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Attention as the primary cognitive domain affected in post-myocardial infarction cognitive impairment: a prospective multicenter study

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We analysed cognitive impairment (CI) during the peri-myocardial infarction (MI) period and after 6 months. The study included 326 patients. Cognitive function was assessed using the Mini–Mental State Examination (*MMSE)* and the Clock Drawing Test (CDT). Routine laboratory and echocardiography data were collected. We distinguished 4 groups of patients: 1 – CI present peri-infarction and after 6 months; 2 – CI present only peri-infarction; 3 – CI present only after 6 months; 4 – without CI. Groups constituted 8.9%, 16.3%, 7.7% and 67.1% of participants (as assessed by MMSE), respectively. In those who improved (group 2) or with worsened cognitive function (group 3), analogous changes in attention function occurred. There was a group of patients with CI on the MMSE who performed the CDT correctly, 12% peri-infarct and 11% at 6-month follow-up, respectively. Patients with a normal CDT score but CI found in the MMSE had impaired attention function. Cognitive function improves in some patients, and deteriorates in others after MI. The uniform type of impaired cognitive function allows us to assume a uniform etiology of CI. Performing the CDT and using the MMSE component assessing attention could prove sufficient for the initial assessment of cognitive functions in patients after MI.

Cardiovascular diseases (CVD) are the leading cause of death worldwide[1]. The central factor in their avoidance is the pursuit of a healthy lifestyle as part of a range of medical interventions known as prevention. Dementia currently affects more than 55 million people worldwide and is the 7th cause of death[2]. Both CVD and dementia share common risk factors for atherosclerosis, with studies showing that the coronary heart disease (CAD) is associated with a 45% increased risk of cognitive impairment (CI)[3]. The prevalence of CI in patients after acute coronary syndrome (ACS) is also highlighted, with a wide disparity in reported prevalence, ranging from 9 to 85%[4]. The mechanisms explaining the association between ACS, including myocardial infarction (MI) and the occurrence of CI and dementia, are still largely unknown and require further study[5–7]. Due to the lack of widespread screening of cognitive function in patients after MI[8,9], those presenting deficits remain undetected, which puts them at a risk of not adhering to secondary prevention, and therefore, achieving poorer treatment outcomes.

Given these implications, we decided to conduct a detailed assessment of neurocognitive function in patients with ACS. Previous research confirmed we concluded that the phenomenon of CI in post-ACS patients is much more common than we might have thought and what might be implied from the relatively good general mental state of the patients[10]. This has major clinical implications, as it requires a thorough and attentive involvement of medical staff to assess neurocognitive function in post-ACS patients, and a subsequent referral of the patients for specialised diagnosis, for instance to a neurologist.

The main hypothesis addressed in this study states that the group of patients representing CI at MI do not always overlap with patients representing symptoms at a 6 months follow-up, and vice versa (this finding has not been yet published). The specific objectives of this study include to characterise these particular groups and

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to assess whether those presenting CI throughout the entire follow-up period differ in any particular way from those presenting them only at the time of MI or at the follow-up visit. Another specific aim of the study is also to assess the type of CI in patients after ACS. In addition, we want to test whether the same or perhaps different cognitive functions are impaired in these particular groups of patients. We want to increase the impact of our project by using two screening tools to assess CI.

Methods
Study design
The study is a prospective, multicentre study. The study was conducted according to the guidelines of the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee at the Medical University of Poznan (agreement no.1201/16). All participants were informed about the procedures and gave written informed consent to participate. All data were analysed in a secure, anonymised database. All methods were performed in accordance with the relevant guidelines and regulations. The study included 326 patients hospitalised for MI (STEMI and NSTEMI), treated by percutaneous coronary intervention, who completed a 6-month follow-up period and were assessed twice for cognitive function using 2 screening tools. Those excluded from the study were subjects: (1) with a documented diagnosis of dementia (2) not consenting to participate (3) unable to complete the questionnaires independently. Data on baseline health status were obtained using available medical records, laboratory tests and echocardiography.

Assessment of cognitive function
The cognitive status of study participants was assessed during the first MI-related hospitalisation (on day 2–3 after coronary revascularisation) and 6 months later. Two diagnostic screening tools were used: the Mini–Mental State Examination (MMSE)[11] and the Clock Drawing Test (CDT)[12].

The MMSE consists of tests to assess orientation in place and time (total points = 10), registration (total points = 3) and recall (total points = 3), attention and calculation (total points = 5), language (total points = 8), and constructional praxis (total points = 1). The maximum possible score is 30 points; <27 points indicates the presence of mild CI or dementia[11].

The Schulman version of the CDT represents a 5-point error scale, where a higher score indicates a failed attempt to draw a clock. Only a score of 0 indicates correct task performance[12].

We identify the following four groups of patients for further analyses:

- Group 1-CI present peri-infarction and after 6 months;
- Group 2-CI present only peri-infarction;
- Group 3-CI present only after 6 months;
- Group 4- without CI during the study.

The MMSE score of < 27 or a CDT error rate of > = 1 were used as cut-off points for the occurrence of CI, respectively[11,12]. We analysed outcomes for both scales individually. Next, we investigated the misalignments in the cognitive status according to the aforementioned scales.

