COPD mortality and exacerbations in the placebo group of clinical trials over two decades: a systematic review and meta-regression

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Analysis of the placebo arms of controlled trials in COPD patients showed a decrease in mortality of 6% over the last two decades. This is comparable to the decrease in exacerbations. However, the decrease in mortality was insignificant. https://bit.ly/3opvouS

Cite this article as: Andreas S, Röver C, Heinz J, *et al*. COPD mortality and exacerbations in the placebo group of clinical trials over two decades: a systematic review and meta-regression. *ERJ Open Res* 2022; 8: 00261-2021 [DOI: 10.1183/23120541.00261-2021].

Received: 14 April 2021
Accepted: 26 Sept 2021

Abstract

A decreasing trend in exacerbation rates has been observed in COPD. Because mortality is linked to exacerbations, it is of interest to investigate whether a similar time trend is also present in mortality rates.

We performed a systematic review of placebo groups in published randomised controlled trials. Mortality rate was modelled based on a Poisson distribution for the event counts. Adding information on mortality as well as on newly published studies on a previous database, we performed a meta-regression.

Among the 56 included studies representing 14 166 patients, an annual decrease in mortality rates of 6.1% (−0.6%, 12.6%) (p=0.073) was observed. Consistent results were obtained in subgroups as well as when adjusting for potential confounders. The correlation between exacerbation rate and mortality rate was positive but weak as well as insignificant.

In summary, analysis of randomised controlled trials in COPD patients showed a decrease in mortality in the placebo arms over the last two decades. This effect is comparable to the previously observed decrease in annual exacerbation rate. Albeit insignificant, our results suggest that care is needed in the design of new trials or when comparing results from trials published many years apart.

Introduction

COPD is currently a leading cause of death and significant complications worldwide [1, 2], and its prevalence is increasing in many countries [1]. Exacerbations are a critical event in patients with COPD and are followed by worsening of lung function, reduced quality of life and increased mortality [3]. Mortality is particularly high after an exacerbation leading to hospital admission [4].

Previously, we reported on COPD exacerbation rate in a systematic review and meta-regression of the placebo groups in randomised controlled trials [5]. We found a decrease in exacerbations over two decades to a clinically relevant extent and independent of important prognostic factors. The reason for this finding was unclear but adjunct therapies such as vaccination, better treatment of comorbidities, less air pollution or healthier lifestyles might have contributed. Because exacerbations are related to increased mortality, we reasoned that not only exacerbations but also mortality may have decreased in the last two decades.

In recent years, two large randomised controlled COPD trials were published. Both trials showed reduction in the specified secondary end-point of mortality with inhaled triple therapy (*i.e.* inhaled corticosteroid and a dual bronchodilator) [6, 7]. It can be speculated that the reduction in COPD exacerbations in these two large studies might have determined the observed survival gain. Indeed, we demonstrated a strong

relationship (regression analysis: r^2=0.70, p=0.018) between annual exacerbation rate and annual mortality rate for the different treatment groups in the two trials [8]. This was, however, only an exploration of two recent studies with limited validity. To our knowledge the association of exacerbations and mortality in the clinical COPD trials published has not yet been analysed.

We thus performed a meta-regression of the placebo groups in randomised controlled trials published up to 2020 and reporting exacerbations as well as mortality as an outcome. The objective was to evaluate whether there is a time trend in COPD mortality and whether this was affected by baseline characteristics or inhaled corticosteroids. Furthermore, we aimed to explore whether annual exacerbation rate and annual mortality were correlated in the included studies.

Methods

The present systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. We updated the search performed for a previous review [5] that was registered with PROSPERO (CRD42018118823, 2018) [10].

Literature review

A comprehensive literature search was conducted using the databases MEDLINE *via* PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms, including relevant Medical Subject Headings (MeSH) and keywords, were (COPD OR chronic obstructive pulmonary disease OR COLD OR chronic obstructive lung disease OR "Pulmonary Disease, Chronic Obstructive" [MeSH]) AND (double-blind OR double blind) AND exacerba*. The results were filtered for "Clinical Trial" and "Randomized Controlled Trial". In order to also retrieve studies that had only recently been added to the database and may not have been completely indexed, we repeated the search using only the limit "published in the last 180 days". We checked reference lists of included studies and relevant reviews to identify any additional relevant articles not captured by the search. The date of the last search was 23 September 2020.

