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Cardiac Events After Mechanical Thrombectomy in Acute Ischemic Stroke: A Nation-Wide Cohort Study

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Keywords: AIS | cardiac events | cerebrovascular disorders | heart disease after stroke | reperfusion treatment | stroke | stroke-heart syndrome | thrombectomy

ABSTRACT

Introduction: Mechanical thrombectomy (MT) markedly improves the outcome in patients with large vessel occlusion stroke. Given the cardiovascular risk profile of these patients, we wanted to investigate their post-MT risk of cardiac events compared to other patients with acute ischemic stroke (AIS).

Methods: All hospitalizations for AIS in Denmark from 2014 to 2021 were included in this registry-based cohort study. Patients were categorized by reperfusion treatment: MT with or without intravenous thrombolysis (IVT), IVT alone, or no reperfusion treatment (NRT). Cardiac events included ischemic heart disease, heart failure, or cardiac death within 6 months of AIS. Pairwise group comparisons were performed after inverse probability treatment weighting (IPTW).

Results: Among 76,092 AIS patients, 4.4% received MT, 15.2% received IVT alone, and 80.4% received NRT. In the MT group, 9.6% of patients experienced cardiac events. After IPTW, MT patients had the highest risk of cardiac events compared to IVT (absolute risk difference [ARD] 4.6%, cause-specific hazard rate ratio [HRR] 1.42 [95% CI: 1.27–1.60]) and NRT (ARD 4.6%, HRR 1.35 [95% CI: 1.22–1.49]). Pre-existing cardiac disease was similar across groups (9.2%–11.8%) and after exclusion of patients with prior cardiac disease, the HRR of cardiac events remained consistent with the primary analysis (MT vs. IVT: HRR 1.48 [95% CI: 1.31–1.68]; MT vs. NRT: 1.39 [95% CI: 1.24–155]).

Conclusion: 10% of patients with AIS undergoing MT experienced cardiac events within 6 months compared to 5% of other AIS patients. This study identified an unrecognized burden of cardiac disease in this group of AIS patients treated with MT.

1 | Introduction

Cardiovascular disease after ischemic stroke is common and occurs in up to 10%–20% of patients and is associated with poor functional outcome and a two-fold increase in mortality [1, 2]. Previous studies have shown the risk of cardiac events, such as myocardial infarction, heart failure, and cardiac death, to be highest in the first 30 days after ischemic stroke [3]. Suffering a cardiac event within 30 days has been associated with a significantly higher 5-year risk of new events compared to other stroke patients [4]. However, the initial risk of cardiac events may not be evenly distributed in ischemic stroke patients, as subpopulations that bear a disproportionate share of cardiac events might exist. One stroke subpopulation is patients with large vessel occlusion stroke. Large vessel occlusions are present in up to one-third of ischemic stroke patients [5], and before the implementation of mechanical thrombectomy (MT) as standard care [6], these patients accounted for two-thirds of disabilities and deaths within 3 months of stroke [7]. Treatment with MT has markedly improved the outcome of patients with large vessel occlusion stroke [8], and new studies have continually expanded the treatment up to 24 h after onset [9], to patients with basilar-artery occlusions [10], and patients with extended infarctions [11]. A recent projection showed an expected four-fold increase in the number of patients eligible for MT [12], and with an increasing number of patients recovering from large vessel occlusion stroke, a knowledge gap of increasing importance appears: do stroke patients treated with MT constitute a patient group with a greater risk of post-stroke cardiac events?

Our hypothesis was that patients with large vessel occlusion could experience a higher occurrence of cardiac disease compared to other ischemic stroke patients, which could be due to either higher pre-stroke cardiac disease burden, or the stroke event heralds a post-stroke increased risk of cardiac disease. This could have important implications for post-stroke clinical examinations and prophylactic treatment.

In this study, we investigated the incidence of cardiac events (a composite of myocardial infarction, heart failure, and cardiac death) within 180 days of ischemic stroke in patients treated with MT and compared to other ischemic stroke patients using a nation-wide stroke registry.

2 | Methods

We included data from all adult patients (≥ 18 years) admitted to all Danish hospitals with a diagnosis of acute ischemic stroke (ICD-10: I63.0-5, I63.9, and I64.0) between January 1, 2014, and May 31, 2021, using the Danish Stroke Registry [13]. Patients with a diagnosis of intracerebral hemorrhage, transient ischemic attack, and subarachnoidal hemorrhage were excluded. The Danish Stroke Registry is a nation-wide public registry for which it is mandatory for hospitals to report admissions for stroke, and the validity of the registry has been found to be high [14]. Access to acute reperfusion treatment in ischemic stroke is without any direct costs for all residents in Denmark as part of a tax-financed universal health-care system and is provided at public hospitals only [15].

The exposure categories were defined as MT (with or without IVT), IVT alone, or no reperfusion treatment (NRT), and were collected from the Danish Stroke Registry. Danish national guidelines on reperfusion therapy follow guidelines from the European Stroke Organisation [6, 16]. Patients with acute ischemic stroke were excluded if the registration of MT did not include a time of groin puncture, as this was considered integral for the procedure to have been performed. Patients were excluded if they received MT treatment for ischemic stroke prior to the observation period, as it led to unclear exposure categorization. Finally, patients who immigrated to Denmark within 1 year of stroke were excluded, as it would affect the validity of known comorbidities and information on socioeconomic markers.

