Associations between primary care electrocardiography and non-Alzheimer dementia

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Objectives: To determine whether electrocardiogram (ECG) markers are associated with incident non-Alzheimer's dementia (non-AD) and whether these markers also improve risk prediction for non-AD. *Materials and methods:* We retrospectively included 170,605 primary care patients aged 60 years or older referred for an ECG by their general practitioner and followed them for a median of 7.6 years. Using Cox regression, we reported hazard ratios (HRs) for electrocardiogram markers. Subsequently, we evaluated if addition of these electrocardiogram markers to a clinical model improved risk prediction for non-AD using change in area under the receiver-operator characteristics curve (AUC). *Results:* The 5-year cumulative incidence of non-AD was 3.4 %. Increased heart rate (HR=1.06 pr. 10 bpm [95% confidence interval: 1.04−1.08], $p<0.001$), shorter QRS duration (HR=1.07 pr. 10 ms [1.05−1.09], $p<0.001$), elevated J-amplitude (HR=1.16 pr. mm [1.08−1.24], $p<0.001$), decreased T-peak amplitude (HR=1.02 pr. mm [1.01−1.04], $p=0.002$), and increased QTc (HR=1.08 pr. 20 ms [1.05−1.10], $p<0.001$) were associated with an increased rate of non-AD. Atrial fibrillation on the ECG (HR=1.18 [1.08−1.28], p<0.001) Sokolow-Lyon index > 35 mm (HR=1.31 [1.18−1.46], $p<0.001$) and borderline (HR=1.18 [1.11−1.26], $p<0.001$) or abnormal (HR=1.40 [1.27−1.55], $p<0.001$) QRS-T angle were also associated with an increased rate of non-AD. Upon addition of ECG markers to the Cox model, 5-year and 10-year C-statistic (AUC) improved significantly (delta-AUC, 0.36 [0.18−0.50] and 0.20 [0.03−0.35] %-points, respectively). *Conclusions:* ECG markers typical of an elevated cardiovascular risk profile were associated with non-AD and improved both 5-year and 10-year risk predictions for non-AD.

Key Words: Vascular dementia—Electrocardiography—Non-Alzheimer dementia—Dementia prediction—Cardiovascular risk factors

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Introduction

The 2020 report of the Lancet Commission[1] estimated that about 40% of dementia cases are attributed to modifiable risk factors. Given timely risk stratification, up to 40% of dementia cases are thus potentially preventable, making readily available risk markers for dementia relevant. The electrocardiogram (ECG) is a commonly used medical test and thus an ideal candidate for identification of biomarkers for dementia.

Non-Alzheimer dementia (non-AD) consists of all dementias excluding Alzheimer's disease (AD) and constitutes approximately half of all dementia cases. A large proportion of these cases consists of vascular dementia.[2] Across dementia subtypes, the non-AD patient population is characterized by a high cardiovascular risk profile including diabetes, hypertension, stroke, cigarette smoking, and myocardial infarction.[3–7]

An established ECG marker for cognitive decline and dementia is atrial fibrillation.[8,9] Left ventricular hypertrophy by Cornell voltage or Sokolow-Lyon index was previously associated with incident dementia from any cause.[10] However many ECG markers including QT interval,[11,12] P-wave indices,[13–15] and the QRS-T angle[16] have only been investigated as potential biomarkers for the diverse endpoint of cognitive decline – but not for dementia endpoints. Thus, in this study, we focused on the endpoint of non-AD.

To bridge the knowledge gaps, we aimed to assess whether ECG markers were associated with non-AD in a large primary care population, and whether the use of these markers would improve 5-year and 10-year risk predictions for non-AD.

Methods

Population

At the Copenhagen General Practitioners' Laboratory (CGPL), 978,358 ECGs were recorded in a population of 449,191 people during 2001–2015. In the present study, we only included people aged 60 years or older on the day of the ECG because the prevalence and validity of non-AD diagnoses below this age is lower. We excluded outlier ECGs defined as ECGs with measurements outside 4 standard deviations from the mean for any of the continuous ECG measurements used in the study. We also excluded ECGs from people with a pacemaker or implantable cardioverter defibrillator and from people on digoxin at the day of the ECG. We used the first ECG from each individual and excluded people with a lack of history due to emigration or with prevalent dementia (see **Supplementary Figure 1** for a flow chart).

