Association of Circulating MicroRNA-124-3p Levels With Outcomes After Out-of-Hospital Cardiac Arrest
A Substudy of a Randomized Clinical Trial

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IMPORTANCE The value of microRNAs (miRNAs) as biomarkers has been investigated in various clinical contexts. Initial small-scale studies suggested that miRNAs might be useful indicators of outcome after cardiac arrest.

OBJECTIVE To address the prognostic value of circulating miRNAs in a large cohort of comatose patients with out-of-hospital cardiac arrest.

DESIGN, SETTING, AND PARTICIPANTS This substudy of the Target Temperature Management After Cardiac Arrest (TTM) trial, a multicenter randomized, parallel-group, assessor-blinded clinical trial, compared the 6-month neurologic outcomes and survival of patients with cardiac arrest after targeted temperature management at 33°C or 36°C. Five hundred seventy-nine patients who survived the first 24 hours after the return of spontaneous circulation and who had blood samples available for miRNA assessment were enrolled from 29 intensive care units in 9 countries from November 11, 2010, to January 10, 2013. Final follow-up was completed on July 3, 2013, and data were assessed from February 1, 2014, to February 1, 2016.

INTERVENTIONS Blood sampling at 48 hours after the return of spontaneous circulation.

MAIN OUTCOMES AND MEASURES The primary endpoint was poor neurologic outcome at 6 months (cerebral performance category score, 3 [severe neurologic sequelae], 4 [coma], or 5 [death]). The secondary endpoint was survival until the end of the trial. Circulating levels of miRNAs were measured by sequencing and polymerase chain reaction.

RESULTS Of the 579 patients (265 men [80.3%]; mean [SD] age, 63 [12] years), 304 patients (52.5%) had a poor neurologic outcome at 6 months. In the discovery phase with short RNA sequencing in 50 patients, the brain-enriched miR-124-3p level was identified as a candidate prognostic variable for neurologic outcomes. In the validation cohort of 529 patients, mean (SD) levels of miR-124-3p were higher in patients with a poor outcome (8408 [12465] copies/μL, compared with patients with a good outcome (1842 [3025] copies/μL; P < .001). The miR-124-3p level was significantly associated with neurologic outcomes in the univariable analysis (odds ratio, 6.72; 95% CI, 4.53-9.97). In multivariable analyses using logistic regression, miR-124-3p levels were independently associated with neurologic outcomes (odds ratio, 1.62; 95% CI, 1.13-2.32). In Cox proportional hazards models, higher levels of miR-124-3p were significantly associated with lower survival (hazard ratio, 1.63; 95% CI, 1.37-1.93).

CONCLUSIONS AND RELEVANCE Levels of miR-124-3p can be used as prognostication tools for neurologic outcome and survival after out-of-hospital cardiac arrest. Thus, miRNA levels may aid in tailoring health care for patients with cardiac arrest.

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Cardiac arrest is a grave condition with a high risk for a poor outcome. Although early in-hospital mortality of patients admitted to the intensive care unit after an out-of-hospital cardiac arrest is mostly owing to hemodynamic failure, more than half of the initial survivors have irreversible neurologic sequelae or die within a few weeks or months. \(^1\) tk; Withdrawal of life-sustaining therapies in patients with a presumed poor neurologic prognosis commonly precedes death. \(^2,^3\) Decisions to withdraw life-sustaining therapies must rely on accurate prognostication tools. However, commonly used methods, such as pathologic patterns on electroencephalograms or neuroimaging, still lack standardization, whereas some clinical signs, such as absent pupillary reflexes to light or absent somatosensory evoked potentials, lack sensitivity. \(^4,^5\) The biomarker neuron-specific enolase (NSE) is currently recommended in multimodal approaches. \(^6,^7\) and high serial levels are needed for reliable prediction. \(^8\) To increase the accuracy of prognostication and to guide clinical decisions, robust tools are needed. Novel biomarkers would be valuable in consideration of the possibility of adapting health care depending on outcome, maximizing resources in patients likely to survive, and minimizing costly efforts in patients with irreversible neurologic damage. \(^9\)

