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## **Primary complications after cardiac surgery: towards better understanding, prediction, and prevention**

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## **PART THREE**

Preventing lung injury after cardiac surgery

# 6

## Physician's preference-based instrumental variable analysis: is it valid and useful in a moderate-sized study?

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## ABSTRACT

**Background:** Instrumental variable methods can potentially circumvent the unmeasured confounding inherent in observational data analyses.

**Methods:** We investigated the validity and usefulness of physician's preference instrumental variable analysis in the setting of a moderate-sized clinical study. Using routine care data from 476 elective cardiac surgery patients, we assessed the effect of preoperative corticosteroids on mechanical ventilation time and duration of intensive care and hospital stay, occurrence of infections, atrial fibrillation, heart failure, and delirium.

**Results:** Although results of the physician's preference-based instrumental variable analysis corresponded in direction to results of a recent large, randomized trial of the same therapy, the instrumental variable estimates showed much larger effects with very wide confidence intervals.

**Conclusion:** The lesser statistical precision limits the usefulness of instrumental variable analysis in a study that might be of sufficient size for conventional analyses, even if a strong and plausible instrument is available.

## INTRODUCTION

Instrumental variable analysis can potentially circumvent confounding by indication that exists because of unknown or poorly recorded factors in observational data of anticipated therapy effects (1).

Physician's prescribing preference is a promising instrument because differences among physicians in therapy preferences are ubiquitous. We used anesthesiologist's preference in an instrumental variable analysis to investigate whether preoperative high dose corticosteroids are beneficial in cardiac surgery patients because they suppress the procedure-induced inflammatory response (2,3).

We compared instrumental variable analyses to standard regression techniques and to results from the recent Dexamethasone for Cardiac Surgery randomized trial (4).

## METHODS

We used clinical data collected in the context of routine clinical care. The Leiden University Medical Centre review board waived the need of formal ethical approval and written informed consent.

### Study Population

We assessed data on all adult patients who underwent elective cardiac surgery in the Leiden University Medical Centre in 2005. Patients had undergone a range of interventions, including coronary artery bypass grafting, valve repair/ replacement, and heart failure surgery. Patients treated with corticosteroids before admission for cardiac surgery were excluded, leaving 476 patients, of whom 115 received prophylactic corticosteroids. All received regular care according to the fast-track protocol (5).

### Study End Points

Data on demographic features, type of surgical intervention and EuroSCORE were extracted from electronic and paper patient records. The EuroSCORE is a validated prognostic score of in-hospital mortality, based on patient-related, cardiac-related, and operation-related factors (6,7). Primary endpoints were 30-day mortality, ventilation time, and durations of intensive care unit (ICU) and hospital stays. Secondary outcomes were atrial fibrillation, infections, heart failure, delirium, norepinephrine use, glucose, and leukocyte count.

## Statistical Analysis

We first used linear regression to estimate the effect of corticosteroids on the outcomes. This included crude analyses, multivariable analyses (adjusting for age, sex, diabetes, EuroSCORE, and type of surgery), and propensity score adjusted analyses (including the variables in the multivariable model plus the surgeon). Next, we performed 2-stage least squares instrumental variable analysis, with robust standard errors for dichotomous outcomes. The instrument was the proportion of all earlier patients of the same anesthesiologist who received corticosteroids. We selected this instrument based on the first-stage F-statistic and partial  $r^2$  and on the range of predicted treatment probabilities. IV analyses were based on 461 patients (excluding 3 patients with unknown anesthesiologists, the only 2 patients of 1 anesthesiologist, and all first patients of the 10 anesthesiologists). Instrumental variable assumptions for our study were as follows (supplemental figure S6.1): (a) anesthesiologist's preference affects the probability that a patient receives corticosteroids; (b) anesthesiologist's preference for corticosteroids does not affect the outcome other than through the decision whether to administer corticosteroids, and (c) anesthesiologist's preference for corticosteroids is not related to characteristics of his patient population (8,9). The fourth assumption, required to obtain a point estimate (10,11), was the monotonicity assumption: no anesthesiologist would give corticosteroids to a certain patient unless all anesthesiologists with the same or a stronger preference would also give corticosteroids to that patient. The causal effect estimated is a local average treatment effect (11), a weighted average of the treatment effects in patients who would receive corticosteroids from anesthesiologists with a certain preference level, but not from anesthesiologists with a lower preference (10). Statistical analyses were performed with Stata 12 and the extension ivreg2 (12). Additional information regarding study population, data-extraction, study endpoints, conventional analyses, instrumental variable analyses, and sensitivity analyses are available at supplement Chapter 6.1.

