

# Risk of cardiovascular events and pulmonary hypertension following splenectomy – a Danish population-based cohort study from 1996-2012

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Haematologica 2017  
Volume 102(8):1333-1341

## ABSTRACT

Splenectomized patients are at increased risk of cardiovascular events, but it remains unclear whether this is due to lack of the spleen or due to the underlying disease leading to splenectomy. We aimed to assess the risk of myocardial infarction, pulmonary hypertension, and stroke following splenectomy. We identified patients splenectomized in Denmark between 1996 and 2012. We constructed two comparison cohorts: an age- and sex-matched general population cohort and a disease-matched cohort based on the splenectomy-related underlying disease. We computed 5-year cumulative incidences and adjusted hazard ratios of myocardial infarction, pulmonary hypertension, and stroke for the three cohorts. The study included 5,306 splenectomized patients, 53,060 members of the general population, and 11,651 disease-matched patients. During the 5-year follow-up, 1.3% of splenectomized patients had a myocardial infarction *versus* 1.8% of the population cohort. The adjusted hazard ratio for myocardial infarction in splenectomized patients *versus* the population cohort was 1.24 (95% confidence interval: 1.01-1.52). The 5-year cumulative incidence of pulmonary hypertension was 0.4% among splenectomized subjects and 0.2% in the population cohort [adjusted hazard ratio 3.25 (95% confidence interval: 1.93-5.45)], while that of stroke was 3.3% among splenectomized patients *versus* 2.6% in the population cohort [adjusted hazard ratio 2.04 (95% confidence interval: 1.78-2.35)]. When comparing splenectomized subjects with the disease-matched cohort, only stroke risk was elevated, with 5-year risks of 3.0% and 2.3%, respectively [adjusted hazard ratio 1.56 (95% confidence interval: 1.26-1.92)]. In conclusion, splenectomized patients were at increased risk of stroke. Additionally, we found that underlying splenectomy-related diseases explained the increased risk of myocardial infarction and pulmonary hypertension following splenectomy.

## Introduction

Splenectomy is a relatively common surgical procedure performed for various medical and surgical conditions.<sup>1</sup> According to the National Hospital Discharge Survey, approximately 22,000 splenectomies are performed annually in the USA, with trauma and incidental splenectomy as the primary surgical indications and hematologic disorders as the primary medical indications.<sup>2</sup>

Splenectomy is known to be associated with both postoperative and long-term complications.<sup>1,3,5</sup> Common short-term complications have been well described and include postoperative infections, bleeding, and venous thromboembolism.<sup>3,6</sup> The most serious long-term consequence is a lifelong increased susceptibility to infections by encapsulated bacteria. Among such infections, pneumococcal sepsis has a particularly high case fatality rate.<sup>1,5</sup>

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Received: September 22, 2016.

Accepted: May 31, 2017.

Pre-published: June 1, 2017.

doi:10.3324/haematol.2016.157008

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: [www.haematologica.org/content/102/8/1333](http://www.haematologica.org/content/102/8/1333)

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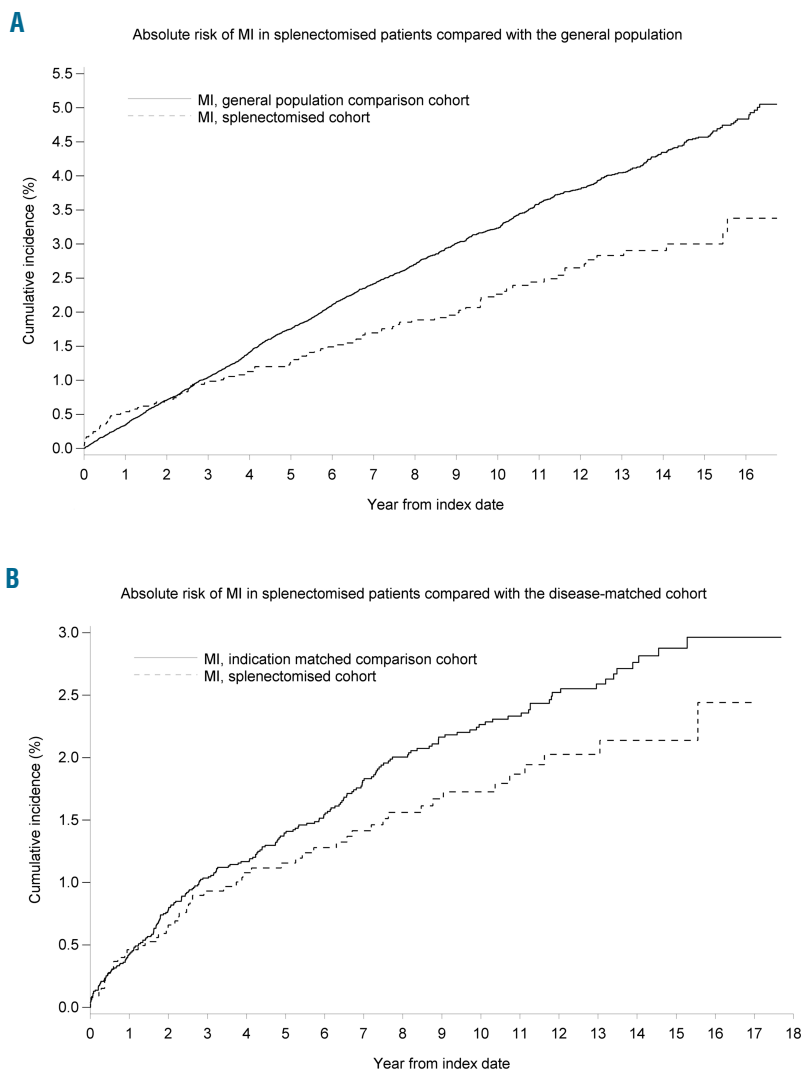


