Studies in the Geriatric population

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Drug use across all age groups in Germany

➢➢ 65-years old persons receive 4-5 different drugs/day
➢➢ 50 % of all octogenarians receive ≥ 5 different drugs/day
Representation of elderly patients in oncology trials submitted to the FDA

55 trials with drugs approved between 1995 and 2002

Mean age of diagnosis in Germany: 72 years

Talarico et al, J Clin Oncol 2004
Heart failure trials and age of patients enrolled

Median age of trial participants versus median age in the Würzburg Heart Failure Registry
Demographic Development and issues for consideration for drug development

- Altered pharmacokinetics and -dynamics
- Multimorbidity
- Polypharmacy
- Interactions
- Adverse drug reactions
- Benefit/Risk-Ratio?
Definition of age groups

- **newborns** (birth to 3 months)
- **infants** (3 months to 2 yrs)
- **children** (2 to 12 yrs)
- **adolescents** (12 to 18 years)

**ADULTS**

- **elderly** (> 65 yrs)
### Definition of age groups

- **newborns** (birth to 3 months)
- **infants** (3 months to 2 yrs)
- **children** (2 to 12 yrs)
- **adolescents** (12 to 18 years)

<table>
<thead>
<tr>
<th>ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>elderly</strong> (&gt; 65 yrs)</td>
</tr>
<tr>
<td><strong>old</strong> (75 yrs &lt; 85 yrs)</td>
</tr>
<tr>
<td><strong>very old</strong> (85 yrs to 100)</td>
</tr>
<tr>
<td><strong>centenarians</strong> (100 yrs and above)</td>
</tr>
</tbody>
</table>
Definitions of age and functional decline

- Calendar age – socio-psycho-biological age
- Biological age – „Frailty“
  - reduced reserve, impaired homeostatic function, reduced stress-resistance based on
  - decline of physiological functions such as
    - Muscle mass (sarcopenia), neuroendocrine function, immune system
  - resulting in an increased vulnerability to adverse events (Rockwood, Age Aging 2005)
- Functional parameters and tests:
  - Charlson Index, Cumulative Illness Rating Scale, Functional Comorbidity Index (Fortin et al, 2005)
  - Handgrip Test, Timed up and go-Test, Tinetti Test, MMSE, …
Some biomarkers of aging

Rosenberg, J Nutr 1997

Koster et al, JAGS 2010
Development of body composition

Minerals 2.0% 3.2% 3.0% 4.2% 4.3% 5.5% 4.0%
Fat 6.0% 13.4% 22.4% 13.7% 13.0% 18.0% 30.0%
Protein 12.0% 13.4% 13.4% 17.3% 18.1% 16.5% 12.0%
Water 80.0% 70.0% 61.2% 64.8% 64.6% 60.0% 54.0%

Premature (2 kg) Full term (3.5 kg) 1 yr (10 kg) 10 yr (31 kg) 15 yr (60 kg) Adult (70 kg) Elder (65 kg)
Kreatinin-Clearance and age: a rough estimate

\[ \text{Cl} = (140 - \text{age}) \times \text{body weight (kg)} \text{ men} \]
\[ \text{Cl} = (140 - \text{age}) \times \text{body weight (kg)} \times 0.72 \text{ serum creatinine} \text{ men} \]
\[ \text{Cl} = (140 - \text{age}) \times \text{body weight (kg)} \times 0.85 \text{ serum Creatinine} \text{ women} \]
Database for physiologically-based pharmacokinetic modeling

Age-associated changes relevant for PK:

- Body weight and composition
- Renal function, metabolism (CYP and transporter function)
- Tissue blood flow, tissue weight
- Heart and lung function
- Frequent comorbidities

Database for physiologically-based pharmacokinetic modeling
Population analysis of atorvastatin clearance in patients living in the community and in nursing homes