The search results were independently screened by two reviewers (LS, JH) using the following inclusion criteria: 1) the study deals with adult COPD patients; 2) the study has a placebo control group; 3) the study design uses parallel group or a crossover design; 4) the trial is double-blind and randomised; 5) exacerbation rates are quoted or can be calculated from the data presented; 6) at least 100 patients (intention-to-treat population) are included in the study; 7) the study has a treatment duration of at least 12 weeks.

Title and abstract were screened and studies that clearly did not meet the inclusion criteria were excluded. Any disagreements between the reviewers were resolved by a third reviewer (CR). For all remaining studies, full texts were reviewed and the decision about inclusion or exclusion of a study was discussed with another independent reviewer (SA).

Data extraction and quality assessment

From the placebo groups of the included studies, we extracted data on patient demographics, trial eligibility criteria, exacerbation rate, the corresponding uncertainties and overdispersion and deaths in a standardised data sheet; these were checked by at least one other author (CR, JH). As exacerbation was not treated as a primary end-point in some of the studies (see table S1), the reporting of exacerbation rates was rather heterogeneous [11]. The joint use of the reported information on exacerbation events in a common statistical model has been described in detail in the previously published systematic review [5, 12]. The concurrent use of inhaled corticosteroids (ICS) was accepted in order to be considered as placebo group for our analysis. Details on sensitivity analyses and ICS proportion were reported previously [5]. As in the previous study we identified two variables that changed over time (SGRQ and FEV_1).

Study quality was rated by dual assessment (CR, JH) using the Oxford quality scoring system [13]. Discrepancies were resolved by a third reviewer (TF).

Data analysis

The data model employed was similar to the one used in our previous investigation [5]. Briefly, the mortality rate is modelled based on a Poisson distribution for the event counts (numbers of patient deaths in a study arm). Covariables are included in the model by assuming a linear effect on the logarithmic rate parameter, and study-specific random effects are included in order to account for between-study heterogeneity. Bayesian methods are used for inference; prior distributions for the unknown parameters are uniform (between log(0.001) and log(1000)) for the intercept, normal (mean zero and SD 10) for the slope,

and half-normal (scale 1.0) for the heterogeneity SD. Models are fitted using Markov chain Monte Carlo (MCMC) methods using JAGS and the "rjags" R package. For the analysis of exacerbation rates, we used the same models as employed previously [5, 12]. In order to investigate potential correlation between exacerbation rates and mortality, we simultaneously fitted regression models for both end-points, adding a correlation parameter ρ to allow for dependence between the study-specific random effects for both end-points. Parameter estimates are given in terms of medians and 95% credible intervals (CIs). Using a Bayesian framework, two-sided posterior tail probabilities p_B are quoted for the regression parameters instead of p-values; values below 5% are considered statistically significant.

Results

The search update resulted in only a single additional eligible study [14] published since our previous literature search (see table S2), which had yielded a total of 55 studies [5]. Data on patient mortality were available and extracted for all 56 studies. The systematic review process is illustrated in the flow chart in figure S1. The 56 studies included comprised 14 166 patients in the placebo arms.

Figure 1(a) and (b) illustrates the two regression analyses for exacerbation rates as well as mortality. The first (top panel) is nearly identical to the one reported previously [5], apart from the inclusion of one additional study (#56, published in 2020). The resulting parameter estimates are also very similar, showing an annual reduction of 6.5% (95% CI 4.3%, 8.7%). Annualised mortalities are overall lower than exacerbation rates, and uncertainties are correspondingly greater, but the data also show a declining trend. With an estimated annual decrease of 6.1% (95% CI −0.6%, 12.6%), the decline is of a similar magnitude as for the exacerbation rate, but the 95% CI is wider and also includes a constant mortality rate (0% decrease) as a possibility ($p=0.073$). The parameter estimates are also shown in table 1 and figure 2.