Over the past 40 years, research has suggested that splenectomized patients are also at increased long-term risk of atherosclerotic events and pulmonary hypertension (PH).<sup>4,5,7</sup> Suggested underlying mechanisms include hypercoagulability, increased platelet counts, platelet activation, disturbance and activation of the endothelium, and altered lipid profiles.<sup>4</sup> Thus, loss of the filtering function of the spleen may permit particulate matter and damaged cells to persist in the bloodstream, thereby perturbing and activating the vascular endothelium and shifting vascular homeostasis towards enhanced coagulation.<sup>4,7</sup>

Since several underlying diseases for which splenectomy is performed may be associated with increased risks of venous and arterial thrombosis,<sup>9-10</sup> it remains unclear whether increased cardiovascular risk arises from removal of the spleen or from the underlying indication for the splenectomy.<sup>11</sup> If lack of a spleen is the cause, then effects would be expected across the underlying reasons for splenectomy. Yet, Kristinsson *et al.* found no increased risks of myocardial infarction (MI) or ischemic stroke in 8,149 cancer-free veterans who underwent splenectomy for various reasons compared with the risk in four million

hospitalized veterans.<sup>5</sup> They did not, however, take into account the underlying reason for splenectomy. In an earlier Danish study, the mortality risk among splenectomized patients more than 1 year after the operation, regardless of the indication, was 2-fold higher than that in the general population. Compared with un-splenectomized patients with similar indications, the risk of death associated with splenectomy was not increased.<sup>12</sup>

Elevated risks of cardiovascular complications may have important clinical implications. Data on these risks are needed to understand and potentially prevent post-splenectomy death. We therefore conducted a nationwide population-based cohort study on the long-term risks of cardiovascular events following splenectomy. We investigated the risks of MI, PH, and stroke among patients splenectomized for a variety of indications and compared these risks with those in the general population. We then examined whether the risks were related to the splenectomy and its consequences or to the underlying diseases by comparing outcomes among patients who underwent splenectomy with outcomes among non-splenectomized patients with similar diseases.



**Figure 1. Cumulative risk of myocardial infarction following splenectomy (in years).** (A) Cumulative risk of myocardial infarction (MI) in splenectomized patients compared with the risk in the general population cohort. (B) Cumulative risk of MI in splenectomized patients compared with the risk in the disease-matched cohort.

## Methods

We used the Danish National Patient Registry (DNPR) to identify patients who underwent splenectomy between January 1, 1996 and December 31, 2012. The DNPR contains information on all admissions to Danish hospitals since 1977 and hospital outpatient clinic visits since 1995. Data include dates of admission and discharge, surgical procedures coded according to the Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures, and up to 20 discharge diagnoses coded by physicians according to the International Classification of Diseases, Eighth Revision (ICD-8) until the end of 1993, and thereafter the ICD-10. We classified splenectomized patients into eight subgroups, according to all previous diagnoses recorded in the patient registry, using the following hierarchy: (i) traumatic rupture of the spleen; (ii) idiopathic thrombocytopenic purpura; (iii) other/unspecified thrombocytopenia; (iv) hematopoietic cancer; (v) hereditary hemolytic anemia; (vi) abdominal cancer; (vii) splenomegaly/other splenic diseases only; and (viii) other indications.<sup>6,12</sup> Accordingly, if a patient had traumatic splenic rupture before the date of splenectomy, he/she was categorized into this first indication group, regardless of the presence/absence of the other indications. Patients in the “other indications” group had none of the selected indications before splenectomy. We excluded splenectomized patients with a prior diagnosis of coronary artery disease, MI, PH, or stroke before the date of surgery. Surgical and diagnostic codes are summarized in *Online Supplementary Table S1*.

We used the Danish Civil Registration System (CRS)<sup>13</sup> to select ten members of the general population for each splenectomized

patient, matched by age, sex, and calendar year of splenectomy. We also constructed a disease-matched comparison cohort, using the CRS and DNPR to identify up to five patients diagnosed with the same underlying disease in the same calendar year as the corresponding splenectomized patient. Members of this comparison cohort could not have a procedure code for splenectomy, or a diagnosis code for coronary artery disease, MI, PH, or stroke before study inclusion. As a comparison group for patients splenectomized due to trauma, we identified trauma patients who underwent surgery for acute injury of the spleen, liver, or gallbladder, with no recorded splenectomy. In our comparison of the splenectomy and disease-matched cohorts, we excluded the “other indications” subgroup from the splenectomy cohort. The date of splenectomy represented the “index date” for the matched sets of patients.

To address potential confounding, we retrieved information on the presence of the following diagnoses recorded prior to the splenectomy/index date: chronic obstructive pulmonary disease, pulmonary embolism, heart failure, diabetes, atrial fibrillation, hypertension and obesity (see *Online Supplementary Table S1* for diagnostic codes). We also retrieved information on all diagnoses of venous thromboembolism recorded prior to cardiovascular outcomes.

Splenectomized patients and members of their comparison cohorts were followed from their surgery/index dates to occurrence of any long-term outcomes of interest, death, or end of follow-up (31 December, 2012), whichever occurred first.

We used cumulative incidence functions with death as a competing event, and plotted the cumulative risks of MI, PH and

**Table 1.** Demographic characteristics of the splenectomized cohort (overall and by indication for splenectomy), the disease-matched comparison cohort, and the general population comparison cohort.

