

Confounding by Contraindication in a Nationwide Cohort Study of Risk for Death in Patients Taking Ibopamine

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Background: Outcomes may differ in treated and untreated patients because of a contraindication for treatment in the latter that is independently associated with the outcome of interest.

Objective: To evaluate the effects of confounding by contraindication on risk factors for death in patients taking ibopamine after its use was restricted in early September 1995.

Design: Retrospective cohort study.

Setting: The Netherlands.

Patients: 1146 patients with congestive heart failure who were prescribed ibopamine at least once and for whom medication history and medical data were available.

Measurements: Cardiovascular risk factors, clinical characteristics, and medication use. Each patient was assigned an index date

(the date of death, or a random date for patients still alive at the end of the study).

Results: In univariate analyses comparing patients with an index date before and those with an index date after 8 September 1995, the relative risk for death associated with current use of ibopamine was 3.02 (95% CI, 2.12 to 4.30) compared with 0.71 (CI, 0.53 to 0.96), respectively. In multivariate analyses, the risk for death was 2.62 (CI, 1.76 to 3.90) and 0.93 (CI, 0.84 to 1.02), respectively.

Conclusion: The marked inversion of the relative risk estimate can be considered a practical example of confounding by contraindication.

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Confounding is one of the major threats to validity in observational studies. However, despite the advantages of randomization in drug effects research, several issues of drug safety can be addressed efficiently only in an observational study (1). Careful study design and appropriate data analysis can strongly reduce the effects of potential confounding in observational studies (2). Confounding by indication and contraindication threatens study validity in nonrandomized comparisons of treatment effects (3). Confounding by indication pertains to differences in outcome between treated and untreated patients that are not attributed to the treatment effect but may occur when the indication for treatment is an independent risk factor for the study outcome. In confounding by contraindication, differences in outcome between treated and untreated patients are attributed at least in part to a contraindication for treatment in the untreated patients. Confounding by contraindication usually leads to an underestimation of the relative risk because patients at risk for the outcome of interest do not receive treatment.

Recently, we completed a cohort study in the Netherlands on risk factors for death in users of ibopamine, an orally administered dopamine agonist (4). Our cohort study was initiated in response to the results of a large trial published in 1995, which showed that ibo-

pamine compared with placebo increased mortality rates in patients with moderate to severe heart failure (5). On the basis of these results, the indication for ibopamine in the Netherlands was restricted to patients with mild heart failure (6). Because the restriction occurred within our study period, we had a unique opportunity to study its influence on estimates of mortality risk.

METHODS

Setting and Design

In early September 1995, all 2147 drug-dispensing outlets in the Netherlands were requested to list all patients to whom they had dispensed ibopamine (4). Of these outlets, 1983 (92%) responded; they reported dispensing ibopamine to 14 024 patients. General practitioners with drug-dispensing outlets received a questionnaire for each patient to whom they had dispensed ibopamine (1573 of 14 024). In addition, we selected a random sample of 1573 patients from the remaining 12 451 patients who obtained ibopamine from community pharmacists; we then sent the same questionnaire to the patients' general practitioners.

The questionnaire assessed cardiovascular risk factors, indication for ibopamine (New York Heart Association [NYHA] class), current use of ibopamine, and

mortality. The drug-dispensing outlets were also asked to provide a printout of the complete computerized medication record for each patient. Patients were followed from the date of the first prescription until death or the end of the study period (15 February 1996), whichever came first.

Exposure and Outcome Assessment

To assess medication use, a drug-exposure window of 3 months preceding an index date was defined for each patient for whom both a questionnaire and a printout of the medication record were available ($n = 1146$). Every patient still alive at the end of the study period was assigned a random date in the printout of the medication record. The index date was defined as the date of death or as the random date in living patients. Drug exposure in the 3 months preceding the index date in deceased patients was compared with drug exposure in a similar 3-month period preceding the index date in patients who were still alive on 15 February 1996. Patients were considered to be current users of every drug for which a prescription was filled within the 3-month drug-exposure window or for which the end date of the legend duration (calculated by dividing the total number of delivered tablets by the prescribed daily number) overlapped the index date (the date of death or, in living patients, the random date).

