THE INCLUSION OF OLDER PEOPLE IN PRE-AUTHORISATION TRIALS

An evaluation of 12 recently authorised medicines

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Patient care
Education
Research

Introduction

- Since 1980s discussion about limited inclusion of older people in clinical trials
  - Upper age limits
  - Eligibility criteria
→ Generalisability of trial efficacy and safety findings towards older population questionable

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ICH E7 guideline (1994)

- In order to improve the inclusion in phase II and phase III trials

- Minimum number of older participants required:
  → Diseases specifically associated with ageing:
    ≥ 50% of the trial participants should be 65+
  → Diseases not unique to, but present in old age:
    ≥ 100 participants 65+
- Numbers and proportions representative for target population
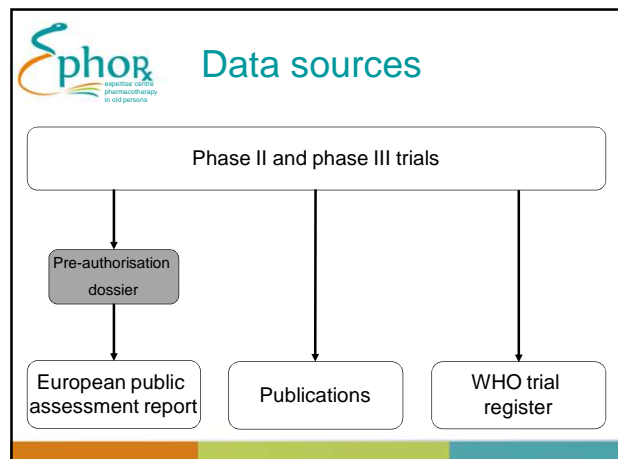

Study aim

To evaluate the number and proportion of older subjects in trials of recently authorised medicines and evaluate the adherence to the ICH E7 guideline

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Methods
Inclusion of medicines

- Diseases characteristically associated with ageing
  - Prevention of venous thromboembolism (VTE) after elective hip or knee replacement surgery
  - Osteoporosis
  - Atrial fibrillation
- Diseases not unique to, but present in old age
  - Type II diabetes mellitus (DM2)
  - Major depression
  - Bipolar disorder
  - Epilepsy
- First time European market approval between January 2008 and January 2011

Data sources

Phase II and phase III trials

Pre-authorisation dossier

European public assessment report

Publications

WHO trial register

Data extraction and analysis

- All phase II and phase III studies

- Variables
  - Number of all randomised participants
  - Number of those aged $\geq$65 and $\geq$75 years

- Descriptive analysis
  - Numbers and proportions (%)

Results

Approved therapeutic indication / generic name	Number of trials	Number of randomised participants
Overall, n (%)	114	88,261
Prevention venous thromboembolism	13	23,777
Dabigatran	4	10,183
Rivaroxaban	9	13,594
Osteoporosis	32	33,109
Bazedoxifene	5	10,660
Lasofoxifene	16 (4)	9,644
Denosumab	11	12,805
Atrial fibrillation	16	8,958
Dronedarone	8	7,495
Vernakalant	8	1,463
Type 2 diabetes mellitus	21	10,883
Liraglutide	12	5,430
Saxagliptin	9	5,453
Depressive disorder – agomelatine	13	4,614
Bipolar disorder – asenapine maleate	12	5,496
Epilepsy – eslicarbazepine	7	1,424

Availability of data

Number of trials providing information about participants aged 65+	Overall number of randomised patients in these trials	Number of trials providing information about participants aged 75+	Overall number of randomised patients in these trials
53 (46.5)	45,697 (51.8)	58 (50.9)	49,890 (56.5)
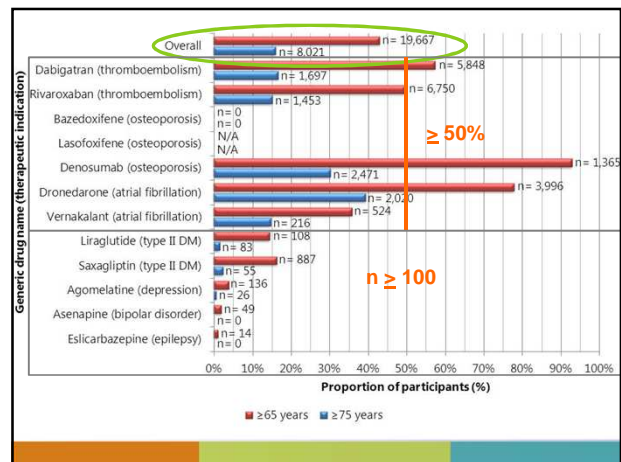
Discussion

- Therapeutic indications specifically associated with ageing proportion almost 50%
  - Number and proportions fairly good
  - Large variations

- Therapeutic indications not unique to old age subjects aged 65+, median 108
  - Numbers and proportions limited

Discussion
ICH E7

- Eight (67%) medicines fulfilled the ICH E7 criteria

Therapeutic indication	Medicines
Prevention VTE	dabigatran, rivaroxaban
Osteoporosis	bazedoxifene, lasofoxifene, denosumab
Atrial fibrillation	dronedarone, vernakalant
Diabetes mellitus	liraglutide, saxagliptin
Major depression	agomelatine
Bipolar disorder	asenapine
Epilepsia	eslicarbazepine

Limitations and strengths

- **Limitations:**
  - Underreporting of number / proportion of older subjects
  - Randomised population ~ population that used trial medication?
  - Small number of trials per therapeutic indication

- **Strengths:**
  - 3 data sources (70% in WHO trial register, 70% published)
  - Focus on categories of therapeutic indications
  - Phase II and Phase III trials

Conclusions

- The number and proportion of older subjects in trials should be improved, especially in trials for diseases not unique to, but present in old age

- They should be representative of the prevalence in the target population

Thank you for your attention

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