Electrocardiogram analysis

All ECGs were analyzed using version 23 of the 12SL algorithm (GE Healthcare, Wauwatosa, WI).[17] We obtained heart rate, QRS duration, QT interval, J-point elevation in lead V5, and T-wave amplitude in V5. The QT interval was corrected by division with the cubic root of the RR-interval (the Fridericia correction, QTcF). Left ventricular hypertrophy was assessed using the Sokolow-Lyon index, calculated as the R-peak amplitude in V5 or V6 (whichever was larger) plus the S-peak amplitude in V1 and considered positive for a value >35 mm (3.5 mV). We pooled atrial flutter and atrial fibrillation, and categorized the variable as follows: Atrial fibrillation or flutter on the ECG coded as: 'AF on ECG'. A history of AF or previous treatment with ablation but no sign on ECG: 'History of AF/paroxysmal AF'. No sign of AF on ECG and no history: 'No'. The QRS-T angle was calculated using the mean QRS and T vectors from the Kors-derived vectorcardiogram, which was previously found superior for associations with mortality,[18] and categorized into 'normal', 'borderline', and 'abnormal' with cut-points at the 80 and 95 percentiles (108 and 151 degrees, respectively).

Endpoint, co-variates, and follow-up

The primary end point, non-AD, was defined as a register diagnosis (using the International Classification of Diseases tenth revision [ICD-10] codes) of vascular dementia (F01), dementia in other diseases (F02), dementia with Lewy bodies (G318E), frontotemporal dementia (G310B), or unspecified dementia (F03). The secondary end point was vascular dementia (F01). AD (F00 and G30) and mortality from any cause were competing risks. If a patient with a first diagnosis of unspecified dementia later received another cause of dementia, we recoded the cause but not the date to reflect the updated clinical information. The validity for all-cause dementia, AD, and (by extension) non-AD was previously found sufficient for register studies, whereas the validity was lower for specific non-AD subtypes.[19]

We identified the following baseline comorbidities using a combination of register diagnoses and/or claimed prescriptions: Stroke (cerebral infarction, intracerebral hemorrhage, and unspecified stroke), diabetes mellitus, ischemic heart disease, congestive heart failure, hypertension, and depression. The ICD-10 and ATC codes that we used are detailed in the **Supplementary Methods**. We identified participants on QT-prolonging drugs on the day of the ECG with the definition from CredibleMeds.org. We also identified participants on beta blockers or calcium antagonists on the day of the ECG.

Participants entered the study on the day of the ECG and were followed until outcome, emigration, death, or 31 December, 2016, whichever occurred first. We reported the median potential follow-up time using the reverse Kaplan-Meier method.[20]

Statistical analyses

We constructed a Cox regression model with non-AD as the outcome, treated death from any cause and incident

AD as competing risks, and reported hazard ratios (HR) for non-AD with 95% confidence intervals (CI). Time-on-study was the underlying time scale, and we stratified the model on sex, age groups (60−64, 65−69, 70−74, 75−79, and ≥80), and stroke at baseline to allow for different baseline hazards and thus relax the proportional hazards assumption. The model included the ECG markers heart rate, atrial fibrillation/flutter, QRS duration, QTcF interval, J-point amplitude in V5, T-wave amplitude in V5, Sokolow-Lyon index, and categorized QRS-T angle. The model also included diabetes mellitus, ischemic heart disease, congestive heart failure, hypertension, depression, use of QT-prolonging medication, and use of beta-blockers or calcium antagonists, all coded as yes/no.

We assessed linearity by categorizing continuous variables into quintiles, but we found no strong departures from linearity and thus used linear predictors. The 5-year and 10-year cumulative incidence was reported using the Aalen-Johanson estimator.

As a secondary analysis, we constructed a model with vascular dementia as endpoint in the same way as the main analysis, with other causes of non-AD dementia pooled as one additional competing risk.

