

OATP1B1-inhibitors in reported cases of statin associated myopathy

Analysis of Swiss pharmacovigilance data

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Background & Objectives

- More than 20% of patients treated with statins experience statin-associated musculoskeletal symptoms (SAMS) [1]
 - It is assumed that this affects medication adherence and thus increases the risk for atherosclerotic cardiovascular diseases (ASCVD) [2]
- Organic anion transporting polypeptide 1B1 (OATP1B1) is a hepatic uptake transporter, encoded by the gene *SLCO1B1*
 - Statins are OATP1B1 substrates
 - Genetic variation in *SLCO1B1* affects OATP1B1 function, influencing systemic exposure and thus tolerability of statins [3]
- OATP1B1-inhibitors, when taken together with statins, may affect statin tolerability and exacerbate SAMS
- To analyze the potential role of OATP1B1 involving interactions with statins in clinical practice:
 - This study aimed to explore the **prevalence of coadministered OATP1B1-inhibitors** in individual case safety reports (ICSR) of suspected SAMS reported to Swissmedic.

Results

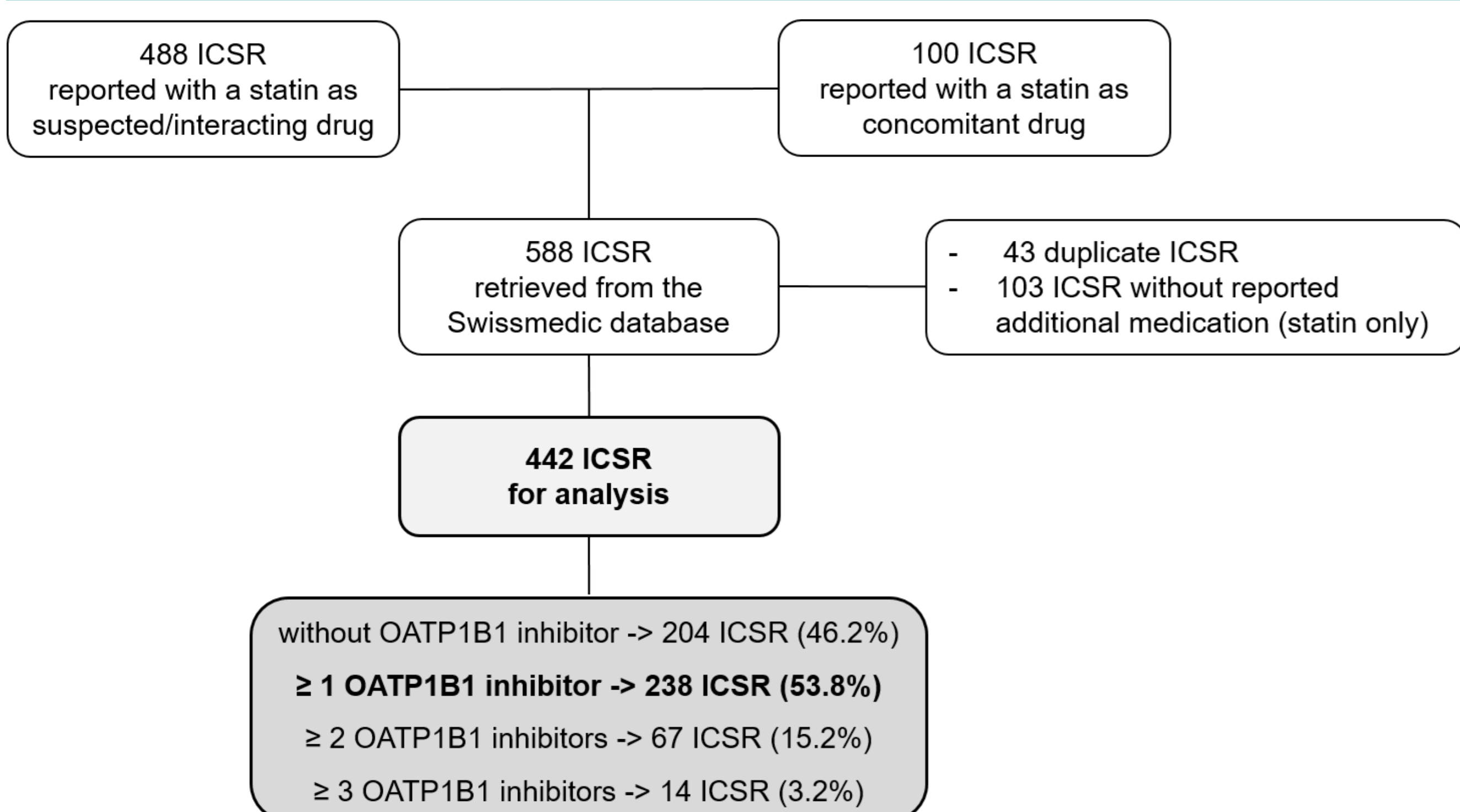


Figure 1. Overview and main results of the individual case safety report (ICSR) analysis concerning the prevalence of OATP1B1-inhibitors in reported cases of suspected statin associated musculoskeletal symptoms (SAMS) reported to Swissmedic.

Characteristic	Type	Number (n), Percentage (%) or Median [IQR]
ICSR statin + additional medication, n	-	442
Gender, %	Female	34.6
	Male	63.8
	Not reported	1.6
Age in years, median [IQR], minimum, maximum	Reported for n=379	65 [55-72] 22, 95
Reported number of substances, median [IQR]	-	5 [3.0-8.0]
Polypharmacy (≥5 prescribed substances), %	-	58.5

Table 1. Overview of individuals' main characteristics from the analysed individual case safety reports (ICSR).

