Poor Sex-Specific Reporting of Results from Phase 3 Studies of New Drugs Approved in Europe between 2017-2021

Rebecca Schulz & Stefan Engeli, M.D., Prof. of Clinical Pharmacology
Institute of Pharmacology, Department of Clinical Pharmacology
University Medicine Greifswald, Germany
stefan.engeli@med.uni-greifswald.de

Background

Given the increasing awareness of of sex- & gender specific differences in clinical medicine, we adressed the following questions:

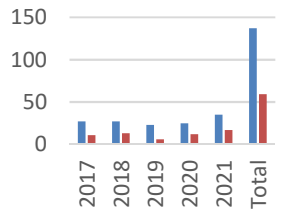
1. How often were sex-specific subgroup analyses published in literature reporting results from Phase 3 trials of newly approved drugs in Europe?
2. What kind of statistical methods were used in these subgroup analyses?
3. How often were sex-specific adverse drug reactions (ADR) reported?
4. What was the sex-ratio in these trials?
5. How did the sex-ratio in trials of specific diseases compare to to the real-life sex-ratio of the diseases in Europe?

Methods

- of 175 identified drugs, 21 are directed against diseases specific for women or men
- for the remaining 154 drugs, we analyzed the European Public Assessment Reports (EPAR), which was missing for 13 drugs
- for the remaining 141 drugs, we identified the relevant Phase 3 studies on which the EPAR was based & retrieved their ClinicalTrials.gov identifiers (NCT)
- using these NCTs, we retrieved the publications of the respective trials in PubMed and ScienceDirect
- losing some drugs along this way (missing information), **our analyses are based on 268 published trials of 137 newly approved drugs**

Results

- the overall ratio of women (49,%) to men (50,3%) in the trials was similar
- for 59 (red) out of 137 (blue) newly approved drugs, sex-specific sub-group analyses were reported (43%; Figure)
- only 89 out of 268 publications (33%) included sex-specific findings
- there was no observable trend over the period 2017-2021 towards reporting more sex-specific results
- 57 of these 59 drugs had similar efficacy data in women and men
- a posthoc analysis described better overall survival for men treated with **Midostaurin** in acute myeloic leukemia
- 1 out of 4 trials with **Bempedoinic Acid** described better LDL-Cholesterol reduction in women
- only 8 publications (3%) on 5 drugs (4%) reported sex-specific data on ADRs
- women appeared to be at higher risk for ADR with **Ertugliflozin** (genital mycosis; 3 publications)
- women had more prevalent antiadrogenic ADR with **Osilodrostat** against endogenous Cushing Syndrome (1 publication)
- heterozygotic women with cystic fibrosis developed more often skin ADRs with **Ivacaftor+Tezacaftor+ Elexacaftor** (counted as 1 drug; 1 publication), whereas in the homozygotic state, no sex difference occurred
- more than 15% difference between the sex-ratio in trials of specific diseases compared to to the sex-ratio of the disease in Europe occurred in **squamous cell carcinoma, psoriasis, atopic dermatitis, schizophrenia, narkolepsy, and chronic heart failure** (women underrepresented); or in **heriditary angioedema** (men underrepresented)



Conclusion

Despite clear demands by regulatory authorities for 20 years to conduct sex-specific analyses in Phase 3 trials for efficacy and safety, the reporting frequency of these analyses (if they were conducted at all) in publications of these trials is poor. Efficacy data are more often reported than safety data.
We found no non-binary sex or transgender data in the analysed 268 publications on 137 new drugs.