	Overall splenectomized cohort N (%)	Population comparison cohort N (%)	Disease-matched comparison cohort N (%)	INDICATION FOR SPLENECTOMY, N (%)							
				Traumatic rupture N (%)	Abdominal cancers N (%)	ITP** N (%)	Hematopoietic cancers N (%)	Splenomegaly/other splenic disease N (%)	Hereditary hemolytic anemias N (%)	Nonspecific thrombocytopenia N (%)	Other N (%)
Total, n (%)	5306 (100)	53,060 (100)	11,651 (100)	1033 (19.5)	880 (16.6)	379 (7.1)	417 (7.9)	321 (6.0)	216 (4.1)	75 (1.4)	1985 (37.4)
Age – years at	58.4	58.4	58.4	36.6	70.8	46.4	63.9	48.0	13.1	56.0	62.9
Median (IQR)	(40.1-70.3)	(40.2-70.3)	(40.2-70.3)	(22.1-53.9)	(78.5-95.2)	(28.9-60.8)	(55.5-71.7)	(32.6-63.0)	(9.7-26.7)	(43.7-66.5)	(51.6-71.8)
Sex											
Female	2485 (46.8)	24,850 (46.8)	5700 (48.9)	300 (29.0)	439 (49.9)	239 (63.0)	183 (43.9)	149 (46.4)	121 (56.0)	38 (50.6)	1016 (51.2)
Male	2821 (53.2)	28,210 (53.2)	5951 (51.1)	733 (71.0)	441 (50.1)	140 (36.9)	234 (56.1)	172 (53.6)	95 (44.0)	37 (49.3)	969 (48.8)
Year of splenectomy/index date											
1996-2001	2113 (39.8)	21,130 (39.8)	4645 (39.9)	427 (41.3)	392 (44.6)	176 (46.4)	137 (32.9)	100 (31.2)	79 (36.6)	29 (38.7)	773 (38.9)
2002-2007	1796 (33.9)	17,960 (33.9)	3935 (33.8)	399 (38.6)	298 (32.8)	117 (30.9)	144 (34.5)	124 (38.6)	90 (41.7)	30 (40.0)	603 (30.4)
2008-2012	1397 (26.3)	13,970 (26.3)	3071 (26.4)	207 (20.0)	199 (22.6)	86 (22.7)	136 (32.6)	97 (30.2)	47 (21.8)	16 (21.3)	609 (30.7)
Comorbid conditions											
COPD*	329 (6.2)	2197 (4.1)	746 (6.4)	37 (3.6)	58 (6.6)	12 (3.2)	28 (6.7)	23 (7.2)	14 (6.5)	8 (10.7)	149 (7.5)
Diabetes	210 (4.0)	1282 (2.4)	503 (4.3)	16 (1.5)	31 (3.5)	15 (4.0)	18 (4.3)	12 (3.7)	3 (1.4)	8 (10.7)	107 (5.4)
Hypertension	437 (8.2)	2610 (4.9)	972 (8.3)	31 (3.0)	93 (10.6)	21 (5.5)	30 (7.2)	23 (7.2)	0 (0)	6 (8.0)	233 (11.7)
Atrial fibrillation	130 (2.5)	1034 (1.9)	399 (3.4)	14 (1.4)	27 (3.1)	8 (2.1)	11 (2.6)	8 (2.5)	0 (0)	3 (4.0)	59 (3.0)
PE	54 (1.0)	187 (0.4)	117 (1.0)	3 (0.3)	14 (1.6)	0 (0)	11 (2.6)	2 (0.6)	0 (0)	2 (2.7)	22 (1.1)
Heart failure	64 (1.2)	436 (0.8)	205 (1.8)	5 (0.5)	16 (1.8)	4 (1.1)	6 (1.4)	2 (0.6)	1 (0.5)	0 (0)	30 (1.5)
Obesity	123 (2.3)	742 (1.4)	270 (2.3)	13 (1.3)	15 (1.7)	12 (3.2)	8 (1.9)	8 (2.5)	2 (0.9)	4 (5.3)	61 (3.1)
5-year mortality	39.4 %	9.5%	38.3%	17.3%	66.4%	7.2%	50.4%	22.3%	4.1%	44.0%	50.1%

IQR: Interquartile range; COPD: chronic obstructive pulmonary disease; PE: pulmonary embolus; ITP: idiopathic thrombocytopenic purpura.

**Table 2.** Five-year risks (cumulative incidence rates with death as a competing event) and adjusted hazard ratios, with 95% confidence intervals, of myocardial infarction, pulmonary arterial hypertension, and stroke in 5,306 splenectomized patients compared with 53,060 age- and gender-matched members of the general population, overall and stratified by indication for splenectomy.

	Myocardial infarction			Pulmonary arterial hypertension			Stroke		
	Splenectomized patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomized patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomized patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio**
Overall	1.28 (0.99-1.63)	1.75 (1.64-1.88)	1.24 (1.01-1.52)	0.35 (0.21-0.56)	0.16 (0.12-0.20)	3.25 (1.93-5.46)	3.34 (2.86-3.89)	2.62 (2.47-2.77)	2.04 (1.78-2.35)
Traumatic rupture	0.54 (0.21-1.21)	0.57 (0.43-0.74)	0.74 (0.34-1.60)	0.21 (0.05-0.74)	0.06 (0.02-0.13)	1.75 (0.31-10.01)	2.78 (1.88-3.96)	0.95 (0.76-1.16)	3.12 (2.19-4.47)
Abdominal cancer	1.50 (0.82-2.55)	2.92 (2.56-3.31)	0.79 (0.47-1.33)	0.12 (0.01-0.68)	0.29 (0.19-0.43)	2.21 (0.46-10.58)	3.08 (2.03-4.48)	4.58 (4.13-5.06)	1.34 (0.96-1.87)
Idiopathic thrombocytopenic purpura	1.13 (0.38-2.71)	1.00 (0.70-1.39)	1.51 (0.70-3.25)	-	0.03 (0.00-0.15)	2.47 (0.25-24.08)	2.09 (0.93-4.09)	1.24 (0.90-1.66)	1.70 (0.99-2.91)
Hematopoietic cancers	1.86 (0.83-3.66)	2.14 (1.69-2.67)	1.12 (0.53-2.38)	0.58 (0.12-1.94)	0.14 (0.05-0.31)	5.13 (0.53 - 49.28)	4.40 (2.62-6.88)	2.83 (2.32-3.42)	2.15 (1.30-3.54)
Splenomegaly/splenic disease	1.73 (0.66-3.79)	0.81 (0.52-1.21)	2.59 (1.15-5.83)	0.77 (0.15-2.57)	0.18 (0.07-0.42)	9.44 (0.95-94.29)	4.51 (2.52-7.36)	1.59 (1.16-2.13)	5.00 (2.85-8.75)
Non-specific thrombocytopenia	2.95 (0.56-9.17)	0.94 (0.39-1.97)	1.73 (0.35-8.43)	-	-	-	3.08 (0.58-9.51)	2.14 (1.23-3.48)	1.02 (0.23-4.52)
Hereditary hemolytic anemia	-	0.17 (0.05-0.47)	3.35 (0.65-17.36)	-	0.56 (0.05-2.86)	-	0.49 (0.05-2.52)	0.57 (0.31-1.00)	4.69 (1.65-13.29)
Other indications	1.50 (1.00-2.16)	2.31 (2.08-2.54)	1.44 (1.08-1.93)	0.49 (0.23-0.94)	0.20 (0.14-0.27)	2.92 (1.33 - 6.43)	3.98 (3.12-5.00)	3.27 (3.01-3.55)	1.96 (1.57-2.44)

