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ORIGINAL RESEARCH ARTICLE

The Sex-Specific Impact of the FORTA (Fit-fOR-The-Aged) List on Medication Quality and Clinical Endpoints in Older Hospitalized Patients: Secondary Analysis of a Randomized Controlled Trial

Ann-Kathrin Schmitt[1] · Christel Weiss[2] · Heinrich Burkhardt[3] · Helmut Frohnhofen[4,5] · Martin Wehling[1] · Farhad Pazan[1]

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Abstract

Background Little is known about the sex-specific impact of drug optimization tools such as the Fit fOR The Aged (FORTA) list on drug use and relevant clinical endpoints in older people.

Objective We aimed to detect gender differences of interventional effects on medication quality and related clinical effects in the VALFORTA trial.

Patients and methods A sex-specific analysis of data from 409 patients (147 men and 262 women, mean age 79.4 and 82.7 years, respectively) in acute geriatric care comparing the control and FORTA intervention groups was performed. Changes of the FORTA score (sum of over- and undertreatment errors per patient), the incidence of adverse drug events (ADEs) during hospitalization, and several clinically relevant endpoints [e.g., the Barthel index (BI)] were tested for equivalence at a 20% margin. "Success" or "failure" for the development of these clinical endpoints was defined and their frequencies compared by a risk reduction analysis.

Results Sex differences were insignificant for the reduction of the FORTA score, the improvement of BI, or over- and undertreatment errors ($p > 0.05$). In women only, the FORTA intervention significantly increased the number of patients without an ADE ($p = 0.010$). Statistical sex equivalence was found for the improvement of the FORTA scores, BI, and the number of prevented events (e.g., falls, confusion, or renal failure) ($p < 0.05$), but not for the improvement of specific mistreatments or over- and undertreatment scores under altered inclusion criteria ($p > 0.05$).

Conclusions Both sexes benefit equally from the FORTA intervention regarding the amelioration of the quality of drug treatment as well as several clinically relevant outcomes. In addition, the positive impact of the FORTA intervention on the number of adverse drug events appears to be greater in women.

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✉ Martin Wehling
martin.wehling@medma.uni-heidelberg.de

1 Clinical Pharmacology Mannheim, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

2 Department of Medical Statistics, Biomathematics and Information Processing, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

3 IV. Medical Department, Medical Faculty Mannheim, University Medical Center, Heidelberg University, Mannheim, Germany

4 Fakultät für Gesundheit, Universität Witten Herdecke, Alfred-Herrhausen-Str. 50, 58455 Witten, Germany

5 Heinrich Heine Universität Düsseldorf, UKD, Moorenstr. 5, 40225 Düsseldorf, Germany

1 Introduction

There is a common ground in clinical research between older people in general and women: both groups are extremely under-represented in clinical trials. In 2018, people with public health insurance aged over 65 years accounted for 22% of the total insured population in Germany but received 55% of the total prescription volume [1]. Based on a recent study, the percentage of people in 17 European countries plus Israel who regularly take five or more different drugs—and therefore comply with a common definition of "polypharmacy" [2]—increases from 25.3% in patients 65 years or older to 46.5% in people older than 85 years [2, 3].

Globally, life expectancy is higher for women than for men [4–6]. In the USA, women aged 85 or older outnumber

Key Points

The FORTA-based intervention improves the quality of drug treatment and clinically relevant outcomes such as the Barthel Index equally in men and women.

Adverse drug events were reduced to a greater extent in women compared to men.

men by two in one and American nursing homes have over four times more women than men [7]. To describe this apparent disparity the term "feminization of aging" was coined [8]. As older women provide a lower self-reported health status [9, 10], the lifespan spent in health is very similar between both sexes and women live longer with impaired health status [4, 6].

Since older people are the biggest consumer group of prescribed medication and women make up the vast majority of this population, increasing efforts to understand their sex-specific characteristics and improve their medical supply is needed [11, 12].

Although the importance of sex aspects in clinical research, drug development, and testing has been more recognized over recent decades, there is still a particular need for further evidence of differences between older men and women [11, 12]. It has been consistently reported that older women have a higher risk for adverse drug events (ADEs) [7, 12–20] than older men, possibly due to a smaller volume of distribution and a more pronounced decrease of renal clearance [7]. In addition, older people often receive multiple medications without an individual dosing adjustment [21]. Consequently, ADEs were thought to be responsible for hospital admissions in 16% of women and 9% of men aged over 80 years [18].

The lack of evidence and guidelines concerning effective and safe treatment of older patients pose great challenges to physicians in primary care as well as in other healthcare settings. To aid physicians in this respect, drug lists have been published that in most cases compile potentially inadequate medications (PIMs) for the treatment of geriatric patients [22–24].

In contrast, the FORTA (Fit-fOR-The-Aged) list is one of the few listing approaches that provides positive drug labels (i.e., recommended in the therapy of geriatric patients) in addition to negative labels (i.e., PIMs) for drugs and drug classes [25]. It is still the only drug list for older people that could be labeled as a positive-negative list as opposed to the START/STOPP criteria comprising both drug AND action recommendations [25].