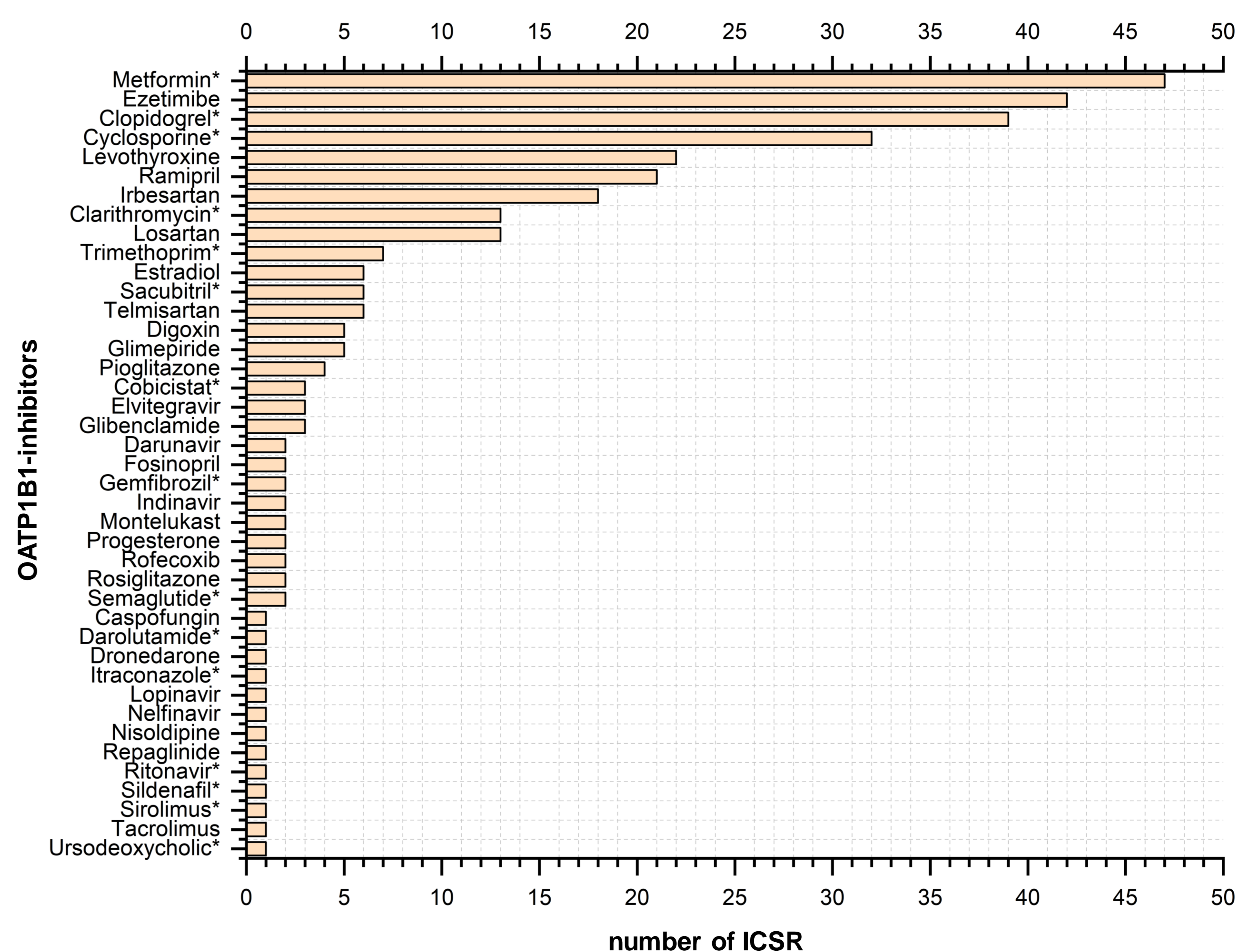


Figure 2. Overview of substances classified as *in vivo* and/or *in vitro* OATP1B1-inhibitors in the Drug Interaction Database (DIDB®, copyright Certara), according to the number of individual case safety reports (ICSR) the substances have been reported. (*) = *in vivo* data indicating OATP1B1 inhibition available in the DIDB®

Method

- Systematic search of the Drug Interaction Database (DIDB®, Copyright University of Washington & Certara USA)
 - in vitro* and *in vivo* data indicating OATP1B1 inhibition ($IC_{50} \leq 10 \mu M$, $AUCR \geq 1.25$)
- Analysis of individual case safety reports (ICSR) in the Swissmedic database
 - reported muscular adverse drug reactions (MedDRA preferred terms: myalgia, myopathy, and rhabdomyolysis)
 - reported statin use (ATC: C10AA)
- Primary endpoint: number of ICSR involving OATP1B1-inhibitors
- Secondary endpoint: prevalence of individual OATP1B1-inhibitors

Conclusions & Outlook

- The concurrent use of OATP1B1-inhibitors with statins is **very common** in ICSR of suspected SAMS (Fig. 1)
- Further investigations are necessary to confirm these associations and to elucidate their clinical relevance in statin therapy
 - for example in patients comedicated for cardiovascular diseases or diabetes type II (Fig. 2)
- In addition, specific attention should be paid to the patients' genetic predisposition (i.a. *SLCO1B1*)
 - currently it is unclear how such a drug-drug-gene interaction (DDGI) should be considered in the evaluation of statin therapy
- We want to highlight the need for further initiatives to collect clinical data on drug-drug-gene interactions in the context of statin therapy

Literature

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- Cooper-Dehoff, RM. et al. *Clin Pharmacol Ther.* 2022; 111(5):1007-1021.

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