\*adjusted for age, sex, chronic obstructive pulmonary disease, pulmonary embolism, heart failure, diabetes, hypertension, and obesity. \*\*additionally adjusted for venous thromboembolism as a time-varying covariate.

stroke for the three study cohorts. Only the first of these outcomes were included in the analyses. We computed the 5-year mortality and 5-year cumulative incidence of MI, PH, and stroke in the three cohorts as a measure of 5-year risk, treating death as a competing event. We used stratified Cox regression analysis to compute the adjusted hazard ratio (aHR) overall and separately for all indications for splenectomy [with the corresponding 95% confidence intervals (CI)] for each outcome, with adjustment for age, sex, and the following comorbid conditions: chronic obstructive pulmonary disease, PE, heart failure, diabetes, hypertension, and obesity while we censored patients who died. In the PH analysis, we additionally included venous thromboembolism as a time-varying covariate. We also analyzed the data categorizing stroke as ischemic or hemorrhagic because of their different underlying mechanisms. Because more than two-thirds of all unspecified strokes are known to be ischemic strokes, we re-categorized unspecified strokes as ischemic strokes.<sup>14</sup> In a separate analysis, we additionally adjusted for atrial fibrillation to explore whether this could be an intermediate step.

All analyses were conducted using SAS 9.2 software. The study was approved by the Danish Data Protection Agency (Jr n. 1-16-02-1-08).

## Results

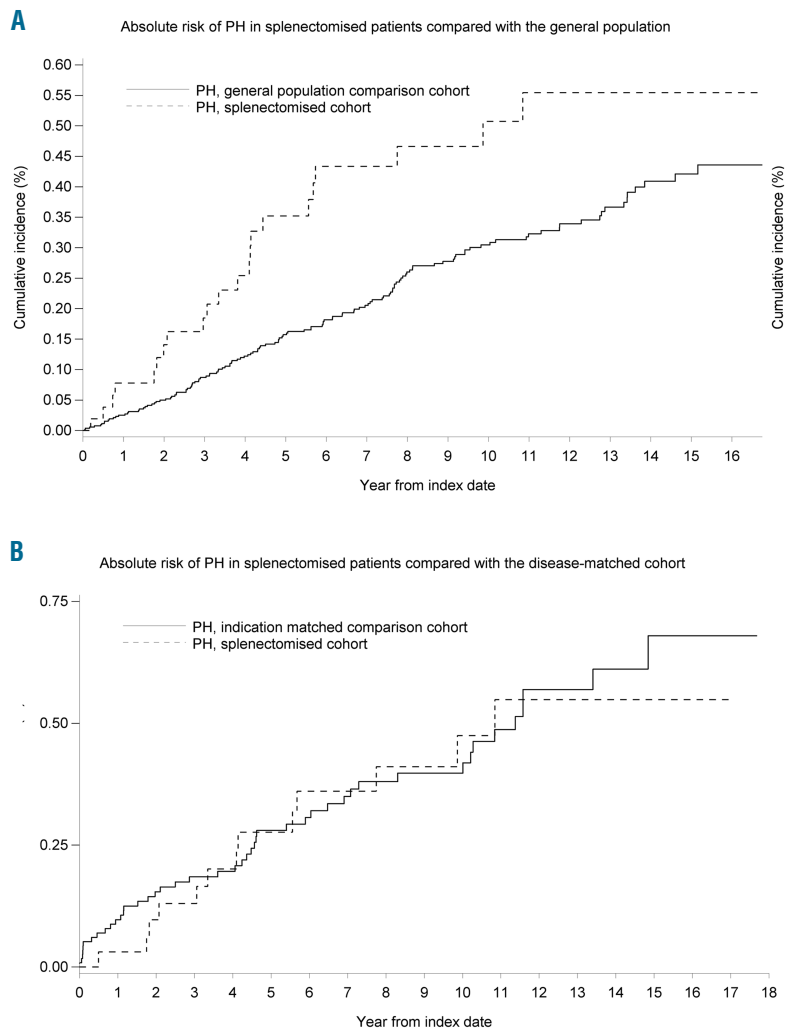
### Patients' characteristics

We identified 5,306 patients who had undergone

splenectomy, 53,060 matched members of the general population, and 11,651 members of a disease-matched cohort. Their characteristics and 5-year mortality rates are summarized in Table 1. The four most frequently recorded indications for splenectomy were traumatic rupture of the spleen [1,033 patients (19.5%)], abdominal cancers [880 patients (16.6%)], hematopoietic cancers [417 patients (7.9%)], and idiopathic thrombocytopenic purpura [379 patients (7.1%)]. In total, 1,985 patients (37.4%) had none of the specified indications. Of the comorbid conditions examined, hypertension and chronic obstructive pulmonary disease were most frequently reported, with a prevalence of 8.2% and 6.2%, respectively, among splenectomized patients overall. The prevalence of comorbidity was generally higher than in the general population comparison cohort (Table 1). Among the general population, 4.9% had hypertension and 4.1% had chronic obstructive pulmonary disease. Patients with other indications were older and had a high prevalence of comorbid conditions. The splenectomy cohort and the disease-matched cohort had almost equal rates of the specified comorbid conditions (Table 1).