Depending on safety, efficacy, and suitability in older patients, the third version of the FORTA list for German-speaking countries includes about 296 items in 30 indication groups labeled FORTA A-D [25, 26]. Since its introduction in 2008, several other country-specific lists have been developed by expert Delphi consensus procedures [26]. The four FORTA categories are:

A: Drugs with clear benefits, their safety is proven in older patients ("A-bsolutely").

B: Drugs with efficacy but limited information regarding safety in the elderly ("B-eneficial").

C: Drugs with a doubtful efficacy-safety ratio; intense monitoring of effects and side effects is necessary ("C-areful").

D: Drugs that should be avoided in older people ("D-on't") [25].

It is important to mention that the FORTA list is a patient-in-focus listing approach (PILA), and therefore its application requires a precise knowledge and evaluation of the patient [22, 25, 26].

In 2016, the trial to VALidate FORTA (VALFORTA) [27] was published as the first randomized controlled trial (RCT) to show that the use of a listing approach—the FORTA list—improves medication quality and several clinical outcomes in geriatric hospitalized patients, such as the rate of in-hospital adverse drug reactions, the Barthel Index (BI) and the termination of common medication errors in older patients.

As far as we know, sex differences of clinical responses to the application of listing approaches have not been adequately studied so far.

With this prospectively planned secondary analysis of VALFORTA trial, we analyzed sex differences for the effects of the FORTA-based intervention that were previously published [27], representing the first sex-specific analysis of an RCT testing a drug listing approach as unidimensional intervention in older patients.

2 Methods

2.1 Study Population and Intervention

The VALFORTA trial was a prospective bicentric RCT at the geriatric departments of "Universitätsmedizin Mannheim" and "Knappschaftsklinikum Essen" in Germany [27]. Patients who met the inclusion criteria (aged 65 years or above with at least three long-term medications or aged 60 years and above with at least six long-term medications, hospitalization for at least 5 days, at least three clinically relevant diagnoses, and written consent by patient or relatives) who were hospitalized between March 2013 and August 2014 were randomly allocated to the control or intervention wards [27]. Physicians working at the intervention ward were instructed on how to use the FORTA principle and the FORTA list. On weekly "PharmaBoard" meetings,

the individual medication of the participants was evaluated according to FORTA by the study physicians. The control group was treated according to standard geriatric care. The study was approved by the Ethical Committees at the Medical Faculty Mannheim, Heidelberg University and the University of Witten-Herdecke.

2.2 Data Collection and the FORTA Score

Admission and discharge medication plans were collected and screened for medication errors according to FORTA. As a measure of medication quality, the FORTA score was designed to quantify the number of over- and undertreatment errors based on the FORTA list. Overtreatment relates to drugs to be removed, undertreatment to those to be added.

In addition, relevant geriatric assessments were performed at admission and discharge, for example the Barthel Index (BI).

Adverse drug events (ADEs) were recorded on both wards in three ways: (1) by teams who were specifically instructed to record ADEs; (2) by explicitly asking for them in patient interviews; and (3) by screening the clinical records for related entries [27].

Further information about the data collection process is available in the original VALFORTA publication [27] and its Online Supplementary Data. The validation and cross-checking of abstracted data were carried out by the statistician as well as by the study physicians. To avoid bias, this process was conducted in a blinded manner after the patient was discharged [27].

3 Endpoints

We compared baseline characteristics (Table 1) as well as changes in the average FORTA score between admission and discharge in the following four groups: Control-Men (CM), FORTA-Men (FM), Control-Women (CW), and FORTA-Women (FW). In addition, data from women versus men were compared for the entire study population. We also compared the two sexes with regard to the group-specific incidence of ADEs during hospitalization.

Furthermore, we defined "success" or "failure" for clinically meaningful changes of endpoints such as BI or over- or undertreatments. Definitions are detailed in the Online Supplementary Material (OSM) 1; those reflecting changes in BI were based on the minimal clinically important difference [28]. The absolute number of successes and failures in the FORTA and control groups were compared by a risk-reduction analysis. We calculated the absolute risk reduction (ARR) for the probability of occurrence of a "failure" for the FORTA intervention as well as the Number Needed to Treat (NNT) to avoid one failure. If no significant differences in the ARR by FORTA between men and women were found, we checked the statistical significance of ARR for not reaching defined goals ("success") in men and women.