Individual patient data was collected from multiple sources: the Danish Stroke Registry, the Danish Civil Registration System (DCRS), the Danish National Patient Registry, the Danish Prescription Database, and Statistics Denmark for socioeconomic data, using a unique personal identification number linking individuals across registries provided by the DCRS. For a detailed description of data sources, see Table S1. Collected variables with definitions are described in Table S2. Variables from the Danish Stroke Registry included the Scandinavian Stroke Scale (SSS) and the modified treatment in cerebral infarction (mTICI) score. The SSS is a scale of stroke symptom severity that, like the National Institute of Health Stroke Scale (NIHSS), is a strong predictor of the 90-day functional outcome after stroke [17]. The SSS ranges from 58 (highest stroke severity) to zero (lowest severity) and was developed to be used by non-neurologists. The mTICI score is used to grade the reperfusion of the target vessel after MT, and a score of 2b or 3 has been considered successful reperfusion [18].

2.1 | Outcome

The primary outcome was cardiac events within 180 days after admission for acute ischemic stroke. Cardiac events included ischemic heart disease (acute myocardial infarction, acute coronary syndrome, and unstable angina [ICD-10: I20-24]), congestive heart failure (acute and chronic [ICD-10: I50]), and cardiovascular death (death according to the DCRS and a diagnosis of ICD-10: I20–25, I30–37, I39, I40–49, I50–52, I70–75). All registered diagnoses were collected from the National Patient Registry. For detailed definitions see Table S3. In a secondary analysis, cardiac events were investigated in a subgroup of patients with no history of cardiac disease.

2.2 | Analysis

Comparisons were performed pairwise for the three exposure groups: MT versus NRT, MT versus IVT, and IVT versus NRT. For each pairwise comparison, propensity scores for the reperfusion therapies were estimated using logistic regression, and these were used to obtain stabilized inverse probability of treatment weights (IPTW) with the intention of estimating the average treatment effect. Propensity scores were estimated separately for the main analysis and the subanalysis, where patients

with a history of cardiac disease were excluded. No trimming was required. The covariates used in the propensity model were age, sex, Charlson Comorbidity Index [19], income (mean household income for 3 years above or below mean national household income for the corresponding 3 years), education level (International Standard Classification of Education definition of low, medium, or high education) and cohabitation status. Multiple imputation with chained equations was used for handling missing values of the balancing covariates. The density functions for the propensity scores were estimated exposure-wise and plotted for each comparison. Covariate balance in the pre- and post-weighted populations was investigated in terms of covariate distributions and strictly standardized mean differences.

We compared baseline clinical and demographic characteristics according to reperfusion therapy group. Cumulative incidences for the primary and secondary outcomes in both the unweighted population (crude) and the weighted pseudo-populations (adjusted) were estimated using the Aalen-Johansen estimator with non-cardiovascular mortality considered a competing event. The cumulative incidence at 180 days of each outcome was used to estimate an absolute risk difference with confidence intervals (CI) in both unweighted and weighted analyses for each pairwise comparison. A Cox proportional hazards model was used to estimate cause-specific hazard rate ratio (HRR) with administrative censoring at 180 days for each pairwise comparison with 95% CI after the proportional hazards assumption was evaluated. The temporal distribution of cardiac events was evaluated by considering subdistribution hazard functions plotted against time. The functions considered were obtained by kernel smoothing numerical derivatives of cumulative subhazard estimates. The temporal distribution of mortality events was similarly investigated. The level of statistical significance was set at a p-value below 0.05, and a CI of 95% was used.

3 | Results

Of 119,046 records in the Danish Stroke Registry between January 1, 2014, and May 21, 2021, a total of 76,607 records were patients diagnosed with acute ischemic stroke, Figure S1. Of the included 76,092 patients, 3370 (4.4%) were treated with MT (with or without IVT), 11,547 (15.2%) were treated with IVT only, and 61,175 patients (80.4%) received no reperfusion therapy. The NRT group was the largest group and had the lowest stroke severity with 70.8% of patients having minor stroke (SSS 45–58), corresponding to 56.7% in the IVT group and 12.5% in the MT group. Patients in the NRT group were more often prescribed anticoagulant treatment compared to the IVT group, 14.3% versus 3.4%, while being comparable to the MT group at 16.0%. The NRT group also tended to have more comorbidities with 37.1% of patients having a CCI above 1, compared to 28.6% in the IVT group and 31.6% in the MT group, and there was a higher proportion of patients aged 80 years or older at 31.3% compared to 23.6% in the IVT group and 25.0% in the MT group. Baseline clinical and demographical characteristics are presented in Table 1 and baseline characteristics for the weighted populations are presented in Tables S4 and S5.