### Study outcomes

We followed the splenectomized cohort for a median of 3.8 years (maximum 17.0 years). Figure 1 illustrates the cumulative risk of MI for the splenectomy and comparison cohorts over the entire follow-up period. After 5 years



**Figure 2. Cumulative risk of pulmonary hypertension following splenectomy (in years).** (A) Cumulative risk of pulmonary hypertension (PH) in splenectomized patients compared with the risk in the general population cohort. (B) Cumulative risk of PH in splenectomized patients compared with the risk in the disease-matched cohort.

of follow-up, the risk of a first-time MI was 1.3% (95% CI: 1.0%-1.6%) among splenectomized patients compared with 1.8% (95% CI: 1.6%-1.9%) among members of the general population cohort, taking death into account as a competing event. However, the unadjusted HR comparing splenectomized patients with the general population cohort was 1.28 (95% CI: 1.04 - 1.57) and the aHR was 1.24 (95% CI: 1.01-1.52) (Table 2). In contrast, splenectomized patients and the disease-matched cohort had similar 5-year risks of MI (Table 3). Considering death as a competing event, the 5-year risk of MI was 1.2% (95% CI: 0.8%-1.6%) in the splenectomy cohort and 1.4% (95% CI: 1.2%-1.6%) in the disease-matched cohort, with an unadjusted HR for MI of 0.92 (95% CI: 0.68 - 1.24) and an aHR of 0.95 (95% CI: 0.70-1.28). Compared with the disease-matched cohort, the relative risk of MI did not vary substantially between subgroups of splenectomized patients.

The 5-year risk of PH was 0.4% (95% CI: 0.2%-0.6%) in splenectomized patients compared with 0.2% (95% CI 0.1%-0.2%) in the general population cohort (Figure 2), with an aHR of 3.25 (95% CI: 1.93-5.46) (Table 2). However, the cumulative incidences were similar in the splenectomy and disease-matched cohorts (Figure 2) with an aHR of 1.03 (95% CI: 0.55-1.93) (Table 3). Comparing

splenectomized patients with those in the disease-matched cohort, the aHR of PH was 7.89 (95% CI: 0.71-87.99) among patients with splenomegaly/splenic disease and 4.16 (95% CI: 0.58-29.88) for patients with idiopathic thrombocytopenic purpura. However, the statistical precision of these estimates was low (Table 3).

Among splenectomized patients, 3.3% (95% CI: 2.9%-3.9%) had a stroke within the first 5 years of follow-up, compared with 2.6% (95% CI: 2.5%-2.8%) of people in the general population cohort (Table 2 and Figure 3), taking death into account as a competing event. The unadjusted HR was 2.05 (95% CI: 1.79-2.36) and the aHR was 2.04 (95% CI: 1.78-2.35) (Table 2). Compared with the general population cohort, the 5-year risk of stroke was consistently higher in all splenectomy indication subgroups, except for the subgroup with non-specific thrombocytopenia (Table 2). The cumulative incidence of stroke was higher in splenectomized patients than in the disease-matched cohort (Figure 3). The 5-year stroke risk was 3.0% (95% CI: 2.4%-3.7%) and 2.3% (95% CI: 2.0%-2.6%) in the two groups, respectively (Table 3). After 10 years of follow-up the stroke risk remained higher in splenectomized patients than in the disease-matched cohort [4.9% (95% CI: 4.1-5.8) versus 4.0% (95% CI: 3.5-4.4), respectively]. The unadjusted HR was 1.48 (95% CI:



1.22-1.80) and the aHR was 1.53 (95% CI; 1.26-1.86) (Table 3). In the disease-matched comparisons, the 5-year stroke risk was higher in splenectomized patients than in non-splenectomized ones in all sub-groups except for those with idiopathic thrombocytopenic purpura or non-specific thrombocytopenia (Table 3). For patients splenectomized because of traumatic rupture of the spleen, the aHR for stroke was 3.12 (95% CI: 2.19-4.47) compared with the general population cohort (Table 2) and 1.95 (95% CI: 1.06-3.58) compared with disease-matched patients who underwent surgery for acute injury of the spleen, liver, or gallbladder, with no recorded splenectomy (Table 3).