3.1 Statistical Analysis

Age and body mass index (BMI) were compared using the *t* test; duration of hospitalization and the number of diagnoses and long-term medications were analyzed by the Mann-Whitney *U* test. The chi-square test was used to assess the

Table 1 Baseline characteristics of men and women in the FORTA and the control group as well as overall characteristics of both sexes

	Control *mean/range/n*	**Men total** *mean/range/n*	FORTA *mean/range/n*	Control mean/range/n	**Women total** *mean/range/n*	FORTA mean/range/n
Age (years)	77.89/60-91/73	**79.39/59-92/147**	80.88/59-92/74*	81.53/62-97/134	**82.73/62-97/262****	83.99/70-96/128***
Duration of stay (days)	16.53/4-43/73	**17.34/4-65/146**	18.15/4-65/73	16.1/2-75/134	**17.66/2-76/262**	19.29/3-76/128
Number of diagnoses	10.19 /3-25/73	**10.67 /3-25/147**	11.15/4-25/73	8.84/3-21/134	**9.35/3-21/262****	9.9/4-20/128**
Number of long-term medications at admission	8.88/3-21/73	**8.78/3-21/147**	8.69/3-19/73	8.25/3-15/134	**8.16/3-26/262**	8.06/3-26/128
Body mass index (kg/m^2)	27.44/10.23-42.52/67	**26.41/10.23-42.52/130**	25.3/15.24-40.48/63*	25.65/13.22-48.89/122	**24.9/13.22-48.89/241***	24.13/16.05-40.56/119*
GFR < 60ml/min (NOC/n/%)	35/72/48.61	**72/145/49.66**	37/73/50.68	65/128/50.78	**138/253/54.55**	73/125/58.4

NOC number of cases; *n* number of patients included; columns that contain "Total" in their heading are in bold

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0025$, ****$p < 0.0001$ for the intergroup comparison

number of patients with a glomerular filtration rate (GFR) less than 60 ml/min. For the comparisons of the changes in the FORTA score, we used the Wilcoxon rank sum test (for intergroup comparisons) and the Mann-Whitney *U* test (for differences between the FORTA and control groups), men and women were compared by Poisson regression analysis. Regarding the incidence of ADEs, intergroup comparisons were performed by chi-square or Fisher's exact tests, respectively; the total number of ADEs was compared by the Cochrane-Armitage trend test. For the risk-reduction analysis, the chi-square test was used to compare the frequency of failure in the FORTA versus control groups, while we used the Wald chi-squared test to check for sex differences in the ARR by FORTA. Finally, we checked the ARR by FORTA of men and women for equivalence at 10% and 20% margins.

Statistical analyses were conducted at the Department of Medical Statistics, Biomathematics and Information Processing, Medical Faculty Mannheim, Heidelberg University. We used SAS Release 9.4 (SAS Institute Inc., Cary, NC, USA) and IBM SPSS Statistics Version 25.

4 Results

Men and women significantly differed in mean age (men: median 80 years; women: median 83 years; Table 1), number of diseases (men: median ten; women: median nine) and body mass index (BMI) (men: median 25.2 kg/m^2; women: median 23.9 kg/m^2). No differences were found for the duration of hospitalization, number of prescribed drugs at admission, and percentage of patients with a glomerular filtration rate (GFR) of less than 60 ml/min. The group-specific analysis showed that men in the intervention group were older (control: median 78 years; FORTA: median 83 years) and had a lower mean BMI (control: median 25.7 kg/m^2; FORTA: median 24.7 kg/m^2) than those in the control group, while there were no differences regarding the other parameters such as number of diagnoses, number of medications, relevant restriction of GFR, or days spent in the hospital. Furthermore, females in the intervention group were also older (control: median 82 years; FORTA: median 84 years), had a higher number of diagnoses (control: median eight; FORTA: median nine) and a lower average BMI (control: median 24.8 kg/m^2; FORTA: median 23.2 kg/m^2) than those in the control group. No differences for women in the FORTA or control groups were found regarding the duration of stay, number of long-term medications at admission, or number of patients with GFR < 60 ml/min (Table 1).

The analysis of changes of the FORTA score between admission and discharge showed that in all four groups, namely Control-Men (CM), FORTA-Men (FM), Control-Women (CW), and FORTA-Women (FW), a significant improvement in the mean FORTA score was achieved (Fig. 1). Significantly greater decreases in the score in the FORTA than the control group were found: the differences in the reduction in the FORTA score between FORTA and control group ("d2") were 1.6 points in men and 1.7 points in women. The positive impact of the FORTA intervention did not differ between men and women. In addition, the difference between "d2" in men and women (so-called "d3") was not significant.

We also evaluated the sex- and group-specific incidence of ADEs (Table 2). A higher rate of falls, dizziness, dyspnea, and renal failure was detected in men compared to women ($p < 0.05$). In addition, nausea was significantly more frequent in women than men ($p < 0.05$). No difference was found for the incidence of confusion, obstipation, diarrhea, cardiac decompensation, and angina pectoris. In total, ADEs were more frequently observed in men as compared to women ($p = 0.0028$). There was no significant sex difference for individual ADEs between the FORTA and control groups. Only women in the FORTA group had a lower incidence of renal failure and total ADE, which was trending to significance. Overall, more than 20% of all events in FM were prevented by using FORTA.

