

**OBJECTIVE**

Approximately 258 Mio DDDs of digitalis glycosides (DGs) are prescribed annually in Germany, mainly digitoxin, followed by  $\beta$ -acetyldigoxin [1]. DGs are well-known for their narrow therapeutic range. Their value in the treatment of heart failure is limited and sex differences in terms of outcome have been reported, where women seem to benefit less than men [2]. Further analyses emphasised importance of digoxin level for clinical outcome in women and men [3,4]. We analysed data from adverse drug reactions (ADRs) associated with DGs resulting in hospitalisation in the German Pharmacovigilance Centers (PVCs) with respect to age, sex, DG-dose, weight-related DG-dose and DG-serum concentrations.

**METHODS**

In 4 German PVCs (situated in Rostock, Greifswald, Jena, Weimar) all non-elective hospital admissions to medical wards are screened prospectively for ADRs since 1999 [5]. Data from 2000 to 2004 focusing digitalis related ADRs are presented here.

- All non-elective admissions to medical wards were screened prospectively using predefined trigger symptoms to detect ADRs as a cause for hospitalisation (e.g. syncope, thrombosis). Patients undergoing cancer chemotherapy were excluded as well as patients with serious cutaneous reactions.
- Suspected ADRs were entered into a relational database (ACCESS 95): demographic data, diagnoses, risk factors, medication, important diagnostic procedures and laboratory values, description of ADRs, their course and outcome.
- Coding of ADRs and medication according to WHO-ART and ATC, standardized causality assessment according to Bégaud Imputability Score [6], quality assurance and plausibility check of ADRs according to Good Pharmacovigilance Practice.
- For incidence calculation (from 2000-2002 for PVCs Rostock and Weimar), the residential postal codes of the patients admitted to the hospitals were checked and the source population was defined as the medication users living in these postal code areas that contributed to the first 75 % (cumulative) of all admissions. Drug dispensing data were obtained from regional pharmacy computing centers. A medication user (exposed person) was defined [5] as one with at least one prescription of a certain drug within 3 months, in case of multiple prescriptions only one was counted per quarter and patient, consequently results are given as incidence per 1000 quarter expositions.
- Statistics: 2-sided t-test, Mann-Whitney-U-test and chi square test (SPSS 13.0)

**RESULTS**

Between 01/2000 and 12/2004 314 patients (244 women, 77.7%) were admitted due to an at least probably digitalis related ADRs (10.2 % of all patients with ADR). Per 1,000 patients exposed to DGs the ADR-incidence (95% CI) was calculated to 1.9 (1.6;2.2) ADRs per quarter for at least possibly digitalis related ADRs. Patients with digitalis ADR were significantly older than patients with other ADRs ( $p < 0.001$ ). Female digitalis ADR patients had a significant lower body weight than their male pendants ( $p < 0.001$ ).

Table 1: Number and age of all ADR patients and patients with digitalis-related ADR (\*\* $p < 0.001$ ).

	Women (W)	Men (M)	total
All ADR-patients [n (%)]	1,888 (61.1%)	1,204 (38.9%)	3092
Age [a]	72.3 ± 15.2	64.9 ± 15.5	69.4 ± 15.7
Digitalis ADR patients [n (%)]	244 (77.7%)	70 (22.3%)	314
Age [a]	82.0 ± 6.9	75.3 ± 9.5	80.5 ± 8.1
bodyweight [kg]	62.1 ± 13.4**	75.9 ± 13.2	65.6 ± 14.7

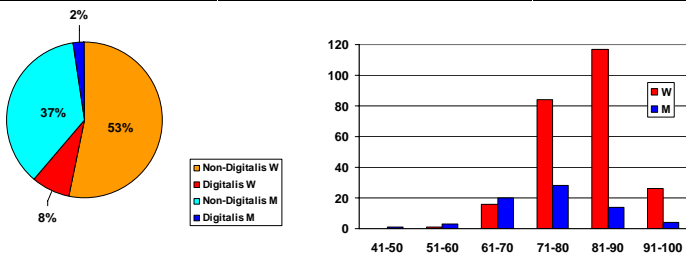


Figure 1: left panel: Proportion of ADRs associated and not associated with DGs between men (M) and women (W) right panel: Sex-specific age-cohorts of digitalis-related ADR patients

There were no significant sex-specific differences in indications for digitalis based therapy.

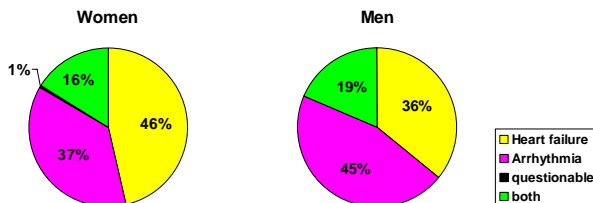


Figure 2: Indications for Digitalis-based therapy for women and men

Proportionally, men suffered more often from cardiac arrhythmia and women more frequently from gastrointestinal disorders (n.s.).

