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ORIGINAL RESEARCH

In-Hospital ECG Findings, Changes in Medical Management, and Cardiovascular Outcomes in Patients With Acute Stroke or Transient Ischemic Attack

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BACKGROUND: In patients with acute ischemic stroke, little is known regarding the frequency of abnormal ECG findings other than atrial fibrillation and their association with cardiovascular outcomes. We aim to analyze the frequency and type of abnormal ECG findings, subsequent changes in medical treatment, and their association with cardiovascular outcomes in patients with acute ischemic stroke.

METHODS AND RESULTS: In the investigator-initiated multicenter MonDAFIS (impact of standardized monitoring for detection of atrial fibrillation in ischemic stroke) study, 3465 patients with acute ischemic stroke or transient ischemic attack and without known atrial fibrillation were randomized 1:1 to receive Holter-ECG for up to 7 days in-hospital with systematic evaluation in a core cardiology laboratory (intervention group) or standard diagnostic care (control group). Outcomes included predefined abnormal ECG findings (eg, pauses, atrial fibrillation, brady-/tachycardias), medical management in the intervention group, and combined vascular end point (recurrent stroke, myocardial infarction, major bleeds, or all-cause death) and mortality at 24 months in both randomization groups. Predefined abnormal ECG findings were detected in 326 of 1693 (19.3%) patients in the intervention group. Twenty of these 326 patients (6.1%) received a pacemaker, and 62 of 326 (19.0%) patients had newly initiated or discontinued β-blocker medication. Discontinuation of β-blockers was associated with a higher death rate in the control group than in the intervention group during 24 months after enrollment (adjusted hazard ratio, 11.0 [95% CI, 2.4–50.4]; *P*=0.025 for interaction).

CONCLUSIONS: Systematic in-hospital Holter ECG reveals abnormal findings in 1 of 5 patients with acute stroke, and mortality was lower at 24 months in patients with systematic ECG recording in the hospital. Further studies are needed to determine the potential impact of medical management of abnormal ECG findings.

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Key Words: beta-blocker ■ ECG ■ mortality ■ stroke ■ transient-ischemic attack

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CLINICAL PERSPECTIVE

What Is New?

- Systematic Holter-ECG recording in addition to usual diagnostic care reveals abnormal findings in ≈20% of patients hospitalized for acute ischemic stroke or patients with transient ischemic attack and is associated with lower mortality within 2 years after stroke.
- Informed adjustment of β-blocker therapy is associated with lower mortality in the intervention than in the control group, in which no systematic Holter ECG was performed in the hospital.

What Are the Clinical Implications?

- Because systematic Holter-ECG recording in-hospital was associated with lower mortality, further efforts to optimize and standardize diagnostic care after acute ischemic stroke or transient ischemic attack are warranted.
- Abnormal ECG findings should lead to consultation with a cardiologist in clinical practice to optimize medical management after acute ischemic stroke or transient ischemic attack.

Nonstandard Abbreviations and Acronyms

CE	composite end point
MonDAFIS	impact of standardized monitoring for detection of atrial fibrillation in ischemic atroke

Patients with ischemic stroke or transient ischemic attack (TIA) often have concomitant heart disease and are susceptible to stroke-related cardiac injury, and a substantial proportion of them die during follow-up.[1,2] Therefore, the identification of patients with stroke at high risk for cardiovascular events is of paramount importance.[1] Several studies have shown that prolonged ECG monitoring has an impact on guiding secondary stroke prevention by detecting atrial fibrillation (AF).[2] Previous prospective studies investigating the detection of AF using prolonged ECG monitoring in patients with acute stroke (without known AF) focused primarily on the detection of AF and not on additional abnormal ECG findings that might have influenced rate and rhythm management and eventually cardiovascular outcomes.[3,4] Thus, it is unclear whether the detection of ECG findings besides AF during prolonged ECG monitoring is associated with cardiovascular outcomes.

In the MonDAFIS (impact of standardized monitoring for detection of atrial fibrillation in ischemic stroke) study, 3465 patients with acute ischemic stroke or TIA were randomized to either systematic Holter-ECG monitoring (up to 7 days in-hospital) in addition to standard diagnostic care (intervention group) or standard of care alone (control group). While systematic ECG monitoring had no statistically significant effect on anticoagulation rates 12 months after the index stroke (primary end point) and the combined vascular end point (recurrent stroke, myocardial infarction, major bleeds, or all-cause death at 6,12, and 24 months after the index stroke), there was a statistically significant decrease in deaths in the intervention group (hazard ratio, 0.7 [95%CI, 0.5–0.9], P=0.017), which could not be explained by fewer recurrent strokes.[5]

Here, we present data on the frequency and type of predefined abnormal ECG findings of extended ECG monitoring in the intervention group. Specifically, we analyzed whether these findings prompted (1) additional ECGs during follow-up, (2) pacemaker implantation during follow-up, or (3) changes in medical rate and rhythm management (specifically β-blocker therapy). Finally, we investigated a potential association between a change in medical rate and rhythm management in patients with abnormal study ECG findings and the combined end point or death and compared the results with the control group, which did not receive systematic ECG monitoring.

METHODS

Data Availability

Deidentified participant data with corresponding data dictionary of the data underlying the current article will be made available upon reasonable request to the corresponding author, Prof. Matthias Endres (matthias.endres@charite.de). Data will be shared with external researchers for scientific noncommercial purposes after approval of the proposal by the MonDAFIS steering board, including a signed data access agreement.

Study Design and Patients

The MonDAFIS study was an investigator-initiated, prospective, multicenter study, sponsored by the Charité - Universitätsmedizin Berlin, Germany, and supported by an unrestricted research grant to the Charité from Bayer Vital GmbH, Germany, which had no influence on study design, study protocol, collection, analysis, interpretation of data, and writing and submitting the paper for publication. The study rationale and design as well as the main results were published previously.[5,6] The MonDAFIS study was approved by the ethics committees of all participating sites, led by the Charité Ethics Committee, Berlin, Germany (EA2_033_14). All study

patients gave written informed consent. A critical event committee blinded to study randomization adjudicated all events (ie, all-cause death, recurrent stroke, myocardial infarction, and major bleeding). Patients were eligible for study enrollment if they had an index stroke defined as ischemic stroke[7] or TIA (with neurological deficit at hospital admission or an acute ischemic lesion on magnetic resonance imaging of the brain) and had no prior diagnosis of AF.[5]

Study Intervention

Treatment allocations were unblinded to patients and treating physicians. Study patients were randomized 1:1 to continuous Holter-ECG recording for up to 7 days during the in-hospital stay in addition to standard diagnostic care (intervention group) or to standard diagnostic care (control group). In the MonDAFIS study, a total of 3465 patients were randomized and assigned to the intervention group (n=1735) or the control group (n=1730, Figures S1).[5] The study ECG core laboratory at the University of Birmingham, UK, received the study ECGs online for evaluation,[5] after which a graded recommendation for cardiology consultation was made based on the abnormal ECG findings identified. Comprehensive reports regarding study ECG findings were returned to the respective study site as soon as possible. If the study patient was discharged at this time, the local study center mailed the core laboratory report to the patient and the treating physician.