The analysis of risk reduction (absolute risk reduction for the probability of "failure" achieved by FORTA) and the NNT to avoid one failure showed that for both sexes the goal of a decrease in the FORTA score of >1 point was reached significantly more often in the intervention than in the control group ($p < 0.0001$ for both sexes). There was no relevant sex difference for the NNT (2.8 vs. 2.7). When applied to participants with lower quality of medication at admission (exclusion of patients with a FORTA score < 2 at admission), the effect was even stronger ($p < 0.0001$), with an NNT of 2 in men and 1.8 in women.

Furthermore, for both sexes the reduction in undertreatment was significantly larger in the FORTA than the control group (male groups $p = 0.002$, female groups $p = 0.0002$). The NNTs to reduce the undertreatment score by one count were not significantly different (4.2 for men and 4.7 for women).

Moreover, reduction of overtreatment was more frequent in both intervention groups than in patients of the control groups (male groups $p = 0.006$, female groups $p = 0.013$). NNTs were 4.4 for men and 6.9 for women; the sex difference that was not significant.

A higher number of participants without ADEs relevant to geriatric patients (those listed in Table 2) were observed in the female intervention group ($p = 0.010$). One out of 6.2 women will not experience an adverse event due to the FORTA approach. This effect could not be observed in the male intervention group ($p = 0.3556$).

An increase in BI by at least 11.4 points [28] was reached more frequently in the female intervention group ($p = 0.0003$) than in the control group, while this effect

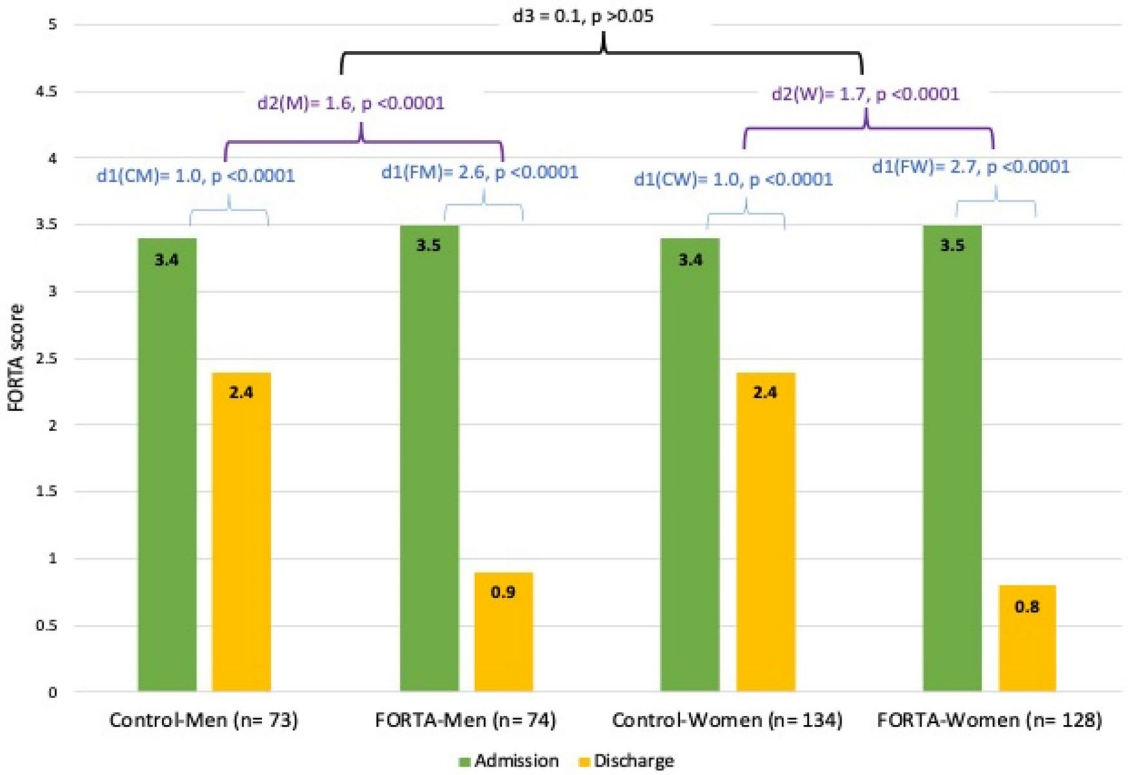


Fig. 1 Group- and sex-specific improvement of the FORTA score during hospital stay. The improvement in FORTA score between admission and discharge for the FORTA-vs. control groups in men and in women was compared. Delta 1 (d1): Decline of intragroup FORTA score between admission and discharge. Delta 2 (d2): Disparity in the intragroup decline (d1) between Control and FORTA group. Delta 3 (d3): Difference in the disparity (d2) between men and women. *CM* Control-Men, *FM* FORTA-Men, *CW* Control-Women, *FW* FORTA-Women

Table 2 Comparison of sex- and group-specific incidence of adverse drug events (ADEs) relevant to geriatric patients during hospital stay for the control and FORTA groups of both sexes as well as for the overall incidence in men and women

