



Multiple factors related to better outcome in out-of-hospital cardiac arrest—is mediation analysis the solution?

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We thank Dr. Goto for his editorial in the *Journal of Emergency and Critical Care Medicine* entitled “Bystander Interventions for Out-of-Hospital Cardiac Arrests: Substantiated Critical Components of the Chain of Survival” (1), commenting on the recent *New England Journal of Medicine* manuscript “Bystander Efforts and 1-Year Outcomes in Out-of-Hospital Cardiac Arrest” conducted by our research group (2). Dr. Goto’s outline of the nationwide initiatives taken in Denmark during the last ten to fifteen years to increase rates of early resuscitative efforts by bystanders is extensively and accurately described. These initiatives include widespread voluntary and mandatory courses in basic life support, introduction and implementation of dispatch-assisted CPR, widespread automated external defibrillator (AED) dissemination and formation of an AED registry and linkage to emergency dispatch centers, enabling healthcare professionals to guide bystanders to the nearest AED (1-4). Bystander CPR and 30-day survival rates have more than tripled since the beginning of the past decade, where the Danish Cardiac Arrest Registry was established (5). In addition to the increased survival rates, Dr. Goto also highlighted from our recent *New England Journal of Medicine* manuscript that 30-day survivors were significantly less likely to be diagnosed with anoxic brain damage or admitted to a nursing home during the first year after out-of-hospital cardiac arrest (OHCA) had they received bystander CPR or bystander

defibrillation relative to no bystander resuscitation (1,2).

Dr. Goto noted that our study was limited by its observational design, and continued that although all known confounders can be accounted for, there may be other unknown or unmeasured confounding factors that may disrupt the causal relationship between bystander CPR and long-term outcome. While this statement is hard to dispute, Dr. Goto suggests that we could have accounted for this limitation by using causal mediation analysis (1). We agree that this could provide further insight, but mediation analysis would be an analysis to investigate intermediate variables (i.e., mediators potentially being witnessed status, delay between cardiac arrest and initiation of CPR, time to defibrillation, bystander resuscitation, time to arrival of ambulance and possibly further factors between the cardiac arrest and outcome), with the possibility of performing sensitivity analysis to test the robustness of the mediator estimate obtained (6). However, our research question was a different one (2), but mediation analyses may in the future be valuable in dissecting out which factors have particular value for improving survival. The problem with possibly missing important confounders is a weakness of any non-randomized study. The best reassurance we can provide are sensitivity analyses and subgroup analyses. We performed an extensive number of such analyses shown in the Supplementary Appendix of the *New England Journal of Medicine* which did not change the conclusion indicating

robust results.

In addition to the main finding of the association between bystander resuscitative efforts and lower risk of brain damage or nursing home admission, there are other factors that also may play an important role in determining the final cerebral outcome of the patient. In our study, we also found an independent association between later years in our study period (2006–2012 relative to 2001–2005) and lower risk of anoxic brain damage or nursing home admission. This finding indicates that other interventions in more recent years also appeared to have had an impact on outcome. In these more recent years of the study period, therapeutic hypothermia in conjunction with standardized post-resuscitation protocols were introduced and implemented in clinical practice as well as coronary angiography and interventions increasingly were used and offered (7). As these data are not systemically available nor are these treatments indicated in all resuscitated patients, it remains difficult to acquire and include such data in statistical models. In 2013, the targeted temperature management trial demonstrated that lowering the body core temperature to 32–34 degrees Celsius was not superior to control of the body core temperature at 36 degrees Celsius (8). Later withdrawal of care until at least 72 hours after cardiac arrest following rewarming after therapeutic hypothermia or temperature management may also play an important role in the increase of survival rates after OHCA (9). Lastly, care and outcomes have the ability to improve regardless of interventions and because of data monitoring (10). Nonetheless, such a “Hawthorne effect” is unlikely to be responsible for the full and incredible tripling of bystander CPR and survival rates in Denmark since the beginning of data monitoring in the beginning of the past decade.

Altogether, with the addition of calendar year in our statistical models, we are likely to have minimized the impact of other and unknown factors on the association of bystander interventions with outcome. In continuation, the independent association between years 2006–2012 relative to years 2001–2005 and outcomes found in our study indicates that other interventions also may have improved outcomes after OHCA. In conclusion, bystander interventions in conjunction with other nationwide initiatives taken to improve resuscitation and post-resuscitation care were related to significantly better survival outcomes in Denmark during and beyond the

most recent decade.

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Footnote

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