Study ECG Findings

ECG recordings were available in 1693 (98.8%) of 1714 patients in the intervention group (Figure S1). Median duration of study ECG recording was 120.6 hours (interquartile range, 73.3–166.1).[5] The following abnormal study-ECG findings were considered "relevant" and were predefined for standardized analysis in the core laboratory: (1) atrial fibrillation, (2) atrial flutter, (3) second-/third-degree atrioventricular block, (4) bradycardia, (5) supraventricular tachycardia, (6) sustained and nonsustained ventricular tachycardia, and (7) pauses. The chosen definitions of these ECG abnormalities are listed in Table 1. "Relevant" ECG abnormalities led to an explicit recommendation requiring immediate attention for an "urgent cardiologic work-up" (in case of sustained ventricular tachycardia, complete heart block, 2:1 atrioventricular block, pauses >5 s, bradycardia) or a "cardiologic work-up" (in case of the other categories) in the written report sent to the study center. Of note, some of these ECG findings may not be pathologic per se, and their relevance depends on clinical circumstances (eg, asymptomatic versus symptomatic pause >5 s). However, all predefined ECG abnormality results were treated as findings that triggered the recommendation for cardiology consultation regardless of clinical circumstances. Additionally, the results of 172 study ECGs (ie, a predefined random 10% sample of the study ECG results) were independently validated from the cardiology core laboratory by an additional cardiology expert, resulting in a confirmation of >99% of abnormal ECG findings of the core laboratory.

Table 1. Definitions of Predefined Abnormal Findings and Their Detection Rates in Patients of the Intervention Group With Analyzable ECG-Recordings Patients

Abnormal ECG findings	Definition	Detection rates of abnormal findings in 1693 patients (n; %)
Atrial fibrillation	>30 s	76 (4.5)
Atrial flutter	Atrial–atrial intervals of <250 ms	0 (0)
Supraventricular tachycardia	>180 bpm, <30 s	61 (3.6)
Nonsustained ventricular tachycardia	4–30 beats	215 (12.7)
Sustained ventricular tachycardia	>30 beats	0 (0)
Pauses (intermediate)	>2 s, <5 s	49 (2.9)
Pauses	≥5 s	9 (0.5)
Atrioventricular block second	Type I and II	11 (0.6)
Atrioventricular block third	Complete heart block	0 (0)
Minimal heart rate	<25 bpm	0 (0)

bpm indicates beats per minute.

Outcomes

In this post hoc analysis, the following outcomes were analyzed: the proportional number of recurrent stroke, myocardial infarction, major bleedings, or all-cause death (composite end point [CE]) and all-cause death within 24 months after the index stroke. CE and all-cause mortality were analyzed and compared in the following groups of study patients: (1) patients with analyzable study-ECG in the intervention group (n=1693); (2) intention-to-treat population of the MonDAFIS study (n=3431; including 1714 patients randomized to the intervention group and 1717 patients randomized to the control group), corresponding to the complete randomized data set of the MonDAFIS study.[5]

Statistical Analysis

Baseline characteristics are reported as frequencies and percentages for categorical variables or median and interquartile range or means and SD for metric variables. We used Fisher exact test, Mann–Whitney *U* test, or *t* test for independent samples when appropriate regarding differences in univariate comparisons. Because there are complex interactions between heart rate, β-blocker therapy, and cardiac and vascular

outcomes, we first focused on changes in β-blocker therapy. To measure changes in β-blocker therapy, we compared β-blocker intake at the time of index hospital admission and 6 months later. We defined 5 types of β-blocker use: continued β-blocker use: yes/yes, no β-blocker use: no/no, discontinuation of β-blocker use: yes/no, initiation of β-blocker use: no/yes, and unknown β-blocker status 6 months after the index event (because of missing data, in case of patient's death, or dropout from the study before 6 months after the index stroke/TIA). Kaplan–Meier curves were used to illustrate descriptively cumulative hazard distributions of the events of interest in patients with known β-blocker status. A comparison of the cumulative event probability in patients with known and unknown β-blocker status is listed in Table S1. We limited our analyses with respect to vascular end points and mortality to drugs that we hypothesized to be clinically associated with the abnormal ECG findings. Other drug groups that are used for secondary prevention of stroke (eg, statins) but are not specifically associated with abnormal ECG findings were not included in our analysis.

Multivariable Cox regression analyses were used to estimate hazard ratios before the effects of the all-cause death and for the combined vascular end point (CE) within 2 years after the index event. Multivariable Cox regression analyses included randomization group (intervention, control) and were adjusted for sex (female/male), age (<65 years/≥65 years), the National Institutes of Health Stroke scale score (ranging from 0–42 points, with higher scores indicating more severe neurological deficits)[8] at baseline (<5/≥5 points), stroke or TIA as an index event, and the dichotomous cardiovascular risk factors at baseline (diabetes, arterial hypertension, coronary heart disease, stroke before index event, TIA before index event, peripheral artery disease, renal insufficiency, heart failure—diagnosed before or during the hospital stay of the index stroke/TIA) and β-blocker administration (see above). In addition, heart rate at admission was included in Cox regression analyses categorized as bradycardia at <60 beats per minute, normal heart rate (60–100 beats per minute), or tachycardia at >100 beats per minute,[9] as well as the interaction of heart rate on admission and randomization group. In order to address possible time-varying misclassifications of β-blocker administration, we additionally performed a Cox regression analysis with a time-varying covariate for discontinuing β-blocker within 6 or 12 months of follow-up. Here, events that occurred before the 6-month follow-up were discarded, and the interaction mentioned above was replaced with the interaction of the time-varying covariate for discontinuing β-blocker and randomization group. Multivariable Cox regression analyses were performed without variable selection. Estimated marginal hazard ratios and corresponding 95% CIs were calculated for the subgroup analyses with interactions. Because this is a hypothesis-generating post hoc analysis, no multiplicity adjustments were done, and the results have to be considered exploratory. All statistical analyses were performed using the statistical software package IBM SPSS Statistics 26.0.

RESULTS

Study Cohort

Mean age was 66.3 years, 40.5% were female, and 29.8% had a TIA as qualifying event. The median National Institutes of Health Stroke Scale score on admission was 2 points (Table S2; for details see also[5]). A total of 1693 patients randomized to the intervention group had an analyzable Holter-ECG.

ECG Findings in the Intervention Group

At least 1 abnormal ECG finding was detected in 326 of 1693 (19.3%) patients of the intervention group, and 90 of 1693 (5.3%) patients had >1 abnormal finding. Overall, 250 of 1693 (14.8%) patients had abnormal findings other than newly detected AF. Of 76 of 1693 (4.5%) patients with newly detected AF, 38 of 1693 (2.2%) patients had additional abnormal ECG findings. The core laboratory recommended "urgent consultation with a cardiologist" in 70 of 1693 (4.1%) patients and "a consultation with a cardiologist" in 210 of 1693 (12.4%) patients (Table 1). Baseline characteristics differed in patients with and without abnormal study ECG findings (Table 2), as patients with abnormal ECG findings were older, less likely to have an index TIA, had a higher National Institutes of Health Stroke Scale score at baseline, a longer in-hospital stay, were more likely to be pretreated with a β-blocker, and were more likely to have coronary artery disease, renal dysfunction, or hypertension.

Management of Patients With Abnormal ECG Findings

Patients with abnormal study ECG findings were relatively more likely to receive at least 1 additional resting ECG and Holter ECG after hospital discharge during the 24 months follow-up compared with patients without abnormal study ECG findings (Table S3).

Within 24 months, there were more pacemaker implantations in patients with abnormal study ECG findings (n=20/326; 6.1%) than in patients without abnormal findings (n=7/1365; 0.5%; $P<0.001$). Of the 578 patients in the intervention group who were on rate or rhythm management at the time of admission, 559 (96.7%) received a β-blocker, followed by 18 patients (3.1%) with calcium channel blocker and 3 (0.5%) patients with a sodium and potassium channel blocker.