Statistical Analysis

We performed stratified analyses for patients with an index date before ($n = 739$) and those with an index date after ($n = 407$) 8 September 1995. On that date, all pharmacists and all general practitioners with a drug-dispensing outlet received a letter from the Inspectorate for Health Care in the Netherlands. The letter asked that the pharmacists and physicians review their records for patients taking ibopamine and contact the prescribers to discuss whether further continuation of ibopamine was still indicated. In addition to crude and stratified univariate relative risk estimates, we performed multivariate analyses by using a generalized linear model with a log link and a binary outcome (GENMOD procedure, SAS, SAS Institute, Inc., Cary, North Carolina). All variables that were significantly associated with death in the univariate analysis were included in the model. Additional multivariate analyses were performed to correct

for potential confounding by severity by introducing two severity indicators into the statistical model; the indicators were based on concomitant cardiovascular drug use within the drug-exposure window. Severity indicator 1 reflected simultaneous use of an angiotensin-converting enzyme inhibitor, a loop diuretic, and digoxin; severity indicator 2 reflected the simultaneous use of an angiotensin-converting enzyme inhibitor, a loop diuretic, digoxin, and a vasodilatory agent.

RESULTS

In the univariate analyses of risk factors for death among deceased and living patients, stratified for index date before and after 8 September 1995, male sex, NYHA class IV at baseline, history of myocardial infarction, and a serum creatinine concentration greater than $151 \mu\text{mol/L}$ (1.7 mg/dL) were associated with a significantly increased risk for death in both groups. Age, severity indicator 2, and syncope within the past 5 years were statistically significantly associated with an increased risk for death in patients with an index date before 8 September 1995 but not in those with an index date after 8 September 1995. Current use of ibopamine was univariately associated with a relative risk for death of 3.02 (95% CI, 2.12 to 4.30) and 0.71 (CI, 0.53 to 0.96) in patients with an index date before and those with an index date after 8 September 1995, respectively. In multivariate analyses (Table), which included all univariately significant variables in combination with severity indicator 2, patients with an index date before 8 September 1995 had an adjusted relative risk for death of 2.62 (CI, 1.76 to 3.90) during current use of ibopamine, and patients with an index date after 8 September 1995 had a relative risk for death of 0.93 (CI, 0.84 to 1.02). The mean ibopamine dosage was 319 mg/d for patients with an index date before 8 September 1995, whereas for patients with an index date after 8 September 1995, the mean dosage decreased slightly toward 293 mg/d ($P = 0.03$).

DISCUSSION

The concept of confounding by contraindication is mostly discussed in theoretical terms. However, we were able to demonstrate confounding by contraindication because the registered indication and contraindications

Table. Analysis of Risk Factors for Death in 1146 Patients Who Had Taken Ibopamine

Variable	Patients with an Index Date before 8 September 1995 (n = 739)			Patients with an Index Date after 8 September 1995 (n = 407)		
	Dead (n = 165)	Alive (n = 574)	Adjusted Relative Risk (95% CI)	Dead (n = 124)	Alive (n = 283)	Adjusted Relative Risk (95% CI)
	n (%)			n (%)		
Age*						
≤64 y	25 (15)	88 (15)	1.0 (referent)	14 (11)	37 (13)	1.0 (referent)
65–74 y	32 (19)	185 (32)	0.54 (0.32–0.91)†	28 (23)	90 (32)	0.93 (0.78–1.10)
75–84 y	70 (43)	214 (37)	1.07 (0.70–1.61)	49 (39)	99 (35)	1.01 (0.85–1.18)
≥85 y	38 (23)	84 (15)	1.48 (0.90–2.44)	32 (26)	55 (19)	1.05 (0.88–1.26)
Information missing		3 (1)		1 (1)	2 (1)	
Male sex	96 (58)	270 (47)	1.50 (1.08–2.08)†	68 (55)	123 (44)	1.08 (0.98–1.20)
New York Heart Association class						
I/II	12 (7)	113 (20)	1.0 (referent)	12 (10)	66 (23)	1.0 (referent)
III	64 (39)	298 (52)	1.24 (0.65–2.37)	53 (43)	153 (54)	1.24 (1.04–1.48)†
IV	73 (44)	135 (23)	2.14 (1.13–4.06)†	49 (39)	47 (17)	1.41 (1.17–1.69)†
Information missing	16 (10)	28 (5)		10 (8)	17 (6)	
History of myocardial infarction	93 (56)	262 (46)	1.36 (1.01–1.84)†	66 (53)	109 (39)	1.07 (0.96–1.19)
Syncope within the past 5 years	45 (27)	106 (19)	0.93 (0.67–1.27)	23 (19)	48 (17)	–
Angina pectoris	101 (61)	314 (55)	–	65 (52)	148 (52)	–
Atrial fibrillation	62 (38)	209 (36)	–	56 (45)	84 (30)	–
Chronic obstructive pulmonary disease	57 (35)	161 (28)	–	30 (24)	75 (27)	–
Diabetes mellitus	43 (26)	118 (21)	–	35 (28)	56 (20)	–
Serum creatinine concentration‡						
<94 μmol/L (1.1 mg/dL)	16 (10)	134 (23)	1.0 (referent)	18 (14)	66 (23)	1.0 (referent)
94–115 μmol/L (1.1–1.3 mg/dL)	34 (21)	119 (21)	1.60 (0.91–2.82)	16 (13)	48 (17)	1.05 (0.90–1.23)
116–151 μmol/L (1.3–1.7 mg/dL)	28 (17)	101 (17)	1.31 (0.73–2.38)	24 (19)	66 (23)	1.04 (0.90–1.20)
>151 μmol/L (1.7 mg/dL)	47 (28)	90 (16)	2.32 (1.35–3.97)†	38 (31)	44 (16)	1.09 (0.93–1.26)
Information missing	40 (24)	130 (23)		28 (23)	59 (21)	
Severity indicator §	22 (13)	48 (8)	1.32 (0.90–2.44)	13 (11)	28 (10)	0.97 (0.82–1.13)
Current use of ibopamine	132 (80)	289 (50)	2.62 (1.76–3.90)†	56 (45)	162 (57)	0.93 (0.84–1.02)