MicroRNAs (miRNAs) are small noncoding RNA molecules that regulate gene expression and that are present and stable in the bloodstream. \(^10\) In the cardiovascular field, miRNAs have been identified as potential novel tools for personalized health care of patients with heart disease such as myocardial infarction. \(^11\) In previous small-scale proof-of-concept studies, \(^12,^13\) the potential of circulating miRNAs to predict neurologic outcome and death after cardiac arrest was revealed. A large-scale investigation was conducted to confirm these initial findings.

The Target Temperature Management After Cardiac Arrest (TTM) trial\(^14\) addressed the potential benefit of targeted temperature management at 33°C vs 36°C for patient outcome after out-of-hospital cardiac arrest. \(^15\) In the present ad hoc substudy of the multicenter TTM trial, we addressed the prognostic value of circulating miRNAs for neurologic outcome and mortality 6 months after cardiac arrest.

**Methods**

**Patients**

From November 11, 2010, to January 10, 2013, participating centers of the TTM trial enrolled 939 unconscious adult patients admitted to an intensive care unit after an out-of-hospital cardiac arrest of presumed cardiac cause. The primary goal of the trial was to investigate the survival benefit provided by targeted temperature management at 33°C vs 36°C. Details on the TTM trial design, protocol, statistical analysis, and results have been published. \(^15-^17\) The TTM trial was approved by ethical committees of the 9 participating countries (Czech Republic, Denmark, Italy, Luxembourg, the Netherlands, Norway, Sweden, Switzerland, and United Kingdom). Informed consent was waived or obtained from each participant or their relatives, according to the legislation in each country and in line with the Declaration of Helsinki. \(^18\)

Of the 36 recruiting centers of the TTM trial, 29 participated in the biobank project and enrolled 700 patients. In the present substudy, we included 579 patients who survived the first 24 hours after the return of spontaneous circulation (ROSC) and who had blood samples available for miRNA assessment (eFigure 1 in the Supplement). This substudy was approved by the steering committee of the TTM trial.

**Outcome**

The primary end point of this study was poor neurologic outcome as defined by a cerebral performance category (CPC) score of 3 to 5 at 6 months. \(^19\) Cerebral performance category scores of 3 or 4 indicate severe neurologic sequelae or coma, respectively, and a CPC score of 5 indicates death. A CPC score of 1 or 2 indicates none or moderate neurologic sequelae, respectively, and is considered a good outcome. Blinded assessment of the CPC score was performed according to the TTM trial protocol. \(^10\) The secondary end point was survival until the end of the trial.

**miRNA Assessment**

Samples used in this study were processed, analyzed, and stored at the Integrated BioBank of Luxembourg in compliance with International Organization for Standards (protocols 9001:2008 and 17025:2005 and NF S96-900:2011) and with the International Society for Biological and Environmental Repositories Best Practices. Circulating levels of miRNAs were first measured using short RNA sequencing in blood samples collected 48 hours after ROSC (discovery phase) \((n = 50)\). Quantitative polymerase chain reaction (PCR) was used subsequently in a validation phase on 48-hour samples \((n = 529)\) and in a time-course experiment with blood samples collected 24, 48, and 72 hours after ROSC \((n = 43)\).

**Short RNA Sequencing**

Short RNA sequencing of plasma samples was performed at Exiqon Services. Library preparation and sequencing were performed following in-house protocols. Briefly, total RNA was extracted from 400 μL of plasma using a proprietary protocol based on organic extraction, followed by column-based filter
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Levels of miR-124-3p

Comparisons of miR-124-3p levels between 2 groups of patients were performed using the Mann-Whitney test. The association between miR-124-3p levels and comorbidities was evaluated using logistic regression. Effect of sampling time on miR-124-3p levels was evaluated using 1-way repeated-measures analysis of variance on ranks.

