

Rischio di ictus ischemico dopo  
un episodio di emorragia  
extracranica nei pazienti con  
fibrillazione atriale

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# Background

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- Atrial fibrillation (AF) is associated with an increased risk of ischemic stroke which is significantly attenuated with anticoagulant therapy, albeit with an increased risk of hemorrhagic complications.
- Oral anticoagulation is routinely withheld in the setting of acute hemorrhage which potentially predisposes patients to an increased risk of thromboembolic complications.
- Patients with AF who develop intracranial hemorrhage while on anticoagulant therapy are at an increased risk of recurrent ischemic stroke and this has been attributed to cessation of anticoagulant therapy and other stroke prevention strategies.
- There is limited data on the risk of ischemic stroke in patients with AF who develop an extracranial hemorrhage (ECH).

# Risk of Ischemic Stroke in Patients With Atrial Fibrillation After Extracranial Hemorrhage

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# Methods

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- Retrospective study using the California State Inpatient Database including all nonfederal hospital admissions in California from 2005 to 2011
- The exposure variable was hospitalization with a diagnosis of ECH with a previous diagnosis of AF
- The outcome variable was a subsequent hospitalization with acute ischemic stroke
- Excluded: patients with stroke before or at the time of ECH diagnosis

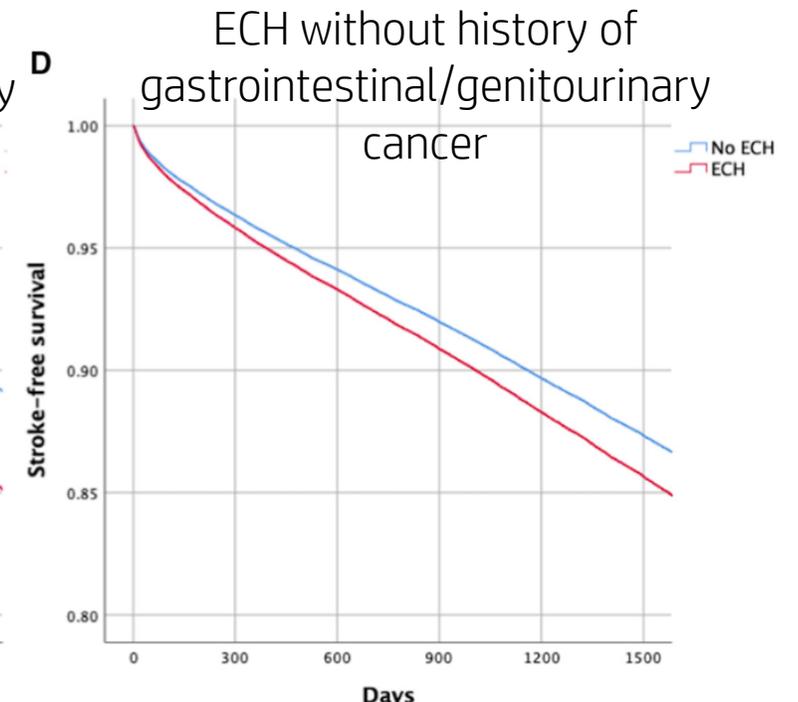
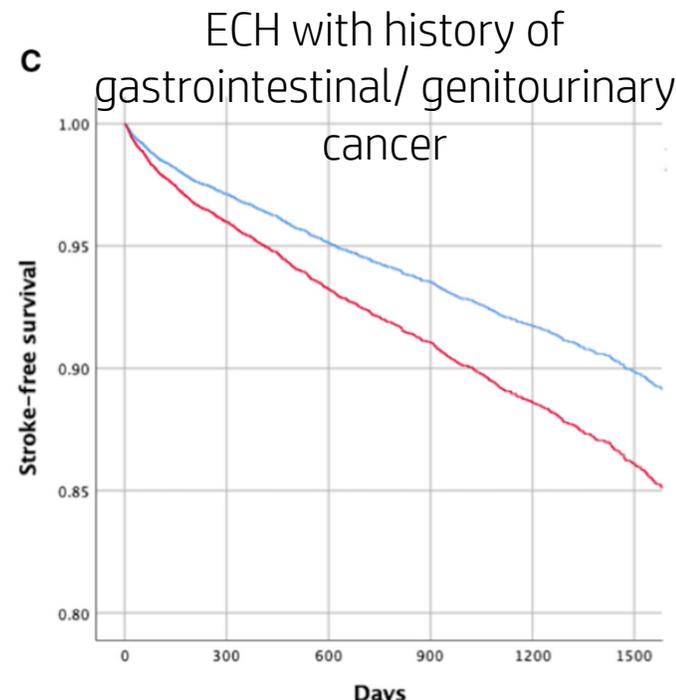
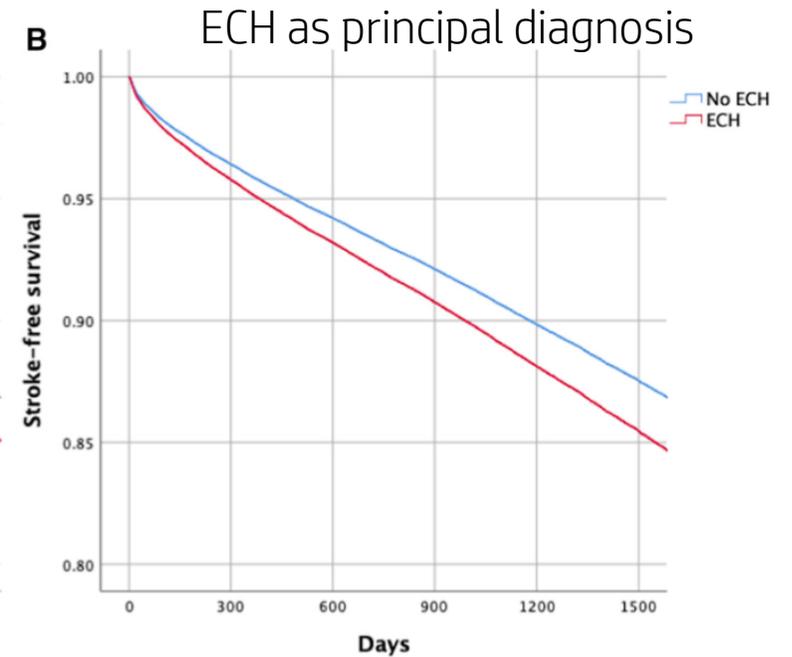
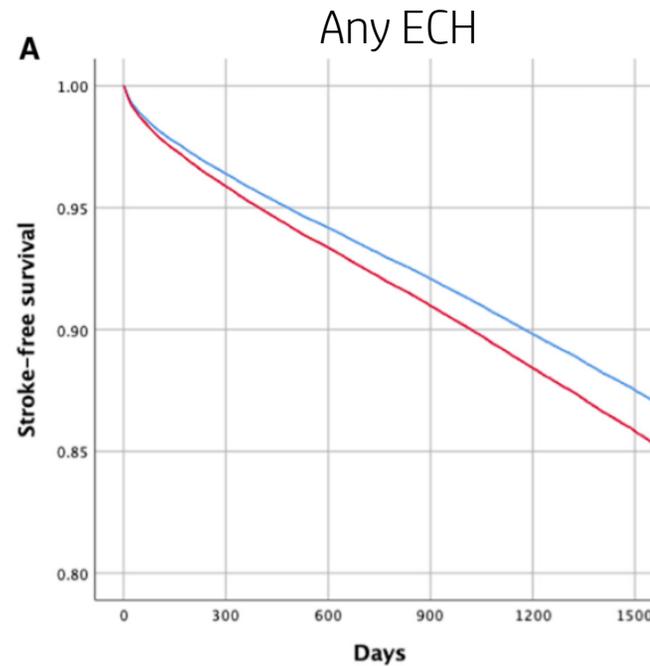
# Characteristics of patients stratified by presence of ECH

- 764257 patients with AF (mean age 75 years, 49% women) without a documented history of stroke
- Of these, 98647 (13%) had an ECH-associated hospitalization

Characteristics	ECH (n=98 647)	No ECH (n=665 610)
Age, y, mean (SD)	77.5 (11.0)	74.9 (12.9)
Women, n (%)	44 799 (45.4)	325 769 (48.9)
Race/ethnicity, n (%)		
White	69 610 (70.6)	486 050 (73.0)
Black	5 193 (5.3)	29 826 (4.5)
Hispanic	11 386 (11.5)	73 507 (11.0)
Asian/Pacific Islander	8 103 (8.2)	42 980 (6.5)
Congestive heart failure, n (%)	60 235 (61.1)	295 756 (44.4)
Hypertension, n (%)	42 083 (42.7)	181 522 (27.3)
Coronary heart disease, n (%)	56 773 (57.6)	304 479 (45.7)
Peripheral vascular disease, n (%)	4,991 (5.1)	19 430 (2.9)
Diabetes, n (%)	37 837 (38.4)	205 843 (30.9)
Chronic kidney disease, n (%)	37 210 (37.7)	152 188 (22.9)
Hyperlipidemia, n (%)	48 195 (48.9)	293 075 (44.0)
Smoking, n (%)	29 607 (30.0)	147 585 (22.2)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score; median (IQR)	3 (2)	3 (2)