ADE	Control *NOE/n/%*	Men total *NOE/n/%*	FORTA *NOE/n/%*	Control *NOE/n/%*	Women total *NOE/n/%*	FORTA *NOE/n/%*
Falls	20/73/27.4	**38/147/25.85**	18/74/24.32	19/134/14.18	**42/262/16.03***	23/128/17.97
Confusion	7/69/10.14	**14/143/9.79**	7/74/9.46	15/131/11.45	**23/257/8.95**	8/126/6.35
Dizziness	10/70/14.29	**24/144/16.67**	14/74/18.92	15/131/11.45	**23/258/8.91***	8/127/6.3
Nausea	2/70/2.86	**6/144/4.17**	4/74/5.41	18/131/13.74	**29/258/11.24***	11/127/8.66
Obstipation	1/69/1.45	**4/143/2.8**	3/74/4.05	5/131/3.82	**11/258/4.26**	6/127/4.72
Diarrhea	5/70/7.14	**7/144/4.86**	2/74/2.7	2/131/1.53	**8/258/3.1**	6/127/4.72
Dyspnea	11/70/15.71	**20/144/13.89**	9/74/12.16	11/131/8.4	**16/258/6.2****	5/127/3.94
Cardiac decompensation	8/70/11.43	**12/144/8.33**	4/74/5.41	9/131/6.87	**14/258/5.43**	5/127/3.94
Angina pectoris	1/70/1.43	**4/143/2.8**	3/73/4.11	2/131/1.53	**3/257/1.17**	1/126/0.79
Renal failure	21/70/30.0	**37/144/25.69**	16/74/21.62	26/131/19.85	**40/257/15.56***	14/126/11.11°
Total ADE ***NOE/n/range/per person***	**85/69/0-4/1.23**	**165/142/0-5/1.16**	**80/73/0-5/1.1**	**121/131/0-4/0.92**	**207/255/0-4/0.82****	**96/124/0-4/0.69^**

NOE number of events, *n* total number of patients assessed, *%* incidence of ADEs in the respective group, *range* minimum to maximum number of ADEs per patient, *per person* mean number of events per patient; columns and rows that contain "Total" in their heading are in bold

*$p < 0.05$, **$p < 0.01$, °$p = 0.0534$, ^$p = 0.0775$

was only trending to significance in the male FORTA group ($p = 0.0508$, Fig. 2). The NNT was 6.4 in men and 5.1 in women ($p > 0.05$). Similar results were observed when participants with high scores at admission were excluded (NNT: men 5.6, $p = 0.0453$; women: 4.8, $p = 0.0008$).

Within the 20% margins, the FORTA intervention was statistically equivalent for the primary endpoint (improvement of FORTA score) with ($p = 0.003$) and without exclusion ($p = 0.032$), and for the over- ($p = 0.019$) and undertreatment score without exclusion ($p = 0.004$) in men and women. With the exclusion of patients without over- or undertreatments at admission, the statistical equivalence of men and women in this regard disappeared ($p = 0.082$ or $p = 0.23$).

In addition, no sex difference but equivalence on a 20% level in the "successful" improvement of BI (based on all three definitions provided in OSM 1) as a secondary clinical endpoint was recorded (Fig. 3).

The ARR for the occurrence of at least one ADE showed equivalence within the 20% margin between men and women ($p = 0.006$) (Fig. 3).

The NNTs in men and women for successful termination of overtreatment with proton pump inhibitors (men: 2.6; women: 3.1), undertreatment of osteoporosis (men: 3.2; women: 2.6), and undertreatment of ischemic heart disease (men: 1.7; women 2.8) were not significantly different, but yet showed no equivalence on a 20% level ($p > 0.05$) (Fig. 3). In the original paper [27] several other over- and undertreatments were successfully terminated by the application of the FORTA list; here, we only analyzed three of the most relevant medical errors that were present in at least 20% of the participants and, thus, appeared to be interpretable despite the smaller case numbers in the gender subgroups.

5 Discussion

No sex differences were found for medication improvement by the FORTA intervention as measured by the FORTA score. This absence of statistically significant differences was corroborated by the proof of statistical equivalence within the 20% margins.

This is the first analysis of sex differences for the clinical effects of a listing approach that is focused on older patients (patient-in-focus listing approach, PILA) [22]. The use of PIMs is associated with a decline in functional aspects and worse outcomes regarding activities of daily living (ADLs) [30, 31]. It was shown that the equivalent improvement of the FORTA score in both sexes is accompanied by an equivalent improvement of the BI. Specifically, a similar number of men and women were able to improve their ADLs by 11.4 points, the MCID for this particular assessment [28], as a result of the FORTA intervention. As the MCID is defined as the smallest improvement of a (functional) scoring system that has a positive impact on a patient's life quality [28, 32], the FORTA approach offers the potential not just to "embellish" one's medication plan at an academic level for the purpose of drug optimization based on a specific listing approach, but also to improve the clinical outcomes. This impact immediately affects patients` quality of daily life; here we demonstrate for the first time that men and women