Table 2. Baseline Characteristic of 1693 Patients in the Intervention Group With and Without Abnormal Study ECG Findings According to Study ECG

	No abnormal finding (n=1367)	Abnormal finding(s) (n=326)	*P* value
Age, y (mean [SD])	65.1 (13.0)	71.0 (10.7)	<0.001*
Female sex (n; %)	558 (40.8)	125 (38.3)	0.451
Index event: TIA (n; %)	431 (31.6)	70 (21.5)	<0.001*
NIHSS score on admission (median [IQR])	2 [1, 4]	3 [1, 5]	0.007
Intravenous thrombolysis (n; %)	284 (20.8)	82 (25.2)	0.099
Endovascular treatment (n; %)	28 (2.1)	12 (3.7)	0.102
Length of hospital stay, d (median [IQR])	7 [5, 9]	8 [6, 11]	<0.001*
Diabetes (n; %)	347 (25.6)	99 (30.5)	0.080
Hypertension (n; %)	1029 (75.9)	275 (84.6)	0.001*
Heart failure (n; %)	143 (10.5)	67 (20.6)	0.0001
Renal impairment (n; %)	84 (6.2)	45 (13.9)	<0.001
Peripheral artery disease (n; %)	52 (3.8)	13 (4.0)	0.873
Hypercholesterolemia (n; %)	715 (52.7)	179 (55.1)	0.458
Coronary artery disease (n; %)	136 (10.0)	61 (18.7)	<0.001*
Prior ischemic stroke (n; %)	222 (16.2)	58 (17.8)	0.508
Prior TIA (n; %)	55 (4.1)	13 (4.0)	1.000
β-blocker on admission (n; %)	426 (31.2)	130 (39.9)	0.003*
Heart rate on admission (mean [SD])	75.3 [13.4]	76.6 [14.5]	0.122

Data are n (%), mean (SD), or median (IQR). IQR indicates interquartile range; NIHSS, National Institutes of Health Scale; and TIA, transient ischemic attack. *P* values were calculated using Fisher exact test, *t* test for independent samples, or Mann–Whitney *U* test.

*$P < 0.05$ is considered statistically significant.

Only 2 patients (0.3%) received a combination of a β-blocker and another antiarrhythmic agent. Because antiarrhythmic drugs other than β-blocker were a small minority treatment group, we restricted further analyses to β-blocker therapy only.

Patients of the study population who received β-blocker treatment at admission were older, more often female, had a higher number of cardiovascular risk factors, had a higher National Institutes of Health Stroke Scale score at admission, and a longer in-hospital stay after the index stroke (Table S4). In addition, patients who received β-blocker treatment at admission were more likely to have abnormal findings on study ECG (130/556; 23.4%) than those without a β-blocker (196/1137; 17.2%; *P*=0.003, Table 2). In particular, there were more frequently changes in the β-blocker therapy in patients with abnormal study ECG findings than in patients without abnormal study ECG findings (67/284; 23.5% abnormal. 172/1235; 13.9%; Table 3). Despite these differences between these 2 subgroups of patients with and without abnormal ECG findings, there were no overall differences in β-blocker change between randomized groups (Table 3). During 24 months follow-up, there were similar numbers of pacemaker implantations in the intervention (n=27/1711) and control (n=30/1715; *P*=0.649; Figure S2) group. Neither differed in the number of additional ECG recordings after hospital discharge (*P*=0.456) nor differed in the number of Holter ECGs performed after hospital discharge between randomization groups (*P*=0.456).

Association of Heart Rate, β-Blocker Treatment, and CE or Death

We analyzed whether or not there was an association between β-blocker treatment regimens (ie, continued treatment: yes/yes, no treatment: no/no, initiation of treatment: no/yes, or discontinuation: yes/no, and unknown β-blocker status) and CE or all-cause death within 24 months follow-up. Kaplan–Meier curves did not show a differential association between β-blocker regimens and CE or all-cause death in the intervention group (Figure 1). In contrast, in the control group, discontinuation of β-blocker therapy had a higher cumulative proportion of patients with CE (22.8% versus 11.0%) and all-cause death (15.3% versus 1.8%) compared with the interventions group at 24 months (Figure 1). Multivariable Cox regression analysis for all-cause death with discontinuation of

Table 3. Alterations of β-Blocker Therapy (β-Blocker Status on Admission Versus Follow-Up)

β-blocker on admission vs at 6-mo follow-up	Intervention group* (n=1531)	Intervention group – abnormal ECG finding(s)† (n=284)	Intervention group – no abnormal ECG finding(s)† (n=1235)	Control group* (n=1487)
Continuing β-blocker (yes/yes, n, %)	445 (29.1%)	94 (33.1%)	350 (28.3%)	433 (29.1)
No β-blocker (no/no, n, %)	844 (55.1%)	123 (43.3%)	713 (57.7%)	833 (56.0)
Discontinuing β-blocker (yes/no, n, %)	62 (4.0%)	20 (7.0%)	41 (3.3%)	54 (3.6)
Starting β-blocker (no/yes, n, %)	180 (11.8%)	47 (16.5%)	131 (10.6%)	167 (11.2)

The type "yes/yes" and "no/no" indicate an unchanged β-blocker regimen, whereas "yes/no" and "no/yes" indicate an altered β-blocker regimen.

*Patients included with available data on β-blocker status at 6 months follow-up.

†Patients included with available data on β-blocker status at 6 months follow-up and data on abnormal ECG findings.