Because the different types of placebo groups considered here (with or without the concomitant use of ICSs) might exhibit differing mortalities, we also considered both subgroups of studies separately. For the group of studies allowing for ICSs (35 studies) we get a somewhat more moderate estimate for the rate reduction of 1.9% (95% CI −8.3%, 10.8%), and for the group of "true" placebos (21 studies) the reduction is estimated at 8.5% (95% CI −2.6%, 19.1%) (see figure S3).

While we did not find a significant change in mortality over time, we investigated whether the tendency would persist if we adjust for covariables that have also shifted over time and that hence might explain a change in mortality. We considered the St. George's Respiratory Questionnaire (SGRQ) score as well as the forced expiratory volume in 1 s (FEV_1) as possible additional covariables in the regression analysis as these two correlated with time. In both cases the estimated change in mortality is slightly reduced while the uncertainty is increased (see figure 2).

Including dependence between mortality and exacerbation rates in the model yielded an estimated correlation coefficient ρ of 0.18 (95% CI −0.24, 0.56), indicating a tendency for a positive relationship (*i.e.* larger exacerbation rates tend to be associated with greater mortality), while the effect magnitude is not large or certain (see also figure S2).

Discussion

Although not statistically significant, our data revealed an annual reduction in mortality of about 6%, which was similar in magnitude to the decrease in exacerbation rate reported previously. This could at least partially be due to the fact that the more recent studies tended to include less severely affected patients. Mortality is a relatively rare event compared to acute exacerbations and therefore larger samples sizes are necessary to detect statistically significant differences. Furthermore, the residual correlation of exacerbation rate with mortality after adjustment for a common time trend was not statistically significant. Interestingly, temporal trends have also been investigated in other disease areas. For instance, a decline in relapse rate as well as disability worsening has been observed in randomised controlled trials in multiple sclerosis [15–17]. Furthermore, temporal trends in mortality and readmission after acute heart failure were recently reported [18].

It is important whether the reduction of exacerbations by inhaled treatment transforms to reduced mortality in this patient group. Because COPD exacerbations are followed by worsening lung function, reduced quality of life and increased mortality [1, 3], a causal relationship is conceivable [19]. Furthermore, exacerbations increase the risk of myocardial infarction, stroke and death [19]. Indeed, many patients with COPD die directly from cardiovascular disease, especially frequent exacerbators [7, 20].