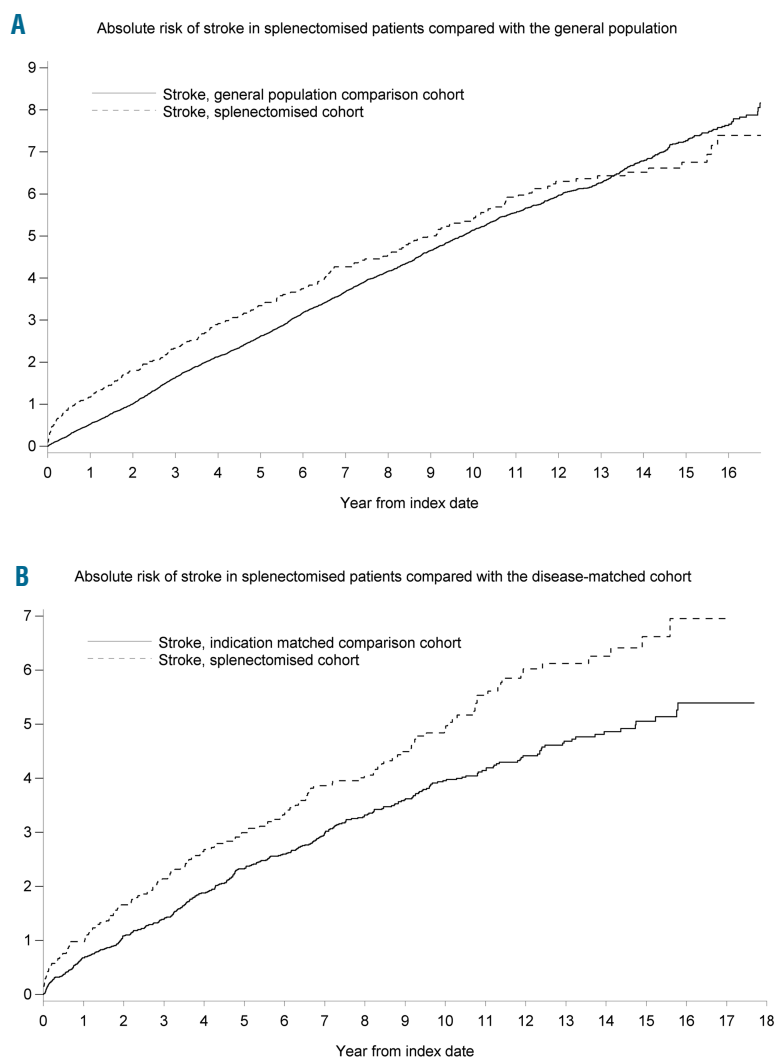
When we analyzed the risk of ischemic and hemorrhagic stroke separately, we found that splenectomized patients had a 2-fold increased risk of ischemic stroke compared with the general population cohort [aHR 2.05 (95% CI: 1.76 - 2.37)] (Table 4) and a 50% increased risk of ischemic stroke, compared with the disease-matched cohort [aHR 1.56 (95% CI: 1.26 - 1.92)]. For haemorrhagic stroke, the aHR were similarly increased: 1.77 (95% CI: 1.17 - 2.70) for the splenectomy cohort compared with the general population cohort and 1.37 (95% CI: 0.81 - 2.31)

for the splenectomy cohort compared with the disease-matched cohort.

Including atrial fibrillation as a covariate did not substantially change the aHR for stroke overall, ischemic stroke, or hemorrhagic stroke (*data not shown*).

## Discussion

Our nationwide population-based study showed that splenectomized patients had, as expected, higher risks of MI, PH, and stroke than people in the general population. When we compared splenectomized patients with a disease-matched cohort, we found similar risks of MI and PH. This indicates that the underlying medical conditions for which the splenectomy was performed caused the increased risk of MI and PH. However, splenectomized patients had a 50% higher risk of ischemic stroke and a 30% increased risk of hemorrhagic stroke compared with patients in the disease-matched cohort. This suggests that the increased risk of stroke was a consequence of the splenectomy, rather than of the underlying disease leading to splenectomy.



**Figure 3. Cumulative risk of stroke following splenectomy (in years).** (A) Cumulative risk of stroke in splenectomized patients compared with the risk in the general population cohort. (B) Cumulative risk of stroke in splenectomized patients compared with the risk in the disease-matched cohort.

The increased risk of cardiovascular events following splenectomy was first suggested in a study of 745 World War II servicemen who had been splenectomized because of trauma.<sup>15</sup> By the end of 1974, the risk of death due to ischemic heart disease was nearly doubled following splenectomy.<sup>15</sup> However, the majority of cardiovascular deaths in splenectomized servicemen (36 out of a total of 41) occurred more than 15 years after the splenectomy. This is in accordance with our finding that splenectomized patients did not have higher risk of MI than the general population cohort during our 17-year follow-up period. When we took death into account as a competing event the 5-year risk of MI was in fact slightly higher in the background population than in splenectomized patients. Still, we found an overall increased hazard ratio of MI and PH when comparing splenectomized subjects with the background population illustrating that although splenectomized people have a higher risk of MI, they also have a higher mortality than the background population and, therefore, fewer of them will live long enough to actually develop MI or PH.

Two previous studies, both restricted to patients with hereditary spherocytosis, indicated that splenectomy increased the risk of arteriosclerotic events (stroke, MI, and coronary or carotid artery surgery) 5- to 7-fold.<sup>16,17</sup> In our study, we categorized hereditary spherocytosis with other hereditary hemolytic anemias and found that the risks of MI and stroke were less than 70% increased, when comparing splenectomized and non-splene-

ctomized patients with hemolytic anemia. This was substantially lower than previous findings.<sup>16,17</sup> Still, due to our low statistical precision, we could not rule out a 7-fold increased risk.

Latency since splenectomy and risk of cardiovascular outcomes were addressed in the large study based on US Veterans Affairs data with up to 27 years of follow-up.<sup>5</sup> Comparing splenectomized veterans with other veterans, the risk of being hospitalized with MI was not increased at any time during the follow-up period. Our study thus corroborates earlier findings that the absolute risk of MI in general is not increased following splenectomy. Because we stratified splenectomy by underlying indication, our study extended these findings. We observed that, compared with risk in the general population, the risk of MI following splenectomy was only increased for patients who were splenectomized due to hematologic disorders. The effect nearly vanished in comparisons with patients with similar hematologic disorders.