Statistical analyses
Statistical analyses were performed using the R language. Continuous variables were reported as means (standard deviation [SD]) or medians (interquartile ranges [IQR]), as appropriate. Qualitative data were presented as number and/or percentage. The differences in the numerical variables were tested using Kruskal Wallis test. Next, the Mann-Whitney test was performed as post-hoc test sequentially for 2 groups and Bonferroni correction was applied. For paired nominal data McNemar's test was applied. All analyses were done using R programming language and two-sided P values < 0.05 were considered to be statistically significant.

Results
The relationships between clinical findings and CI for MI-related hospitalization and 6-month follow-up
According to the MMSE, persistent CI (group 1) was found in 8.9% (N-29), only peri-infarct CI (group 2) in 16.3% (N-53) and only after 6 months (group 3) in 7.7% (N-25) of patients. According to the CDT, persistent CI (group 1) was found in 13.5% (N-44) of patients, peri-infarct (group 2) in 18.1% (N-59), while 9.8% (N-32) occurred only after 6 months (group 3). The results are shown in Fig. 1.

The next stage of the study involved analysing clinical and laboratory parameters in the 4 groups. The results in the groups for the MMSE and the CDT, respectively, are presented in Tables 1, 2, 3 and 4.

For the MMSE, statistically significant differences for the first hospitalization were observed for BNP, which was higher in patients with only peri-infarct CI (group 2) than in those without CI (group 4) [170 (81.4–292.6) vs. 81.2 (47.4–166.4); $p < .001$]. After the follow-up period, BNP was also significantly higher in the group with persistent CI (group 1) compared to group without CI (group 4) [43.1 (23.7–98.5) vs. 30.8 (15.4–54.3); $p < .001$]. Patients with persistent CI (group 1) also scored significantly higher peri-infarction points on the Insomnia Severity Index (ISI) compared to people without CI (group 4) [9 (4–14) vs. 6 (3–10); $p < .001$].

Overall, more statistically significant results were observed when grouping by the CDT. We found that patients with persistent CI (group 1) were significantly older than those without CI (group 4) [65 (59–69) vs. 58 (51–64); $p < .001$], as well as those with only peri-infarct CI (group 2) [65 (59–69) vs. 58 (53–66); $p < .001$]. In addition, those with persistent CI (group 1) were observed to differ significantly from those without CI (group 4) in peri-infarct RBC score (4.4 (4.1–4.6) vs. 4.6 (4.3–4.9); $p < .001$) and BNP (190.3 (108.5–347) vs. 84.6 (46.8–157.9); $p < .001$).
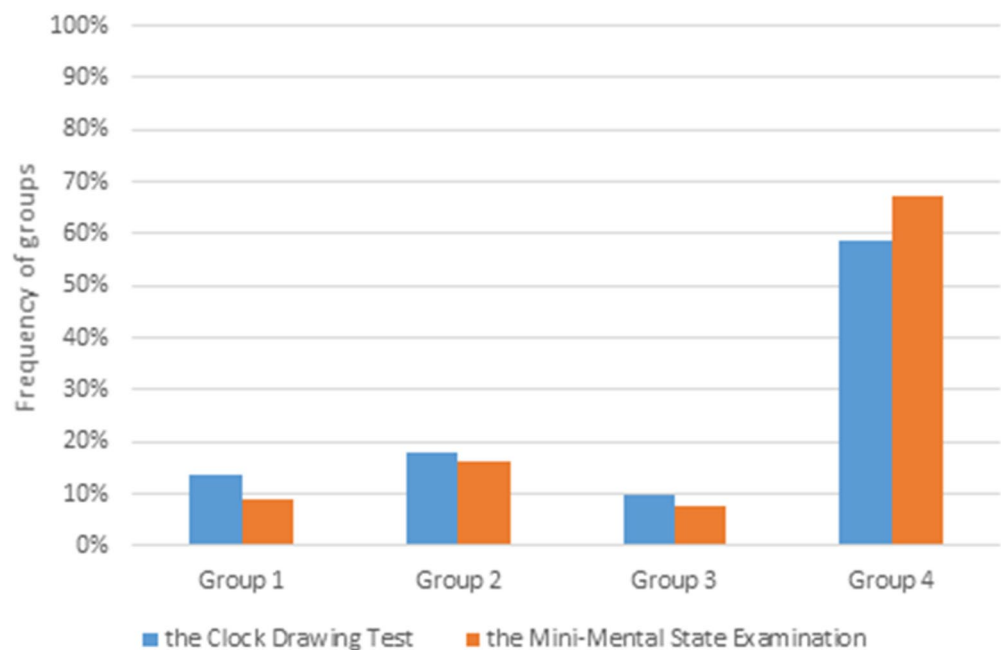
Fig. 1. Change in cognitive status during 6-months follow-up. Groups created according to the Clock Drawing Test and the Mini-Mental State Examination. Group 1- cognitive impairment present peri-infarction and after 6 months; Group 2- cognitive impairment present only peri-infarction; Group 3- cognitive impairment present only after 6 months; Group 4- without cognitive impairment.

Significantly higher peri-infarct TN scores also characterised patients with persistent CI (group 1) compared to those with newly-impaired CI (group 3) (1634 (398–5109.2) vs. 199.5 (56.5–1019.5); $p < .001$).