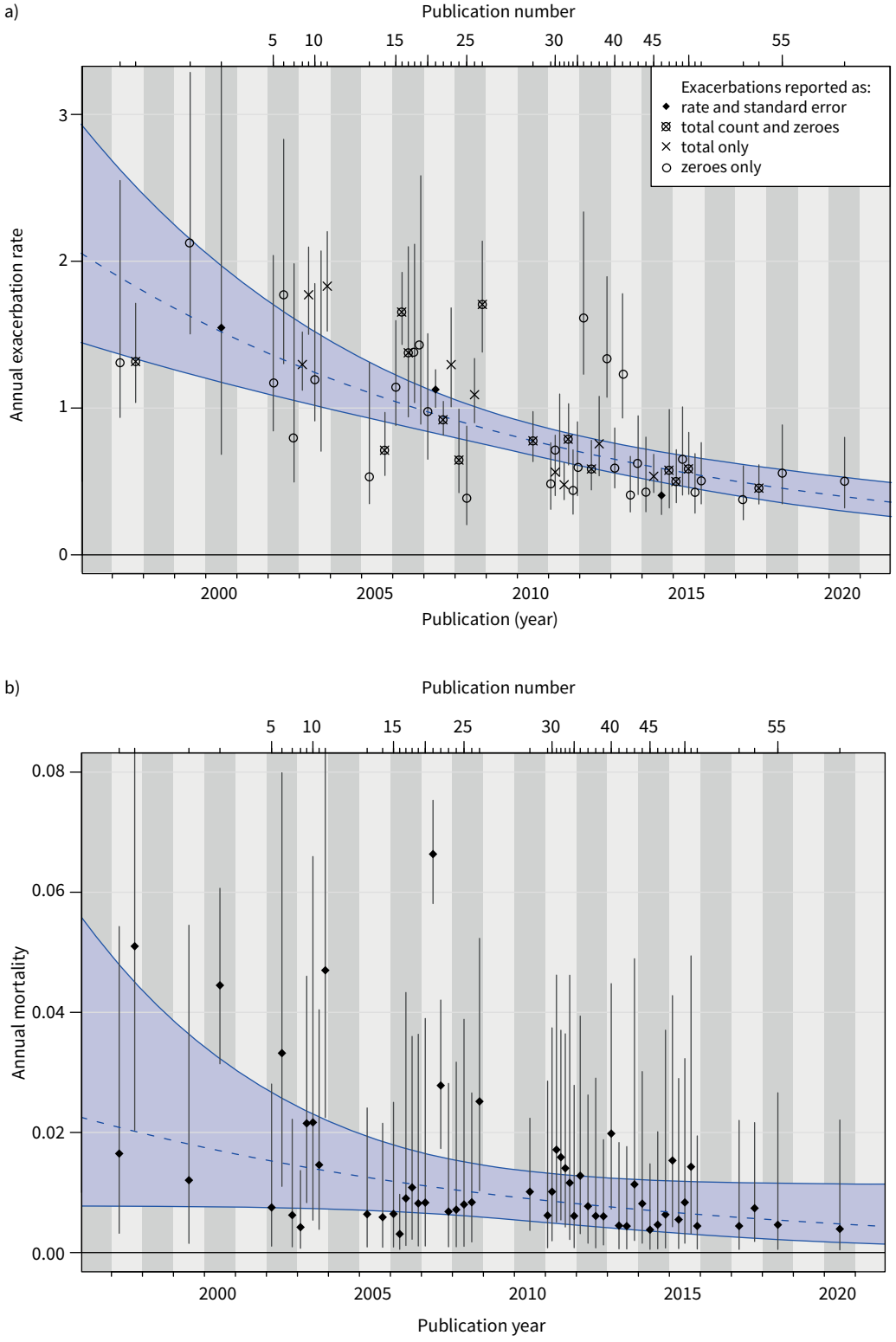

FIGURE 1 The estimated time trends in annualised exacerbation rates (a) as well as mortality rates (b). The analysis of exacerbation rates includes one additional study (#56) compared to the previous results [5] and essentially confirms the earlier findings. The investigation of mortality suggests a similar trend.

TABLE 1 Parameter estimates from the regression analyses, for the main analysis as well as for the sensitivity analyses based on the subsets of "true" and "ICS-" placebos only, or when adjusting for confounders

Model	Parameter	Estimate [95% CI]	Percentage change	p_B
All placebos	Intercept β_0	−4.077 [−4.878, −3.434]		
(56 studies)	Slope β_1 (year)	−0.063 [−0.134, 0.006]	−6.1 [−12.6, 0.6]	0.073
	Heterogeneity τ	0.951 [0.629, 1.426]		
ICS placebos only	Intercept β_0	−4.670 [−5.951, −3.720]		
(35 studies)	Slope β_1 (year)	−0.019 [−0.115, 0.079]	−1.9 [−10.8, 8.3]	0.689
	Heterogeneity τ	0.875 [0.423, 1.564]		
True placebos only	Intercept β_0	−3.620 [−4.756, −2.721]		
(21 studies)	Slope β_1 (year)	−0.089 [−0.212, 0.026]	−8.5 [−19.1, 2.6]	0.116
	Heterogeneity τ	0.988 [0.554, 1.737]		
SGRQ-adjusted	Intercept β_0	−8.117 [−15.186, 0.513]		
(28 studies)	Slope β_1 (year)	−0.010 [−0.140, 0.118]	−1.0 [−13.0, 12.5]	0.873
	Slope β_2 (SGRQ)	0.078 [−0.095, 0.218]	8.1 [−9.1, 24.4]	0.362
	Heterogeneity τ	0.957 [0.551, 1.628]		
FEV_1-adjusted	Intercept β_0	−1.571 [−4.408, 1.509]		
(51 studies)	Slope β_1 (year)	−0.027 [−0.110, 0.063]	−2.6 [−10.4, 6.5]	0.535
	Slope β_2 (FEV_1)	−0.058 [−0.130, 0.004]	−5.6 [−12.2, 0.4]	0.069
	Heterogeneity τ	0.942 [0.610, 1.438]		

