Editorial

Targeted treatment of acute respiratory distress syndrome with statins—a commentary on two phenotype stratified re-analysis of randomized controlled trials

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No immunomodulatory pharmacological interventions have been found effective for the acute respiratory distress syndrome (ARDS) despite identification of potentially effective drugs in preclinical studies (1,2). A frequently mentioned reason is the clinical and biological heterogeneity of ARDS (2). In attempts to quantify this heterogeneity, etiological, physiological-, and biological phenotypes have been explored (2-4). A classification based on a physiological phenotype by PaO_2/FiO_2 ratio, is included in the Berlin definition as 'oxygenation criterion' and discriminates between mild, moderate and severe ARDS (2). Recently, two biological phenotypes have been identified: 'hyper-inflammatory' and 'hypo-inflammatory', depending on levels of; pro-inflammatory markers, coagulopathy, severe shock, and metabolic derangement (4). These two biological phenotypes, also called "subphenotypes", have different outcomes with a high mortality in the 'hyper-inflammatory' phenotype and a low mortality in the 'hypo-inflammatory' phenotype. Furthermore, the biological phenotypes show a differential treatment responses to PEEP-strategies and fluid management (4,5). There is no data on a differential response to immunomodulatory treatments.

Subgroup analysis for treatment responsiveness is often done by post-hoc analysis in randomized controlled trials (RCTs). RCTs enable researchers to investigate the effectiveness of treatments with decreased bias due to double-blinding and randomization assignments. However, in ARDS, the study population is a highly-heterogeneous, unselected group (6). Post-hoc analysis provides useful information of effects in subgroups to mitigate or highlight the influence of heterogeneity. These subgroups are generally not predefined, because reliable researches into subgroups require large trials. This is not reasonably achievable for every disease. The results of post-hoc analysis can be eminently useful to initiate new research (7).

In this editorial, we review the recently published post-hoc analyses of 'Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction' (HARP-2)-, and 'Statin for Acutely Injured Lungs From Sepsis' (SAILS) randomized controlled trials. The well-known effect of statins is hypolipidemic by depletion of mevalonate pathway products via HMG-CoA reductase. Research shows that statins also have many other pleiotropic effects, like anti-inflammatory and anti-

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proliferative (8-10). These anti-inflammatory properties are a result of the modification of underlying mechanisms, which are also involved in the development of ARDS.

Simvastatin in ARDS: the HARP-2 trial

The HARP-2 trial included intubated and ventilated ARDS-patients regardless of underlying cause, within 48h of onset, based on a PF ratio <300, bilateral pulmonary infiltrations/pulmonary edema, and no evidence of left atrial hypertension. Five hundred and forty patients were randomized between 80 mg Simvastatin (259 patients) and placebo once a day (281 patients). The aim was to investigate whether Simvastatin improved clinical outcomes with as primary outcome the number of ventilator free days up to 28 days. Simvastatin did not increase the number of ventilator-free days, nor improve clinical outcome (11). In a post-hoc analysis of the baseline data, the two aforementioned biological phenotypes were identified based on sTNFR1, IL-6, platelet counts, and vasopressure use. Simvastatin improved the 28-day survival of the 'hyper-inflammatory' phenotype with an absolute risk (AR) reduction of 13%, versus 0.01% in the 'hypo-inflammatory' phenotype (12).

Rosuvastatin in ARDS: the SAILS trial

The SAILS trial investigated the effect of Rosuvastatin on clinical outcomes, with in-hospital mortality or mortality until study day 60 as primary outcome. The study included intubated and ventilated ARDS patients selected on PF ratio <300, bilateral infiltrations, no evidence of left atrial hypertension, and with a known or suspected infection (sepsis-criteria). Within 48 h after onset the patients were randomized between 40 mg loading dose and 20 mg maintenance dose of Rosuvastatin and placebo. The trial was prematurely stopped due to futility after 745 of 1,000 included patients. Rosuvastatin did not reduce the in-hospital mortality, nor improved clinical outcomes. Possible detrimental effects on kidney and hepatic function were reported (13). Post-hoc analysis of the baseline data identified similar biological phenotypes based on sTNFR1, Il-8 and bicarbonate. No phenotype-specific benefit of Rosuvastatin treatment, nor difference in outcome were observed (14).

Discussion

The SAILS- and HARP-2 trials both identified similar 'hyper-inflammatory' and 'hypo-inflammatory' phenotypes by post-hoc latent class analysis. Although HARP-2 observed phenotype stratified improved survival with Simvastatin, SAILS did not with Rosuvastatin. With the anti-inflammatory properties of statins in mind, the difference between the reported results of both trials is surprising, but can be explained through pathophysiological and pharmacological reasoning (15).