* For patients with an index date before and those with an index date after 8 September 1995, the mean age ± SD was 76 ± 0.8 years and 77.0 ± 0.9 years, respectively, for deceased patients and 73.7 ± 0.5 years and 75.0 ± 0.7 years, respectively, for living patients.

† Values are statistically significant.

‡ For patients with an index date before and those with an index date after 8 September 1995, the mean serum creatinine concentration ± SD was 152 ± 7.6 μmol/L (1.7 ± 0.09 mg/dL) and 161 ± 11.3 μmol/L (1.8 ± 0.1 mg/dL), respectively, for deceased patients and 123 ± 2.8 μmol/L (1.4 ± 0.03 mg/dL) and 124 ± 3.3 μmol/L (1.4 ± 0.04 mg/dL), respectively, for living patients.

§ Simultaneous use of an angiotensin-converting enzyme inhibitor, a loop diuretic, digoxin, and a vasodilatory agent during the 3-month drug-exposure window.

abruptly changed within our study period. In current users of ibopamine with an index date before 8 September 1995, we demonstrated an adjusted relative risk for death of 2.62, a statistically significant increase. In patients with an index date after 8 September 1995, however, current use of ibopamine was associated with a neutral or even protective effect (although this effect was no longer statistically significant in multivariate analyses).

These seemingly contradictory findings can be explained by confounding by contraindication. Confounding was caused by restriction of the indication for ibopamine in the Netherlands in early September 1995 and the issuing of two direct mailings from the Inspectorate for Health Care to physicians and pharmacists regarding ibopamine use. Until September 1995, ibopamine was considered a useful drug in the treatment of

congestive heart failure. The unexpected and sudden reversal of the relative risk toward a neutral or even protective effect of ibopamine in current users with an index date after 8 September 1995 constitutes, in the absence of any other likely explanation, a practical example of confounding by contraindication in an epidemiologic study. According to the information obtained from the general practitioners, 76% of the patients who died before 8 September 1995 had used ibopamine until the date of death, whereas after 8 September 1995 only 46% of the deceased patients had used ibopamine until the date of death ($P < 0.001$). Patients with severe congestive heart failure are most susceptible to death, and our findings indicated that ibopamine was gradually withdrawn from such patients after 8 September 1995. Our findings also nicely illustrate the phenomenon of

depletion of susceptibles (7), a concept that is directly related to confounding by contraindication. Patients who are most susceptible to the outcome of interest (death) are withdrawn from exposure (ibopamine) and move to the untreated category. Consequently, the association between exposure and outcome may disappear, or exposure may seem to have a protective effect, as shown in the analysis of patients with an index date after 8 September 1995.

Our study is strengthened by the unbiased collection of data on both exposure and outcome and the random assignment of the index date in controls before or after 8 September 1995. Information on medication use was obtained from the computerized printouts of the medication record, which was compiled before the outcome of interest occurred. Although filled prescriptions do not guarantee medication adherence, exposure based on the legend duration of filled prescriptions provides a valid approximation of the actual drug exposure (8). Substantial misclassification bias for the outcome of death is highly unlikely.

In conclusion, confounding by contraindication may have a profound effect on risk estimates in epidemiologic studies. In most studies, however, the data do not allow a detailed quantification of this confounding effect, and its impact remains speculative. Because of widespread communication of an abrupt regulatory decision, we were able to quantify the effect of confounding by contraindication on risk estimates.

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