### Table 1 Patient data

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Nursing home</td>
<td>Community dwelling</td>
<td>Total</td>
</tr>
<tr>
<td>n</td>
<td>64</td>
<td>6</td>
<td>58</td>
<td>79</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>64.6 ± 12.1, 36–97</td>
<td>83.2 ± 8.95, 74–97</td>
<td>62.7 ± 10.7, 36–92</td>
<td>69.3 ± 13.0, 43–93</td>
</tr>
<tr>
<td>Range</td>
<td>90.0 ± 24.9, 52.5–194.5</td>
<td>75.9 ± 14.1, 52.4–94.8</td>
<td>91.5 ± 25.4, 61–194.5</td>
<td>83.1 ± 26.3, 47.6–168.9</td>
</tr>
<tr>
<td><strong>Total body weight (kg)</strong></td>
<td>62.6 ± 7.21, 43.5–82.3</td>
<td>57.3 ± 7.93, 43.5–67.9</td>
<td>63.1 ± 6.98, 49–82.3</td>
<td>46.2 ± 7.37, 18.6–67.1</td>
</tr>
<tr>
<td><strong>Comedications (n)</strong></td>
<td>142 ± 28, 137 ± 24</td>
<td>142 ± 28</td>
<td>142 ± 28</td>
<td>160 ± 28</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/dl)</strong></td>
<td>76 ± 24</td>
<td>66 ± 11</td>
<td>72 ± 23</td>
<td>80 ± 25</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mg/dl)</strong></td>
<td>142 ± 28</td>
<td>137 ± 24</td>
<td>142 ± 28</td>
<td>160 ± 28</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

LDL, low-density lipoprotein.

*P = 0.063, for dose in men vs. women, unpaired t-test; **P < 0.002 for living-site effect, analysis of variance; no sex × living-site interaction.
Population analysis of atorvastatin clearance in patients living in the community and in nursing homes

a. Men by dosing time

b. Women by dosing time

c. INH vs. non-INH

Schwartz & Verotta, CPT 2009
## Decline of cognitive functions associated with anticholinergic drugs over 4 years (3 Cities Study)

<table>
<thead>
<tr>
<th>Test</th>
<th>Women odds ratio</th>
<th>Men odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isaac Set Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>verbal fluency</td>
<td>1.49 (1.00-2.22)</td>
<td>0.63 (0.30-1.34)</td>
</tr>
<tr>
<td></td>
<td>1.53 (1.13-2.05)*</td>
<td>1.48 (0.87-2.51)</td>
</tr>
<tr>
<td><strong>Benton Visual Retention Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>verbal memory</td>
<td>0.90 (0.60-1.35)</td>
<td>1.18 (0.59-2.37)</td>
</tr>
<tr>
<td></td>
<td>1.27 (0.95-1.71)</td>
<td>2.07 (1.24-3.45)*</td>
</tr>
<tr>
<td><strong>Trail Making Test A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>0.81 (0.47-1.41)</td>
<td>0.49 (0.17-1.44)</td>
</tr>
<tr>
<td></td>
<td>1.14 (0.79-1.64)</td>
<td>1.12 (0.58-2.17)</td>
</tr>
<tr>
<td><strong>Trail Making Test B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor executive function</td>
<td>1.06 (0.65-1.73)</td>
<td>0.97 (0.39-2.44)</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.64-1.34)</td>
<td>2.23 (1.23-4.03)*</td>
</tr>
<tr>
<td><strong>Minimental State Examination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cognitive function</td>
<td>1.07 (0.71-1.62)</td>
<td>1.34 (0.67-2.66)</td>
</tr>
<tr>
<td></td>
<td>1.48 (1.10-1.97)*</td>
<td>1.41 (0.84-2.36)</td>
</tr>
</tbody>
</table>

Carriere et al, Arch Intern Med 2009
**Figure 3**

Tissue concentrations of antimuscarinic agents following subcutaneous administration in rats. Mean concentrations of compounds in plasma, brain and CSF determined following subcutaneous dosing to three animals are shown, where error bars represent SDs. Unbound fractions in plasma ($f_{unp}$) and brain ($f_{unb}$) are shown underneath each compound: plasma (ng mL$^{-1}$) [ ]; brain (ng g$^{-1}$) [ ]; CSF (ng mL$^{-1}$) [ ].
### CNS penetration potential of overactive bladder agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Predicted CNS penetration</th>
<th>P-gp substrate</th>
<th>CNS penetration in rats in vivo</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trospium</td>
<td>Not significant</td>
<td>Yes</td>
<td>Not significant</td>
<td>NR</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Significant</td>
<td>Yes</td>
<td>Not significant</td>
<td>NR</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>Significant</td>
<td>Yes</td>
<td>Not significant</td>
<td>~ 2 % dizziness</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Significant</td>
<td>No</td>
<td>Significant</td>
<td>~ 2 % dizziness</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Significant</td>
<td>No</td>
<td>Significant</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>significant</td>
<td>No</td>
<td>Significant</td>
<td>somnolence</td>
</tr>
</tbody>
</table>