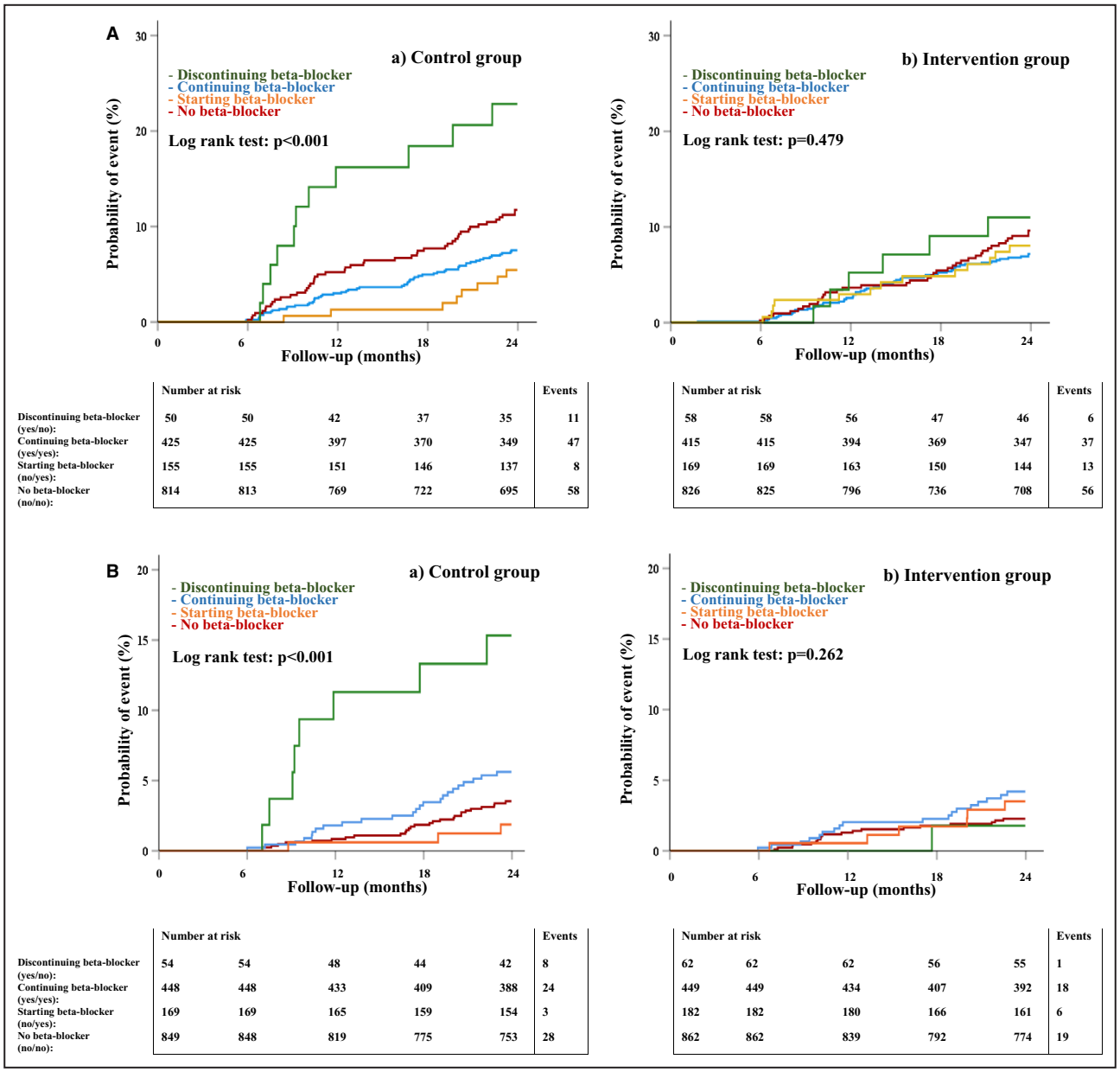

Figure 1. Kaplan–Meier curve for the probability of (A) the CE (ie, mortality, stroke, myocardial infarction, or major bleeding; intervention group, n=1468 and control group, n=1444) and (B) all-cause death (intervention group, n=1555 and control group, n=1520) within 24 months after the index stroke/transient ischemic attack in patients with different regimens of β-blocker depicted for each study group separately (patients with missing data at 6 months with regard to β-blocker status excluded: CE, n=519 and all-cause death, n=356).

Log-rank test was used to test group differences. CE indicates composite end point.

β-blocker therapy as time-varying covariate revealed that there was an interaction of discontinuation of β-blocker therapy (yes/no) and randomization group (*P*=0.025). Specifically, discontinuation of β-blockers was associated with an increased risk for death (adjusted HR [aHR], 11.0 [95% CI, 2.4–50.4]; *P*=0.002) in the control group compared with the intervention group (Figure 2B). The corresponding interaction for CE was less pronounced (aHR, 2.2 [95% CI, 0.9–5.0]; *P*=0.149, Figure 2A). Event rates for all-cause death and CE within 24 months were similar between intervention and control group in patients who did not discontinue β-blocker therapy (all-cause death: aHR, 1.3 [95% CI, 0.8–1.9]; *P*=0.253 and CE: aHR, 1.1 [95% CI, 0.8–1.5]; *P*=0.451, Figure 2A and 2B).

A separate multivariable Cox regression analysis revealed that tachycardia on admission was associated with an increased risk for CE (aHR, 3.1 [95%

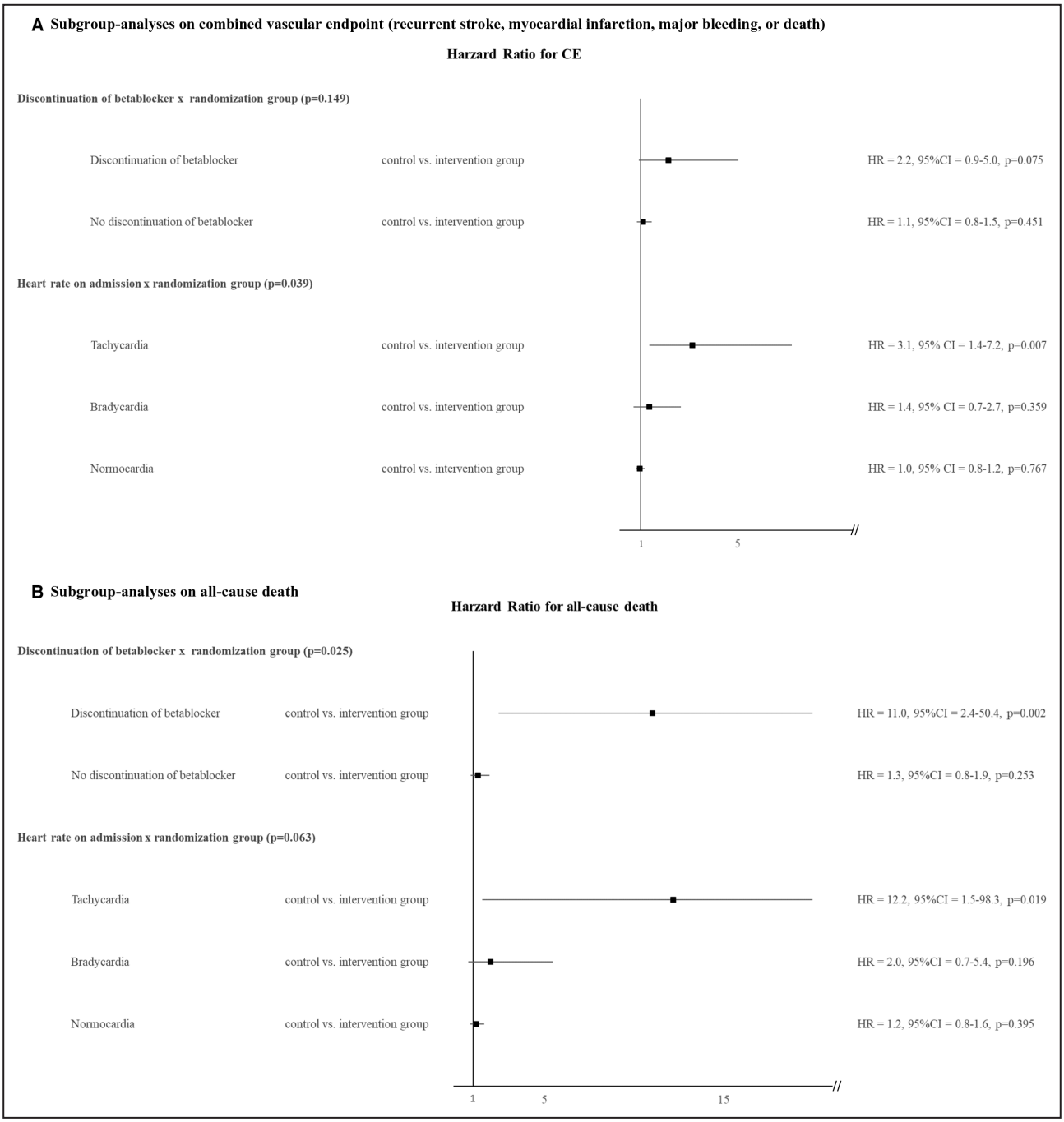

Figure 2. Estimated marginal hazard ratios and corresponding 95% CIs are depicted to illustrate the interaction between randomization groups and β-blocker discontinuation as well as the interaction between randomization groups and heart rate on admission and corresponding 95% CIs.

