Diabetes and 30-Day Mortality From Peptic Ulcer Bleeding and Perforation

A Danish population-based cohort study

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OBJECTIVE — Diabetes may influence the outcome of complicated peptic ulcer disease, due to angiopathy, blurring of symptoms, and increased risk of sepsis. We examined whether diabetes increased 30-day mortality among Danish patients hospitalized with bleeding or perforated peptic ulcers.

RESEARCH DESIGN AND METHODS — This population-based cohort study took place in the three Danish counties of North Jutland, Viborg, and Aarhus between 1991 and 2003. Patients hospitalized with a first-time diagnosis of peptic ulcer bleeding or perforation were identified using the counties' hospital discharge registries. Data on diabetes, other comorbidities, and use of ulcer-associated drugs were obtained from discharge registries and prescription databases. The Danish Civil Registry System allowed complete follow-up for mortality. The outcome under study was 30-day mortality in diabetic versus nondiabetic patients, adjusted for potential confounders.

RESULTS — We identified 7,232 patients hospitalized for bleeding ulcers, of whom 731 (10.1%) had diabetes. The 30-day mortality among diabetic patients was 16.6 vs. 10.1% for other patients with bleeding ulcers. The adjusted 30-day mortality rate ratio (MRR) for diabetic patients was 1.40 (95% CI 1.15–1.70). We also identified 2,061 patients with perforated ulcers, of whom 140 (6.8%) had diabetes. The 30-day mortality among diabetic patients was 42.9 vs. 24.0% in other patients with perforated ulcers, corresponding to an adjusted 30-day MRR of 1.51 (1.15–1.98).

CONCLUSIONS — Among patients with peptic ulcer bleeding and perforation, diabetes appears to be associated with substantially increased short-term mortality.

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n addition to well-established risks among diabetic subjects for vascular diseases, renal disease, blindness, and amputations (1,2), diabetes also is associated with a poorer outcome from several acute medical conditions, including myocardial infarction (3), possibly stroke (4), and certain severe infections (5). Diabetes may also be a risk factor for complicated peptic ulcer disease. A recent British case-control study of 1,121 patients with bleeding peptic ulcers indicated that diabetes was associated with a clearly increased relative risk for this condition (odds ratio [OR] 3.1 [95% CI 1.2–4.3]) (6).

Peptic ulcer bleeding and perforation are common medical emergencies, with an in-hospital or 30-day mortality of ~10% for bleeding ulcers (7,8) and up to 25–40% for ulcer perforation (9). Patients with diabetes may have poorer outcomes after peptic ulcer complications due to diabetic angiopathy (6), delayed ulcer healing (10), blurring of symptoms due to autonomic neuropathy, and increased risk of bacterial sepsis (11). Very limited data on the association between diabetes and outcome after peptic ulcer complications are available, due to the very large sample size needed to study this issue.

Research resources available in Denmark allowed us to undertake a cohort study within a population of 1.4 million people in three Danish counties to examine the influence of diabetes on 30-day mortality among patients with peptic ulcer bleeding and perforation.

RESEARCH DESIGN AND METHODS

The study population consisted of patients with bleeding peptic ulcers and patients with perforated peptic ulcers identified from population-based health registries in the three Danish counties of North Jutland, Aarhus, and Viborg, encompassing 26% of the Danish population. The Danish national health service provides tax-supported health care for all residents, guaranteeing free access to hospitals and primary medical care and partially reimbursing the costs of most physician-prescribed drugs. Study periods were based on availability of prescription data records in the counties, commencing on 1 January 1991 in North Jutland County, on 1 January 1996 in Aarhus County, and on 1 January 1998 in Viborg County. The study period concluded on 31 December 2002.

Record linkage
Civil registration numbers, assigned to every Danish citizen since 1968, code for age, sex, and date of birth and allow for electronic record linkage among multiple databases. Using civil registration numbers, we were able to obtain complete prescription and hospital discharge histories for study patients.