Increased incidences of PH following splenectomy were previously observed in patients with sickle cell anemia and thalassemia<sup>18</sup> and also in patients referred for lung transplantation.<sup>7</sup> When we compared our splenectomized and disease-matched cohorts, we did not find an increased risk of PH. This also suggests that it is not the absence of a spleen, but factors related to the underlying indication for splenectomy that may be the primary causes of PH. Pulmonary embolism is a risk factor for PH, and it is well documented that many of the underlying conditions for

**Table 3.** Five-year risks (cumulative incidence rates with death as a competing event) and adjusted hazard ratios with 95% confidence intervals of myocardial infarction, pulmonary arterial hypertension, and stroke in 3,321 splenectomized patients with a known underlying indication compared with 11,651 members of a disease-matched cohort. Patients with other indications for splenectomy (N=1985) were not included in the overall analyses.

	Myocardial infarction			Pulmonary arterial hypertension			Stroke		
	Splenectomized patients, 5-year risk, %	Disease-matched comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomized patients, 5-year risk, %	Disease-matched comparison cohort, 5-year risk, %	Adjusted hazard ratio*	Splenectomized patients, 5-year risk, %	Disease-matched comparison cohort, 5-year risk, %	Adjusted hazard ratio**
Overall	1.16 (0.82-1.59)	1.40 (1.18-1.64)	0.95 (0.70-1.28)	0.28 (0.13-0.53)	0.28 (0.19-0.40)	1.03 (0.55-1.93)	2.99 (2.42-3.65)	2.32 (2.04-2.64)	1.53 (1.26-1.86)
Traumatic rupture	0.54 (0.21-1.21)	0.69 (0.27-1.55)	0.55 (0.18-1.70)	0.21 (0.05-0.74)	0.14 (0.01-0.74)	1.27 (0.11 - 15.17)	2.78 (1.88-3.96)	1.53 (0.78-2.73)	1.95 (1.06-3.58)
Abdominal cancer	1.50 (0.82-2.55)	1.59 (1.24-2.02)	1.07 (0.58-1.99)	0.12 (0.01-0.68)	0.28 (0.15-0.49)	0.86 (0.17-4.32)	3.08 (2.03-4.48)	2.53 (2.06-3.06)	1.37 (0.90-2.09)
Idiopathic thrombocytopenic purpura	1.13 (0.38-2.71)	1.30 (0.83-1.95)	0.75 (0.33-1.74)	–	0.37 (0.16-0.79)	4.16 (0.58-29.88)	2.09 (0.93-4.09)	2.56 (1.87-3.42)	1.02 (0.57-1.80)
Hematopoietic cancers	1.86 (0.83-3.66)	1.80 (1.26-2.51)	1.04 (0.46-2.37)	0.58 (0.12-1.94)	0.12 (0.03-0.43)	–	4.40 (2.62-6.88)	2.46 (1.80-3.29)	1.63 (0.91-2.91)
Splenomegaly/splenic disease	1.73 (0.66-3.79)	1.22 (0.68-2.04)	2.20 (0.79-6.09)	0.77 (0.15-2.57)	0.39 (0.13-0.97)	7.89 (0.71-87.99)	4.51 (2.52-7.36)	2.33 (1.53-3.40)	1.99 (1.02-3.85)
Non-specific thrombocytopenia	2.95 (0.56-9.17)	1.49 (0.57-3.28)	0.65 (0.08-5.67)	–	0.27 (0.03-1.42)	–	3.08 (0.58-9.51)	2.46 (1.16-4.61)	0.92 (0.19-4.40)
Hereditary hemolytic anemia	–	0.29 (0.06-1.03)	1.57 (0.13-15.15)	0.56 (0.05-2.86)	0.45 (0.13-1.25)	1.30 (0.13-12.60)	0.49 (0.05-2.52)	0.82 (0.34-1.72)	2.00 (0.65- 6.10)

\*adjusted for age, sex, chronic obstructive pulmonary disease, pulmonary embolism, heart failure, diabetes, hypertension, and obesity. \*\*additionally adjusted for venous thromboembolism as a time-varying covariate.

**Table 4.** Five-year risks (cumulative incidence rates with death as a competing event) and adjusted hazard ratios with 95% confidence intervals of ischemic stroke and hemorrhagic stroke in 5,306 splenectomized patients compared with 53,060 members of an age- and gender-matched general population comparison cohort, overall and stratified by indication for splenectomy.

	Ischemic stroke			Hemorrhagic stroke		
	Splenectomized patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio* (95% CI)	Splenectomized patients, 5-year risk, %	General population comparison cohort, 5-year risk, %	Adjusted hazard ratio* (95% CI)
Overall	2.94 (2.48-3.46)	2.35 (2.21-2.49)	2.05 (1.76-2.35)	0.40 (0.25-0.61)	0.27 (0.22-0.32)	1.77 (1.17-2.70)
Traumatic rupture	1.98 (1.23-3.02)	0.80 (0.64-1.00)	2.82 (1.90-4.19)	0.80 (0.38-1.52)	0.14 (0.08-0.24)	5.05 (2.06-12.35)
Abdominal cancer	2.96 (1.93-4.34)	4.17 (3.74-4.63)	1.47 (1.05-2.06)	0.12 (0.01-0.68)	0.41 (0.29-0.58)	0.28 (0.04-2.08)
Immune thrombocytopenia	1.56 (0.59-3.43)	1.03 (0.73-1.43)	1.41 (0.76-2.64)	0.53 (0.11-1.79)	0.20 (0.09-0.41)	3.27 (0.81-13.13)
Hematopoietic cancers	3.67 (2.05-6.01)	2.62 (2.12-3.18)	2.09 (1.21-3.60)	0.74 (0.21-2.02)	0.22 (0.10-0.42)	2.92 (0.78-11.01)
Splenomegaly/splenic disease	3.87 (2.04-6.59)	1.41 (1.01-1.92)	5.18 (2.82-9.50)	0.64 (0.13-2.15)	0.18 (0.07-0.42)	7.98 (1.44-44.12)
Non-specific thrombocytopenia	3.08 (0.58-9.51)	1.98 (1.11-3.28)	1.21 (0.27-5.46)	–	–	–
Hereditary hemolytic anemia	0.49 (0.05-2.52)	0.47 (0.23-0.87)	6.29 (2.18-18.20)	–	0.10 (0.02-0.35)	–
Other indications	3.74 (2.91-4.72)	2.95 (2.69-3.21)	2.02 (1.60-2.40)	0.25 (0.08-0.61)	0.33 (0.25-0.43)	1.10 (0.51-2.40)