Prediction Analyses

We conducted univariable and multivariable analyses. Logistic regression was used to assess the potential association of miR-124-3p levels after log transformation with neurologic outcome as determined by the dichotomized CPC score at 6 months, with a CPC score of 1 to 2 considered a good neurologic outcome (0 value) and a CPC score of 3 to 5 considered a poor neurologic outcome (1 value). Odds ratios (ORs) were computed for an increase of 1 unit for continuous variables. Continuous variables were centered and scaled to unit to have them on the same scale. The area under the receiver operating characteristic curve (AUC) was used to estimate prediction ability of multivariable models. The procedure was corrected for overfitting using 150-fold bootstrap internal validation, which was combined with 10-fold multiple imputation to account for missing data. P values of variables included in the model correspond to the last iteration of the multiple imputation of missing values. The incremental prognostic value of miR-124-3p levels to a clinical model that included demographic and arrest-related factors and NSE levels was evaluated by computation of the integrated discrimination improvement. No marked non-linear effects, as evaluated using restricted cubic splines, were detected.

Survival Analysis

We used Kaplan-Meier survival analysis and Cox regression to evaluate the association of miR-124-3p levels and survival after log-transformation. In Kaplan-Meier analysis, expression levels of miR-124-3p were divided into quartiles. In Cox regression, the association of miR-124-3p and survival was assessed after adjustment with clinical variables using 10-fold multiple imputation.

Statistical Analysis

Demographic and Clinical Data

Follow-up was completed on July 3, 2013, and data were assessed from February 1, 2014, to February 1, 2016. Comparisons of continuous clinical characteristics between 2 groups of patients were performed using the Mann-Whitney test. The χ2 test or the Fisher exact test was used to compare categorical clinical characteristics. P < .05 was considered statistically significant.

Results

Patients

A flowchart describing the study design is presented in eFigure 1 in the Supplement. A total of 939 patients were included in the primary analysis of the TTM trial. In the present study, 579 patients who survived the first 24 hours after ROSC were included (265 men [80.3%]; mean [SD] age, 63 [12] years). Blood samples were collected 48 hours after ROSC. This point was...
Table 1. Clinical Features of 579 Patients With Good and Poor Neurologic Outcomes Within the miRNA Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient Outcome*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good (n = 304)</td>
<td>Poor (n = 275)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>60 (20-90)</td>
<td>68 (35-94)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>251 (82.6)</td>
<td>214 (77.8)</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>98 (32.2)</td>
<td>131 (47.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31 (10.2)</td>
<td>50 (18.2)</td>
</tr>
<tr>
<td>Known IHD</td>
<td>61 (20.1)</td>
<td>90 (32.7)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>45 (14.8)</td>
<td>64 (23.3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (2.3)</td>
<td>25 (9.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>17 (5.6)</td>
<td>29 (10.5)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (0.3)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Previous cerebral stroke</td>
<td>17 (5.6)</td>
<td>29 (10.5)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>7 (2.3)</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>First monitored rhythm, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF or nonperfusing VT</td>
<td>271 (89.1)</td>
<td>185 (67.3)</td>
</tr>
<tr>
<td>Asystole or PEA</td>
<td>18 (5.9)</td>
<td>76 (27.6)</td>
</tr>
<tr>
<td>ROSC after bystander defibrillation</td>
<td>6 (2.0)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (3.0)</td>
<td>12 (4.4)</td>
</tr>
<tr>
<td>Witnessed arrest, No. (%)</td>
<td>277 (91.1)</td>
<td>240 (87.3)</td>
</tr>
<tr>
<td>Bystander CPR, No. (%)</td>
<td>243 (79.9)</td>
<td>182 (66.2)</td>
</tr>
<tr>
<td>Time from cardiac arrest to ROSC, min</td>
<td>20 (0-111)</td>
<td>30 (0-170)</td>
</tr>
<tr>
<td>Initial serum lactate level, mg/dL</td>
<td>42.3 (4.5-180.2)</td>
<td>58.6 (4.5-225.2)</td>
</tr>
<tr>
<td>Circulatory shock on admission, No. (%)</td>
<td>24 (7.9)</td>
<td>46 (16.7)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; IHD, ischemic heart disease; MI, myocardial infarction; miRNA, microRNA; PEA, pulseless electric activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