Patients with peptic ulcer bleeding or perforation
County hospital discharge registries contain key information on all patient discharges from nonpsychiatric hospitals

since 1977 (since 1972 in Viborg County). This information includes patients' civil registration numbers, admission and discharge dates, and up to 20 discharge diagnoses, assigned exclusively by physicians according to the ICD-8 until the end of 1993 and the ICD-10 thereafter. The discharge registries permitted us to identify all patients hospitalized with a first-time diagnosis of peptic ulcer bleeding or peptic ulcer perforation during the study periods. The ICD-8 codes for peptic ulcer bleeding were 53190, 53192, 53195, 53290, 53390, and 53490, and the ICD-10 codes were K250, K254, K260, K264, K270, K274, K280, and K284. The ICD-8 codes for peptic ulcer perforation were 53100, 53101, 53108, 53109, 53209, 53309, and 53409, and the ICD-10 codes were K251, K252, K255, K256, K261, K262, K265, K266, K271, K272, K275, K276, K281, K282, K285, and K286.

Data on diabetes

Data on the presence of diabetes among study patients were obtained from the counties' hospital discharge registries and prescription databases (12). The prescription databases (established in 1991 in North Jutland County, in 1996 in Aarhus County, and 1998 in Viborg County) contain information on prescriptions for all reimbursed drugs dispensed from every pharmacy in the counties (13). These data include patients' civil registration numbers, the type of drug prescribed according to the Anatomical Therapeutical Chemical classification system and dates when prescriptions were filled. Diabetes was considered present if *1*) at least one prescription for insulin or an oral antidiabetic drug was recorded and/or *2*) there was a hospital discharge diagnosis of type 1 or type 2 diabetes (ICD-8 codes 249–250 and ICD-10 codes E10–E11) before the date of hospitalization for a bleeding or perforated ulcer. We have recently evaluated the predictive value of diabetes identified by this approach among patients with community-acquired pneumococcal bacteremia during 1992–2001. In a review of 63 hospital records and laboratory charts, we found that 97% (95% CI 89–100) of diabetes diagnoses met the World Health Organization diagnostic criteria (12).

Data on possible confounding factors

To adjust for possible confounders associated with both diabetes and mortality after peptic ulcer complications, we examined data on drug use and comorbidities. The prescription databases provided data on whether, within 60 days before the date of admission for peptic ulcer bleeding or perforation, study subjects had filled a prescription ("yes" or "no") for antiulcer drugs or for systemic corticosteroids, nonsteroidal anti-inflammatory drugs, or low- or high-dose aspirin. For the subset of patients with peptic ulcer bleeding, we also obtained data on preadmission use of paracetamol, vitamin K antagonists, calcium channel blockers, and/or antidepressants. To adjust for existing comorbid diseases, we computed a summary measure of comorbidities developed by Charlson et al. (14) for each patient based on his or her complete hospital discharge history preceding the date for hospitalization with peptic ulcer bleeding or perforation. The Charlson Index includes 19 major disease categories: cardiovascular diseases, diabetes, chronic pulmonary, liver, renal, and connective tissue diseases, peptic ulcer disease, and solid and hematological malignancies, among others. For calculating the Charlson Index score, a weight is assigned to each disease category and the score is the sum of these weights. The index has been adapted and validated for use with hospital discharge registry data in ICD databases for the prediction of short- and long-term mortality (15). For this study, diabetes was excluded from the Charlson Index as it constituted our exposure variable. Diagnoses of previous uncomplicated peptic ulcer disease (excluding peptic ulcer bleeding and perforation) were also removed from the index and included as a separate variable in the analyses. Three comorbidity index levels were defined, on the basis of Charlson Index scores: 0 (low), 1–2 (medium), and 3+ (high).

Mortality

Data on mortality among study patients were obtained from the Danish Civil Registration System, which is electronically updated daily and includes records of all changes in vital status and migration in the entire Danish population since 1968, including exact date of death. The study's outcome variable was death within 30 days of hospital admission for a bleeding or perforated peptic ulcer.