## RESULTS

Table 1 displays patient characteristics and outcomes according to received treatment. The EuroSCORE was higher in patients who received corticosteroids, suggesting confounding. For the selected instrument the first-stage F-statistic was 126 and the partial  $r^2$  was 0.22 (see supplement Chapter 6.1 and Table S6.1). Table 2 shows patient characteristics across physician's preference quintiles. There was no clear pattern across physician's preference quintiles in EuroSCORE (see supplement Figure S6.2) for EuroSCORE per anesthesiologist) or other patient characteristics, suggesting physicians' preference for corticosteroids was not related to differences in patients' prognosis.

**Table 1.** Patient Characteristics and Outcomes by Treatment Status

	Prophylactic Corticosteroids			
	No. (n=361)		No. (n=116)	
<b>Patient Characteristics</b>				
Male	246	(68)	69	(60)
Age (years); mean (SD)	64.5	(13.5)	63.9	(12.9)
BMI (kg/m <sup>2</sup> ); mean (SD)	26.6	(4.2)	26.4	(4.2)
Diabetes mellitus	54	(15)	15	(13)
EuroSCORE; median (IQR)	4	(2–8)	5	(3–10)
EuroSCORE category				
1–2%	115	(32)	23	(20)
3–5%	110	(31)	35	(31)
≥ 6%	134	(37)	55	(49)
Type of Surgery				
Off-pump CABG	36	(10)	6	(5)
On-pump CABG	100	(28)	29	(25)
Valve	116	(32)	39	(34)
Combination/other	109	(30)	41	(36)
<b>Outcomes</b>				
Mortality (30 days)	10	(2.8)	4	(3.5)
Ventilation time (hrs); median (IQR)	10	(7–19)	11	(7–20)
ICU stay (days); median (IQR)	1	(1–3)	2	(1–4)
Hospital stay (days); median (IQR)	7	(6–11)	8	(6–13)
Highest norepinephrine dos > 0,1 µg/kg/min	112	(33)	35	(32)
Highest glucose (mmol/l); Mean (SD)	10.4	(2.4)	11.4	(2.5)
Highest leukocyte count (10 <sup>9</sup> /L); mean (SD)	13.4	(4.0)	15.6	(5.1)
Atrial fibrillation	173	(48)	50	(44)
Infection	52	(15)	15	(13)
Heart failure	48	(13)	22	(19)
Delirium	54	(15)	20	(18)

aNo. (%), unless otherwise indicated.

BMI, body mass index; CABG, coronary artery bypass graft; IQR, interquartile range

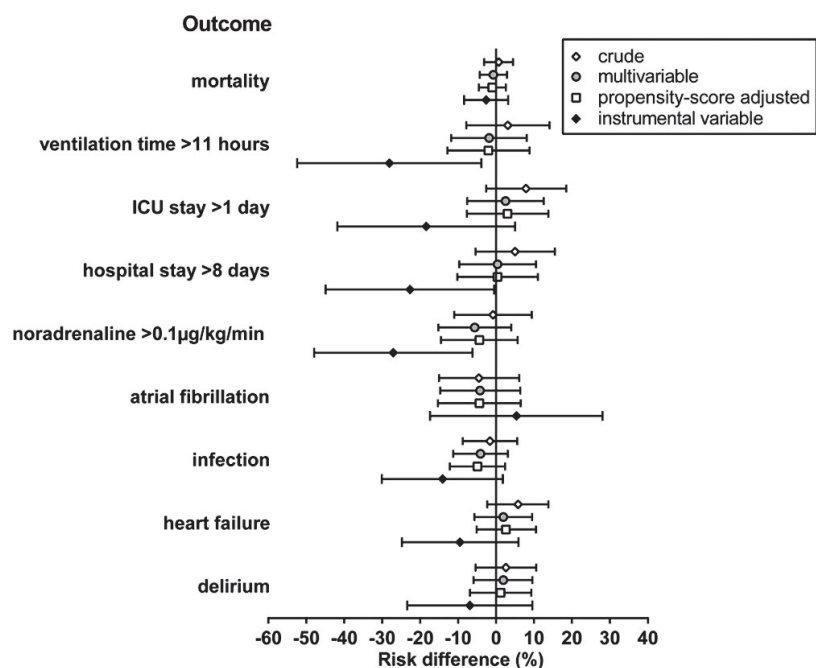
Table 2 shows a decreasing pattern across physician's preference categories for duration of ventilation and infections.