* Good outcomes indicate cerebral performance category score of 1 to 2; poor outcomes, 3 to 5. Scores are described in the Outcome subsection of the Methods section.

chosen for consistency with previous studies and because NSE levels were maximal 48 hours after cardiac arrest and provided an optimal prognostic value. The miRNA study cohort had similar demographic and clinical features to those of the whole TTM cohort (eTable 1 in the Supplement). Three hundred four patients (52.5%) had a good neurologic outcome at 6 months (CPC scores 1-2) and 275 patients (47.5%) had a poor neurologic outcome or died (CPC scores 3-5) (Table 1).

Patients with a poor neurologic outcome or who died within the 6-month follow-up period were older and had more comorbidities compared with patients with a good neurologic outcome. The incidence of an initial nonshockable rhythm, time from cardiac arrest to ROSC, initial serum lactate levels, and frequency of circulatory shock on admission were higher in patients with poor outcomes (Table 1).

**Discovery Phase**

Short RNA sequencing was used to profile the expression of miRNAs in 2 groups of 25 patients (eFigure 1 in the Supplement). Twenty-five patients had a good neurologic outcome and 25 patients had a poor neurologic outcome or died within the 6 months after cardiac arrest. Consistent with the entire cohort, patients with a poor outcome were older and had a longer time from cardiac arrest to ROSC compared with patients with good outcomes (eTable 2 in the Supplement). However, comorbidities, initial rhythm, lactate levels, and shock on admission were not statistically significantly different between the 2 groups, presumably owing to the small sample size.

After a sample quality check attesting for the suitability of plasma samples for small RNA sequencing (eResults in the Supplement), the sequencing generated a mean of 18.5 million reads per sample (total, 926 million reads for the entire experiment). The data set has been deposited at the Gene Expression Omnibus under the accession number GSE74198. Of the sequencing reads, 84.8% mapped to the human genome and 26.0% mapped to human miRNAs. eFigure 3 in the Supplement depicts the relative contribution of different small RNA species and the percentages of differentially expressed RNAs among different RNA species. Two hundred thirty-six miRNAs were detected in all 50 samples with tags per million greater than or equal to 1. The brain-enriched miR-124-3p was the most differentially expressed miRNA (46-fold change; false discovery rate, $2 \times 10^{-15}; P = 7 \times 10^{-14}$; eFigure 4 in the Supplement) and was selected for validation. Of note, the mean expression level of miR-124-3p was 14 tags per million.

Serum levels of miR-124-3p were measured in 43 of the 50 patients of the discovery phase for whom blood samples at 24, 48, and 72 hours after cardiac arrest were available (eFigure 5 in the Supplement). Although miR-124-3p levels tended to increase over time in the group with poor outcomes, no statistically significant effect of time of sampling was detected ($P = .83$ in the group with good outcomes and $P = .40$ in the group with poor outcomes).

**Validation Phase**

Circulating levels of miR-124-3p were measured using quantitative PCR in a validation cohort of 529 patients from the miRNA cohort (n = 579) after removal of the 50 patients of the discovery phase (eFigure 1 in the Supplement). In this validation cohort, 231 patients (43.7%) were allocated to 33°C...
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48 hours after ROSC did not differ between temperature groups. NSE levels only to the preceding model that included clinical variables, NSE levels, and miR-124-3p levels. Inclusion of miR-124-3p levels slightly improved prognostic accuracy as attested by a modest, albeit significant, increase of the AUC from 0.89 to 0.90 (P = .02). However, miR-124-3p levels did not reclassify a significant number of patients as attested by an integrated discrimination improvement of 0.005 (95% CI, −0.003 to 0.013). When NSE levels were omitted from the prediction models, miR-124-3p levels provided a most prominent improvement of prognostic ability, with an AUC of 0.78 and 0.84 for the models without and with miR-124-3p levels, respectively (P < .001). In this case, the integrated discrimination improvement generated by miR-124-3p levels was 0.11 (95% CI, 0.08-0.14).