To assess if ECG markers improved 5-year and 10-year risk predictions, we calculated area under the receiver-operator characteristics curve (AUC) in the main Cox models versus a reference model without ECG markers but with sex, age, stroke, diabetes, ischemic heart disease, congestive heart failure, hypertension, depression, use of QT-prolonging medication, and use of beta-blockers or calcium antagonists. To obtain a robust AUC and calculate the statistical certainty (95% CI) of the AUC, we used 100-fold cross validation, with a split of 63 % training and 37 % validation. Using the full Cox models, we calculated the absolute 5-year risk for eight example patients to illustrate the influence of the ECG markers on risk of AD.

A two-sided p-value ≤0.05 was considered statistically significant. Analyses were conducted using R (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) with use of the riskRegression package.[21]

Results

Population characteristics

In total, 170,605 participants met the inclusion criteria and were followed for a median of 7.6 years (interquartile range, IQR: 3.9 to 11.3 years), yielding a total of 969,989 person-years. During follow-up, 7,857 participants were registered with non-AD. Vascular dementia was the most common subtype with 1402 cases, there were 323 cases of dementia with Lewy bodies, 98 cases of dementia in other diseases, 39 cases of frontotemporal dementia, and the remaining 5,995 cases were unspecified dementia. The 5-year and 10-year risks of non-AD were 3.4 % and 5.8 %, respectively. The median age was 71 years (IQR: 65 to 79 years) and 58 % of the participants were females (Table 1).

Table 1. *Baseline clinical characteristics and ECG findings.*

Variable	Entire population
n, (%)	170,605
Male sex, % (n)	42.2% (72,039)
Age, years	70.5 [64.5;78.7]
Follow up, years	7.6 [3.9;11.3]
Stroke, % (n)	7.4% (12,574)
Diabetes mellitus, % (n)	12.5% (21,346)
Hypertension, % (n)	46.0% (78,421)
Heart failure, % (n)	20.8% (35,405)
Ischemic heart disease, % (n)	15.6% (26,611)
Depression, % (n)	27.5% (46,957)
On QT-prolonging drugs, % (n)	3.9% (6,636)
On beta blockers	4.7% (7,980)
On calcium blockers	7.4% (12,617)
Heart rate, bpm	72 [63;82]
Atrial fibrillation or flutter	
No AF	90.3% (154,098)
AF on ECG	5.9% (10,003)
History of AF/paroxysmal AF	3.8% (6,504)
QRS duration, ms	92 [84;100]
QT interval, ms	398 [376;420]
QTc Fridericia, ms	420 [407;435]
J-point elevation V5, μV	-20 [-40;4]
T-wave amplitude V5, μV	263 [161;375]
Sokolow-Lyon index > 35 mm, % (n)	3.6% (6,089)
QRS-T angle	
Normal (≤108 deg)	80.0% (136,491)
Borderline (109−151 deg)	15.0% (25,584)
Abnormal (>151 deg)	5.0% (8,530)

Values are median [inter-quartile range] or % (n). AF, atrial fibrillation or flutter; ECG, electrocardiogram

Associations between ECG markers and non-AD

Hazard ratios for development of non-AD are depicted on Fig. 1. Increased heart rate, atrial fibrillation on ECG, shorter QRS duration, increased QTcF interval, elevated J-point, decreased T-peak amplitude, increased QRS-T angle, and left ventricular hypertrophy by Sokolow-Lyon index were associated with an increased rate of non-AD.

Non-AD risk prediction using ECG markers

Risk prediction for non-AD improved significantly upon addition of ECG markers to the reference model for the 5-year time frame (ΔAUC = 0.36 [0.18 to 0.50] %-points, AUC for final model = 77.2 %) and for the 10-year time frame (ΔAUC = 0.20 [0.03 to 0.35] %-points, AUC for final model = 72.0 %).

Fig. 2 depicts predicted risks for sample patients with an average ECG and with an ECG that according to Fig. 1 would be associated with an increased rate of non-AD (high-risk ECG). For both females and males with and without stroke, respectively, we found that the risk of non-AD was substantially higher for patients with a high-risk ECG compared to those with an average ECG. The 5-