The parameters originally refer to the mortality rate on the logarithmic scale, the slope parameters are expressed in terms of an annual percentage change; these are shown in a separate column, where applicable. Bayesian posterior tail probabilities (p_B) are also provided for the regression coefficients instead of frequentist two-sided p-values. Between-study heterogeneity is quantified in terms of the SD parameter τ.

So far, efficacy of inhaled treatments has never been demonstrated based on effects on mortality as primary end-point in randomised controlled COPD trials. For instance, the largest randomised controlled COPD trial ever, the SUMMIT trial investigating all-cause mortality as the primary end-point, was negative despite the trial being enriched by patients with cardiovascular disease [21]. This negative finding was in part attributed to the inclusion of patients with less severe respiratory disease [22, 23]. Thus, it is consequent that the current GOLD report noticed a lack of convincing evidence for a survival benefit with inhaled COPD therapy despite relevant improvements in lung function, exacerbations and patient-reported outcomes [24].

The decrease in mortality over time we observed in our data, albeit insignificant, is in line with the results of a previous large population study. The Chronic Respiratory Disease Collaborators reported that the

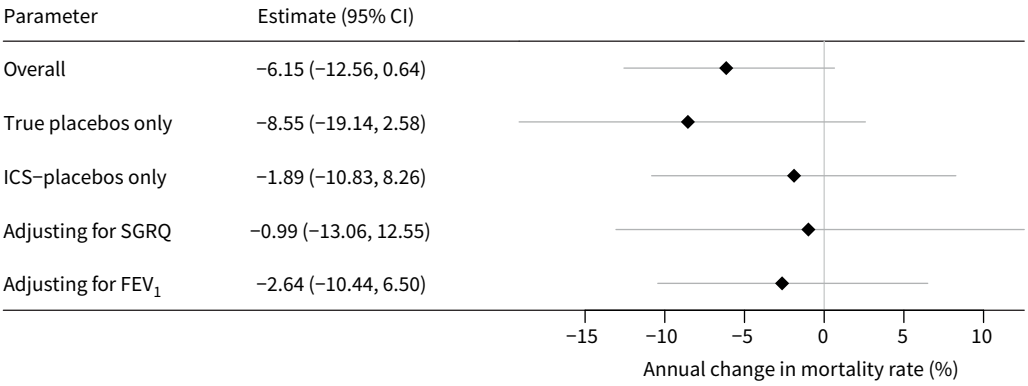

FIGURE 2 Parameter estimates corresponding to the annual change in mortality rate for the sensitivity analyses in comparison to the main analysis (see also table 1). All estimates suggest a decline in mortality over time of slightly differing magnitude, but in all cases the 95% CIs also include 0%, *i.e.*, the possibility of no change. FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroids; SGRQ: Saint George's Respiratory Questionnaire.

global age-standardised mortality rate for COPD dropped by 43% between 1990 and 2017 [2]. As the authors discussed, these data might be explained by changes in smoking prevalence or the environment. There may also have been ambiguities in diagnoses and data reporting.

Our data showed a weak association between exacerbations and mortality explaining only about 4% of the variance. Thus, our data are unable to support a meaningful relationship between exacerbations and mortality. Due to the limitations discussed below, such as a low number of mortality events and the lack of individual patient data, our findings are also unable to disprove a causal association. Furthermore, low correlation across the placebo populations of patients does not mean that a treatment would not be able to reduce exacerbations and mortality at the same time.