Among the results collected after 6 months, significant differences were observed between the group with persistent CI (group 1) and without CI (group 4) for: (a) red blood cell counts, respectively: RBC (4.7 (4.5–4.9) vs. 4.9 (4.6–5.1); $p < .001$) and HCT (42(40.9–43.8) vs. 43.7 (41.7–45.4); $p < .001$), (b) BNP [41.2 (27.7–159. 8) vs. 27 (15–54.1); $p < .001$], as well as for (c) potassium [4.8(4.6–5) vs. 4.6 (4.4–4.8); $p < .001$ and (d) ALAT [19 (14–30) vs. 26 (20–33); $p < .001$].

Patients with CI only after 6 months (group 3) were also found to have a history of diabetes significantly more often compared to those without CI (group 4) [44% vs. 15%; $p < .001$.

Evaluation of cognitive deficits for MI-related hospitalization and the 6-month follow-up

Next, the study sample was analysed for changes in specific cognitive domains assessed by the MMSE. We observed that for the 3 cognitive domains: registration, praxis, language, the score did not change at follow-up in 100%, 90% and 88% of patients, respectively. Changes were observed for 3 cognitive domains: attention, orientation and recall. For attention, the score improved in 27% of patients and worsened in 23%. For recall, changes occurred in 49% of patients, of which 33% had an improved score. For the orientation function, the score changed in 37% and improved in 30%. The results are presented in eFigure 1–6.

Next, the 4 specific groups were analysed for changes in specific cognitive domains. It was shown that individuals who experience improvement (group 2) or deterioration in cognitive function during follow-up (group 3), show analogous changes in attention. In the group of patients with only peri-infarct CI (group 2), 81% also improved in attention, whereas among patients with CI only after 6 months (group 3), 100% deteriorated in attentional outcome. We also observed that the orientation function improved in 53% of those whose mental status returned to normal (group 2), as well as in 47% of the recall function. For the registration, language and praxis, we did not observe significant changes. The results are presented in eFigure 7–12.

Comparison MMSE and CDT

The next stage of the study was aimed at comparing the results obtained on the MMSE and the CDT. We decided to check whether the 4 groups of patients correspond to each other regardless of the screening tool used. The results are presented in Fig. 1. Next, we examined how the MMSE scores changed in these 4 groups identified on the basis of the CDT. Among patients presented CI only peri-infarct in the CDT (group 2), an improvement in the MMSE score was observed in 58% after 6 months. Similarly, among patients with CI only after 6 months in the CDT (group 3), the MMSE score deteriorated in 48% during follow-up.

Further analyses done separately for both hospitalisations showed that there was a group of patients with CI found only in one test (MMSE or CDT), with a normal result in the other. As shown in Table 5, during MI hospitalisation, the results did not overlap in 34% (N-111) of patients, and after 6 months in 27% (N-89). CI on