**Table 2.** Patient characteristics and Outcomes by instrumental Variable Status

	Instrumental Variable Quintile				
	1 (n=104)	2 (n=84)	3 (n=89)	4 (n=92)	5 (n=92)
% Prophylactic corticosteroids in all previous patients	0	2-8	9-19	19-42	43-100
Prophylactic corticosteroids in current patient	8 (8)	2 (4)	19 (21)	27 (29)	57 (62)
<b>Patient Characteristics</b>					
Male	69 (66)	52 (62)	59 (66)	63 (68)	61 (66)
Age (years); mean (SD)	62.6 (13.6)	65.2 (12.9)	65.1 (13.6)	64.0 (13.4)	63.8 (13.1)
BMI (kg/m <sup>2</sup> ); mean (SD)	25.9 (3.7)	26.5 (4.2)	26.4 (4.2)	26.3 (3.8)	27.1 (4.6)
Diabetes mellitus	14 (14)	9 (11)	13 (15)	11 (12)	16 (17)
EuroSCORE; median (IQR)	4 (2-9)	4 (2-8)	5 (3-8)	4 (2-9)	4 (2-9)
EuroSCORE category					
1-2%	34 (33)	28 (33)	18 (20)	29 (32)	28 (31)
3-5%	27 (26)	22 (26)	28 (32)	28 (30)	32 (35)
≥6%	41 (40)	34 (40)	42 (48)	35 (38)	31 (34)
Type of surgery					
Off-pump CABG	8 (8)	10 (12)	9 (10)	8 (9)	7 (8)
On-pump CABG	26 (25)	25 (30)	15 (17)	27 (29)	28 (30)
Valve	32 (31)	30 (36)	35 (39)	23 (25)	32 (35)
Combination/ Other	38 (37)	19 (23)	30 (34)	34 (37)	25 (27)
<b>Outcomes</b>					
Mortality (30 days)	2 (1.9)	2 (2.4)	5 (5.6)	4 (4.4)	1 (1.1)
Ventilation time (hrs); median (IQR)	12 (8-20)	11 (7-23)	12 (7-24)	10 (7-20)	9 (6-14)
ICU stay (days); median (IQR)	2 (1-4)	1 (1-3)	2 (1-3)	2 (1-4)	1 (1-1)
Hospital stay (days); median (IQR)	8 (6-13)	7 (5-9)	8 (6-11)	8.5 (6-14)	8 (5.5-9)
Highest norepinephrine dose > 0.1µg/kg/min	28 (31)	30 (37)	32 (39)	39 (45)	14 (16)
Highest glucose (mmol/l); mean (SD)	10.6 (2.3)	10.6 (2.5)	10.6 (3.0)	10.2 (1.8)	11.2 (2.6)
Highest leukocyte count (10 <sup>9</sup> /L); mean (SD)	13.0 (3.3)	12.8 (3.3)	14.7 (5.2)	14.4 (4.9)	15.0 (4.8)
Atrial fibrillation	42 (41)	40 (48)	45 (51)	44 (48)	44 (48)
Infection	18 (18)	16 (19)	12 (13)	12 (13)	9 (10)
Heart failure	18 (17)	9 (11)	19 (21)	14 (15)	9 (10)
Delirium	16 (16)	15 (18)	16 (18)	16 (18)	9 (10)

<sup>a</sup>No. (%), unless otherwise indicated.