Survival Analysis

The association of circulating levels of miR-124-3p measured 48 hours after ROSC with survival until the end of the trial was evaluated using Cox proportional hazards models. Maximum follow-up time was 956 days after cardiac arrest. Median time from cardiac arrest to death was 275 days. Combined with clinical and demographic variables, miR-124-3p levels had significant prognostic value for a shorter survival (Table 2), as did age, first monitored rhythm, initial serum lactate levels, and NSE levels. Targeted temperature regimen was not associated with survival, consistent with a previous report. Inclusion of miR-124-3p levels improved the predictive value with an integrated discrimination improvement of 0.06 (95% CI, 0.02-0.10). In Kaplan-Meier analysis, miR-124-3p levels were strongly associated with shorter survival (Figure 2D), even after adjustment for age. Overall, patients with high levels of miR-124-3p 48 hours after ROSC were at high risk for death.
Discussion

In this predefined substudy of the multicenter TTM trial, we addressed the prognostic value of circulating miRNAs after cardiac arrest. We report that the miR-124-3p level is associated with neurologic outcome and death, independently of the targeted temperature management regimen.

Animal experiments and in vitro studies have shown that mild induced hypothermia affects the expression of some miRNAs in the brain. In our study, circulating levels of miR-124-3p were not affected by targeted temperature. This finding is consistent with the observed absence of effect of hypothermia on the predictive value of miR-124-3p levels and with the equal effect of targeted temperature management at 33°C or 36°C to protect the brain from severe neurologic sequelae induced by hypoxia and ischemia.

Patients with high levels of miR-124-3p were at high risk for poor neurologic outcome and death. This outcome confirms the results of a previous study and is consistent with the concept that circulating levels of brain-enriched miRNAs reflect neurologic damage. Several other studies support this concept. First, the blood-brain barrier is disrupted after cerebral ischemia, allowing the release of brain-enriched miRNAs into the bloodstream. Second, exosomes carrying miRNAs have the ability to cross the blood-brain barrier.

Circulating levels of miR-124-3p were assessed using quantitative polymerase chain reaction in blood samples obtained 48 hours after the return of spontaneous circulation in 529 patients of the validation cohort. A-C, The prognostic value for neurologic outcome at 6 months assessed by dichotomized cerebral performance category score was determined using logistic regression for all patients and those in the 33°C (n = 231) and 36°C (n = 298) treatment groups. Areas under the receiver operating characteristics curve (95% CI) are shown for each group. D, The prognostic value of microRNA 124-3p (miR-124-3p) levels for death at the end of the trial was determined using Kaplan-Meier curves and the log-rank test. Quartile 1 indicates patients with miR-124-3p serum levels of 3 to 688 copies/μL; quartile 2, 690 to 1565 copies/μL; quartile 3, 1572 to 4817 copies/μL; and quartile 4, 4882 to 83,373 copies/μL.
Third, brain-enriched miRNAs have been identified in the blood samples of patients at an early stage of neurodegenerative disease. Furthermore, in the present study, levels of miR-124-3p were positively correlated with the time from cardiac arrest to ROSC and with NSE levels, but not with age. Because most patients with cardiac arrest die of irreversible brain injury, the prognostic ability of brain-enriched miRNAs for death after cardiac arrest is biologically plausible. We expect that patients with high serum levels of brain-enriched miR-124-3p, attesting to an extensive brain damage, are at high risk for death.

Sex differences in circulating levels of miRNAs have been reported in some but not all miRNA studies. We did not detect different levels of miR-124-3p between male and female patients. Of note, sex was not associated with outcome in the present substudy, in the main TTM trial, and in the previous proof-of-concept study. 