A, The CE (ie, mortality, stroke, myocardial infarction, or major bleeding) and all-cause death (**B**) within 24 months after the index stroke or TIA in multivariable Cox regression models. A time-varying covariate was used for the discontinuation of β-blocker during follow-up discarding patients with unknown β-blocker status (CE, n=2894, number of events=235; all-cause death, n=3042, number of events =106, intervention group as reference category) and heart rate on admission (tachycardia >100 bpm and bradycardia <60 bpm, normocardia 60–100 bpm) using separate multivariable Cox regression analyses (CE, n=3367, number of events=477; all-cause death: n=3354, number of events =174, intervention group as reference category). Cox regression analyses were additionally adjusted for age, sex, stroke severity (National Institutes of Health Stroke Scale score on admission), ischemic stroke or TIA as index event, cardiovascular risk factors at baseline (diabetes, hypertension, coronary artery disease, prior stroke, peripheral artery disease, renal insufficiency, heart failure: diagnosed before or during the hospital stay of the index stroke/TIA). *P* value for interaction within Cox regression analyses. bpm indicates beats per minute; CE, composite end point; HR, hazard ratio; and TIA, transient ischemic atack.

CI, 1.4–7.2]; *P*=0.007) and for all-cause death (aHR, 112.2 [95% CI, 1.5–9.3]; *P*=0.019) in the control group compared with the intervention group (Figure 2). The interaction of heart rate on admission and randomization group had for CE within 24 months (a *P* value of 0.039) and for all-cause death (a *P* value of *P*=0.063) within 24 months. In addition, we performed a sensitivity analysis to examine whether the cause of the index event was associated with mortality within 24 months of follow-up. The Kaplan–Meier analysis showed that the subgroups "cardioembolic stroke" and "stroke of other determined cause" had the highest mortality rates at 24 months after the index event (Figure S3). Even though the proportions of assumed causes of the index event were similar between randomization groups at baseline (Fisher exact test *P*=0.788), patients with a cardioembolic index event had a 3-fold higher mortality rate in the control group compared with the intervention group (hazard ratio, 3.09 [95% CI, 1.39–6.88]; *P*=0.006). All other subgroups of the assumed cause of the index event did not differ between randomization groups (Table S5).

DISCUSSION

This exploratory post hoc analysis of the MonDAFIS study shows that predefined abnormal ECG findings are detected by systematic Holter ECG recording in ≈20% of patients hospitalized with acute ischemic stroke or TIA. Differences in ECG use, pacemaker implantation, and especially β-blocker use in response to abnormal ECG findings were evident during follow-up. Our analyses suggest that these changes in medical treatment may have been influenced by abnormal study ECG findings and subsequent recommendations to consult a cardiologist. The individual decisions to continue, discontinue (eg, because of bradycardia or high-grade atrioventricular block), or initiate (eg, because of tachycardia) β-blocker therapy might have been better justified in the intervention group than in the control group. In particular, our data support the notion that ill-considered discontinuation of β-blocker therapy that is not informed by specific ECG findings may be associated with recurrent vascular events and death in the control group.

Because the intervention group did not receive more diagnostic and therapeutic interventions overall compared with the control group, it is conceivable that the specific selection of these interventions was better qualified to manage the underlying cardiovascular pathology. Overall, these differences in medical management may have contributed to the statistically significantly lower mortality in the intervention versus the control group observed at 24 months in our study.[5]

Interestingly, tachycardia on admission was associated with a higher death rate in the control group compared with the intervention group. There is evidence from cohort- and registry-based studies that an increased heart rate on admission in patients with acute ischemic stroke (and without atrial fibrillation) is associated with increased in-hospital mortality[10,11] and also with mortality within 90 days[12] or within a median follow-up of 2.4 years.[13] Because no patient with tachycardia on admission and abnormal ECG findings in the intervention group died within 2 years, these results can be cautiously interpreted as further indirect evidence that the intervention of additional ECG monitoring with systematic recommendation for cardiology consultation might have altered the risk profile of patients with acute stroke, resulting in a lower event rate over time. Moreover, our finding that patients with a cardioembolic stroke as an index event had a 3-fold higher mortality within 24 months in the control group compared with the intervention group could be interpreted accordingly.

β-blocker therapy lowers heart rate, may prevent the development of potentially fatal arrhythmias, and has been associated with a reduction of sudden cardiac death and mortality in patients with myocardial infarction.[14,15] In addition, abrupt discontinuation of β-blocker therapy can lead to a rebound phenomenon, which usually manifests as tachycardia, arrhythmia, blood pressure elevation, angina, and worsening of heart failures symptoms, and can be fatal.[16] In a recent meta-analysis that included 18 observational studies and 2 randomized controlled trials, no benefit in mortality, functional outcomes, or infection rates were found within the first 12 months in >100 000 patients who received a β-blocker within the first week after acute ischemic stroke.[17] In a Cochrane meta-analysis of 2 double-blinded randomized controlled trials testing atenolol versus placebo in 2193 patients with stroke, β-blocker therapy did not reduce the risk of stroke recurrence or fatal stroke, and adverse events occurred more frequently in the β-blocker group.[18] These meta-analyses are based on mean differences between groups. Our analysis suggests that targeted changes in β-blocker therapy could lead to improved cardiovascular outcomes that are independent of mean differences between treatment groups.

An open issue is how long and with which technique of ECG monitoring should be performed in patients with stroke. In the MonDAFIS study, we have shown that Holter ECG monitoring for up to 7 days in the hospital, evaluated in a core laboratory, can detect more AF than regular care in a certified stroke unit. Here, we show that, in addition, other abnormal ECG findings are detected that may be clinically relevant and lead to significant changes in medical management. We also believe that the cardiology consultation triggered by

the abnormal ECG findings is an important element in the improved care of patients with stroke, although we cannot rule out the possibility that this simply reflects good clinical practice in a stroke unit by careful monitoring and prompting action when an abnormality is detected.

Our study has limitations. First, there was no systematic information on abnormal study ECG findings in the control group because standard diagnostics were not analyzed in the cardiology core laboratory. Second, changes in medication were assessed for the first time at 6 months after the index stroke. Hence, the effect on all-cause mortality between randomization groups at 24 months can only be explained by extrapolation of the early changes, assuming a continued effect of the changes in medical management. Third, we have no information on changes in daily drug dose in patients who continued their β-blocker therapy. Fourth, we cannot rule out bias based on indication because of a nonrandom treatment exposure. However, the types of β-blocker therapy were similarly distributed in both randomization groups. In addition, the increased risk of mortality and CE in patients who discontinued β-blocker therapy remained stable after multivariable adjustment. Furthermore, although cardiology work-up was explicitly recommended for patients with abnormal ECG findings in the intervention group, we have no information on how frequently and timely cardiologists were consulted. It should be noted that the abnormal ECG findings were evaluated in a cardiology core laboratory. Unfortunately, apart from AF, we do not have information on abnormal ECG findings diagnosed in the control group. Furthermore, we have no information on abnormal ECG findings during routine diagnostic care in the intervention group in the hospital. Fifth, because of the small sample size for the reported exposures of β-blocker discontinuation (n=112) and tachycardia on admission (n=162), a chance finding cannot be excluded. Sixth, even though we cautiously conclude from our data that informed medical management of patients based on the specific ECG findings may have positively influenced their outcome, the design of our post hoc analysis limits any conclusions regarding causality. Finally, the observed difference in mortality rates between the 2 study groups may be because of informative censoring (ie, when study patients were lost to follow-up because of reasons related to the study). However, a comparison of the baseline characteristics of patients who dropped out of the study (for reasons other than death) during the 24-month follow-up period showed that there was no difference between the 2 randomization groups (data not shown).