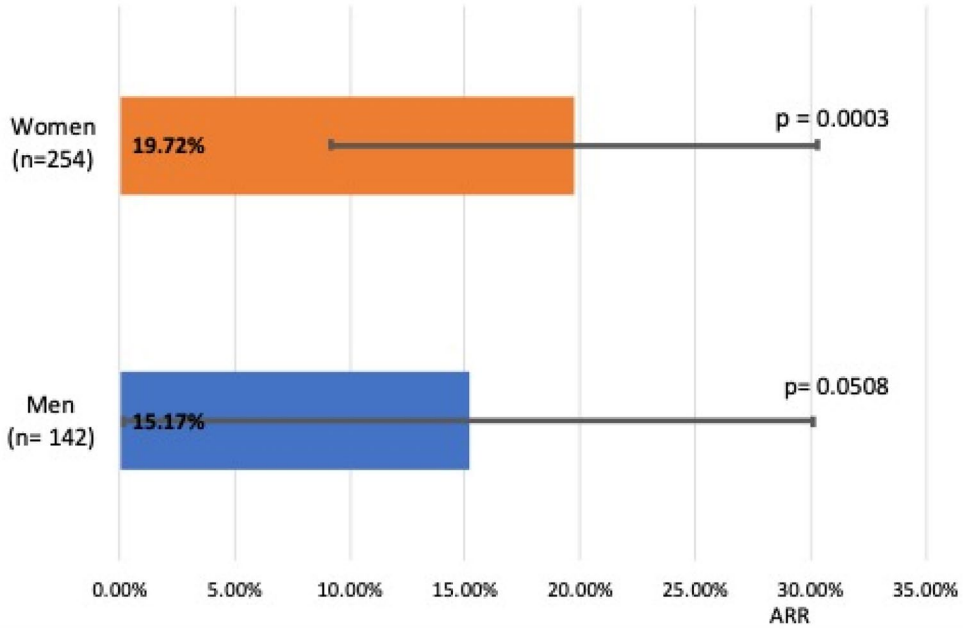
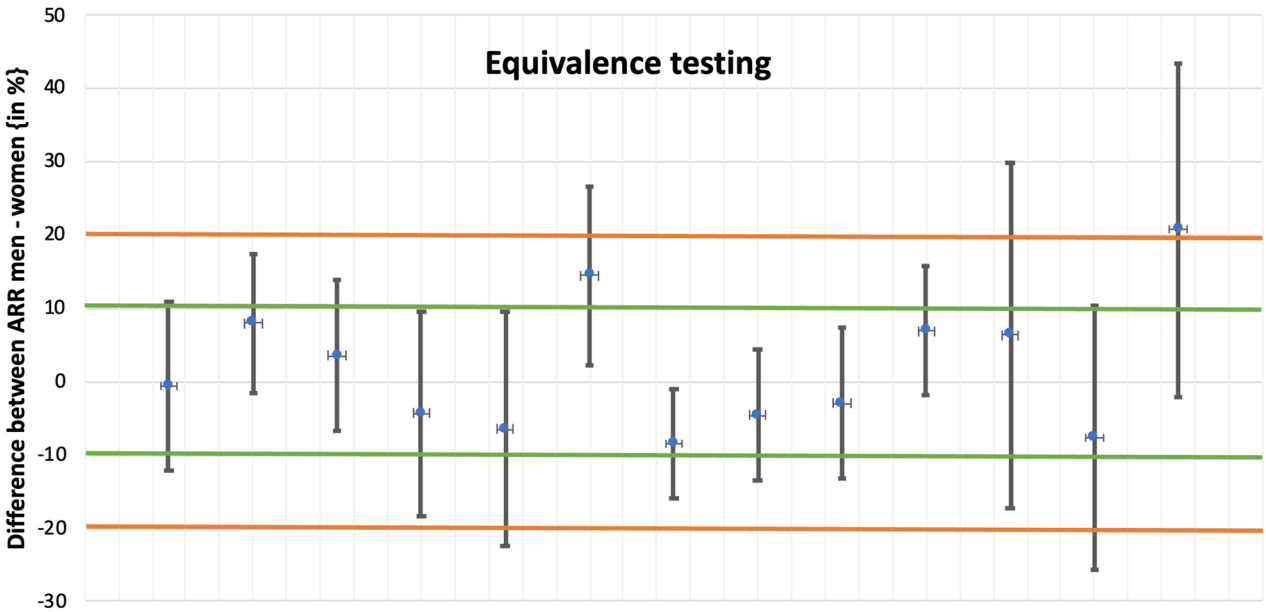


Fig. 2 Absolute risk reduction of "failure" for the improvement in the Barthel index. The figure shows the absolute risk reduction (ARR) of the intervention groups to receive "failure" compared with the control groups. "Success": increase of at least 11.4 points between admission and discharge as this marks the Minimal Clinical Important Difference (MCID) [28]. "Failure": increase by less than 11.4 points, no change or decrease in the Barthel index. 95% confidence intervals are plotted: men 0.22–30.12 (NNT 6.4), women 9.17–30.28 (NNT 5.1). *NNT* number needed to treat