3.1 | Incidence of Cardiac Events

The crude cumulative incidence of cardiac events within 180 days was 9.6% (95% CI: 8.6, 10.6) in the MT group, 4.8% (95% CI: 4.5, 5.3) in the IVT group, and 5.8% (95% CI: 5.7, 6.0) in the NRT group, Table 2, Figure 1. The corresponding risk difference was 4.7% (95% CI: 3.6, 5.8) in MT versus IVT, 3.7% (95% CI: 2.7, 4.7) in MT versus NRT, and −1.0% (95% CI: −1.4, −0.6) in IVT versus NRT. After IPTW, the adjusted risk differences were 4.6% (95% CI: 3.6, 5.7) in MT versus IVT, 4.6% (95% CI: 3.4, 5.7) in MT versus NRT, and 0.3% (95% CI: −0.2, 0.8) in IVT versus NRT. The crude HRR for cardiac events was 1.43 (95% CI: 1.28, 1.59) in MT versus IVT, 1.32 (95% CI: 1.21, 1.44) in MT versus NRT, and 0.90 (95% CI: 0.83, 0.97) in IVT versus NRT and after IPTW, the adjusted HRRs were 1.42 (95% CI: 1.27, 1.60), 1.35 (95% CI: 1.22, 1.49), and 0.99 (95% CI: 0.91, 1.07), respectively. When estimating the temporal distribution, cardiac events occurred earlier in the MT group compared to both the IVT and NRT groups, Figure 2. The temporal distributions for adjusted estimates are provided in Figures S2–S4.

3.2 | Types of Cardiac Events

For each type of cardiac events (ischemic heart disease, congestive heart failure, and cardiac death), the cumulative incidence at 180 days was highest in the MT group and lowest in the IVT group in both crude and adjusted analyses (except for a lower adjusted cumulative incidence of cardiovascular death in the NRT group). The highest adjusted risk difference was for congestive heart failure at 2.6% (95% CI: 1.8, 3.5) for MT vs. IVT and 2.6% (95% CI: 1.7, 3.5) for MT versus NRT. The range of HRR for ischemic heart disease, congestive heart failure, and cardiac death was 1.33–1.43 for MT compared to IVT or NRT in both crude and adjusted analysis, while for NRT compared to IVT, the range of HRR was 0.90–1.05.

3.3 | Patients With No History of Cardiac Disease

Across groups, 9.2%–11.8% had a history of cardiac disease, and in a subanalysis with these patients excluded, the cumulative incidence of incident cardiac events was lower for all groups, but still highest in the MT group at 6.1% (95% CI: 5.3, 7.0%) and lowest in the IVT group at 3.3% (95% CI: 3.0, 3.7%). The lower incidence resulted in correspondingly lower absolute risk differences, but the adjusted HRRs were consistent with the main analysis at 1.48 (95% CI: 1.31, 1.62) for MT versus IVT, 1.39 (95% CI: 1.24, 1.55) for MT versus NRT, and 0.96 (95% CI: 0.89, 1.05) for IVT versus NRT.

3.4 | Cardiac Death and All-Cause Mortality

In addition to a higher risk of cardiac death, the all-cause mortality within 180 days was also highest in the MT group at 20.1% (95% CI: 18.7, 21.4%) compared to both the IVT group, adjusted risk difference of 12.6% (95% CI: 11.2, 14.0), and NRT group, 10.8% (95% CI: 9.2, 12.4). Most fatalities occurred within the first few weeks, Figure 3, Figures S5–S7 for adjusted estimates.

TABLE 1 | Baseline characteristics.

	NRT ($n = 61,175$)	IVT ($n = 11,547$)	MT ($n = 3370$)
Age categories			
18–49, *n* (%)	3013 (4.9%)	1000 (8.7%)	259 (7.7%)
50–59, *n* (%)	7070 (12%)	1599 (14%)	421 (12%)
60–69, *n* (%)	12,701 (21%)	2623 (23%)	693 (21%)
70–79, *n* (%)	19,231 (31%)	3603 (31%)	1154 (34%)
80–89, *n* (%)	14,735 (24%)	2224 (19%)	705 (21%)
≥ 90, *n* (%)	4425 (7.2%)	498 (4.3%)	138 (4.1%)
Sex (Male), *n* (%)	33,949 (55%)	6959 (60%)	1900 (56%)
Treatment with IVT, *n* (%)	0 (0%)	11,547 (100%)	1815 (54%)
NIHSS at baseline, median (IQR)	NA[a]	4 (2, 7)	16 (10, 20)
Missing (%)	NA[a]	203 (1.8%)	68 (2.0%)
Scandinavian stroke scale			
Minor (SSS 45–58), *n* (%)	43,289 (71%)	6543 (57%)	420 (12%)
Moderate (SSS 30–44), *n* (%)	10,167 (17%)	3333 (29%)	790 (23%)
Severe (SSS 15–29), *n* (%)	3855 (6.3%)	1059 (9.2%)	1056 (31%)
Very severe (SSS 0–14), *n* (%)	2813 (4.6%)	502 (4.3%)	970 (29%)
Missing (%)	1051 (1.7%)	110 (1.0%)	134 (4.0%)
Comorbidities			
History of cardiac events, *n* (%)	6455 (11%)	1061 (9.2%)	399 (12%)
History of atrial fibrillation, *n* (%)	11,735 (19%)	1308 (11%)	1022 (31%)
History of hypertension, *n* (%)	36,219 (60%)	6167 (54%)	1798 (54%)
History of diabetes, *n* (%)	10,692 (18%)	1517 (13%)	439 (13%)
History of chronic kidney disease, *n* (%)	3431 (5.6%)	405 (3.5%)	167 (5.0%)
History of peripheral arterial disease, *n* (%)	3574 (6.0%)	480 (4.2%)	166 (5.1%)
mRS at baseline			
0, *n* (%)	NA[a]	6913 (60%)	1608 (48%)
1–2, *n* (%)	NA[a]	3071 (27%)	666 (20%)
≥ 3, *n* (%)	NA[a]	730 (6.3%)	114 (3.4%)
Missing (%)	NA[a]	833 (7.2%)	982 (29%)
Charlson Comorbidity Index			
0, *n* (%)	25,159 (41%)	5773 (50%)	1684 (50%)
1, *n* (%)	13,343 (22%)	2476 (21%)	619 (18%)
> 1, *n* (%)	22,673 (37%)	3298 (29%)	1067 (32%)
Medications at admission			
Statin treatment, *n* (%)	22,178 (36%)	4212 (36%)	1245 (37%)
Antiplatelet treatment, *n* (%)	22,533 (37%)	4256 (37%)	968 (29%)
Anticoagulant treatment, *n* (%)	8773 (14%)	396 (3.4%)	539 (16%)
Tobacco smoking			