In conclusion, this post hoc analysis of the prospective MonDAFIS study demonstrates that systematic ECG recording for up to 7 days identifies abnormal ECG findings in ≈20% of hospitalized patients with ischemic stroke and TIA. The fact that patients with systematic ECG recording in the intervention had a statistically lower mortality compared with the control group may at least in part be explained by the fact that abnormal study ECG findings triggered cardiology consultation and allowed better-informed changes in therapy. Our results warrant further studies to explore the potential of systematic ECG monitoring and intensified interdisciplinary management of patients with ischemic stroke.

APPENDIX

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Disclosures

Dr Haeusler reports speaker's honoraria, consulting fees, lecture honoraria and/or study grants from Abbott, Alexion, Amarin, AstraZeneca, Bayer Healthcare, Sanofi, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, Biotronik, Medtronic, Portola, Getemed AG, Premier Research, W.L. Gore and Associates, SUN Pharma, and Edwards Lifesciences. Dr Kirchhof receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, has received honoraria from several such companies in the past, and is listed as inventor on 2 patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). Dr Thomalla has received speaker's honoraria or consulting fees from Acandis, Bayer Healthcare, Boehringer Ingelheim, Covidien, Bristol-Myers-Squibb, Portola, Stryker, and Pfizer. Dr Nabavi has received speaker's honoraria and consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi Sankyo, Novartis, and Pfizer. Dr Schurig has received speaker's honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Pfizer, Daiichi Sankyo, Alexion, and Astra Zeneca. Dr Laufs reports honoraria/reimbursements for lectures, participation in studies, scientific cooperations (with Saarland University), consulting, travel, support (of colleagues) or support of scientific meetings by Amgen, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, MSD, Sanofi, and Servier outside the submitted work. RV reports grants, personal fees and other from Bayer, grants from Boehringer, grants and personal fees from BMS, grants from Daiichi Sankyo, grants from Medtronic, personal fees from Javelin, grants from Biogen, grants and personal fees from Pfizer, personal fees from Abbott, personal fees from Astra Zeneca, other from Novartis, outside the submitted work. Dr Veltkamp is an investigator of Imperial BRC and partially funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No. 754517 (PRESTIGE-AF). Dr Heuschmann reports grants from Charité - Universitätsmedizin Berlin during study conduct (within MonDAFIS for biometry; member scientific board); research grants from German Ministry of Research and Education, German Research Foundation, research grants from Bavarian State (ministry for science and the arts) (within STAAB COVID-19), European Union, Charité – Universitätsmedizin Berlin, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, Federal Joint Committee (G-BA) within the Innovationsfonds, University Hospital Heidelberg (within RASUNOA-prime; supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo), University Göttingen (within FIND-AF randomized; supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), outside the submitted work. Dr Endres reports grants from Bayer and fees paid to the Charité from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Covidien, Daiichi Sankyo, Glaxo Smith Kline, Novartis, Pfizer, and Sanofi. Dr Dimitrijeski reports travel support and support of scientific meetings by Boehringer and Daiichi Sankyo. Dr Kraft reports lecture honoraria and/or study grants from Daiichi Sankyo and Pfizer, outside the submitted work. Dr Günther reports speakers honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi Sankyo, Pfizer, and a research grant from Ipsen. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S5
Figures S1–S3

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Supplemental Material

Table S1. Cumulative probability of myocardial infarction of (A) CE (recurrent stroke, myocardial infarction, major bleedings, or all-cause death) and of all-cause death (B) at 6 and 24 months after the index stroke/TIA in patients with known and unknown status of beta-blocker (on admission vs. 6 months follow-up) listed separately for the intervention (n=1714) and control group (n=1717). The status of beta-blocker is unknown due to missing data, ín case of patient's death or drop out the study prior to 6 months after the index stroke/TIA.

		CE					**All-cause death**			
		Cumulative probability					Cumulative probability			
		at 6 months		at 24 months			at 6 months		at 24 months	
		(%)	95 % CI	(%)	95 % CI		(%)	95 % CI	(%)	95 % CI
Control group										
beta-blocker status										
	Known (n=1,444)	0.00	0.00 - 0.00	8.76	7.27 - 10.26	Known (n=1,520)	0.00	0.00 - 0.00	4.30	3.25 - 5.35
	Unknown (n=273)	52.84	45.70 - 59.99	72.62	62.91 - 82.33	Unknown (n=197)	20.35	13.03 - 27.68	48.42	33.56 - 63.28
Intervention group										
beta-blocker status										
	Known (n=1,468)	0.07	0.00 - 0.20	7.82	6.42 - 9.23	Known (n=1,555)	0.00	0.00 - 0.00	2.96	2.10 - 3.82
	Unknown (n=246)	59.90	52.67 - 67.13	70.03	61.17 - 78.88	Unknown (n=159)	24.22	15.49 - 32.96	41.74	25.50 - 57.98

Table S2. Baseline characteristics of patients included in the ITT analysis secondary endpoints (complete randomized set)

	Control n=1,717	Intervention n=1,714	Overall n=3,431
Age, years (mean (SD))	66.2 (13.0)	66.3 (12.8)	66.2 (12.9)
Female sex (n; %)	662 (38.6)	694 (40.5)	1,356 (39.5)
Body-mass index, kg/m2 (mean (SD))	27.5 (5.06)	27.5 (4.88)	27.5 (4.97)
Index stroke			
TIA (n; %)	520 (30.4)	510 (29.8)	1,030 (30.1)
NIHSS score on admission (median [IQR])	2 [1, 4]	2 [1, 4]	2 [1, 4]
Intravenous thrombolysis (n; %)	375 (21.9)	370 (21.6)	745 (21.8)
Endovascular treatment (n; %)	57 (3.4)	41 (2.4)	98 (2.9)
Hemicraniectomy (n; %)	1 (0.1)	3 (0.2)	4 (0.1)
Carotid surgery or stenting (n; %)	36 (2.1)	42 (2.5)	78 (2.3)
Hospital stay, days (median [IQR])	7 [5, 9]	7 [5, 10]	7 [5, 9]
Medication on admission			
Oral anticoagulation (n; %)	10 (0.6)	9 (0.5)	19 (0.6)
Heparin, therapeutic dose	15 (0.9)	16 (0.9)	31 (0.9)
Antiplatelet drug (n; %)	587 (34.2)	576 (33.6)	1,163 (33.9)
Statin (n; %)	461 (26.8)	437 (25.5)	898 (26.2)
Beta-blocker on admission (n; %)	573 (33.4)	559 (32.6)	1132 (33.0)
metoprolol (n; %)	245 (14.3)	242 (14.1)	487 (43.0)
bisoprolol (n; %)	223 (13.0)	213 (12.4)	436 (38.5)
nebivolol (n; %)	54 (3.1)	50 (2.9)	104 (9.2)
others (n; %)	53 (3.1)	56 (3.3)	109 (9.6)
Heart rate on admission (mean (SD))	75.8 (13.9)	75.6 (13.6)	75.7 (13.8)
Normocardia (n; %)	1492 (87.1)	1483 (86.6)	2975 (86.9)
Bradycardia (n; %)	138 (8.1)	150 (8.8)	288 (8.4)
Tachycardia (n; %)	83 (4.8)	79 (4.6)	162 (4.7)
Cardiovascular risk factors			
Diabetes mellitus (n; %)	434 (25.6)	448 (26.4)	882 (26.0)
Hypertension (n; %)	1,295 (76.4)	1,314 (77.4)	2,609 (76.9)
Heart failure (n; %)	221 (13.0)	212 (12.5)	433 (12.8)
Hypercholesterolemia (n; %)	898 (53.0)	900 (53.0)	1,798 (53.0)
Coronary heart disease	216 (12.7)	199 (11.7)	415 (12.2)
Peripheral arterial disease (n; %)	66 (3.9)	67 (4.0)	133 (3.9)