# Stroke-free survival probabilities for patients

- 22748 patients (3%) developed an ischemic stroke during follow-up
- In unadjusted Cox regression, ECH was associated with an increased risk of incident ischemic stroke during follow-up (over-all hazard ratio, 1.15 [95% CI, 1.11–1.19])  
*Stroke*. 2020;51:00–00.



Overall Hazard Ratios for Ischemic Stroke in ECH Patients Compared With Non-ECH Patients in the 4 Different Cox Regression Models, Adjusting for Pertinent Covariates

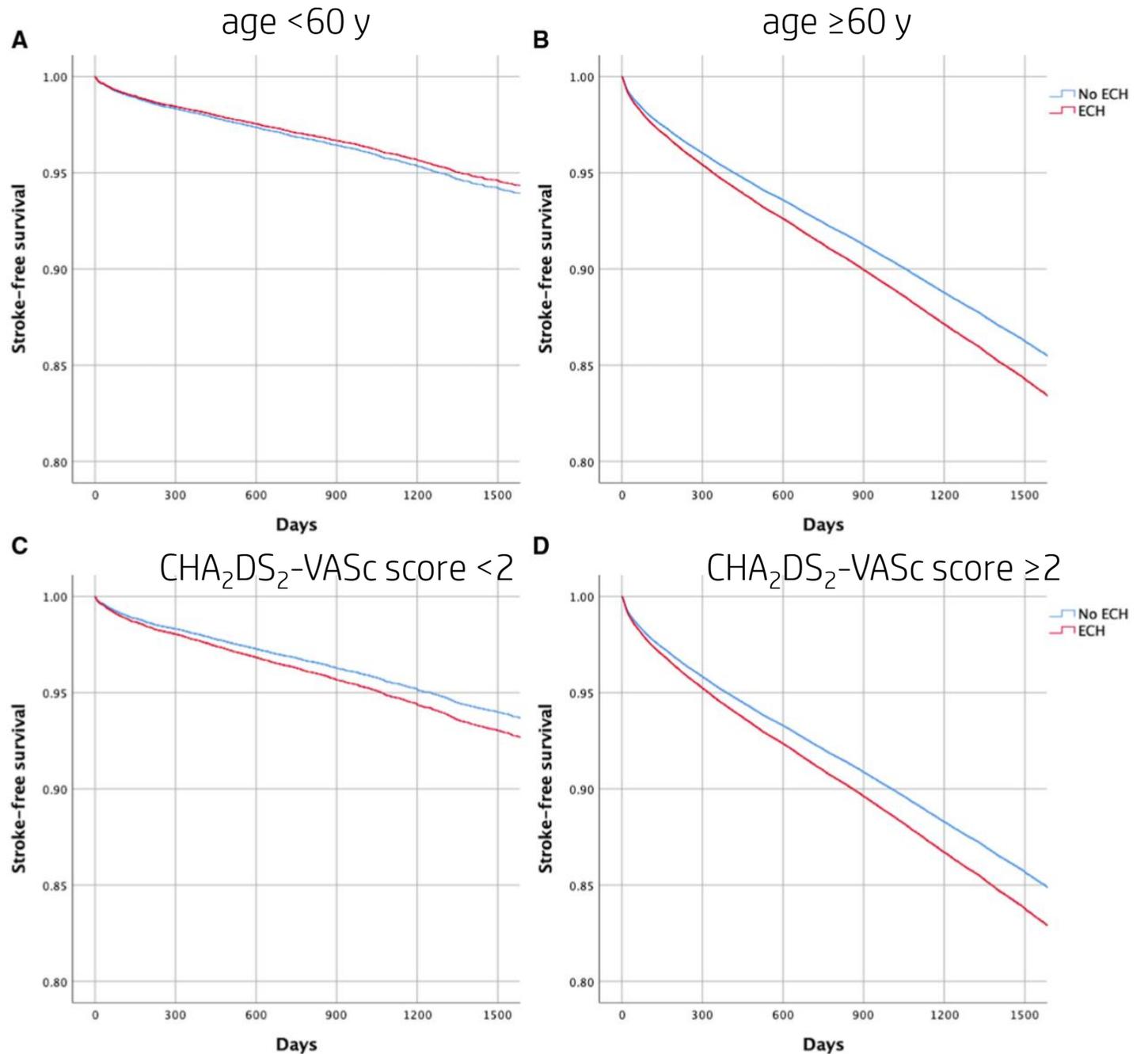
Model	Overall hazard ratio (95% CI)
1	1.15 (1.11–1.19)
2	1.12 (1.09–1.17)
3	1.15 (1.11–1.19)
4	1.09 (1.05–1.13)