Callegari et al, BJCP 2011
Die Anwendung von Efient bei Patienten ≥ 75 Jahre wird im Allgemeinen nicht empfohlen und sollte nur mit Vorsicht nach einer sorgfältigen, individuellen Nutzen-Risiko Abwägung durch den verschreibenden Arzt erfolgen, wenn der Nutzen im Hinblick auf die Prävention von ischämischen Ereignissen das Risiko für schwerwiegende Blutungen überwiegen kann. In der klinischen

\[ P_{\text{int}} = 0.36 \]

\[ -13 \]
Thrombolysis with alteplase in acute stroke
Thrombolysis with alteplase in acute stroke

Actilyse®

Anwendung bei älteren Patienten
Actilyse ist nicht angezeigt zur Therapie des akuten Schlaganfalls bei Erwachsenen, die älter als 80 Jahre sind.
In clinical trials submitted to the EMA/FDA patients > 80 years were excluded!

Very old patients have a poorer prognosis than younger old patients.
### Benefit of thrombolysis in octogenarians

<table>
<thead>
<tr>
<th>Age group</th>
<th>Treated</th>
<th>Control</th>
<th>Odds ratio (95% CI)</th>
<th>Cochran-Mantel-Haenszel P value</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>170</td>
<td>12</td>
<td>0.88</td>
<td>0.86 (0.29 to 2.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>31-40</td>
<td>632</td>
<td>104</td>
<td>1.5</td>
<td>1.5 (1.0 to 2.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>41-50</td>
<td>1642</td>
<td>358</td>
<td>1.5</td>
<td>1.5 (1.2 to 1.8)</td>
<td>1.5</td>
</tr>
<tr>
<td>51-60</td>
<td>3658</td>
<td>830</td>
<td>1.6</td>
<td>1.6 (1.4 to 1.8)</td>
<td>1.6</td>
</tr>
<tr>
<td>61-70</td>
<td>6193</td>
<td>1422</td>
<td>1.5</td>
<td>1.5 (1.4 to 1.7)</td>
<td>1.5</td>
</tr>
<tr>
<td>71-80</td>
<td>8527</td>
<td>2203</td>
<td>1.5</td>
<td>1.5 (1.5 to 1.8)</td>
<td>1.5</td>
</tr>
<tr>
<td>81-90</td>
<td>2069</td>
<td>1158</td>
<td>1.5</td>
<td>1.5 (1.3 to 1.7)</td>
<td>1.5</td>
</tr>
<tr>
<td>91-100</td>
<td>133</td>
<td>77</td>
<td>0.73</td>
<td>1.2 (0.69 to 2.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>≤80</td>
<td>20 860</td>
<td>4929</td>
<td>&lt;0.001</td>
<td>1.6 (1.5 to 1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;80</td>
<td>2202</td>
<td>1237</td>
<td>&lt;0.001</td>
<td>1.4 (1.3 to 1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All age groups</td>
<td>23 062</td>
<td>6166</td>
<td>&lt;0.001</td>
<td>1.6 (1.5 to 1.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**SITS-ISTR (Registry) versus Placebo-treated controls from thrombolysis studies (VISTA)**

Mishra et al, BMJ 2010
Current Guidance/Guidelines for the Geriatric population

Patients entering clinical trials should be reasonably representative

- Geriatric: age 65 and older
- 75 y. and above to the extent possible
- in Phase 2/3 approx. 100 geriatrics
- PK related to renal function
- formal PK studies in elderlies not mandatory, sparse sampling from phase 2/3 trials
- PD: focussing on CNS (side) effects
Adequacy of guidance on the elderly regarding medicinal products for human use

• Age cut offs and definition of frailty should be defined by the European Union of Geriatric Medicine Society (EUGMS)

• Reviews how current guidelines (CHMP, EWP etc.) address ICH E 7
  - Some of them need improvement, e.g. urinary incontinence in women

• Analyses of 10 recently approved drugs (CHMP assessment reports)
How was ICH E 7 addressed in the assessment report of duloxetine?