Clinical values, median (IQR)	Persistent CI (1)	Peri-infarct CI (2)	CI after 6 months (3)	Without CI (4)	p (1 vs. 2)	p (1 vs. 3)	p (1 vs. 4)	p (2 vs. 3)	p (2 vs. 4)	p (3 vs. 4)
Age [years]	62 (54–68)	62 (53–67)	58 (52–63)	59 (52–65)	0.77	0.14	0.08	0.18	0.13	0.62
BMI [kg/m^2]	28.1 (25.1–31.6)	28.3 (25.9–30.5)	27.7 (24.8–30)	27.8 (25.3–31.7)	0.85	0.44	0.93	0.37	>0.99	0.36
Clinical factors, n (%)										
History of diabetes	15 (27)	14 (23)	5 (24)	34 (18)	0.6	0.8	0.16	0.91	0.45	0.53
History of heart failure	5 (9)	4 (7)	0 (0)	14 (8)	0.62	0.16	0.73	0.24	0.79	0.2
History of hypertension	34 (61)	32 (52)	12 (57)	114 (61)	0.32	0.78	0.97	0.67	0.2	0.74
History of MI	8 (14)	8 (12)	2 (10)	21 (11)	0.83	0.59	0.54	0.69	0.72	0.82
MI type, n (%)										
STEMI	30 (55)	37 (60)	13 (65)	114 (61)	0.58	0.57	0.4	0.86	0.86	0.94
NSTEMI	25 (45)	25 (40)	7 (35)	72 (39)	0.58	0.35	0.36	0.58	0.8	0.65
Laboratory values, median (IQR)										
Hgb [g/dl]	13.6 (12.6–14.4)	13.6 (12.4–14.4)	13.7 (12.8–14.7)	14 (13.1–14.9)	0.86	0.85	0.03	0.76	0.02	0.2
Hct [%]	40.1 (36.6–42.4)	40.5 (36.7–42.5)	40.6 (38.5–43.2)	41.2 (38.8–43.7)	P>.99	0.42	0.02	0.38	0.02	0.53
RBC [mln/µl]	4.6 (4.2–4.8)	4.4 (4.1–4.7)	4.6 (4.3–5)	4.6 (4.3–4.9)	0.39	0.3	0.11	0.11	0.01	0.98
WBC [tys/µl]	9.3 (7.7–12.2)	9.1 (6.9–11.7)	9.5 (7.7–11.7)	9.6 (7.7–11.7)	0.53	0.91	0.85	0.8	0.51	0.89
PLT [tys/µl]	217.5 (191.2–260.2)	225 (191.8–257)	227 (196–284)	228 (194.5–267.5)	0.95	0.32	0.66	0.27	0.59	0.35
Na [mmol/l]	140 (139–142)	140 (138.2–142)	141 (140–143)	140 (139–142)	0.6	0.36	0.6	0.15	0.84	0.15
K [mmol/l]	4.2 (4.1–4.4)	4.2 (3.9–4.5)	4.4 (4.2–4.5)	4.3 (4–4.5)	0.42	0.21	0.96	0.09	0.45	0.23
Creatinine [µmol/l]	74.5 (68.8–89.2)	79.5 (71.5–92.5)	82 (73–86)	81 (68.2–91)	0.11	0.49	0.21	0.58	0.56	0.84
Urea [mmol/l]	5.3 (4.3–6.2)	5.8 (4.6–6.5)	5.1 (4.3–6.4)	5.1 (4.3–6.3)	0.21	0.94	0.77	0.46	0.25	0.87
Uric acid [mmol/l]	305.5 (288.2–342.5)	318 (274–383)	376 (313.8–427.5)	337 (284.5–384.5)	0.81	0.3	0.21	0.36	0.47	0.45
GFR [ml/min/1,73 m^2]	90.5 (77.2–102)	83.5 (70.2–99)	91 (82–104)	89 (75–104)	0.06	0.64	0.96	0.05	0.03	0.46
TN [ng/l]	527 (98.8–3591.8)	1043 (73.5–4382.5)	421.5 (74–2606.2)	487.5 (70–2888.2)	0.84	0.61	0.46	0.46	0.28	0.87
ALAT [U/l]	34 (23–62.5)	35 (25–49.5)	29 (23–47)	37 (26–52)	0.79	0.29	0.88	0.3	0.7	0.21
HDL [mmol/l]	1.2 (1–1.4)	1.1 (0.9–1.3)	1.2 (1–1.4)	1.1 (1–1.3)	0.25	0.79	0.63	0.19	0.29	0.49
LDL [mmol/l]	3 (2.2–3.9)	3.2 (2.4–3.7)	3.3 (2.4–3.7)	3.1 (2.4–3.9)	0.56	0.94	0.52	0.79	0.80	0.86
TG [mmol/l]	1.4 (1.1–2)	1.5 (1.1–2)	1.5 (1–2.2)	1.4 (1.1–2.1)	0.80	0.96	0.93	0.91	0.78	0.93
TSH [µIU/ml]	1.2 (0.7–1.7)	1 (0.6–1.8)	0.8 (0.6–1.2)	1.3 (0.7–2)	0.61	0.13	0.48	0.23	0.2	0.02
CK [IU/l]	75 (30–153)	55 (24–155.8)	142 (22–232.5)	49 (25–112)	0.28	0.72	0.06	0.27	0.65	0.17
BNP [pg/ml]	120.2 (59.4–263.5)	170 (81.4–292.6)	85.1 (59.8–137.2)	81.2 (47.4–166.4)	0.25	0.19	0.08	0.02	**P<.001**	0.94
EF [%]	0.5 (0.4–0.5)	0.5 (0.4–0.5)	0.5 (0.4–0.5)	0.5 (0.4–0.6)	0.69	0.68	0.16	0.48	0.05	0.58
Psychiatric scale, points, median (IQR)										
BDI	10 (6.8–13)	10 (6–15.8)	8 (5–13)	7 (4–12)	0.81	0.45	0.02	0.36	0.01	0.5
The Overt Aggression Scale Modified	0 (0–1)	1 (0–1)	1 (0–1)	0 (0–1)	0.38	0.27	0.78	0.68	0.16	0.15
ISI	9 (4–14)	8.5 (3–13)	7 (3–12)	6 (3–10)	0.29	0.30	**P<.001**	0.95	0.16	0.46
AIS	7.5 (3–11)	7.5 (3.2–10)	6 (4–7)	5 (3–8)	0.83	0.22	0.03	0.36	0.08	0.74
Epworth Sleepiness Scale	6 (4–9)	5 (4–8)	7 (4.8–9)	6 (4–9)	0.30	0.86	0.92	0.28	0.25	0.76

Table 1. Baseline characteristics and comparison of participants according to cognitive status for the first MI-related hospitalization detected by the MMSE. p-values from Mann–Whitney test are presented which was performed as post-hoc test sequentially for 2 groups and Bonferroni correction was applied. The statistical threshold for significance for the P value was 0.008. Boldface indicates statistical significance. *AIS* Athens Insomnia Scale, *ALAT* alanine transaminase, *BDI* Beck Depression Inventory, *BMI* Body Mass Index, *BNP* brain natriuretic peptide, *CK* creatine kinase, *EF* ejection fraction, *GFR* glomerular filtration rate, *Hct* hematocrit, *HDL* high-density lipoprotein, *Hgb* hemoglobin, *ISI* Insomnia Severity Index, *K* potassium, *LDL* low density lipoprotein, *MI* myocardial infarction, *MMSE* Mini Mental State Examination, *Na* sodium, *PLT* platelet count, *RBC* red blood cells, *TG* triglycerides, *Tn* troponin, *TSH* thyroid stimulating hormone, *WBC* white blood cells.