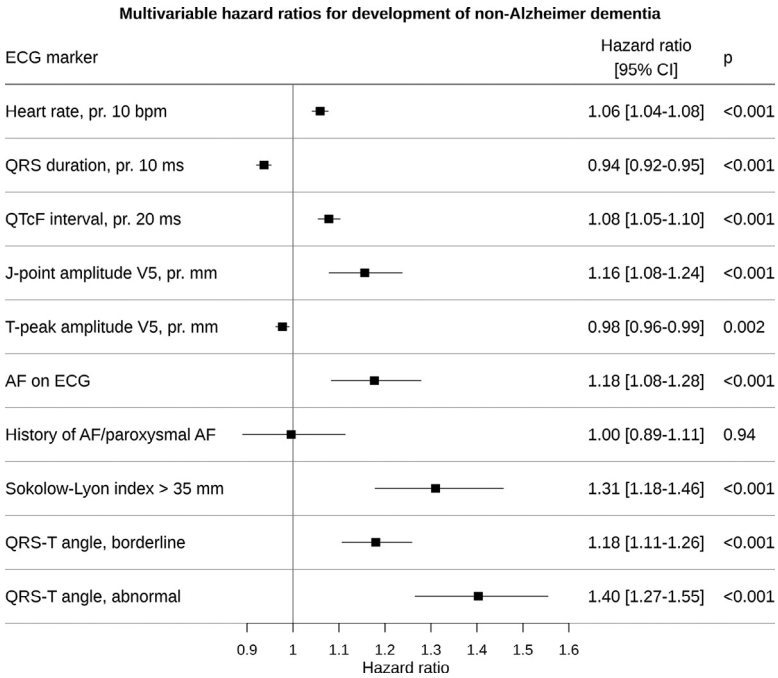

Fig. 1. *Hazard Ratios for development of non-Alzheimer dementia by ECG markers. The model was stratified by sex, age groups, and stroke, and adjusted for ischemic heart disease, congestive heart failure, hypertension, diabetes mellitus, depression, use of QT-prolonging medication, beta blockers, and calcium channel blockers. AF, atrial fibrillation of flutter; CI, confidence interval; ECG, electrocardiogram; QTcF, QT corrected by the method of Fridericia.*

year risk of non-AD was more than doubled from 3.8% to 9.5% for a 78 year old woman with a high-risk ECG profile compared to a peer with an average ECG.

Vascular dementia

The 5-year and 10-year risks of vascular dementia were 0.7 % and 1.0 %, respectively. With the lower number of events, the precision of the estimates was lower for vascular dementia than for non-AD although directionality of HRs remained the same for vascular dementia as for non-AD (Fig. 3). The most notable differences were found for heart rate and J-point amplitude, which were not significantly associated with vascular dementia, and for Sokolow-Lyon index > 35 mm, which was associated with a HR of 1.45 [1.15 to 1.83], p=0.002, similar to that of abnormal QRS-T angle (HR=1.44 [1.13 to 1.82]).

Compared to non-AD, risk prediction with ECG markers for vascular dementia yielded a higher point estimate on the 5-year time frame (ΔAUC = 0.80 [0.20 to 1.33]