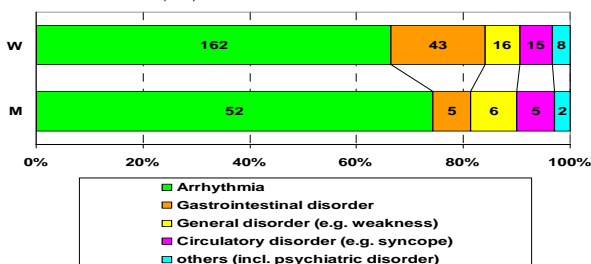


Figure 3: Leading symptom of digitalis related ADRs for women and men

50 of 244 women (20.5%) and 17 of 70 men (24.3%) were admitted to an intensive care unit. Probability for lethal outcome due to digitalis therapy was non-significantly increased in female patients (2.0% vs. 1.4%). In women, more ADRs were preventable in 110 out of 244 cases (45.1%) but only 23 of 70 cases (32.9%) in men ( $p = 0.068$ ). DGs alone were suspected to cause ADR in 197 (62.7%) of all cases, whereas in 117 cases (92 women) at least one co-medication was suspected, predominantly beta-blockers (61.2%) and verapamil (18.6%). There were no significant sex-specific differences (figure 4).

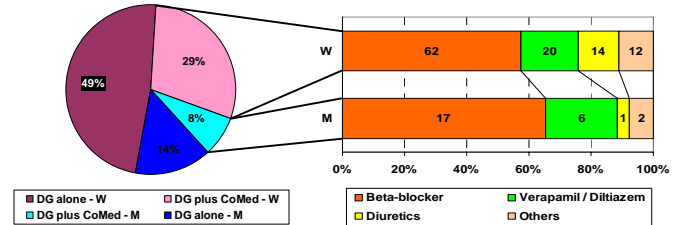


Figure 4: left panel: Sex-specific proportion of ADRs associated with DG alone or with DG plus interacting co-medication right panel: Sex-specific proportion of ADR suspected co-medication

In 296 cases (228 women; 68 men) oral digitoxin was involved. 103 women but only 17 men (64.4% of 160 women vs. 29.3% of 58 men with documented body weight) received more than the recommended dose of 1  $\mu$ g digitoxin/kg body weight [7].

Table 2: Digitoxin doses (absolute and weight-related) and digitoxin serum levels

	Women	Men	p-value
Daily dose [mg/d] (n=296)	0.068 ± 0.010	0.070 ± 0.012	0.232
Daily weight-related dose [ $\mu$ g/(kg bodyweight per day) (n=218)	1.14 ± 0.27	0.96 ± 0.26	<0.001
Digitoxin serum level [ng/ml] (n=269)	35.7 ± 16.3	30.1 ± 12.2	0.018

Elevated digitoxin levels (> 25 ng/ml [8]) were detected in 156 women but in only 40 men (75.4% of female vs. 64.5% of male patients with measured digitoxin levels).

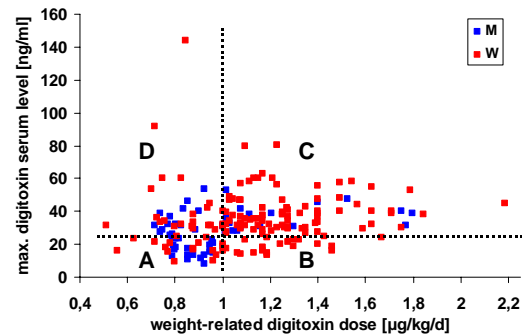


Figure 5: Sex-specific relationship between weight-related daily digitoxin dose and maximal serum digitoxin level

Regarding grouped weight-related daily digitoxin dose and digitoxin serum level, proportion of male and female patients differed significantly from expected values (table 3).

Table 3: Sex-specific comparison of body weight related daily digitoxin dose and maximal digitoxin serum level (NC: not calculated)

	All	Women	Men	p-value
Patients with documented body weight and determined digitoxin serum level	196	143	53	NC
A: Dose and serum level o.k	37 (18.9%)	18 (12.6%)	19 (35.8%)	0.003
B: Dose too high, serum level o.k.	21 (10.7%)	21 (14.7%)	0	NC
C: Dose and serum level too high	99 (50.5%)	82 (57.3%)	17 (32.1%)	0.027
D: Dose o.k., but serum level too high	39 (19.9%)	22 (15.4%)	17 (32.1%)	0.02

**CONCLUSION**

More women than men have been admitted to hospital due to DG-related ADRs, of which most were associated with digitoxin. Prescription data from Germany suggest, that more men than women receive DGs [9]. As our data suggest, the most likely reason for the female predominance in DG-related ADRs is the neglect of body weight when prescribing DGs. Taking into account the importance of the DG dose for clinical outcome [3,4], women are probably overdosed in many cases even without clinical manifestation of ADRs.

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