Prior ischemic stroke (n; %)	299 (17.6)	283 (16.7)	582 (17.1)
Prior TIA (n; %)	81 (4.8)	69 (4.1)	150 (4.4)
Renal impairment (n; %)	131 (7.7)	131 (7.7)	262 (7.7)
Sleep apnoea (n; %)	45 (2.7)	51 (3.0)	96 (2.8)
Current smoker (n; %)	825 (48.5)	848 (49.8)	1,673 (49.2)

Data are n (%), mean (SD), or median (IQR). TIA=transient ischaemic attack. NIHSS=National Institutes of Health Scale.

Table S3. Rate of patients who received at least one resting ECG or Holter ECG after hospital discharge during the 24 months follow-up in patients* with or without abnormal study ECG findings in the intervention group. In addition, the post-discharge ECG rate of the control group is listed.

	Intervention group – abnormal study ECG finding	Intervention group - no abnormal study ECG finding	Intervention group - abnormal vs. no abnormal findings p-value**	Control group
At least one resting ECG	201/271 (74.2)	~~738~~783/1,191 (65.7)	p=0.008	952/1,443 (66.0)
At least one Holter ECG	138/270 (51.1)	523/1,192 (43.9)	p=0.036	672/1,436 (46.8)

Data are n (%).

*Data of ECGs performed during 24 months of follow-up were available in 1,462/1,693 patients in the intervention (for both resting and Holter ECG, 86.4%) and in 1,443 patients (for resting ECG, 84.0%) and in 1,436 patients (for Holter ECG, 83.6%) of 1,717 patients in the control group, respectively.

**P < 0.05 is considered statistically significant using exact Fisher Test.

Table S4. Baseline characteristic for patients in the complete randomized set (n = 3,431) with and without beta-blocker on admission.

	No beta-blocker on admission (n=2,299)	Beta-blocker on admission[a] (n=1,132)	p-value
Age, years (mean (SD))	64.1(13.4)	70.5 (10.6)	< 0.001
Female sex (n; %)	853 (37.1)	503 (44.4)	< 0.001
Index event TIA (n; %)	711 (31.0)	319 (28.3)	0.104
NIHSS score on admission (median, [IOR [10,25,75,90 percentile])	2 [0, 1, 4, 6]	2 [1, 1, 4, 7]	0.011
Intravenous thrombolysis (n; %)	493 (21.5)	252 (22.3)	0.597
Endovascular treatment (n; %)	65 (2.9)	33 (2.9)	0.913
Length of hospital stay, days (median [IQR])	7 [5, 9]	7 [5, 10]	0.007
Diabetes mellitus (n; %)	450 (19.8)	432 (38.5)	< 0.001
Hypertension (n;%)	1,532 (67.5)	1,077 (96.0)	< 0.001
Heart failure (n;%)	246 (10.8)	187 (16.7)	< 0.001
Renal impairment (n;%)	118 (5.2)	144 (12.9)	< 0.001
Peripheral artery disease (n;%)	71 (3.1)	62 (5.5)	0.001
Hypercholesterolemia (n; %)	1,167 (51.4)	631 (56.3)	0.007
Coronary artery disease (n; %)	144 (6.3)	271 (24.2)	< 0.001
Prior ischemic stroke (n; %)	315 (13.9)	267 (23.8)	< 0.001
Prior TIA (n; %)	90 (4.0)	60 (5.4)	0.075
Heart rate on admission (mean (SD))	77.0 (13.5)	73.1 (13.9)	< 0.001

Data are n (%), mean (SD), or median (IQR). TIA=transient ischaemic attack. NIHSS=National Institutes of Health Scale. P < 0.05 is considered statistically significant using exact Fisher Test, t-test for independent samples, or median (IQR): Mann-Whitney-U test.

Table S5. Unadjusted HR for all-cause death within 24 months after the index stroke or TIA of the control group compared to the intervention group stratified for the assumed etiology of the index stroke/TIA.

Assumed etiology of the index stroke/TIA		**HR** (unadjusted)	**95% CI**	**p-value**
large artery atherosclerotic stroke	control vs. intervention group	1.1	0.6-1.8	0.799
cardioembolic stroke	control vs. intervention group	3.1	1.4-6.9	0.006
small artery occlusion	control vs. intervention group	1.2	0.6-2.2	0.670
cryptogenic stroke	control vs. intervention group	1.7	0.9-3.3	0.106
stroke of other determined etiology	control vs. intervention group	0.7	0.2-3.0	0.612

Figure S1: Flow chart of the post hoc analysis of the MonDAFIS cohort (see also Haeusler et al.[5])