- **Model 1:** unadjusted.
- **Model 2:** Adjusted for age and sex.
- **Model 3:** Adjusted for age, sex, smoking status, congestive heart failure, coronary heart disease, hyperlipidemia, hypertension, diabetes mellitus, peripheral vascular disease, chronic kidney disease.
- **Model 4:** Adjusted for CHA2DS2-VASc score.

# Hazard Ratios of Subgroup Analysis for ECH Patients

	Overall HRs			
	Model 1	Model 2	Model 3	Model 4
Primary ECH diagnosis (n=710 693)	1.22 (1.16–1.27)	1.16 (1.11–1.21)	1.18 (1.13–1.24)	1.17 (1.12–1.22)
Severe ECH (n=708 532)	1.23 (1.17–1.30)	1.17 (1.11–1.24)	1.21 (1.14–1.27)	1.12 (1.06–1.18)
Nonsevere ECH (n=721 335)	1.10 (1.06–1.15)	1.09 (1.05–1.14)	1.11 (1.06–1.16)	1.07 (1.02–1.12)
GI ECH (n=732 383)	1.23 (1.17–1.28)	1.16 (1.11–1.21)	1.18 (1.13–1.24)	1.15 (1.10–1.20)
Non-GI ECH (n=667 827)	1.01 (0.88–1.17)	1.05 (0.91–1.21)	1.09 (0.94–1.26)	0.96 (0.83–1.11)
History of GI/GU cancer (n=43 117)	1.46 (1.25–1.71)	1.39 (1.19–1.62)	1.40 (1.20–1.64)	1.40 (1.20–1.63)
No history of GI/GU cancer (n=718 666)	1.15 (1.11–1.19)	1.12 (1.08–1.16)	1.14 (1.10–1.19)	1.09 (1.05–1.13)
Age <60 y (n=91 959)	1.01 (0.83–1.22)	1.00 (0.82–1.20)	0.93 (0.77–1.13)	0.94 (0.78–1.14)
Age ≥60 y (n=671 807)	1.13 (1.09–1.17)	1.13 (1.09–1.17)	1.16 (1.12–1.20)	1.09 (1.06–1.14)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score <2 (n=130 424)	1.21 (1.05–1.41)	1.18 (1.02–1.37)	1.17 (1.00–1.36)	1.20 (1.03–1.39)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 (n=633 833)	1.11 (1.07–1.15)	1.12 (1.08–1.16)	1.15 (1.10–1.19)	1.08 (1.04–1.12)

# Stroke-free survival probabilities for subgroup analyses based on patient characteristics



# Limitations

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- Observational studies: selection, indication, and follow-up bias.
- No data on anticoagulation status in patients both before and after the ECH
- No data on serum and imaging markers (ex. INR).
- Only included inpatient hospitalizations, and thus patients with hemorrhagic complications managed on an outpatient basis were not captured.
- The competing risk of death may have led to underestimating our ischemic stroke in patients with ECH.
- Possibility of information bias through miscoding.
- Performed between 2005 and 2011, before the advent of direct oral anticoagulants and left atrial appendage occlusion

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# Conclusions

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- Hospitalized patients with AF and ECH may be at increased risk for ischemic stroke.
- This association was stronger in subgroups of patients with advanced age, more severe hemorrhage, and gastrointestinal-type hemorrhage, and concomitant gastrointestinal or genitourinary cancer history.
- The effect size remained relatively stable for at least 18 months from the initial ECH hospitalization suggesting that the elevated risk continues over time which is also supported by the survival curves continued separation over time.
- The results may have significant implications for future research to test the safety and efficacy of stroke prevention strategies, such as anticoagulation resumption and left atrial appendage closure to reduce the risk of ischemic stroke in this patient population.