(Continues)

TABLE 1 | (Continued)

	NRT ($n = 61,175$)	IVT ($n = 11,547$)	MT ($n = 3370$)
Never, *n* (%)	19,325 (32%)	3974 (34%)	1045 (31%)
Current or former, *n* (%)	33,785 (55%)	6357 (55%)	1591 (47%)
Missing (%)	8065 (13%)	1216 (11%)	734 (22%)
Alcohol use			
Within guidelines, *n* (%)	41,211 (67%)	8302 (72%)	2224 (66%)
Above guidelines, *n* (%)	5858 (9.6%)	999 (8.7%)	271 (8.0%)
Missing (%)	14,106 (23%)	2246 (19%)	875 (26%)
Household income			
Above average, *n* (%)	12,730 (22%)	3309 (31%)	932 (30%)
Education level			
Low, *n* (%)	24,345 (40%)	4082 (35%)	1255 (37%)
Medium, *n* (%)	24,060 (39%)	4897 (42%)	1370 (41%)
High, *n* (%)	10,808 (18%)	2296 (20%)	680 (20%)
Missing (%)	1962 (3.2%)	272 (2.4%)	65 (1.9%)
Cohabitation			
Cohabitant, *n* (%)	32,138 (53%)	7784 (67%)	2241 (66%)
Living alone, *n* (%)	26,145 (43%)	3427 (30%)	1022 (30%)
Other or undisclosed, *n* (%)	2892 (4.7%)	336 (2.9%)	107 (3.2%)

Abbreviations: IVT, intra-venous thrombolysis; mRS, Modified Rankin Scale; MT, mechanical thrombectomy; NA, not available; NIHSS, National Institutes of Health Stroke Scale; NRT, no reperfusion treatment; SSS, Scandinavian Stroke Scale.
[a]Data not collected by the Danish Stroke Registry for this patient group.

The rate of procedural or postprocedural hemorrhage was 3.1%, Table 3, which could not account for the higher mortality in the MT groups. We observed a two-fold higher all-cause mortality in MT patients without successful reperfusion (mTICI score < 2b) compared to patients with successful reperfusion, 38.0% (95% CI: 33.5%, 42.2%) and 17.5% (95% CI: 16.1%, 18.9%), respectively. While a higher mortality was observed, an mTICI score < 2b was associated with a lower incidence of cardiac events compared to mTICI 2b–3, 6.8% (95% CI: 9.0%–11.2%) and 10.1% (95% CI: 9.0%–11.2%).

4 | Discussion

In this nation-wide registry study, one in 10 patients treated with MT (with or without IVT) for acute ischemic stroke had a cardiac event within 180 days compared to one in 20ischemic stroke patients who received IVT alone or no reperfusion therapy. For each cardiac event type investigated (myocardial infarction, heart failure, and cardiac death), the risk was consistently highest in the MT group. Furthermore, in a subanalysis where patients with a history of cardiac disease were excluded, we continued to observe a significantly higher risk of cardiac events in MT patients compared to other ischemic stroke patients.

Post-stroke cardiac events have been investigated in previous studies [2–4], but not specifically in a cohort of MT patients. A single insurance data-based study with an observation period of 2003–2014 investigated myocardial infarctions after ischemic stroke, with MT patients accounting for 0.5% of the study population. In that study, MT was significantly associated with myocardial infarction [20]. Another population-based study reported a higher incidence of cardiac events following ischemic stroke compared to the general population using the inclusion years of 2002–2012 [3]. They collected the same type of cardiac events as in our study and reported an incidence of 5% in stroke patients with no history of cardiac disease. This was comparable to the 3.3%–6.6% in the subanalysis of our study in patients with no history of cardiac disease. In agreement with our findings, the study reported the highest risk of cardiac disease in the first 30 days after stroke, and that the most frequent event was heart failure [3]. However, there were no data on the use of MT, or any reperfusion treatment. In our study, patients were categorized according to reperfusion treatment, while other categorizations could potentially identify other risk groups for clinicians to be aware of. We considered stratifying on stroke etiology; however, simpler classification systems such as TOAST yield a high proportion of undetermined cases [21], while more complex systems like ASCOD [22] would likely not provide a classification for the individual patient in the first week after stroke, where the risk is highest.

Recent studies have investigated post-stroke cardiac events, and it has been hypothesized that cerebral infarctions may have a direct negative cardiac effect, which has been called the stroke-heart syndrome [23]. Studies have shown increased levels of

TABLE 2 | Primary and secondary outcomes in unweighted and weighted populations.