To the best of our knowledge this is the first meta-regression analysis of randomised clinical trials investigating a time trend in COPD mortality. Network meta-analyses are commonly used to indirectly compare treatments that have not been compared directly in a clinical trial. The interpretation rests on the assumption of a relatively stable rate of the investigated end-point over time. Indeed, large trials have been performed in COPD for over two decades and thus network meta-analysis included studies over a 20-year period [25]. Our results of a decrease in mortality rate over time, albeit insignificant, raises concern about the robustness of such work.

Recently it was suggested that the observed mortality reduction with inhaled triple therapy was mediated mainly by the ICS [7]. The beneficial effect on cardiovascular outcomes with ICS is a possible explanation [26]. Indeed, in a very recent network meta-analysis, ICS/LAMA/LABA and ICS/LABA, unlike other combinations, were associated with reduced mortality as compared to placebo [25]. Albeit not significant, our findings showed a reduced time trend in the ICS-treated patients as compared to the group without ICS. This finding may support a protective effect of ICS on mortality compared to the patients not treated by ICS. However, the observed difference was again insignificant due to the low event number. Interestingly, in our previous analysis on exacerbation rate, the time trend was very similar in the ICS and the non-ICS group [5].

There is ambiguity in the definition of what exactly constitutes an exacerbation, mainly in the older studies. Indeed, the use of different conventions may make substantial differences [27]. This is especially true for mild exacerbations. The more recent trials used standardised definitions, especially for moderate and severe exacerbations [10], which increased the comparability of events.

Our approach was to use data for moderate to severe exacerbations, if more than one category of exacerbations was reported. However, the incomplete reporting of exacerbations, mainly in the older trials, did not allow for a distinct analysis according to the severity of exacerbations.

Limitations and strengths

The mortality rate in patients with COPD is much lower compared to the exacerbation rate. For instance, the exacerbation rate in recent large randomised trials was about one per patient and year, while the mortality rate was only 1–2% per patient and year [6, 7]. Therefore, the time trend in mortality relies on fewer events as compared to the time trend in exacerbations and thus is associated with larger uncertainties. We further acknowledge that we present only data aggregated at study level and not individual patient data. Furthermore, patients included in clinical trials might not be representative of a general COPD population. Finally, it should be kept in mind that the correlation demonstrates an association and not necessarily a causal relationship. Potentially the correlation could be explained by a time trend in a variable we were unable to control for.

The main strength of our study lies in the long period of time evaluated, the large number of studies included and the adjustment for a number of well-known confounders including baseline symptoms and lung function.

In conclusion, the present analysis of more than 50 clinical trials in COPD patients showed that mortality rate did decline, by about 6% per year. This decline is of similar magnitude to the decline in exacerbation rate but did not reach statistical significance. Nevertheless, our findings indicate that care is needed in the design of new trials given the observed shifts in study populations. In future trials, these planning risks might be mitigated by the application of adaptive designs [28]. Furthermore, one needs to be cautious when comparing results from older trials with more recent ones, *e.g.* indirectly comparing treatments in network meta-analyses. The association between exacerbation rate and mortality rate was weak as well as insignificant and does not allow for inferences.

Acknowledgements: The authors thank Lejla Sahovic for her support in literature screening, data extraction and manuscript submission.

Provenance: Submitted article, peer reviewed.

Conflict of interest: S. Andreas reports receiving a prize from Oskar Helene during the conduct of the study; and grants and personal fees from Boehringer Ingelheim, grants from Pfizer, and personal fees from Novartis, AstraZeneca, GSK, Chiesi and Merini, outside the submitted work. C. Röver has nothing to disclose. J. Heinz has nothing to disclose. C. Taube has nothing to disclose. T. Friede reports consultancy fees from Novartis, Bayer, Janssen, Roche, Boehringer Ingelheim, Daiichi-Sankyo, Galapagos, Penumbra, Parexel, Vifor, BiosenseWebster, CSL Behring, Fresenius Kabi, Coherex Medical, LivaNova and Minoryx, outside the submitted work.

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