Insufficient cardiovascular treatment is a major risk factor for stroke in RA patients:

a matched case-control study from the German biologics register RABBIT

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Background & Objectives

Patients with rheumatoid arthritis (RA) are at increased risk for stroke. The particular impact of RA and its treatment in addition to known risk factors is not clear.

We examined the impact of RA on the risk of stroke taking risk factors of cardiovascular disease (CVD) and age into account.

Patients & Methods

We performed a nested case-control study within the prospectively followed cohort of the German biologics register RABBIT. We considered all non-haemorrhagic strokes reported until October 2015 as cases. For each case two RABBIT patients were matched as controls by an extensive algorithm [1] using: sex, age, enrolment period, smoking status, BMI and comorbidities at baseline. Three cases could not be matched to a control. A multivariable Cox proportional hazard model with a random component (shared frailty model) was applied. Missing data were considered by multiple imputations.

Reference: [1] Hansen B., et al. "Optimal full matching and related designs via network flows." Journal of Computational and Graphical Statistics (2012).

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Results

In total, 158 non-haemorrhagic strokes occurred with a mean time to event of 4 years. The strokes comprised:

- 91 ischaemic strokes
- 43 TIAs
- 18 unclassified strokes.

The yearly incidence of stroke did not change over the first five years of follow up with an overall rate of 2.63/1,000 patient years [95%CI 2.20; 3.12].

Case and control patients were similar in matching criteria and in most of the unmatched criteria. Compared to the remaining cohort they were considerably different (Table 1).

Table 1: Baseline characteristics of cases, controls and the remaining cohort.

		Cohort N=12,598	Controls N=316	Cases N=158
MATCHING CRITERIA	Female patients, N(%)	9648 (76.6)	236 (74.7)	118 (74.7)
	Age in years	**55.8 (12.6)**	62.7 (10.2)	63.4 (10.8)
	Hypertension, N(%)	**4638 (36.8)**	176 (55.7)	88 (55.7)
	Coronary heart disease, N(%)	727 (5.8)	26 (8.2)	13 (8.2)
	Heart failure, N(%)	283 (2.2)	6 (1.9)	3 (1.9)
	Diabetes mellitus, N(%)	**1229 (9.8)**	52 (16.5)	26 (16.5)
	Smoking, N(%) ever unknown	5499 (46.3) 1219 (10.3)	161 (50.9) 27 (8.5)	83 (52.5) 11 (7.0)
	Enrolment (prior 2007), N(%)	**4916 (39.0)**	172 (54.4)	86 (54.4)
UNMATCHED CRITERIA	Observation time in months	**46.1 (34)**	**74.8 (32.9)**	69.1 (32.2)
	Disease duration in years	9.7 (9)	11.5 (9.8)	10.9 (9.3)
	CRP in mg/l	**18.2 (25.9)**	21.8 (40.1)	23.8 (30.6)
	DAS28	**5.1 (1.3)**	5.4 (1.4)	5.5 (1.3)
	FFbH (% of full physical function)	**64.1 (23.2)**	**60.5 (22.9)**	54.4 (24.1)
	No. of bDMARD failures	0.3 (0.8)	**0.3 (0.6)**	0.4 (0.9)
	≥2 comorbidities, N(%)	**4928 (39.1)**	**173 (54.7)**	98 (62.0)

Values are means (SD) unless otherwise specified. Values in bold are significantly different compared to cases ($p < 0.05$).

Treatment of patients

Underlying CV comorbidities were less often treated in cases compared to controls and the cohort (Table 2). This was not found in other comorbidities.

Treatment with DMARDs and glucocorticoids during follow up did not differ between cases and controls.

Table 2: Selected baseline comorbidities and their treatment of cases, controls and the cohort.

	Cohort N=12,598	Controls N=316	Cases N=158
Cardiovascular disease*	5162 (41.0)	187 (59.2)	100 (63.3)
No treatment	1102/5162 (21.3)	38/187 (20.3)	33/100 (33.0)
Diabetes	1229 (9.8)	52 (16.5)	26 (16.5)
No treatment	239/1229 (19.4)	15/52 (28.8)	3/26 (11.5)
Osteoporosis	2195 (17.4)	76 (24.1)	47 (29.7)
No treatment	332/2195 (15.1)	13/76 (17.1)	6/47 (12.8)

Values are No. of patients (%) | *Comprises hypertension, coronary heart disease, heart failure, and hyperlipoproteinemia.

Case-control analysis

Untreated CV comorbidities, impaired physical function, hospitalizations due to other serious adverse events (SAEs) and numbers of previous bDMARD failures were significantly associated with the risk for stroke.

Table 3: Risk factors for stroke in the matched case-control design.

	Univariate analysis	Adjusted frailty model
logCRP	1.34 [1.11; 1.62]	1.20 [0.99; 1.45]
DAS28	1.37 [1.20; 1.56]	0.96 [0.82; 1.12]
FFbH (% of full physical function)	0.93 [0.87; 0.99]	0.86 [0.78; 0.94]
≥2 comorbidities	1.86 [1.31; 2.63]	1.28 [0.73; 2.25]
No CV disease (Reference)		
CV disease with therapy	1.40 [0.87; 2.24]	1.41 [0.66; 3.01]
CV disease and no therapy	2.98 [1.75; 5.07]	3.10 [1.41; 6.79]
csDMARD (Reference)		
TNFi	1.31 [0.92; 1.87]	0.87 [0.56; 1.35]
Other bDMARDs	0.81 [0.52; 1.26]	0.70 [0.40; 1.21]
No. of bDMARD failures	1.30 [1.06; 1.60]	1.44 [1.06; 1.97]
GC, current by 5mg/d	1.36 [1.06; 1.75]	0.90 [0.69; 1.15]
Selected hospitalized SAEs (6 months prior to index date)	2.22 [1.32; 3.75]	2.15 [1.16; 3.99]

Conclusions

Treatment of RA was not associated with an elevated risk of stroke. The risk was significantly increased by impaired physical function and hospitalization due to other serious adverse events. However, the strongest risk factor for a future stroke in the RABBIT cohort was insufficient treatment of cardiovascular comorbidities. These results strengthen the need for a better CVD management in RA patients.

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