	FORTA score w/o exclusion	Overtreatment score w/o exclusion	Undertreatment score w/o exclusion	FORTA score with exclusion	Overtreatment score with exclusion	Undertreatment score with exclusion	Adverse events	Barthel index score w/o exclusion	Barthel index score with exclusion	Barthel index score with different success criteria	Overtherapy with PPI	Undertherapy of Osteoporosis	Undertherapy of Ischemic heart disease
ARR Women	36.63%	14.54%	21.48%	55.37%	45.39%	22.04%	16.12%	19.72%	20.74%	11.52%	32.35%	38.95%	36.29%
ARR Men	36.09%	22.53%	25.04%	51.06%	38.94%	36.54%	7.61%	15.17%	17.83%	18.40%	38.67%	31.29%	57.05%
p_10	0.089	0.364	0.15	0.251	0.358	0.727	0.371	0.161	0.127	0.28	0.399	0.415	0.781
p_20	**0.003**	**0.019**	**0.004**	**0.032**	0.082	0.23	**0.006**	**0.003**	**0.003**	**0.007**	0.17	0.13	0.522

Fig. 3 Test for equivalence of the impact by FORTA on clinical measures in men and women. The sex differences for the ARR by the FORTA approach was tested. Negative values stand for higher ARRs in women than men. We tested the equivalence for two different margins: ± 10% (green lines) and ± 20% (orange lines). If the 90% confidence interval of differences (depicted as black vertical bars) is within a margin, equivalence on this level can be assumed [29]. The related *p* values are depicted as well. *ARR* absolute risk reduction

participate in the clinical benefits to the same extent. The ARR resulting from the FORTA intervention was higher in women, most likely due to a lower success rate in the women's control group (16.3% vs. 23.2% in the male control group, not significant), whereas the success rate in both intervention groups was fairly similar (FORTA women: 36% vs. FORTA men: 38.4%, not significant). This might be an indicator that women may suffer more from the presence of PIMs in terms of decline in ADLs than men do. In addition, the FORTA intervention also eliminated potentially omitted drugs (POMs), as shown, for example, in the case of osteoporosis treatment. Adequate treatment of osteoporosis may prevent about 50% of hip fractures—especially in women—which are known to have a risk for functional decline [33].

In the D-PRESCRIBE-trial, Martin et al. [34] found no differences between older men and women in the absolute discontinuation rates of PIMs based on Beer's criteria by a pharmacist-led intervention; unlike VALFORTA, clinical endpoints were not analyzed in this trial.

A recent Finnish study analyzed sex differences for the improvement of geriatric assessments by an interprofessional intervention in nursing home residents. The Database of Medication for the Elderly (Meds75+ [35]) was applied in this multifactorial trial as one of the undiscernible contributors of the intervention; only weak or inconsistent effects could be detected [36].

Notably, in the VALFORTA trial female patients were less often affected by ADEs than men. This finding is

contrary to the frequently stated observation that (older) women are more vulnerable to adverse drug reactions than men [7, 12–20]. Several explanations for this sex difference have been discussed. Firstly, women are more likely to report on subjective symptoms associated with (newly prescribed) drugs than men [20, 37, 38]. In the VALFORTA trial, ADEs were detected by more objective methods like chart review and explicit questioning, which is proven to document more events than spontaneous reporting [14]. Secondly, the ADEs registered in the VALFORTA trial did not include all events that are known to appear more frequently in females such as cough with ACE inhibitors [20, 39]. The registered incidents could better be described as "adverse drug events" than "adverse drug reactions" because they have not been proven to be a consequence of the use of a drug [14]. In addition, being female and/or taking multiple medications is known to be a risk factor for the prescription of PIMs [12, 40, 41] . Some authors state female sex as a risk factor for polypharmacy [7, 42], others found no difference between men and women in this regard [2, 3]. The prescription of PIMs as well as polypharmacy are risk factors for the development of ADEs [7, 14, 15, 17, 18, 43–45]. For inclusion in the VALFORTA-trial, exposure to at least three long-term medications and at least three clinically relevant diagnoses were necessary. Hence, 87.5% of the study participants took at least five medications at hospital admission with a mean number of 8.16 in women and 8.78 in men (no significant difference), so polypharmacy was a widespread phenomenon with all of them, not just in females. Furthermore, the FORTA score at admission as well as at discharge (which includes the overtreatment with drugs that should be avoided (i.e., PIMs) in the elderly) did not differ between the sexes. Thus, a common reason for increased rates of ADEs in women was absent in the VALFORTA trial, and arguments to explain the lower incidence of ADEs in women in VALFORTA remain speculative and unproven.