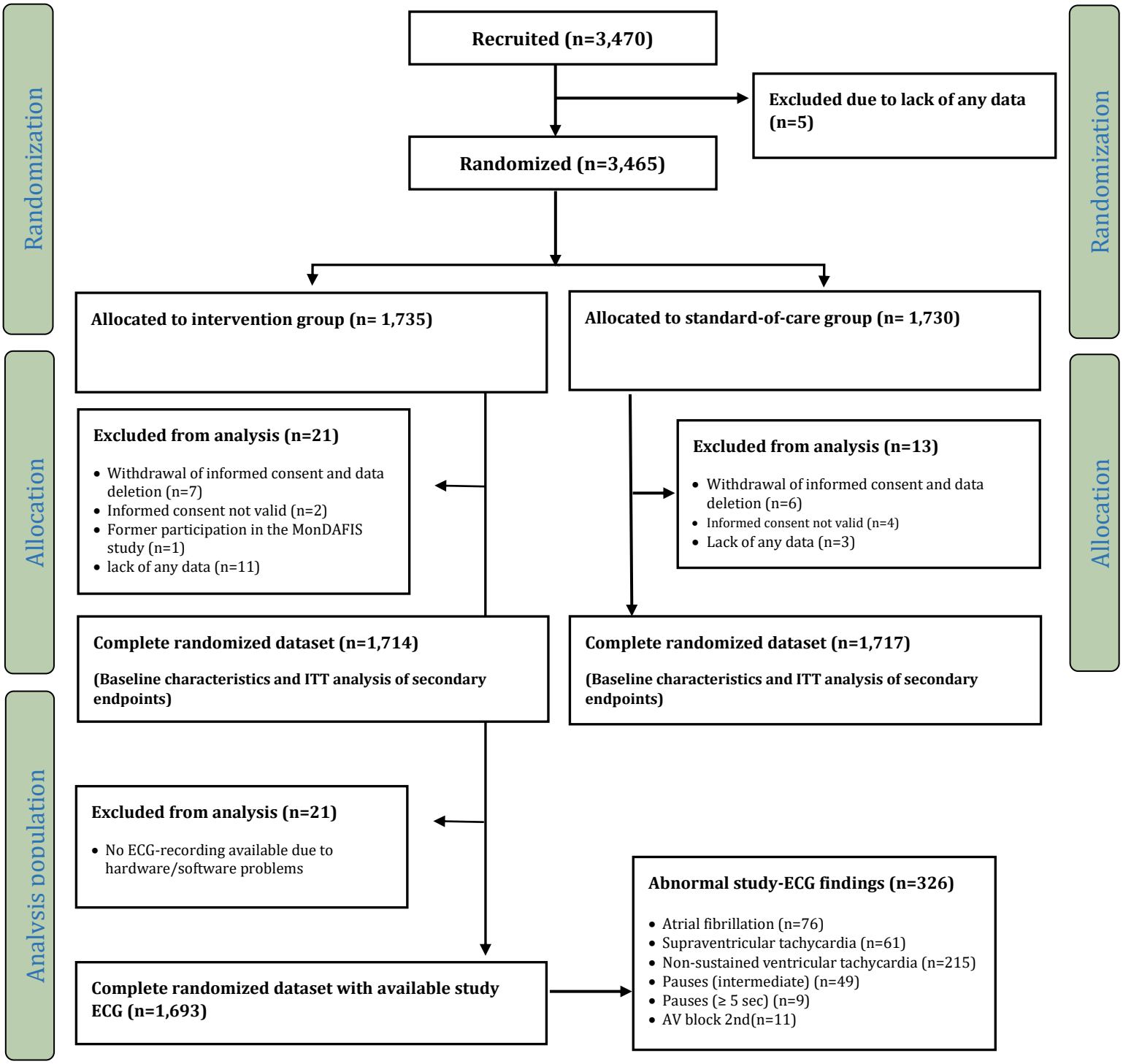
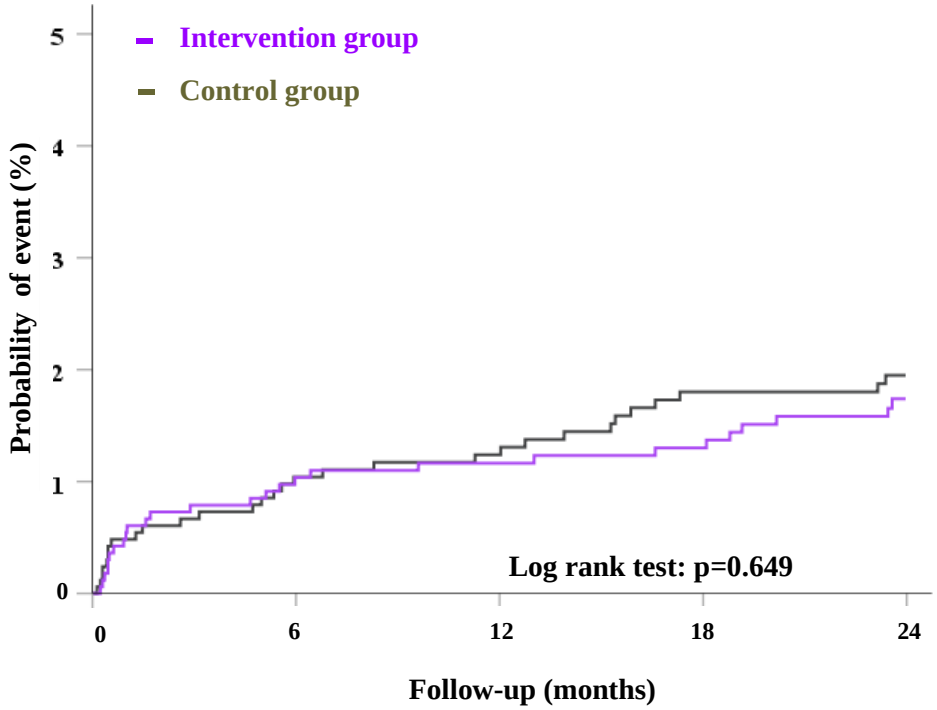
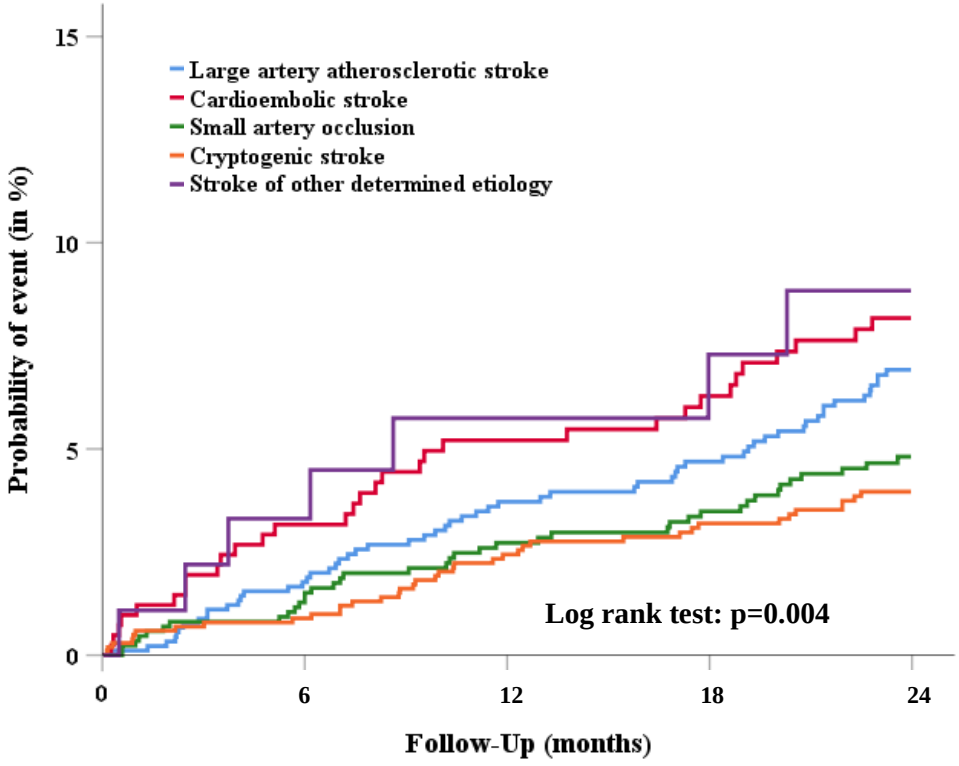


Figure S2: Kaplan Meier curve for the probability of a pacemaker-implantation within 24 months after the index stroke/TIA in the intervention group and control group (complete randomized set): P-value Log-Rank test was used to test the significance.



	Number at risk					Events
Intervention group	1,711	1,607	1,519	1416	1,370	27
Control group	1,715	1,593	1,470	1374	1,319	30

Figure S3: Kaplan Meier curve for the probability of mortality within 24 months after the index stroke/TIA stratified for the typo of assumed etiology of the index event (n=3,353): P-value Log-Rank test was used to test the significance.



	Number at risk					Events
Large artery atherosclerotic stroke	**921**	**889**	**834**	**744**	**921**	**59**
Cardioembolic stroke	**421**	**397**	**371**	**340**	**421**	**32**
Small artery occlusion	**875**	**852**	**795**	**724**	**875**	**39**
Cryptogenic stroke	**1027**	**993**	**947**	**869**	**1027**	**38**
Stroke of other determined etiology	**109**	**87**	**74**	**59**	**109**	**7**