	Persistent CI (1)	Peri-infarct CI (2)	CI after 6 months (3)	Without CI (4)	p (1 vs. 2)	p (1 vs. 3)	p (1 vs. 4)	p (2 vs. 3)	p (2 vs. 4)	p (3 vs. 4)
Laboratory values, median (IQR)										
Hgb [g/dl]	14 (13.2–15)	14.3 (13.6–14.9)	14.2 (13.5–15.6)	14.6 (13.7–15.3)	0.42	0.32	0.05	0.73	0.28	0.98
Hct [%]	42.3 (40.4–44.2)	42.7 (41.2–45.4)	42.5 (41.8–45.5)	43.3 (41.1–45.3)	0.12	0.18	0.01	0.73	0.63	0.97
RBC [mln/µl]	4.7 (4.5–5)	4.8 (4.6–5)	5 (4.5–5.3)	4.8 (4.6–5.1)	0.38	0.07	0.06	0.26	0.35	0.32
WBC [tys/µl]	7.7 (6.4–9)	7.3 (6.4–8.4)	8 (6.7–8.9)	7.6 (6.3–8.8)	0.41	0.82	0.5	0.31	0.74	0.44
PLT [tys/µl]	230 (204.5–271.5)	235 (204–264)	253.5 (212.8–266)	238.5 (205–283.8)	0.66	0.4	0.42	0.61	0.8	0.67
Na [mmol/l]	141 (139–142.5)	141 (139–142)	139.5 (138–141.2)	141 (140–143)	0.84	0.08	0.28	0.08	0.14	0.01
K [mmol/l]	4.7 (4.5–4.9)	4.6 (4.4–4.8)	4.7 (4.4–5.1)	4.6 (4.4–4.8)	0.08	0.92	0.05	0.31	0.98	0.28
Creatinine [µmol/l]	79 (66–87.5)	80 (71.8–88.2)	85 (70.8–95)	83.5 (72–95.2)	0.37	0.32	0.03	0.64	0.21	0.87
Urea [mmol/l]	5.8 (4.4–7)	5.8 (4.9–7.1)	5.4 (4.6–5.9)	5.6 (4.7–6.6)	0.63	0.47	0.74	0.24	0.3	0.38
GFR [ml/min/1,73 m²]	87 (74–100.5)	83 (69.8–94.8)	87.5 (74.8–104.2)	85 (70.8–97.2)	0.21	0.84	0.35	0.28	0.5	0.45
ALAT [U/l]	24 (19–32.8)	24 (18–30)	28 (17–33)	26 (20–35)	0.63	0.82	0.38	0.5	0.14	0.96
HDL [mmol/l]	1.4 (1.1–1.6)	1.2 (1–1.6)	1.4 (1.1–1.5)	1.2 (1–1.4)	0.47	0.93	0.03	0.54	0.25	0.11
LDL [mmol/l]	1.9 (1.6–2.5)	2 (1.6–2.8)	2.2 (1.8–2.8)	1.9 (1.5–2.2)	0.40	0.15	0.45	0.43	0.05	0.02
TG [mmol/l]	1.3 (0.9–1.6)	1.4 (1–1.9)	1.2 (1–1.7)	1.4 (1–1.8)	0.07	0.71	0.19	0.38	0.38	0.61
TSH [µIU/ml]	1.2 (0.8–2)	1.1 (0.8–1.6)	1 (0.6–1.2)	1.2 (0.8–1.7)	0.75	0.08	0.73	0.16	0.82	0.05
CK [IU/l]	116 (85.5–155.2)	106.5 (82.2–139.8)	125.5 (83.8–183.8)	117 (92–170)	0.62	0.39	0.3	0.28	0.09	0.78
BNP[pg/ml]	43.1 (23.7–98.5)	41.2 (19.7–87.2)	23 (16.2–39.8)	30.8 (15.4–54.3)	0.43	0.03	**P<.001**	0.12	0.05	0.59
EF [%]	0.5 (0.4–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.6)	0.5 (0.5–0.6)	0.45	0.05	0.21	0.19	0.72	0.15
Psychiatric scale, points, median (IQR)										
BDI	9 (5–13.2)	9 (5–13)	6 (4–9)	7 (3–12)	0.68	0.1	0.03	0.19	0.09	0.78
The Overt Aggression Scale Modified	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–1)	0.95	0.11	0.55	0.12	0.59	0.17
ISI	6 (3–11.2)	6 (3–11)	5 (3–10)	4.5 (2–10)	0.89	0.63	0.12	0.67	0.14	0.51
AIS	4 (3–8)	6 (3–9)	5 (3–6)	5 (3–8)	0.19	0.58	0.93	0.12	0.07	0.57
Epworth Sleepiness Scale	5 (3–9)	6 (4–9)	5 (4–9)	6 (4–9)	0.41	0.55	0.24	0.97	0.72	0.74