Statistical analysis

The duration of follow-up extended from the admission date for peptic ulcer bleeding or perforation until death or migration or until 30 days after that date. We constructed survival curves and 30-day mortality estimates for the following study variables: diabetes, sex, age-group (<50, 50–59, 60–69, 70–79, and ≥80 years), level of comorbidity (Charlson score = 0, 1–2, or 3+), previous uncomplicated peptic ulcer disease, use of antiulcer drugs, and use of drugs associated with peptic ulcer complications. Cox regression analyses were used to compute mortality rate ratios (MRRs) with 95% CIs for diabetic compared with nondiabetic patients, adjusted for sex, age, level of comorbidity, previous uncomplicated peptic ulcer disease, and drug use. To evaluate variations in peptic ulcer complication mortality from diabetes according to the presence of heart or renal disease, we examined 30-day mortality and adjusted MRRs stratified by these morbidities. Diagnoses of heart disease, i.e., previous myocardial infarction and/or congestive heart failure, and renal disease were excluded from the Charlson Index when stratified by either of these variables. The assumption of proportional hazards in the Cox model was assessed graphically and found to be appropriate. All statistical analyses were performed with SAS software (Version 9.1.3; SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency and the Aarhus University Hospital Registry Board.

RESULTS — We identified 7,232 patients with a first-time hospitalization for peptic ulcer bleeding, and 2,061 patients with a first-time hospitalization for peptic ulcer perforation.

Peptic ulcer bleeding

Among patients with peptic ulcer bleeding, 731 (10.1%) had diabetes. Compared with nondiabetic patients, diabetic patients were slightly older and were more likely to have a history of hospital-diagnosed comorbidity and thus higher Charlson Index score levels (Table 1). The use of ulcer-associated drugs was similarly high in diabetic and nondiabetic patients. Overall, 16.6% of diabetic vs. 10.1% of nondiabetic patients with peptic ulcer bleeding died within 30 days of hospital admission, resulting in a 30-day MRR of 1.69 (95% CI 1.39–2.01). Survival curves for diabetic and nondiabetic patients with ulcer bleeding diverged early after admission; diabetic patients were at increased risk of dying throughout the observation period (Fig. 1). After

Table 1—*Characteristics of 7,232 patients with a first-time hospitalization for peptic ulcer bleeding in North Jutland, Aarhus, and Viborg counties, Denmark*

	Diabetic patients	Other patients
n	731	6,501
Age		
<50 years	25 (3)	676 (10)
50–59 years	64 (9)	773 (12)
60–69 years	135 (18)	1,078 (17)
70–79 years	230 (31)	1,879 (29)
≥80 years	277 (38)	2,095 (32)
Sex		
Male	401 (55)	3,361 (52)
Female	330 (45)	3,140 (48)
Comorbidity		
Score low (0)*	244 (33)	3,402 (52)
Score medium (1–2)	338 (46)	2,390 (37)
Score high (>2)	149 (20)	709 (11)
Previous uncomplicated peptic ulcer disease	95 (13)	747 (11)
Use of drugs associated with peptic ulcer bleeding†	635 (87)	4,973 (76)
Use of antiulcer drugs	119 (16)	1,106 (17)

Data are *n* (%). *Level of Charlson Index score (see RESEARCH DESIGN AND METHODS). †Filled prescription for systemic corticosteroids, nonsteroidal anti-inflammatory drugs, low- or high-dose aspirin, paracetamol, vitamin K antagonists, calcium channel blockers, and/or antidepressants within 60 days before admission.

adjustment for sex, age, comorbidity, previous ulcer disease, and drug use, the MRR for diabetic patients with peptic ulcer bleeding compared with that for nondiabetic patients with this condition was 1.40 (1.15–1.70) (*P* < 0.001). The 30-day mortality and the adjusted MRRs for diabetic patients increased considerably if heart disease or, in particular, renal disease was also present (Table 2).

Peptic ulcer perforation
Of 2,061 patients with perforated ulcers, 140 (6.8%) had diabetes (Table 3). Sixty-six percent of patients in this diabetic group compared with half of the patients in the nondiabetic group were >70 years old. Diabetic patients were also more likely to have medium or high Charlson Index score levels. The use of drugs potentially related to ulcer perforation was high among diabetic patients, similar to that in the nondiabetic group. The 30-day mortality among diabetic patients with perforated peptic ulcers was 42.9% compared with 24.0% among nondiabetic patients with this condition (MRR 2.01 [95% CI 1.54–2.63]). As a point of comparison, 30-day mortality in patients with peptic ulcer perforation and a history of cancer was 37.3%. Figure 2 shows survival curves during 30 days of follow-up after hospital admission for ulcer perforation. After adjustment for sex, age, comorbidity, previous ulcer disease, and drug use, the MRR for diabetic patients compared with that for nondiabetic patients was 1.51 (1.15–1.98) (*P* = 0.003). The presence of heart disease but not renal disease strengthened the association between diabetes and mortality from peptic ulcer perforation (Table 2).