4.2.1 Cymbalta

<table>
<thead>
<tr>
<th>Product (INN)/year of start of the procedure</th>
<th>Cymbalta (duloxetine)/2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Major depression</td>
</tr>
</tbody>
</table>

**TOTAL EXPOSURE**

<table>
<thead>
<tr>
<th>Total number of patients exposed for efficacy</th>
<th>1310</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients exposed for safety (primary indication)</td>
<td>2774</td>
</tr>
</tbody>
</table>

| Number of patients exposed 12 months or longer | 445 |
| Mean age of participants                      | 43.6 |

**GERIATRICS EXPOSURE**

<table>
<thead>
<tr>
<th>Total exposed elderly patients</th>
<th>143 for efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>261 for safety</td>
</tr>
<tr>
<td>Number of specific trials in the elderly (type)</td>
<td>2 (E, PK)</td>
</tr>
<tr>
<td>% efficacy exposure</td>
<td>10.9</td>
</tr>
<tr>
<td>% safety exposure</td>
<td>9.4</td>
</tr>
</tbody>
</table>

One additional study in the elderly was requested: phase III with 206 elderlies, only 64 were > 75 years.
Current Guidance/Guidelines for the Geriatric population

Final Concept Paper
E7(R1): Studies in Support of Special Populations: Geriatrics
(Revision of the ICH E7 Guideline)
23 October 2008
Endorsed by the Steering Committee on 24 September 2008*

- N = 100 no longer sufficient
- > 65 years, but also very elderly
- Other endpoints (QoL, function) rather than living longer
- Access to trials (!)
- Frailty
- Adapted dosages and formulations
- PopKin or formal PK-studies
- In some indications, e.g. Parkinson, strata > 75 and > 85
- Adequate characterisation of safety in very elderly!!
- Development plan
- Specific elements in trials to consider comorbidities/comedication
Current Guidance/Guidelines for the Geriatric population

Guidance for Industry
E7 Studies in Support of Special Populations: Geriatrics
Questions and Answers

CDER, FDA February 2012

- Every effort should be made to include geriatric patients in clinical trials …
- … enrollment of these patients could be challenging …
- … insufficient, a specific plan to collect data postmarketing should be presented
- Age-related efficacy endpoints and adverse effects, e.g. cognition, falls, urinary retention …should be actively thought in the geriatric population
EMA geriatric medicines strategy

17 February 2011
EMA/CHMP/137793/2011

• Identification of current gaps in guidelines and knowledge
• Updating current regulatory guidelines
• Specific pharmacovigilance activities (e.g. ENCePP project ADR related hospitalisations in the geriatric population in Europe chaired by Ulf Bergman)
• Provide advice to applicants in this regard
• Fostering and using an expert pool
• Template of the assessment report will include a new section for geriatric population
• CHMP Advisory group on geriatrics now established
The **Geriatric Expert Group** (GEG) provides scientific advice to the **Committee for Medicinal Products for Human Use** (CHMP) and the European Medicines Agency secretariat on issues related to the elderly. Its work includes:

- giving input related to geriatrics on guidelines under consultation;
- giving advice on geriatric aspects of the development, assessment or safety monitoring of medicines;
- taking part in meetings where expertise on geriatrics is needed;
- contributing to the geriatric implementation plan.

[Link to EMA website](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000249.jsp&mid=WC0b01ac058004cbb9&jsenabled=true)
Barriers to include elderly patients in clinical drug trials

- In/exclusion criteria
- Old Age
- Comorbidities, comedication
- Life expectancy
- Difficulties of communication
- Explanation of informed consent / involving family and caregivers
- study-associated office/hospital visits (mobility)
- Ethical aspects in dementia
European Medicines Agency workshop on medicines for older people

• **Date:** 22/03/2012 - 23/03/2012

• **Location:** European Medicines Agency, London, UK

• The European Medicines Agency is hosting a two-day workshop on medicines for older people. Although speakers will be by invitation and capacity will be limited, the Agency is inviting interested experts and stakeholders to send an expression of interest to attend this workshop by 9 December 2011 to geriatricsworkshop@ema.europa.eu.
Thank you!