which splenectomy is performed are associated with increased risk of venous thromboembolism and/or PH, including malignancies, trauma, myeloproliferative neoplasms, idiopathic thrombocytopenic purpura, and hemolytic anemia.<sup>19,20</sup> Some studies have also shown that splenectomy is a risk factor for chronic thromboembolic pulmonary hypertension (defined by the absence of thrombus resolution after acute pulmonary embolism), particularly in patients splenectomized for a hemolytic disorder.<sup>11,21</sup> Unfortunately, even our large cohort did not allow us to study specific types of PH such as chronic thromboembolic pulmonary hypertension.<sup>10</sup> Moreover, a previous case series demonstrated that chronic thromboembolic pulmonary hypertension may occur more than 20 years after splenectomy for trauma.<sup>21</sup> Accordingly, our follow-up may not have been sufficiently long to capture such cases. Still, when we included venous thromboembolism as a time-varying covariate in comparisons of the splenectomized and general population cohorts, the HR was not substantially lowered. Our study additionally highlighted that the absolute risk of PH was very low.

Our finding of a nearly 2-fold increased risk of stroke among splenectomized patients compared to a disease-matched cohort with traumatic rupture of the spleen, and a nearly 3-fold increased risk of stroke compared with the general population are in line with previous research.<sup>18,22</sup> A nationwide cohort study from Taiwan considered 11,273 patients with splenic injury during 1998-2010, including 5,294 patients who were splenectomized. Compared with a control cohort from the background population splenectomized subjects had a 2-fold higher incidence of stroke while patients with splenic injury but no splenectomy

only had a 20% increased incidence.<sup>22</sup> As comparisons for those splenectomized due to trauma we similarly used patients with traumatic injury of the spleen, the liver or the gallbladder who were not splenectomized and found a higher risk of stroke in the splenectomized patients. Although we cannot completely rule out confounding by indication, our study extends the findings from the Taiwanese study by showing an increased risk of stroke across varying underlying reasons for splenectomy. In the Taiwanese study, patients with splenectomy had higher prevalences of liver cirrhosis, hypertension, hyperlipidemia, diabetes, and chronic obstructive pulmonary disease compared with the control cohort. This suggests that lifestyle may differ between splenectomized subjects and the general population and thus may confound comparisons between splenectomized people and the background population. Nevertheless, the prevalence of these factors did not differ between splenectomized subjects and those with splenic injury who were not splenectomized.<sup>22</sup> The US Veterans study showed no increase in risk of hospitalization due to ischemic stroke;<sup>5</sup> however, the risk of death due to stroke was nearly doubled in splenectomized veterans (standardized mortality ratio 1.89; 95% CI: 0.91-3.90).

The mechanisms underlying the increased risk of stroke following splenectomy remain unclear. MI and stroke have broadly comparable risk factors.<sup>23</sup> We did not, however, observe an increased risk of MI, which speaks against a generally increased risk of arteriosclerosis caused by platelet activation, disturbance and activation of the endothelium, and altered lipid profiles.<sup>4</sup>

Several potential study weaknesses should be consid-



ered in interpreting our data. As discussed above, one major weakness is that we cannot rule out confounding by disease severity. Furthermore, our study relied on diagnoses recorded in the DNPR and it is well known that coding errors occur.<sup>24</sup> We did not validate the underlying diagnoses in splenectomized or disease-matched subjects. However, diagnoses in the DNPR are validated on an *ad hoc* basis,<sup>24</sup> and it has been shown that the surgical procedures used to identify splenectomized patients have high validity.<sup>25</sup> Moreover, the positive predictive value of a diagnosis of MI in the DNPR was previously found to be above 90%,<sup>26</sup> and that of acute ischemic stroke was found to be 97%.<sup>14</sup> We, therefore, do not think that misclassification of the underlying disease constitutes a major source of bias in our study. We were able to adjust for selected comorbid conditions such as chronic obstructive pulmonary disease, diabetes, hypertension, and obesity, which are known to be associated with increased risk of cardiovascular events. However, we based our comorbidity information on hospital-related diagnoses and did not capture diagnoses made by general practitioners. It has been recognized that the diagnosis of obesity may be severely underreported in the DNPR.<sup>27</sup> The prevalence of hypertension in our general population cohort was 5%, which is lower than expected based on an age-adjusted

prevalence.<sup>28</sup> Consequently, residual confounding is likely to be present in comparisons of splenectomized patients with the general population. Although we cannot rule out residual confounding in the comparisons with a disease-matched cohort either, the reported prevalences of comorbid diseases were similar between the splenectomized and disease-matched cohorts so that we assume residual confounding was smaller in these comparisons. More than 30% of the patients in our splenectomy cohort had another underlying diagnosis than the indications that we *a priori* had specified as the major underlying causes of splenectomy. This “other group” was not included in the indication-matched analyses; when compared with their matched cohort from the general population the relative estimates did not suggest that this group had a higher relative risk of the outcomes than those with selected underlying indications. Finally, even in our nationwide study, the statistical precision in some of our strata did not allow us to make firm conclusions.

In conclusion, our study showed that splenectomy is associated with an increased risk of stroke, across the underlying indications for splenectomy. In contrast, any increased risk of MI and PH in splenectomized patients seemed to be related to the underlying indication rather than to the splenectomy itself.

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