	Before IPTW				After IPTW				
	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ratio	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ration	*p*
Cardiac events									
Comparison 1									
IVT	11,547	4.8% (4.5, 5.3%)	—	Ref.	10,619	4.9% (4.5, 5.3%)	—	Ref.	—
MT	3370	9.6% (8.6, 10.6%)	4.7 (3.6, 5.8)	1.43 (1.28, 1.59)	4298	9.5% (8.5, 10.5%)	4.6 (3.6, 5.7)	1.42 (1.27, 1.6)	<0.001
Comparison 2									
NRT	61,175	5.8% (5.7, 6%)	—	Ref.	60,329	5.8% (5.6, 6%)	—	Ref.	—
MT	3370	9.6% (8.6, 10.6%)	3.7 (2.7,4.7)	1.32 (1.21, 1.44)	4209	10.4% (9.3, 11.5%)	4.6 (3.4,5.7)	1.35 (1.22, 1.49)	<0.001
Comparison 3									
NRT	61,175	5.8% (5.7, 6%)	—	Ref.	62,014	5.7% (5.5, 5.9%)	—	Ref.	—
IVT	11,547	4.8% (4.5, 5.3%)	−1.0 (−1.4, −0.6)	0.9 (0.83, 0.97)	10,710	5.4% (5, 5.9%)	0.3 (−0.2, 0.8)	0.99 (0.91, 1.07)	0.75
Ischemic heart disease									
Comparison 1									
IVT	11,547	1% (0.8, 1.2%)	—	Ref.	10,619	1% (0.8, 1.2%)	—	Ref.	—
MT	3370	1.5% (1.2, 2%)	0.5 (0.1, 1.0)	1.41 (1.27, 1.56)	4298	1.5% (1.1, 2%)	0.5 (0.0, 0.9)	1.42 (1.28, 1.58)	<0.001
Comparison 2									
NRT	61,175	1.1% (1, 1.2%)	—	Ref.	60,329	1.1% (1, 1.2%)	—	Ref.	—
MT	3370	1.5% (1.2, 2%)	0.4 (0.0, 0.8)	1.4 (1.29, 1.51)	4209	1.6% (1.2, 2.2%)	0.6 (0.1, 1.0)	1.41 (1.29, 1.55)	<0.001
Comparison 3									
NRT	61,175	1.1% (1, 1.2%)	—	Ref.	62,014	1.1% (1, 1.2%)	—	Ref.	—
IVT	11,547	1% (0.8, 1.2%)	−0.1 (−0.3, 0.1)	0.96 (0.89, 1.03)	10,710	1.1% (0.9, 1.3%)	0.0 (−0.2, 0.2)	1 (0.93, 1.08)	0.952

(Continues)

TABLE 2 | (Continued)

	Before IPTW				After IPTW				
	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ratio	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ration	*p*
Heart Failure									
Comparison 1									
IVT	11,547	3.4% (3.1, 3.8%)	—	Ref.	10,619	3.4% (3.1, 3.8%)	—	Ref.	—
MT	3370	6% (5.3,6.9%)	2.6 (1.7, 3.5)	1.41 (1.27, 1.57)	4298	6.1% (5.3, 7%)	2.6 (1.8, 3.5)	1.41 (1.27, 1.57)	<0.001
Comparison 2									
NRT	61,175	3.8% (3.6, 3.9%)	—	Ref.	60,329	3.7% (3.6, 3.9%)	—	Ref.	—
MT	3370	6% (5.3, 6.9%)	2.3 (1.4, 3.1)	1.34 (1.24, 1.46)	4209	6.4% (5.5, 7.3%)	2.6 (1.7, 3.5)	1.36 (1.24, 1.5)	<0.001
Comparison 3									
NRT	61,175	3.8% (3.6, 3.9%)	—	Ref.	62,014	3.7% (3.5, 3.8%)	—	Ref.	—
IVT	11,547	3.4% (3.1, 3.8%)	−0.3 (−0.7, 0.0)	0.93 (0.86, 1)	10,710	3.8% (3.4, 4.2%)	−0.1 (−0.5, 0.3)	1 (0.93, 1.07)	0.928
Cardiac death									
Comparison 1									
IVT	11,547	1% (0.8, 1.1%)	—	Ref.	10,619	1% (0.8, 1.2%)	—	Ref.	—
MT	3370	2.9% (2.4, 3.5%)	2.0 (1.4,2.5)	1.33 (1.19, 1.48)	4298	2.8% (2.3, 3.4%)	1.8 (1.2, 2.4)	1.35 (1.21, 1.51)	<0.001
Comparison 2									
NRT	61,175	1.7% (1.6, 1.8%)	—	Ref.	60,329	1.7% (1.6, 1.8%)	—	Ref.	—
MT	3370	2.9% (2.4, 3.5%)	1.2 (0.6, 1.8)	1.41 (1.29, 1.53)	4209	3.4% (2.8, 4.1%)	1.7 (1.0, 2.4)	1.4 (1.27, 1.55)	<0.001
Comparison 3									

(Continues)

TABLE 2 | (Continued)