**Figure 1.** Estimates of the effect of prophylactic corticosteroids on clinical outcomes in cardiac surgery patients, from crude, multivariable, propensity-score-adjusted, and instrumental variable analyses. Risk differences with 95% confidence interval are shown.



Results of conventional and instrumental variable analyses are displayed in the Figure 1 (dichotomous outcomes only) and supplement Table S6.2.

In general, unadjusted conventional analyses showed poorer outcomes in patients treated with corticosteroids (except for atrial fibrillation, infections, and norepinephrine dose). Multivariable and propensity-score-adjusted analyses generally showed a null effect. Instrumental variable results indicated a decreased risk of adverse outcomes (except atrial fibrillation) after corticosteroid administration. However, confidence intervals of IV estimates were much wider than those of conventional estimates. For example, crude analysis indicated the risk of a ventilation time >11 hours was 3.1% higher (95% confidence interval = -7.8% to 14.1%), propensity-score-adjusted analysis indicated it was 2.0% lower (-12.8% to 8.8%), and instrumental variable analysis indicated it was 28.1% lower (-52.4% to -3.9%) for patients who received corticosteroids. Instrumental variable estimates of differences in glucose and leukocyte count were slightly higher than estimates from the other analyses (Supplement Table S6.2).

Because of our small sample size, we could compare our results only to secondary outcomes of the Dexamethasone for Cardiac Surgery randomized clinical trial (4). In general, effects in our instrumental variable analyses were similar in direction to the randomized clinical trial results (supplement Chapter 6.2) but with considerably larger effect sizes. For example, whereas our instrumental variable analyses estimated the risk of a ventilation time >24 hours to be 16.3% lower (-33.2% to 0.5%) for patients who received corticosteroids, the randomized clinical trial estimated this difference to be -1.5% (-2.7% to -0.3%) (4).

Neither adjusting the instrumental variable analysis for patient characteristics, nor using an instrumental variable based on the last 5 patients materially changed the results (supplement Table S6.3) Sensitivity analyses estimating relative risks yielded similar effect sizes (supplement Table S6.4).

## DISCUSSION

We investigated whether physician's preference-based instrumental variable analysis was valid and useful in a moderate-sized study for the question whether preoperative corticosteroids are beneficial in cardiac surgery. In contrast to crude and propensity score-adjusted analyses, instrumental variable analysis using anesthesiologists' preferences as an instrument showed beneficial effects, similar in direction to the Dexamethasone for Cardiac Surgery randomized clinical trial results (4), and compatible with pathophysiologic insights concerning prevention of operation-induced systemic inflammation (13–15). However, compared with the trial results, the instrumental variable estimates were extremely large and confidence intervals were so wide as to preclude useful conclusions.

A reason for the difference in magnitude between our instrumental variable estimates and the randomized clinical trial results could be effect modification because of baseline prognostic differences between the study populations. Our patients seemed to be more high risk, as indicated by longer ventilation and ICU stay times and higher incidences of most outcomes.

There are also design-inherent explanations for the large size of the instrumental variable effect estimates. First, our smaller number of patients, compared with the randomized clinical trial, gives rise to less statistical precision, which is further aggravated in the IV analysis because of its 2-stage approach (16). This lack of precision, reflected in the large confidence intervals, could lead to the instrumental variable estimates being more extreme by chance.

Second, main instrumental variable assumptions may be violated. We would not expect differences in patient characteristics depending on anesthesiologist's preference for corticosteroids (independence assumption), as patients are assigned to the anesthesiologist on duty on the day of surgery. The lack of a consistent pattern in measured patient characteristics across quintiles of the instrumental variable is therefore reassuring. The assumption that preference for corticosteroids does not affect outcomes other than through administration of corticosteroids is more difficult to assess but seems plausible, as anesthesiologists took care of the patients only during surgery and were not involved in subsequent ICU care.

Third, violation of the monotonicity assumption could contribute to the extreme estimates. For example, if patients who receive corticosteroids from an anesthesiologist with a weak preference would not receive them from an anesthesiologist with a strong preference and if corticosteroids are of relatively little benefit to these patients, then the estimate of the effect of corticosteroids would be too favorable.