Apart from sex differences in ADEs, we were able to show that equal improvement of medication quality by FORTA is associated with the occurrence of fewer ADEs in women. In line with this, O'Connor et al. [46] found a significantly greater reduction of in-hospital ADEs in the intervention group (ARR 9.3%, NNT 11), which was supported by a trained physician optimizing individual prescriptions according to the START/STOPP-criteria; however, the proportion of women was significantly higher in the intervention group (63.9% vs. 49.7% in the control group, $p < 0.0001$). Both groups were balanced in terms of comorbidities. From these findings the authors concluded that sex had no influence on the occurrence of ADEs or on incidence rates of medication errors [46]. Nevertheless, the reduction of ADEs by the intervention has not been analyzed sex specifically. In line with these results, a 12-year population-based retrospective cohort study of 64,446 patients [47] showed that comorbidities, chronic diseases, and severity of illness, but not higher age and female sex, may affect the likelihood of ADEs. As the ADEs recorded in our study have the potential to cause subsequent symptoms that might impair the recovery or even lead to functional decline, their prevention through medication optimization should be regarded as a major goal in acute geriatric care, the achievement of which may be supported by the FORTA approach.

As reported in Table 1, significant sex heterogeneities in baseline parameters were found; for example, patients in the FORTA groups were older than control groups or women had a lower BMI. All significant differences, however, should have weakened rather than enhanced the significance of findings. As an example, the higher age in women should have worsened the occurrence of ADEs in female patients as compared to male patients.

Based on the findings in our study, we can highly recommend the application of the FORTA principle at least once during acute hospitalization of geriatric patients. As an easy-to-apply tool, FORTA can assist physicians to reduce medical errors (PIMs as well as POMs), support gain of function in older patients, and prevent the occurrence of ADEs in this vulnerable population. With a NNT of less than 10 (in all proven effects in both sexes), the implementation of FORTA should make a noticeable improvement in health status and might especially in women become a tool for use toward improved self-rated health quality.

5.1 Limitations

Although preplanned, the sex-specific analysis of the VALFORTA study resulted in sub-groups being too small for comparison of less common circumstances, such as comparisons of drug groups or individual FORTA labels.

In line with this limitation of subgroup sizes, some differences (or strong similarities) between men and women did not reach significance (or equivalence) due to wide standard deviations.

Since patients admitted to acute geriatric wards have a higher prevalence of frailty (about 40% [48, 49]) as compared to others in their age group, the results of this study might not be transferable to all people aged 65 years and over.

Whereas some ADEs can be judged objectively (e.g., falls or renal insufficiency), others are subjective complaints (e.g., dizziness or dyspnea) and therefore difficult to quantify or verify.

Furthermore, the short observation period does not allow for detection of long-term effects of the improvement of medication according to FORTA principle. As medication errors may only become evident through events like falls, pathological fractures, or cardiovascular events [50], the overall impact of FORTA in an individual patient cannot be

assessed by this short study. Further research is needed to determine whether sex differences may affect the impact of a FORTA-based medication improvement on quality of life or self-reported health.

The fact that we proved equivalence even for preventing ADEs points to the limits of the statistical analysis: unlike women, men in the FORTA group showed an insignificant ARR for the occurrence of at least one event. Moreover, statistically significant differences could have been missed by the application of a comparably wide equivalence margin.

5.2 Conclusion

Our study revealed that the two sexes benefit equally from the FORTA intervention regarding the amelioration of medication quality as well as several clinical outcomes including BI. In addition, the positive impact of the FORTA intervention on the rate of ADEs appears to be stronger in women.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-022-00292-9.

Declarations

Funding DFG-German Research Foundation (WE 1184/15-1).

Ethics approval The study was approved by the ethics committees at the Medical Faculty Mannheim, Heidelberg University, and at the University of Witten-Herdecke.

Data sharing The data can only be provided to other researchers upon submission of a written request and evaluation by our study group.

Conflict of interest MW was employed by AstraZeneca R&D, Mölndal, as director of discovery medicine (translational medicine) from 2003 to 2006, while on sabbatical leave from his professorship at the University of Heidelberg. Since returning to this position in January 2007, he has received lecturing and consulting fees from Bristol Myers, Bayer, Boehringer-Ingelheim, LEO, Mundipharma, Novartis, Pfizer, Polyphor, Helsinn, Allergan, Allecra, Novo-Nordisk, Heel, AstraZeneca, Roche, Santhera, Sanofi-Aventis, Shire, Berlin-Chemie und Daichii-Sankyo. HF received a grant from Paul-Kurth-Stiftung. HB, CW, AKS, and FP declare that they have no conflicts of interest.

Consent to participate Written consent for participation by patients or their proxies was provided [27].

Consent for publication Consent for publication was provided by AKS, CW, HB, HF, MW, and FP.

Availability of data and material Please see our data-sharing policies above.

Code availability Not applicable.

Author contributions Original study conduct: MW, FP, HF, HB, CW. Design and ideas: MW, FP, AKS. Data analysis: CW, MW, FP, AKS.

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