	Before IPTW				After IPTW				
	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ratio	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ration	*p*
NRT	61,175	1.7% (1.6, 1.8%)	—	Ref.	62,014	1.6% (1.5, 1.7%)	—	Ref.	—
IVT	11,547	1% (0.8, 1.1%)	−0.7 (−0.9, −0.5)	1.02 (0.95, 1.1)	10,710	1.2% (1, 1.5%)	0.4 (0.2, 0.7)	1.05 (0.97, 1.13)	0.235
All-cause mortality									
Comparison 1									
IVT	11,547	7.4% (6.9%–7.9%)	—	Ref.	10,619	7.5% (7%–8%)	—	Ref.	—
MT	3370	20.6% (19.2%–21.9%)	13.2 (11.7, 14.6)	3.03 (2.74–3.35)	4298	20.1% (18.7%–21.4%)	12.6 (11.2, 14.0)	2.91 (2.63–3.22)	<0.001
Comparison 2									
NRT	61,175	12.9% (12.6%–13.1%)	—	Ref.	60,329	12.7% (12.5%–13%)	—	ref.	—
MT	3370	20.6% (19.2%–21.9%)	7.7 (6.3, 9.1)	1.72 (1.59–1.85)	4209	23.5% (21.9%–25.1%)	10.8 (9.2, 12.4)	2.03 (1.87–2.2)	<0.001
Comparison 3									
NRT	61,175	12.9% (12.6%–13.1%)	—	Ref.	62,014	12.4% (12.1%–12.6%)	—	Ref.	—
IVT	11,547	7.4% (6.9%–7.9%)	−5.4 (−6.0, −4.9)	0.56 (0.52–0.6)	10,710	9.7% (9.1%–10.3%)	−2.7 (−3.4, −2.0)	0.78 (0.72–0.83)	<0.001
Incident cardiac disease									
Comparison 1									
IVT	10,486	3.3% (3, 3.7%)	—	Ref.	9671	3.3% (3, 3.7%)	—	Ref.	—
MT	2971	6.1% (5.3, 7.1%)	2.8 (1.9, 3.7)	1.48 (1.31, 1.67)	3786	6.1% (5.3, 7%)	2.8 (1.8, 3.7)	1.48 (1.31, 1.68)	<0.001
Comparison 2									
NRT	54,720	3.6% (3.4, 3.7%)	—	Ref.	53,955	3.6% (3.4, 3.7%)	—	Ref.	—

(Continues)

TABLE 2 | (Continued)

	Before IPTW				After IPTW				
	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ratio	Population, *n*	Cumulative incidence, %	Absolute risk difference	Hazard-rate ration	*p*
MT	2971	6.1% (5.3, 7.1%)	2.5 (1.7, 3.4)	1.35 (1.23, 1.48)	3728	6.6% (5.7, 7.7%)	3.1 (2.1, 4.1)	1.39 (1.24, 1.55)	<0.001
Comparison 3									
NRT	54,720	3.6% (3.4, 3.7%)	—	Ref.	55,404	3.5% (3.4, 3.7%)	—	Ref.	—
IVT	10,486	3.3% (3, 3.7%)	−0.2 (−0.6, 0.1)	0.9 (0.83, 0.97)	9803	3.6% (3.2, 4%)	−0.1 (−0.5, 0.3)	0.96 (0.89, 1.05)	0.369

Note: Values are presented with 95% confidence intervals.
Abbreviations: IPTW, inverse probability treatment weight; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NRT, no reperfusion treatment.

high-sensitivity cardiac troponins (hs-cTn) [23, 24], ventricular dysfunction with decreased ejection fraction [25, 26], and autonomic dysfunction with cardiac involvement [27, 28] to be common phenomena after ischemic stroke. These cardiac changes were more frequent if the dorsal insular cortex of the right hemisphere was involved in the lesion [23, 25, 27], which plays a role in autonomic function. The most frequent site of the treated large vessel occlusion in our population was the first segment of the middle cerebral artery (M1), which supplies the insular cortex, and could possibly contribute to the observed group differences. We could not investigate this possibility because we had no data on the parenchymal location of the acute ischemia. Blood-based biomarkers have been investigated to predict cardiac events in the general stroke population, and studies on myocardial infarctions after ischemic stroke have investigated hs-cTn to identify stroke patients who could benefit from coronary angiography, but no cut-off has been established [29]. The biomarkers copeptin and brain natriuretic peptide have been shown to be associated with cardiac death after stroke [30, 31]. Furthermore, a recent study suggests that inflammatory markers were associated with post-stroke cardiac complications [32]. As shown in this study, MT patients have an increased risk of cardiac events and could constitute a particularly suitable population for future studies.

Strengths of our study include that we compared cardiac events across a complete national cohort of ischemic stroke patients over a period spanning 8 years where treatment with MT was performed at four comprehensive stroke centres in Denmark. We studied the cumulative incidence of cardiac events and used non-cardiac mortality as a competing event to reduce the risk of biased estimates [33]. Data was collected using registries of high quality; the stroke patients were identified from the Danish Stroke Registry, which has a high validity of stroke diagnoses with a sensitivity of 97% and a positive predictive value of 90% [14], whereas cardiac events were collected using the Danish National Patient Registry, where the positive predictive value of 76%–97% has been found for cardiovascular diagnoses [34]. Registration of all MT procedures to the health authorities for reimbursement was mandatory and the risk of non-registration of MT procedures was considered negligible. Denmark has a universal taxpayer financed health care system, which minimized the risk of selection bias due to socio-economic differences.