CONCLUSIONS — In this large cohort study of >9,000 patients hospitalized with peptic ulcer complications, including 871 diabetic subjects, diabetes was associated with a 40–50% increase in short-term mortality for both peptic ulcer bleeding and perforation.

This study has several methodological strengths. Denmark's national health care system allowed a population-based design. Ascertainment of comorbidity and drug use through administrative registries reduced potential patient-related or investigator-related information bias. In addition, follow-up for mortality was complete.

Several limitations of this observational study also must be noted. Use of routine hospital discharge data could be associated with coding errors, leading to inclusion of some patients without ulcer bleeding or perforation. Still, the positive predictive value of recorded gastrointestinal site-specific discharge diagnoses has been reported to be high (16,17), and misclassification of ulcer complications is unlikely to be associated with diabetes. Diabetic patients with ulcers may have been hospitalized more readily than nondiabetic patients because of closer surveillance by physicians and other caregivers, but this would probably cause underestimation of their mortality.
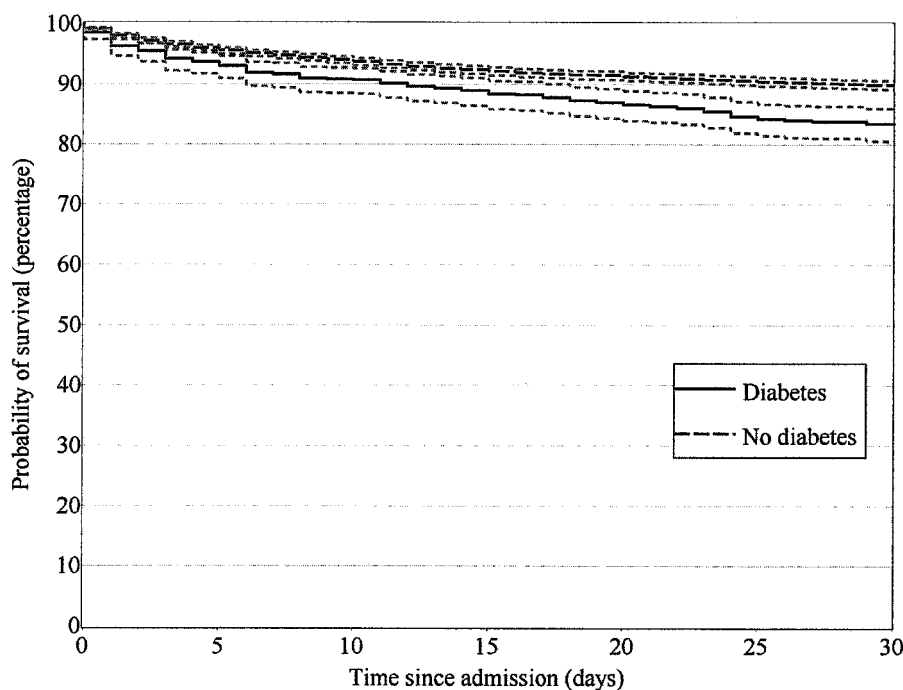

Figure 1—*Survival curves (with 95% CIs) (grey dashed lines) for patients with diabetes* (n = *731) and without diabetes* (n = *6,501) hospitalized for peptic ulcer bleeding.*

Table 2—Cumulative 30-day mortality and adjusted 30-day MRRs for patients with peptic ulcer bleeding and perforation, according to the presence of diabetes