In a recent report from the International Cardiac Arrest Registry, men were more likely than women to survive after out-of-hospital cardiac arrest despite similar neurologic outcomes. Thus, whether sex is an important determinant of outcome after cardiac arrest is still a matter of debate.

Identification of novel biomarkers associated with outcomes after cardiac arrest is important because currently available biomarkers for prognostication are insensitive when aiming for a low false-positive rate and may be hindered by confounders such as hemolysis. Previous investigations demonstrated the potential of brain-derived proteins such as NSE and S-100B to identify patients at high risk for a poor outcome. Combined determination of clinical examination, biomarkers, and neurophysiologic variables has shown some added prognostic value. Herein, we have shown that circulating miR-124-3p can aid in the prediction of outcome after cardiac arrest. The observation that miR-124-3p levels do not provide an added predictive value to a clinical model that includes NSE is consistent with the fact that NSE and miR-124-3p levels reflect cerebral damage. Other miRNAs indicative of multiple organ injury may have an added value and should be considered in further investigations.

From a clinical perspective, our findings are appealing because diagnostic assays to measure miRNA levels are being implemented. These assays require a low volume of blood, are sensitive, can be automated and multiplexed, and may thus be cost-effective. However, the added value in a prognostic algorithm involving clinical examination, neurophysiology, and brain imaging remains to be established. In future investigations, the focus should be on the added value of miRNA levels for early prognostication. Because high, serial levels of NSE are necessary for reliable prediction, one may expect that miRNAs, which are small molecules that easily cross the blood-brain barrier, may be detectable in the blood earlier than NSE. In addition, brain-enriched miR-124-3p might also serve as a biomarker in other rapidly progressive neurodegenerative or neurovascular disorders such as stroke or subarachnoid hemorrhage.

This study has a number of strengths and limitations. Our examination of miR-124-3p level as a prognostic factor was a predefined substudy of the largest prospective multicenter randomized clinical trial—to our knowledge—to address the therapeutic value of target temperature regimens in patients with cardiac arrest. In addition, assessment of miR-124-3p levels was performed in a single laboratory to maximize consistency of sample handling and processing and measurement of miRNA levels. We have implemented a computational method to determine the absolute concentrations of miR-124-3p, whereas most past miRNA studies reported relative concentrations.

As far as limitations are concerned, the predictive value of only 1 miRNA is reported, and other miRNAs may also have a prognostic value. We must acknowledge that short RNA sequencing of plasma samples is prone to multiple biases that may prevent the discovery of novel candidates. Also, the study was performed in a subgroup of patients of the TTM trial for whom blood samples were available. However, demographic and clinical features of this subgroup are comparable to those of the whole cohort. The discovery phase with sequencing was undertaken in plasma samples, whereas the validation phase with PCR was achieved in serum samples. Although this process might appear inconsistent, the ability to confirm initial findings obtained in plasma samples in additional serum samples validates the suitability of both sample types to be used for miRNA testing. No mechanistic link between miR-124-3p levels and outcome are provided in this biomarker study, although we expect that patients with high circulating levels of brain-enriched miR-124-3p, reflecting extensive brain injury, are at high risk for poor outcomes. Finally, serial measurements were performed in a subgroup of 43 patients, and the best time points for outcome prognostication remain to be determined.

Conclusions

The miRNA-124-3p level is associated with neurologic outcome and survival after cardiac arrest. This finding motivates future research to determine the additive value of measurement of miR-124-3p levels for early prognostication after cardiac arrest.
Research Original Investigation

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Acquisition, analysis, or interpretation of data: Devaux, Dankiewicz, Salgado-Somoza, Stammet, Collignon, Zhang, Vausort, Hassager, Wise, Kuiper, Croneberg, Erlinge, Nielsen.

Drafting of the manuscript: Devaux, Collignon.

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Obtained funding: Devaux, Cronberg, Erlinge, Nielsen.

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Study supervision: Devaux, Cronberg, Nielsen.

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MicroRNA-124-3p Levels in Cardiac Arrest

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