Limitations of this study include those inherent to observational studies, as we cannot dismiss unmeasured confounding despite known potential confounding factors being adjusted for using IPTW. Follow-up time in this study was restricted to 6 months as the purpose was to investigate if MT patients were at an immediate risk of cardiac events. A longer follow-up time may have yielded different results. Another limitation was that not all patients with large vessel occlusion stroke would be treated with MT and would subsequently be categorized as either IVT or NRT. This would likely attenuate the group differences, as more cardiac events would potentially be registered in the IVT and NRT groups, and our estimates were therefore likely conservative. The high all-cause mortality in the MT group may also have led to an underestimation of cardiac events due to a *depletion of susceptibles* bias as the competing event had a high frequency [35]. In other words, patients dying without experiencing an event cannot experience one later. This is consistent with the

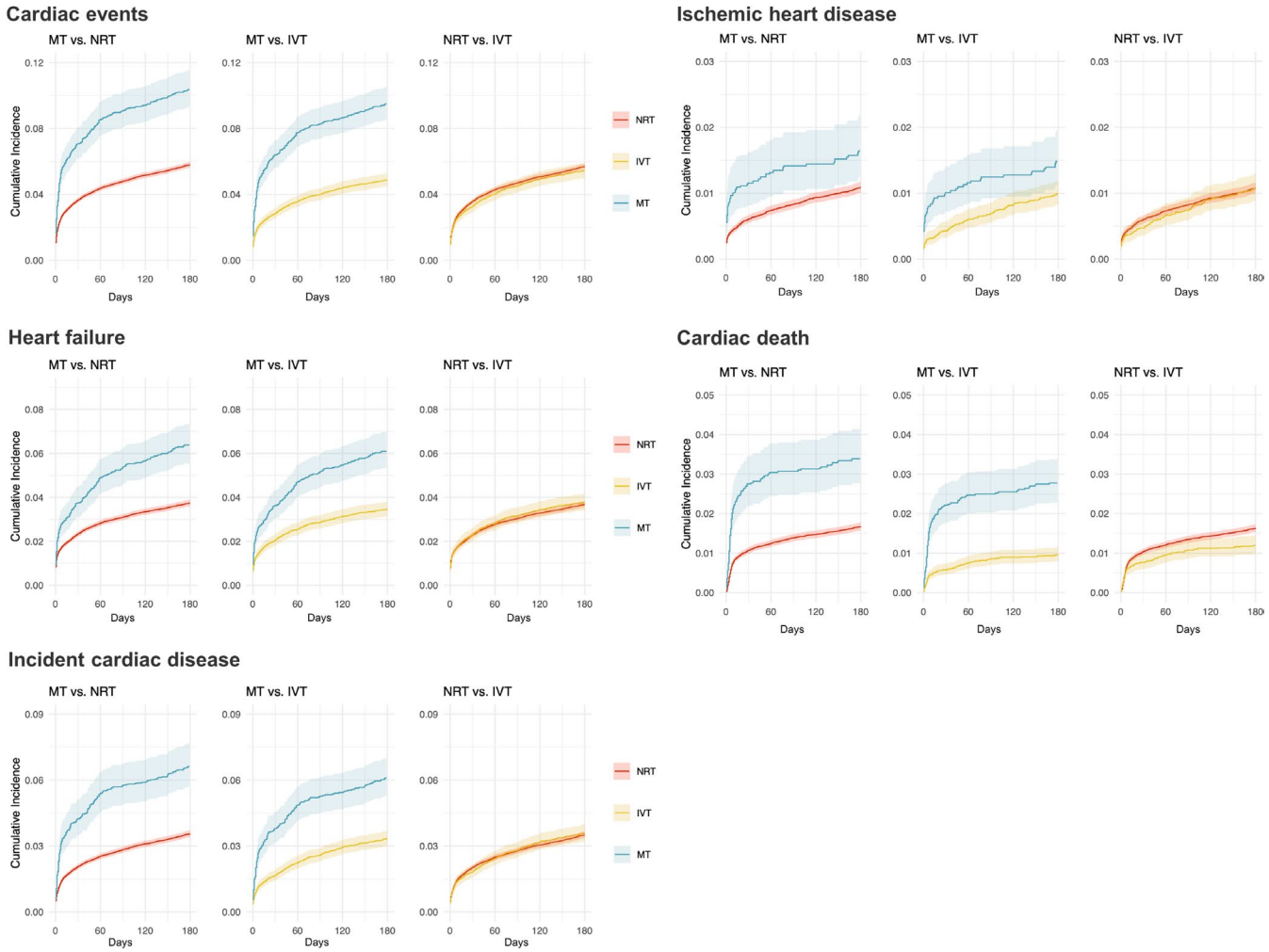

FIGURE 1 | Cumulative incidence of cardiac events in pair-wise comparisons of reperfusion treatment groups.

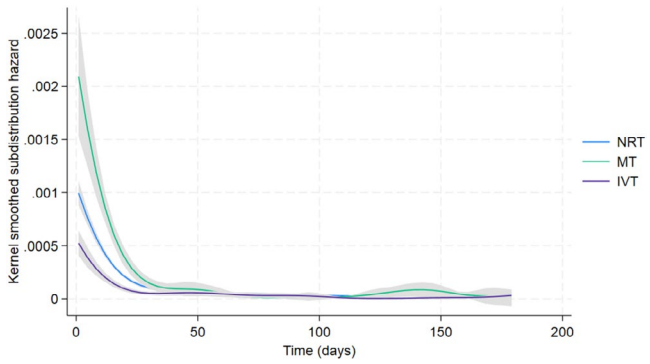

FIGURE 2 | Kernel smoothed subdistribution hazard for cardiac events by exposure (unadjusted estimates).