		Peptic ulcer bleeding				Peptic ulcer perforation		
	n	30-day mortality (%)	Adjusted 30-day MRR (95% CI)*	P value (for adjusted 30-day MRR)	n	30-day mortality (%)	Adjusted 30-day MRR (95% CI)*	P value (for adjusted 30-day MRR)
Unstratified								
No diabetes	6,501	10.1	1.0 (reference)		1,921	24.0	1.0 (reference)	
Diabetes present	731	16.6	1.40 (1.15–1.70)	<0.001	140	42.9	1.51 (1.15–1.98)	0.003
Stratified by heart disease								
No heart disease								
No diabetes	5,552	9.5	1.0 (reference)		1,712	21.9	1.0 (reference)	
Diabetes present	508	13.8	1.28 (0.99–1.64)	0.06	99	35.4	1.41 (0.99–2.01)	0.05
Heart disease present								
No diabetes	976	13.5	1.11 (0.91–1.34)	0.32	209	41.2	1.37 (1.08–1.74)	0.01
Diabetes present	223	22.9	1.86 (1.39–2.49)	<0.001	41	61.0	2.29 (1.51–3.46)	<0.001
Stratified by renal disease								
No renal disease								
No diabetes	6,317	9.9	1.0 (reference)		1,895	23.8	1.0 (reference)	
Diabetes present	692	16.0	1.39 (1.13–1.70)	0.002	132	42.4	1.55 (1.17–2.05)	0.003
Renal disease present								
No diabetes	184	15.2	1.42 (0.97–2.07)	0.07	26	38.5	1.48 (0.79–2.80)	0.22
Diabetes present	39	25.6	2.46 (1.31–4.62)	0.005	8	50.0	1.40 (0.52–3.78)	0.51

Unstratified estimates and values stratified for the presence of heart and renal disease. Heart disease = previous discharge diagnoses of acute myocardial infarction and/or congestive heart failure as evidenced in the Charlson Index; renal disease = previous discharge diagnoses of moderate to severe renal disease as evidenced in the Charlson Index. *Adjusted for sex, age, Charlson Index score level, previous uncomplicated peptic ulcer disease, use of antiulcer drugs, and use of drugs associated with peptic ulcer complications. Heart and renal disease were excluded from the Charlson Index when stratified by this variable.

We examined total mortality, but we did not address cause-specific mortality. We find that total mortality is a clinically relevant, robust, and unbiased measure. It is very difficult to separate the contribution of the peptic ulcer bleeding or perforation from that of the underlying disorders when examining 30-day mortality.

We were able to adjust for a range of important potential confounding factors included in the Charlson Index, the most extensively validated comorbidity index for predicting mortality (15). Nevertheless, misclassification of comorbidity due to inaccuracy in hospital discharge diagnoses, as well as misclassification of drug use due to lack of compliance, may have produced some residual confounding and could have resulted in lowered or inflated mortality estimates. Given the higher likelihood of previous hospitalization among diabetic patients, documentation of comorbidity and thus control of confounding may have been more complete in this patient group, leading to conservative mortality estimates. We may have missed some diabetic patients in our study sample who had never previously been hospitalized or treated with drugs; again, this also would lead to underestimation of differences in outcome between diabetic and nondiabetic patients.

In Danish hospitals, standard treatment for peptic ulcer bleeding is early diagnostic endoscopy with hemostasis if required. For ulcer perforation, standard treatment is immediate intervention with either simple closure or a more complex surgical procedure (8,9). Delayed treatment is probably a major prognostic fac-

Table 3—Characteristics of 2,061 diabetic and nondiabetic patients with a first-time hospitalization for peptic ulcer perforation in North Jutland, Aarhus, and Viborg counties, Denmark*

Characteristic	Diabetic patients	Other patients
n	140	1,921
Age		
<50 years	16 (11)	298 (16)
50–59 years	8 (6)	296 (15)
60–69 years	24 (17)	378 (20)
70–79 years	50 (36)	478 (25)
≥80 years	42 (30)	471 (25)
Sex		
Male	66 (47)	889 (46)
Female	74 (53)	1,032 (54)
Comorbidity		
Score low (0)†	47 (34)	1,105 (58)
Score medium (1–2)	67 (48)	635 (33)
Score high (>2)	26 (19)	181 (9)
Previous uncomplicated peptic ulcer disease	22 (16)	210 (11)
Use of drugs associated with peptic ulcer perforation‡	104 (74)	1,351 (70)
Use of antiulcer drugs	28 (20)	337 (18)