Table 2. Baseline characteristics and comparison of participants according to cognitive status for the follow-up visit detected by the MMSE. p-values from Mann-Whitney test are presented which was performed as post-hoc test sequentially for 2 groups and Bonferroni correction was applied. The statistical threshold for significance for the P value was 0.008. Boldface indicates statistical significance. *AIS* Athens Insomnia Scale, *ALAT* alanine transaminase, *BDI* Beck Depression Inventory, *BMI* Body Mass Index, *BNP* brain natriuretic peptide, *CK* creatine kinase, *EF* ejection fraction, *GFR* glomerular filtration rate, *Hct* hematocrit, *HDL* high-density lipoprotein, *Hgb* hemoglobin, *ISI* Insomnia Severity Index, *K* potassium, *LDL* low density lipoprotein, *MI* myocardial infarction, *MMSE* Mini Mental State Examination, *Na* sodium, *PLT* platelet count, *RBC* red blood cells, *TG* triglycerides, *Tn* troponin, *TSH* thyroid stimulating hormone, *WBC* white blood cells.

the CDT despite a normal MMSE score (median 28) presented 15% (N-49) of patients during MI hospitalization and 16% (N-53) of patients after 6 months. Moreover, among patients with a normal CDT score and yet the presence of CI in the MMSE, the attention function was impaired regardless of the time of assessment.

Discussion

CI is common in patients after MI. Moreover, it can be found both immediately after an ACS incident and during follow-up. The design of our study involved assessing cognitive function twice over a 6-month period. This allowed us to distinguish 4 groups of patients according to changes in their mental status. We found that in more than half of the study participants with peri-infarct CI, it was transient and had resolved at follow-up. However, there is a group of approximately 8–10% in whom, despite normal test results peri-infarct, CI developed during follow-up. Studies indicate that there is also a higher risk of progression to dementia for those whose cognitive status has returned to normal, compared to those who never develop CI[13]. It is also important to emphasise that even subtle CI detected by only one test, is an indicator of increased risk of adverse health outcomes and functional impairment in people over 50 years of age[14]. With this in mind, it would be advisable to monitor the cognitive status of patients after ACS on a regular basis. Unfortunately, we are currently unable to predict the direction of these changes.

In our project, we set out to see if there were specific clinical differences between the 4 groups. We observed that these differences existed mainly between two groups: those presenting with persistent CI (group 1) and those without CI (group 4). We found no specific differences between those with only peri-infarct CI and those with CI only after 6 months (group 2 vs. 3). In our study, those with persistent CI (group 1) were older, had worse red-blood cell parameters, and features indicative of greater myocardial damage, i.e. higher BNP and troponin. In addition, patients with CI only after 6 months (group 3) presented significantly more often with a history of