First of all, there are inter-drug differences in statins, like bioavailability and intracellular concentrations. A study by Gbelcová *et al.* showed that Simvastatin reaches considerably higher intracellular concentrations (156.4 nmol/100,000 cells) compared to Rosuvastatin (26.6 nmol/100,000 cells) in pancreatic cancer cells. Simvastatin also altered gene expression (total genes with changed expression: 166) while Rosuvastatin didn't (total genes with changed expression: 0). The latter is interesting, because alterations in gene expression are believed to cause the anti-inflammatory properties of statins (8). Furthermore, the effects seem cell-type dependent. For example anti-proliferative effects are observed in pancreatic cancer cells (MiaPaCa-2) (8), but the anti-inflammatory and anti-coagulatory (by decreased tissue factor expression due to PTX3 suppression) are seen in vascular cells (HUVEC) but not in hepatocarcinoma cells (Hep G2 cells) (10). This implicates that statins have a wide range of cell-dependent, pleiotropic, and highly inter-individual effects.

Additionally, the trials had different inclusion criteria. The SAILS trial added systemic inflammatory response to the inclusion criteria, selecting a narrower group of ARDS-patients. Baseline characteristics showed a lower PaO_2/FiO_2 in the HARP-2 population, indicating more severe ARDS. Since the effect of statins might depend on the severity of ARDS, this could be a confounding factor (16). Although both trials identified two phenotypes based on a comparable set of biomarkers, it is uncertain that both phenotypes are identical. A recently published observational study identified and validated a different set of biomarkers from HARP-2 and SAILS to distinguish between 'hyper-inflammatory' (referred to as 'reactive') and 'hypo-inflammatory' (17). It is unclear whether both distinguished subgroups are biologically and/or phenotypically comparable, as also mentioned by Shankar-Hari *et al.* (18). The next step would be a study explicitly defining phenotypes, which can be validated and then subsequently used in other studies.

The future of clinical trials in ARDS

A pitfall frequently seen in subgroup analysis of randomized

Table 1 Sufficient-component cause model for mortality stratified per ARDS phenotype. Prevalence hypo-inflammatory: 65% and hyper-inflammatory: 35% (12)

Phenotype	Outcome if exposed to		Individual causal effect	Type	Proportion of total	
	Placebo	Drug			HARP-2	Enrichment hyper-inflammatory
Hypo-inflammatory	1	1	1–1=0	Doomed	0.10	–
Hyper-inflammatory	1	1	1–1=0	Doomed	0.11	0.32
Hypo-inflammatory	1	0	1–0=1	Benefit	0	–
Hyper-inflammatory	1	0	1–0=1	Benefit	0.05	0.13
Hypo-inflammatory	0	1	0–1=–1	Harmed	0.01	–
Hyper-inflammatory	0	1	0–1=–1	Harmed	0	0
Hypo-inflammatory	0	0	0–0=0	Immune	0.54	–
Hyper-inflammatory	0	0	0–0=0	Immune	0.19	0.55

Table 2 Estimated size effect of treatment with Simvastatin and required sample size

Study population	Mortality rate placebo group (%)	Absolute effect size (%)	NNT	Required sample size
HARP-2	25	4.5	22	2,722
Enrichment hyper-inflammatory phenotype	45	13	8	438

NNT, number needed to treat.

controlled trials is a false positive outcome. This is caused by underpowering for subgroup analysis, multiple-testing, and only stratifying on one variable at a time, thereby excluding other clinical relevant variables from the analysis. This can be mitigated by predefining subgroups, ideally based on clinical relevance, and/or including a bigger cohort. Additionally, although the AR provides a better and solid impression of the effect size, the relative risk (RR) is generally used in clinical trials to express the effect size despite distorting in small groups (19).

In order to help to put the positive HARP-2 trial results into perspective and to generate an absolute effect size for a future clinical trial-design, a sufficient-component cause model for mortality stratified per ARDS phenotype was applied (20). This model shows that the 'hyperinflammatory' ARDS-patients benefitting from Simvastatin represent 5% of the total HARP-2 population, leading to an effect size of 13% when translated to an exclusively 'hyper-inflammatory' study population (*Table 1*). Based on this effect size, a future trial into the effect of Simvastatin on 28-day mortality in 'hyper-inflammatory' ARDS patients should include 438 patients (*Table 2*). The corresponding number needed to treat of 8 seems worth the efforts to further investigate in a future RCT.

The HARP-2 trial showed that 'phenotype-dependent treatment response' is a possible new strategy for heterogeneous syndromes like ARDS, but needs to be investigated more thoroughly. In advance of future RCTs, phenotypes need to be defined, validated, and standardized. With the 10% incidence of ARDS in all ICU-patients in mind, phenotype-based research in ARDS will remain challenging.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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