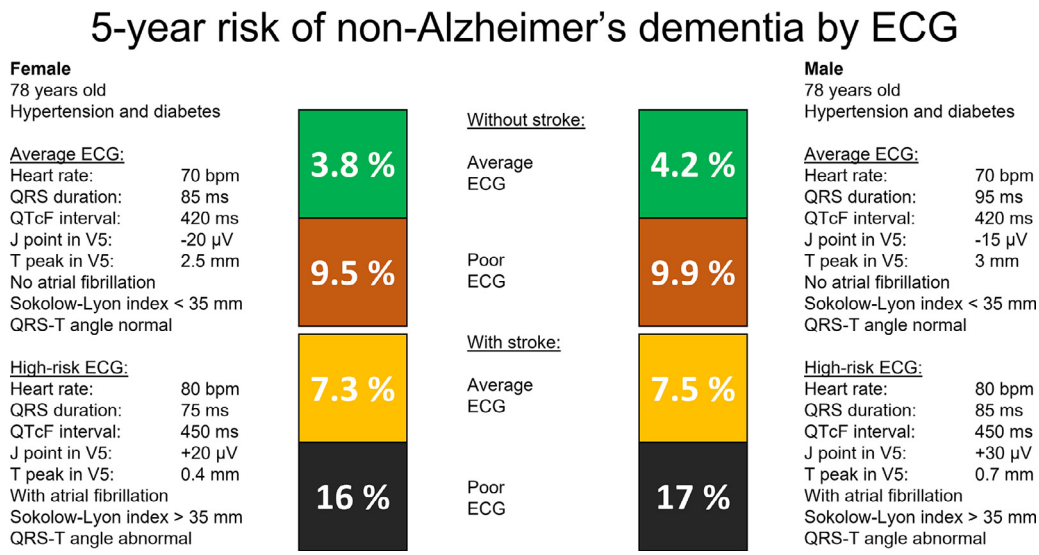

Fig. 2. *Absolute risk of non-Alzheimer's dementia by different ECG profiles, stratified by sex and prior stroke. With a high-risk ECG, the predicted 5-year risk of non-Alzheimer's dementia is substantially higher than with an average ECG. The specific example is a 78 year old patient with diabetes and hypertension. The ECG values are shown left (females) and right (males). ECG, Electrocardiogram.*

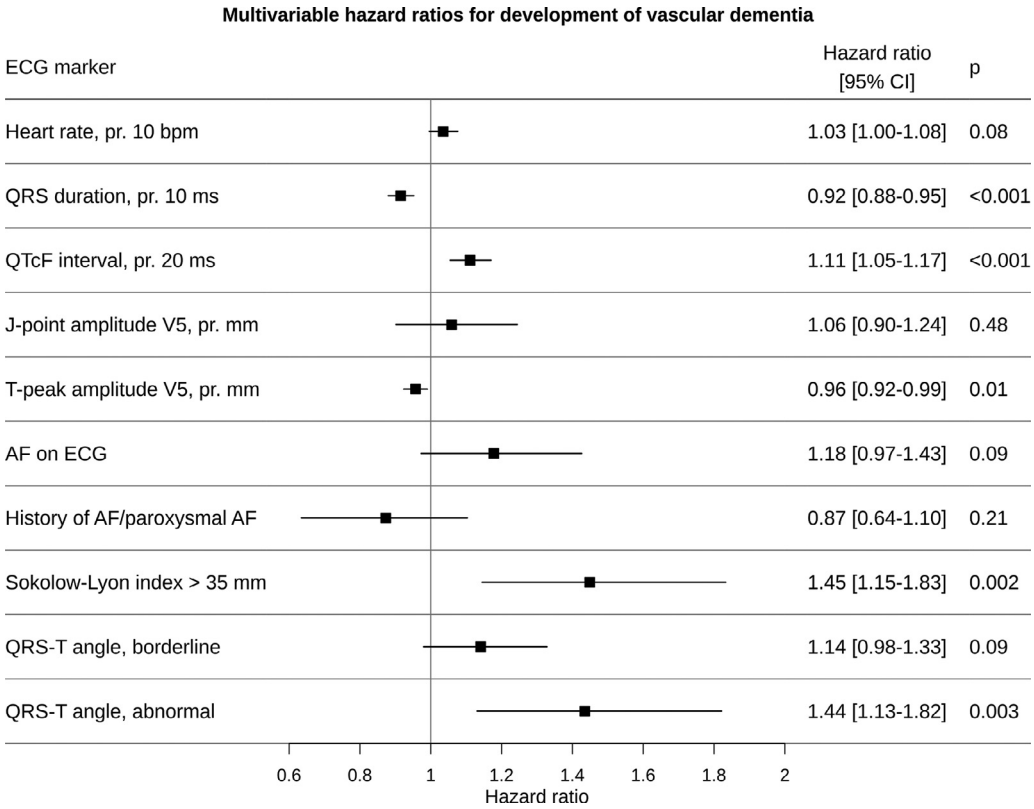

Fig. 3. *Hazard ratios for development of the secondary end point of vascular dementia by ECG markers. The model was stratified and adjusted as the main model (see text or Fig. 1). AF, atrial fibrillation of flutter; CI, confidence interval; ECG, electrocardiogram; QTcF, QT corrected by the method of Fridericia.*

%-points, AUC for final model = 75.5 %). However, on the 10-year time frame the increase in risk prediction was non-significant (ΔAUC = 0.38 [-0.28 to 0.89] %-points, AUC for final model = 70.5 %).