Clinical values, median (IQR)	Persistent CI (1)	Peri-infarct CI (2)	CI after 6 months (3)	Without CI (4)	p (1 vs. 2)	p (1 vs. 3)	p (1 vs. 4)	p (2 vs. 3)	p (2 vs. 4)	p (3 vs. 4)
Age [years]	65 (59–69)	58 (53–66)	62 (57–66)	58 (51–64)	**0.001**	0.11	**<0.001**	0.13	0.43	0.02
BMI [kg/m²]	27.8 (25.1–29.8)	28.4 (25.1–30.5)	29 (26–31.4)	28 (25.3–32.1)	0.84	0.31	0.38	0.4	0.6	0.64
Clinical factors, n (%)										
History of diabetes	14 (32)	12 (20)	14 (44)	28 (15)	0.19	0.29	0.01	0.02	0.31	**<0.001**
History of heart failure	5 (11)	4 (7)	2 (6)	12 (6)	0.42	0.46	0.25	0.93	0.90	0.99
History of hypertension	23 (52)	36 (61)	17 (53)	115 (61)	0.38	0.95	0.32	0.47	0.95	0.43
History of MI	5 (11)	4 (7)	4 (13)	25 (13)	0.42	0.89	0.75	0.36	0.18	0.92
MI type, n (%)										
STEMI	28 (64)	31 (53)	19 (63)	115 (61)	0.26	0.71	0.73	0.54	0.26	0.88
NSTEMI	16 (36)	28 (48)	11 (37)	74 (39)	0.26	0.86	0.73	0.23	0.26	0.61
Laboratory values, median (IQR)										
Hgb [g/dl]	13.4 (12.6–14.2)	13.8 (12.6–14.7)	13.8 (13.2–14.7)	13.9 (13–14.8)	0.33	0.15	0.02	0.67	0.29	0.7
Hct [%]	38.9 (36.7–41.7)	40.6 (37.6–43.1)	40 (38.5–43.4)	41.2 (38.5–43.5)	0.15	0.13	0.01	0.85	0.29	0.5
RBC [mln/µl]	4.4 (4.1–4.6)	4.6 (4.2–4.8)	4.4 (4.3–4.7)	4.6 (4.3–4.9)	0.09	0.3	**<0.001**	0.6	0.25	0.21
WBC [tys/µl]	9.4 (8.1–11.8)	9.5 (7.8–12.1)	9.7 (7.6–10.7)	9.4 (7.4–11.7)	0.66	0.41	0.41	0.75	0.85	0.79
PLT [tys/µl]	221 (191–254.8)	237 (200.5–271)	212 (187–272.2)	227 (195–265)	0.24	>0.99	0.37	0.39	0.49	0.53
Na [mmol/l]	140 (138.5–142)	140 (138–142)	141 (139–141)	140 (139–142)	0.32	0.74	0.65	0.43	0.32	0.98
K [mmol/l]	4.2 (4–4.5)	4.3 (3.9–4.5)	4.2 (4–4.5)	4.3 (4–4.5)	0.81	0.81	0.83	0.69	0.88	0.71
Creatinine [µmol/l]	83 (68.5–94)	77 (70–88)	81.5 (71.5–89.2)	79 (68–91)	0.34	0.9	0.35	0.47	0.85	0.51
Urea [mmol/l]	5.4 (4.9–7)	4.8 (4.1–5.8)	6 (5.2–7.3)	5.2 (4.3–6.3)	0.01	0.42	0.13	0.01	0.15	0.03
Uric acid[mmol/l]	312 (280–373)	362 (301–429.8)	378 (336.5–414.5)	323 (278–369)	0.18	0.16	0.78	0.73	0.03	0.08
GFR [ml/min/1,73 m²]	82 (69.5–89)	91 (76.5–102)	85.5 (75.5–97.2)	91 (75–104.8)	0.02	0.28	0.01	0.3	0.79	0.18
TN [ng/l]	1634 (398–5109.2)	1104.5 (105.2–8838.5)	199.5 (56.5–1019.5)	456 (65–2540)	0.72	**<0.001**	0.01	0.04	0.05	0.29
ALAT [U/l]	36.5 (25.2–50.2)	40 (23–51.5)	33 (23–51)	36 (25–53)	0.96	0.6	0.97	0.81	0.95	0.67
HDL [mmol/l]	1.2 (1–1.3)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.1 (1–1.4)	0.88	0.72	0.88	0.52	0.71	0.65
LDL [mmol/l]	3.2 (2.5–3.9)	3.4 (2.4–4)	2.9 (2.4–3.4)	3.1 (2.4–3.8)	0.57	0.17	0.75	0.05	0.25	0.18
TG [mmol/l]	1.3 (1.1–1.9)	1.6 (1.3–2.1)	1.4 (1.1–2)	1.5 (1.1–2.1)	0.1	0.72	0.54	0.33	0.15	0.98
TSH [µIU/ml]	0.9 (0.6–1.4)	1.3 (0.7–1.8)	1.4 (0.7–2.2)	1.1 (0.7–2)	0.27	0.34	0.23	0.72	0.95	0.81
CK [IU/l]	108 (37–214)	63 (26–142)	38.5 (23.5–123.5)	47.5 (23–120)	0.21	0.07	0.02	0.23	0.23	0.73
BNP [pg/ml]	190.3 (108.5–347)	115.7 (54.7–271)	125.7 (52.7–256.8)	84.6 (46.8–157.9)	0.02	0.05	**<0.001**	0.95	0.1	0.2
SYNTAX [points]	12.5 (6–16)	10 (8–16.8)	9 (7.2–11)	9 (6–13)	0.7	0.36	0.27	0.14	0.05	0.92
EF [%]	50 (40–50)	50 (40–50)	50 (40–50)	50 (40–60)	0.17	0.18	0.01	0.8	0.3	0.64
Psychiatric scale, points, median (IQR)										
BDI	10 (7–13)	8 (4–13)	9 (5–12.5)	8 (4–13)	0.07	0.21	0.03	0.7	0.82	0.8
The Overt Aggression Scale Modified	0 (0–1)	1 (0–1)	1 (0–2)	0 (0–1)	0.57	0.21	0.87	0.33	0.32	0.09
ISI	8 (4–12)	8 (4–11.5)	7 (4–14)	6.5 (3–12)	0.96	0.81	0.32	0.99	0.31	0.3
AIS	7 (4–9.5)	6 (3.5–10)	7 (3–9.2)	5 (3–9)	0.68	0.75	0.3	0.98	0.12	0.24
Epworth Sleepiness Scale	5 (3–8.5)	5 (3.5–9.5)	8 (4.5–9.5)	6 (4–9)	0.50	0.05	0.22	0.2	0.62	0.18

Table 3. Baseline characteristics and comparison of participants according to cognitive status for the first MI-related hospitalization detected by the clock drawing test. p-values from Mann-Whitney test are presented which was performed as post-hoc test sequentially for 2 groups and Bonferroni correction was applied. The statistical threshold for significance for the P value was 0.008. Boldface indicates statistical significance. *AIS* Athens Insomnia Scale, *ALAT* alanine transaminase, *BDI* Beck Depression Inventory, *BMI* Body Mass Index, *BNP* brain natriuretic peptide, *CDT* Clock Drawing Test, *CK* creatine kinase, *EF* ejection fraction, *GFR* glomerular filtration rate, *Hct* hematocrit, *HDL* high-density lipoprotein, *Hgb* hemoglobin, *ISI* Insomnia Severity Index, *K* potassium, *LDL* low density lipoprotein, *MI* myocardial infarction, *Na* sodium, *PLT* platelet count, *RBC* red blood cells, *TG* triglycerides, *Tn* troponin, *TSH* thyroid stimulating hormone, *WBC* white blood cells.

diabetes compared to those without CI (group 4). Analysis of psychological factors also showed no differences between the 4 groups with depressive symptoms, aggression or sleep disorders. We did, however, find greater severity of insomnia symptoms in the group with persistent CI (group 1 vs. 4). These observations are in line with the results of our first paper[10].

