
2011-2020	462	3.23	1.749	1.229	[1.07, 1.39]	<0.001

Abbreviations: CI = confidence interval, mg = milligram(s), N = number of patients, SD = standard deviation.

Table 3: Starting dose for age subgroups compared to guidelines (2 mg)

Age groups	N	Mean (mg)	SD	SEM	Mean difference	95% CI	p
70-74	273	3.51	1.643	0.099	1.505	[1.31, 1.70]	<0.001
75-79	316	3.46	1.628	0.092	1.456	[1.28, 1.64]	<0.001
80-84	255	3.39	1.776	0.111	1.392	[1.17, 1.61]	<0.001
85-90	125	2.81	0.998	0.089	0.808	[0.63, 0.98]	<0.001
>90	50	2.84	1.621	0.229	0.840	[0.38, 1.30]	0.001

Abbreviations: CI = confidence interval, mg = milligram(s), N = number of patients, SD = standard deviation, SEM = Standard error of the mean

Table 4: Mean starting dose per year between 1991 and 2020

Years	Mean	N	Std. Deviation
1991	4.00	5	0.000
1992	3.09	11	1.044
1993	3.14	7	1.069
1994	3.22	18	1.003
1995	3.00	14	1.038
1996	3.67	18	0.767
1997	3.75	16	1.000
1998	3.89	19	1.696
1999	3.14	7	1.069
2000	3.14	7	1.069
2001	4.00	3	0.000
2002	4.00	8	1.852
2003	3.03	37	1.301
2004	3.75	57	1.735
2005	3.41	61	1.283
2006	3.37	67	1.774
2007	3.49	83	1.525
2008	3.16	62	1.601
2009	3.65	46	1.479
2010	3.67	79	1.767
2011	3.56	68	1.790
2012	3.27	70	2.050
2013	2.82	60	1.359
2014	3.62	63	2.121
2015	3.40	50	1.818
2016	3.56	27	1.601
2017	2.61	33	1.273
2018	2.86	37	1.294
2019	3.33	39	1.675
2020	2.94	34	1.575
Total	3.37	1106	1.625

Table 5a: Starting dose distribution between 1991 and 2020

		Frequency	Percent	Valid Percent	Cumulative Percent
Dose	1	5	0.5	0.5	0.5
	2	475	46.6	46.6	47.1
	4	464	45.5	45.5	92.6
	6	2	0.2	0.2	92.8
	8	73	7.2	7.2	100.0
	Total	1019	100.0	100.0	

Table 5b: Starting dose distribution between 1991 and 2010

		Frequency	Percent	Valid Percent	Cumulative Percent
Dose	1	1	0.2	0.2	0.2
	2	223	40.0	40.0	40.2
	4	298	53.5	53.5	93.7
	6	2	0.4	0.4	94.1
	8	33	5.9	5.9	100.0
	Total	557	100.0	100.0	

Table 5c: Starting dose distribution between 2011 and 2020

		Frequency	Percent	Valid Percent	Cumulative Percent
Dose	1	4	0.9	0.9	0.9
	2	252	54.5	54.5	55.4
	4	166	35.9	35.9	91.3
	8	40	8.7	8.7	100.0
	Total	462	100.0	100.0	