Fourth, estimands of the conventional and the instrumental variable analyses are different: the conventional analyses estimate average treatment effects in the population, whereas the instrumental variable analyses estimate local average treatment effects (as explained in the Methods section).

Fifth, finite sample bias might be a reason for the large instrumental variable effect estimates. However, the first-stage F-statistic of 126 should be sufficient for finite sample bias to be negligible (1). We further explored this use of simulations under conditions similar to our study (100–500 patients; mean partial  $r^2$  of 0.17; unmeasured confounding and a binary outcome occurring in 50% of patients; see supplement. Mean instrumental variable estimates were close to the “true” treatment effect of 0.10, even when the sample size was reduced to 100 patients, indicating no substantial finite sample bias with an instrument of this strength.

## CONCLUSION

In conclusion, despite availability of a strong instrument, plausibly fulfilling main instrumental variable assumptions, physician's preference-based instrumental variable analysis in a moderate-sized study population showed results that differed greatly in magnitude from results of a major randomized clinical trial on the same intervention. We have explored possible reasons and conclude that this phenomenon is most likely because of the reduced statistical precision of the instrumental variable analysis in datasets of moderate size.

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## LIST OF ABBREVIATIONS

ICU:	Intensive Care Unit
IV:	Instrumental Variable

## REFERENCES

1. Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. Instrumental variables: application and limitations. *Epidemiology*. 2006;17:260–267.
2. Ng CS, Wan S, Arifi AA, Yim AP. Inflammatory response to pulmonary ischemia-reperfusion injury. *Surg Today*. 2006;36:205–214.
3. Clark SC. Lung injury after cardiopulmonary bypass. *Perfusion*. 2006;21:225–228.
4. Dieleman JM, Nierich AP, Rosseel PM, et al.; Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA*. 2012;308:1761–1767.
5. Silbert BS, Santamaria JD, O'Brien JL, Blyth CM, Kelly WJ, Molnar RR. Early extubation following coronary artery bypass surgery: a prospective randomized controlled trial. The Fast Track Cardiac Care Team. *Chest*. 1998;113:1481–1488.
6. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999;16:9–13.
7. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. *Eur Heart J*. 2003;24:881–882.
8. Brookhart MA, Wang PS, Solomon DH, Schneeweiss S. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiology*. 2006;17:268–275.
9. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S. Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. *J Clin Epidemiol*. 2009;62:1226–1232.
10. Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? *Epidemiology*. 2006;17:360–372.
11. Swanson SA, Hernán MA. Commentary: how to report instrumental variable analyses (suggestions welcome). *Epidemiology*. 2013;24:370–374.
12. Baum CF, Schaffer ME, Stillman S. ivreg2: stata module for extended instrumental variables/2SLS, GMM and AC/HAC, LIML and k-class regression; 2010.
13. Warren OJ, Smith AJ, Alexiou C, et al. The inflammatory response to cardiopulmonary bypass: part 1—mechanisms of pathogenesis. *J Cardiothorac Vasc Anesth*. 2009;23:223–231.
14. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood*. 2003;101:3765–3777.
15. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. *Crit Care Med*. 2001;29(7 suppl):S99–106.
16. Ionescu-Iltu R, Delaney JA, Abrahamowicz M. Bias-variance trade-off in pharmacoepidemiological studies using physician-preference-based instrumental variables: a simulation study. *Pharmacoepidemiol Drug Saf*. 2009;18:562–571.

## SUPPLEMENTARY MATERIAL

### Contains:

6.1 Methods

6.2 Comparison to DECS trial results

Figure S6.1 Instrumental Variable assumptions on 5 different preference assignments

Figure S6.2 Proportion of patients to whom an anesthesiologist administered prophylactic corticosteroids (lower part) and distribution of the EuroSCORE of these patients (upper part). Search strategy

Table S6.1 Strength of instruments based on 5 different preference assignments

Table S6.2 Outcomes by treatment status and estimates of the treatment effect from four different analyses.

Table S6.3 Sensitivity analysis

Table S6.4 Relative Risk estimates.