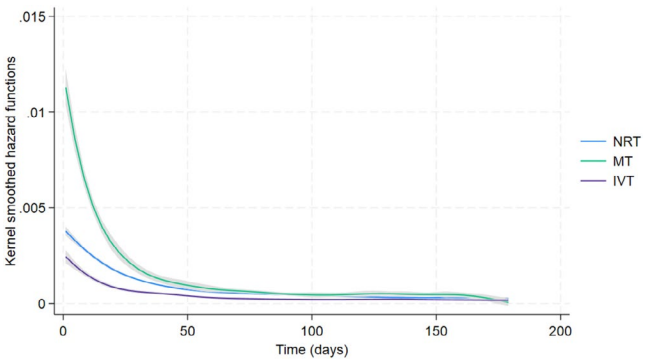

FIGURE 3 | Kernel smoothed hazard functions for all-cause mortality by exposure (unadjusted estimates).

low frequency of cardiac events in the MT patients without successful reperfusion. A further limitation was that no data on the cardiac investigations performed was available, such as echocardiography and troponin sampling. A higher number of investigations performed in one group could lead to subclinical or mild cardiac disease being diagnosed and increase the number of events in that group. The higher incidence of cardiac death in the MT group is not consistent with this. Last, the MT procedure itself was not considered the cause of cardiac events, as catheter-based interventional radiological procedures for both treatment and diagnostic purposes are considered safe in both neurological disorders and other fields with low complication rates [36]. Procedure-related complications would be expected to occur in immediate relation to the procedure and not in the following weeks.

In conclusion, in this large nation-wide cohort study, ischemic stroke patients treated with MT had an incidence of cardiac

TABLE 3 | Procedural and treatment data of the MT group.

	MT ($n = 3370$)
Symptom onset to groin puncture, median (IQR)	233 (163, 350)
Missing, *n* (%)	180 (5.3%)
Groin puncture to end of procedure, median (IQR)	40 (22, 68)
Missing, *n* (%)	196 (5.8%)
Door-to-needle, median (IQR)[a]	31 (20, 42)
Missing, *n* (%)	99 (5.5%)
Site of occlusion	
Extracranial occlusion, *n* (%)	683 (20%)
Only extracranial occlusion, *n* (%)	271 (8.0%)
Intracranial occlusions	
T occlusion, *n* (%)	368 (11%)
M1, *n* (%)	1529 (45%)
M2, *n* (%)	566 (17%)
BA/VA, *n* (%)	306 (9.1%)
Other, *n* (%)	298 (8.8%)
Missing, *n* (%)	32 (0.9%)
Reperfusion result	
Successful reperfusion, *n* (%)[b]	2765 (82%)
No reperfusion, *n* (%)	482 (14%)
Missing, *n* (%)	123 (3.6%)
Conscious sedation, *n* (%)	829 (25%)
General anesthesia or missing, *n* (%)	2541 (75%)
Pre-cerebral stent placement	456 (14%)
Missing, *n* (%)	256 (7.6%)
Complications	
Periprocedural ICH, *n* (%)	21 (0.6%)
Periprocedural SAH, *n* (%)	54 (1.6%)
Postprocedural ICH, *n* (%)	15 (0.4%)
Postprocedural SAH, *n* (%)	16 (0.5%)
Missing, *n* (%)	282 (8.4%)
Procedural iatrogenic embolism, *n* (%)	83 (2.5%)
Missing, *n* (%)	16 (0.5%)
Perforation after procedure, *n* (%)	32 (0.9%)
Missing, *n* (%)	282 (8.4%)

Abbreviations: BA, basilar artery; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; VA, vertebral artery.
[a]For 1815 patients with IVT pre-treatment.
[b]Successful reperfusion: mTICI 2b-3.

events twice that of other ischemic stroke patients. This result was consistent also in patients without pre-stroke cardiac disease. This study emphasizes that MT-treated patients, while having an improved prognosis, have a significantly increased risk of developing cardiac disease, and could benefit from a distinct clinical approach aimed specifically at preventing future cardiac events.

Author Contributions

Nicolaj Grønbæk Laugesen: conceptualization, methodology, writing – original draft, investigation, data curation, formal analysis. **Jakob Nebeling Hedegaard:** data curation, formal analysis, methodology, validation. **David Gaist:** writing – review and editing, resources, supervision. **Claus Ziegler Simonsen:** resources, supervision, writing – review and editing. **Boris Modrau:** supervision, resources, writing – review and editing. **Klaus Hansen:** resources, writing – review and editing. **Søren Paaske Johnsen:** project administration, conceptualization, writing – review and editing. **Thomas Truelsen:** conceptualization, supervision, writing – review and editing, funding acquisition.

Disclosure

Dr. Simonsen received speaker honoraria from Pfizer outside the submitted work. Dr. Gaist received speaker honoraria from Pfizer and Bristol Myers Squibb outside the submitted work and participated in research outside the submitted work funded by Bayer with funds paid to the institution where he is employed.

Ethics Statement

No individual patient consent or approval from the ethics committee was required under Danish law. The study was approved by the Danish Data Protection Agency (Journal no. 2019-899/10-0033).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The public sharing of the study data is not permitted under Danish law. Upon individual requests to the Danish Data Protection Agency, access to Danish clinical registry data can be obtained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.