Discussion

The present study is to our knowledge the largest study to assess the association between electrocardiographic markers and non-AD and vascular dementia. We found that repolarization abnormalities quantified by increased QTcF, widened QRS-T angle, and decreased T-wave amplitude as well as shortened depolarization time by QRS measurements, left ventricular hypertrophy by Sokolow-Lyon index, and increased heart rate were associated with non-AD. Upon addition of ECG markers to a clinical reference model, 5-year and 10-year risk predictions of non-AD improved significantly. Risk of non-AD was markedly higher for people with a high-risk ECG irrespective of sex and history of stroke. The incidence of non-AD in this primary care population was a little higher compared to other studies of the general population.[22,23]

High cardiovascular risk profile and ECG markers

Many of the ECG markers that were associated with an increased rate of non-AD are well-established ECG markers of a cardiovascular high risk profile, which has been associated with non-AD and particularly vascular dementia.[1,2] These markers, including increased heart rate,[24] QTc interval,[25] Sokolow-Lyon index[26], and QRS-T angle,[18] have each been associated with mortality. Autonomic dysfunction was previously associated with dementia with Lewy bodies,[27] however accurate assessment of autonomic dysfunction with ECG requires more than 10 seconds of recording.

The association between shortened QRS duration and increased rate of non-AD is unexpected, since prolonged QRS duration is a well-known predictor of mortality.[28,29] This would suggest that a traditional high cardiovascular risk profile is not the only driver of the associations, but the mechanism remains unknown.

The association between the QTc interval and non-AD is novel despite previous attempts to establish one. One study found no relationship between incident QTc-prolongation in mid-life and cognitive decline in late-life.[11] Another study of n=4,627 older participants found some association between QTc and baseline cognitive performance, but not with cognitive decline over time.[12] The association between QTc and Alzheimer's disease is negative, whereas the association with non-AD is positive, and these associations would cancel each other out and mask the association when the outcome is all-cause dementia or cognitive decline instead of cause-specific dementia.

We found that atrial fibrillation or flutter on the ECG was associated with an increased risk of non-AD, albeit with a smaller hazard ratio compared to earlier studies.[8] The mechanism is formation of clots in the left atrium which leads to subclinical or clinical cerebral infarctions, hypoperfusion, and cognitive decline. The smaller hazard ratio in this study may be caused by improved anticoagulant treatment compared to earlier.

The association between ECG markers of high cardiovascular risk and non-AD may also be enhanced by reverse causation. Particularly the association between the QTcF interval and non-AD, which was positive, because people with a prior vascular insult (and a longer QTc[30]) are more likely to receive a diagnosis of non-AD than AD in unclear cases.

Vascular dementia

Vascular dementia was the only subtype of non-AD with enough events to justify as a cause-specific outcome. J-point elevation in V5 was not associated with vascular dementia, but the results for vascular dementia were otherwise similar to those for non-AD. 5-year risk prediction for vascular dementia was significantly improved upon addition of ECG markers, and the point estimate was larger than for non-AD. These results speak to both similarities and differences among the diverse causes of AD. However, to further assess the nuances and different ECG risk profiles between dementia subtypes, a cohort with a higher incidence of these dementias is needed. Perhaps, then, the differences are so small that cause-specific models are not necessary in non-AD risk stratification.

Strengths and limitations

The primary strengths of the present study include 1) a large sample of people from primary care, 2) long and complete follow-up using national registers, and 3) the use of automated ECG measurements.

We did not have data on smoking, body mass index, or level of physical activity, but we were able to adjust for diabetes, hypertension, ischemic heart disease, and other relevant comorbidities. We only had sufficient power to investigate the vascular dementia subtype of non-AD. This was in part caused by a high number of non-AD cases being diagnosed with unspecified dementia. Furthermore, a part of the non-specific group may have had Alzheimer's disease, although the distinction of Alzheimer's disease and non-AD in Danish registers was previously considered sufficient for register studies.[19]

Conclusion

We have identified novel associations between ECG markers related to a high cardiovascular risk profile and non-Alzheimer dementia. 5-year and 10-year risk predictions for non-Alzheimer dementia was improved with the use of ECG markers.

Conflict of Interests

A.G.H. is an employee of Acesion Pharma. J.B.N is employed by Regeneron Pharmaceuticals, Inc. The remaining authors have no conflict of interests to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106640.

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