Data are n (%). *Level of Charlson Index score (see RESEARCH DESIGN AND METHODS). †Filled prescriptions for systemic corticosteroids, nonsteroidal anti-inflammatory drugs, and/or low- or high-dose aspirin within 60 days before admission.
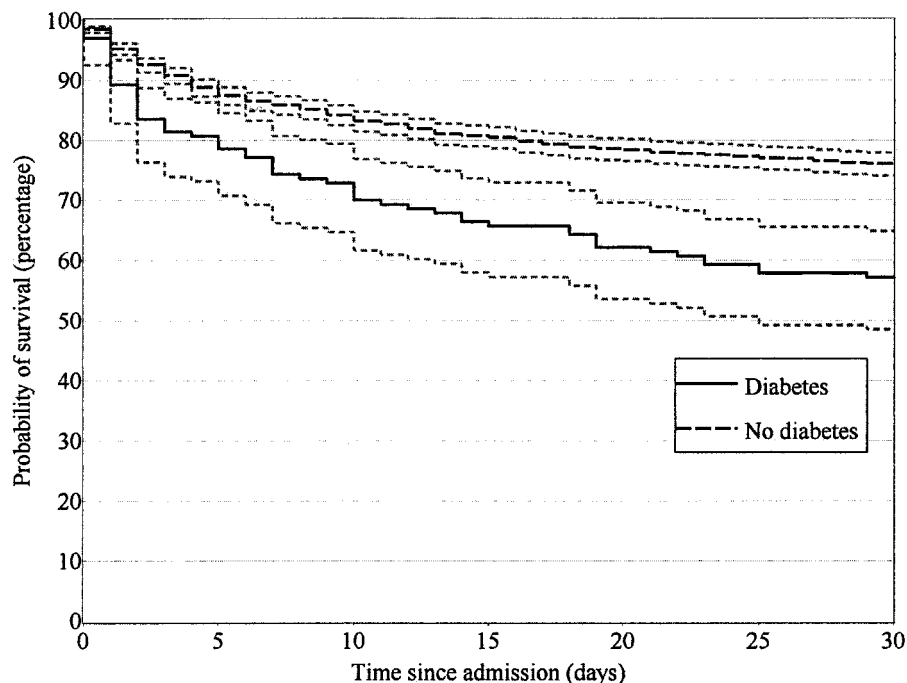
Figure 2—*Survival curves (with 95% CIs) (grey dashed lines) for patients with diabetes (n = 140) and without diabetes (n = 1,921) hospitalized for peptic ulcer perforation.*

tor for both peptic ulcer complications (18). Unfortunately, it was not possible to obtain valid information on the duration from symptom onset to initiation of treatment in this study. Thus we cannot rule out the possibility that differential treatment delay influenced our findings.

Several mechanisms may be involved in the poorer outcome observed among patients with diabetes. Diabetic angiopathy may impair mucosal integrity and lead to more severe ulcers (6) and may also make it more difficult to stop bleeding from the ulcers. In rats, diabetes has been associated with delayed gastric ulcer healing due to increased release of pro-inflammatory cytokines and attenuated angiogenesis (10). Symptoms may be vaguer in diabetic patients with perforated ulcers, because of autonomic neuropathy, and this may lead to delayed surgical treatment and poorer outcomes. However, a recent cross-sectional study found that diabetes was not a risk factor for "silent" peptic ulcer disease (19). Severe sepsis, abdominal infections, and wound infections are frequent complications and causes of death after ulcer perforation (20), and diabetes has been associated with an increased risk for these infections (5,21). The general decrease in tissue oxygenation, as well as the risk of metabolic disturbance in diabetic patients with acute disease, may further contribute to a poorer outcome compared with nondiabetic patients. We found a particularly

strong association between diabetes and mortality from peptic ulcer complications if heart or renal disease was also present, probably indicating that increased severity of diabetes was associated with a worse outcome.

We conclude that diabetes is an important prognostic factor for short-term mortality among patients with either bleeding or perforated peptic ulcers. Our findings suggest that efforts to improve outcomes from these medical emergencies in diabetic persons should be directed to reducing preventable diabetes complications. Further studies might help clarify the influence of both acute and long-term glycemic control in diabetes on the outcome from peptic ulcer complications.

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