	Persistent CI (1)	Peri-infarct CI (2)	CI after 6 months (3)	Without CI (4)	p (1 vs. 2)	p (1 vs. 3)	p (1 vs. 4)	p (2 vs. 3)	p (2 vs. 4)	p (3 vs. 4)
Laboratory values, median (IQR)										
Hgb [g/dl]	14.2 (13.5–14.8)	14.4 (13.4–15.2)	14 (13.1–15.1)	14.6 (13.8–15.3)	0.52	0.92	0.03	0.58	0.23	0.09
Hct [%]	42 (40.9–43.8)	42.7 (40.8–45.2)	42 (40–44.5)	43.7 (41.7–45.4)	0.28	0.84	**<0.001**	0.56	0.1	0.05
RBC [mln/µl]	4.7 (4.5–4.9)	4.9 (4.6–5)	4.6 (4.4–4.9)	4.9 (4.6–5.1)	0.06	0.85	**<0.001**	0.15	0.36	0.02
WBC [tys/µl]	7.8 (6.9–8.4)	7.5 (6.5–8.8)	7.7 (6.6–8.5)	7.5 (6.2–9.1)	0.7	0.8	0.57	0.9	0.96	0.96
PLT [tys/µl]	231 (203.5–274.8)	240 (199–280)	231 (202–274.5)	239 (208–281)	0.74	0.96	0.52	0.77	0.76	0.47
Na [mmol/l]	140 (139–142)	141 (139–142)	141 (138.8–143)	141 (140–143)	0.76	0.47	0.09	0.58	0.18	0.70
K [mmol/l]	4.8 (4.6–5)	4.7 (4.4–4.9)	4.7 (4.4–5.1)	4.6 (4.4–4.8)	0.4	0.59	**<0.001**	0.72	0.05	0.08
Creatinine [µmol/l]	82 (73.2–88.8)	78 (71–92)	88 (74–93.2)	82 (71–92)	0.6	0.21	0.95	0.25	0.56	0.23
Urea [mmol/l]	6 (5.1–7.3)	5.7 (4.9–6)	6.5 (5.3–8.2)	5.4 (4.7–6.6)	0.07	0.31	0.03	0.02	0.8	0.01
GFR [ml/min/1.73 m^2]	82.5 (66.5–91.2)	88 (72–101)	80 (66–91.2)	86 (74–100)	0.09	0.97	0.06	0.3	>0.99	0.16
ALAT [U/l]	19 (14–30)	27 (20–35)	27.5 (19–36.8)	26 (20–34)	**<0.001**	0.01	**<0.001**	0.88	0.56	0.54
HDL [mmol/l]	1.2 (1.1–1.5)	1.2 (1.1–1.5)	1.3 (1.1–1.6)	1.2 (1–1.5)	0.79	0.71	0.78	0.88	0.54	0.59
LDL [mmol/l]	2 (1.6–2.4)	1.9 (1.4–2.5)	1.8 (1.4–2.2)	1.9 (1.6–2.4)	0.7	0.32	0.61	0.5	0.95	0.44
TG [mmol/l]	1.3 (1–1.5)	1.4 (1.1–1.8)	1.4 (0.8–1.8)	1.4 (1–1.9)	0.27	0.94	0.38	0.43	0.73	0.46
TSH [µIU/ml]	1.1 (0.6–1.9)	1.2 (0.9–1.6)	1.2 (0.9–1.9)	1.1 (0.8–1.6)	0.58	0.29	0.64	0.7	0.67	0.39
CK [IU/l]	108.5 (85–156.2)	127 (91–171)	115 (78–144)	112.5 (88–167.2)	0.21	0.88	0.53	0.15	0.27	0.42
BNP [pg/ml]	41.2 (27.7–159.8)	38.8 (20.2–65.6)	30.9 (13.9–68.6)	27 (15–54.1)	0.09	0.04	**<0.001**	0.59	0.07	0.52
EF [%]	50 (40–50)	50 (50–60)	50 (50–60)	50 (50–60)	0.06	0.05	0.01	0.57	0.62	0.78
Psychiatric scale, points, median (IQR)										
BDI	9 (7–12)	7 (3.5–11.5)	9.5 (5–17)	7 (3–12)	0.06	0.77	0.02	0.19	0.72	0.07
The Overt Aggression Scale Modified	0 (0–1)	1 (0–1)	0 (0–1)	0 (0–1)	0.33	0.89	0.25	0.33	0.01	0.44
ISI	5.5 (3–10)	6 (2–11)	5.5 (3–12.2)	6 (2–10)	0.97	0.96	0.47	0.89	0.5	0.53
AIS	5 (3–8)	4 (3–7)	6 (3.8–10)	5 (3–8)	0.69	0.38	0.94	0.24	0.65	0.27
Epworth Sleepiness Scale	7 (4–9)	6 (3–8)	6 (4–9)	6 (4–9)	0.41	0.76	0.71	0.33	0.18	>0.99

Table 4. Baseline characteristics and comparison of participants according to cognitive status for the follow-up visit detected by the clock drawing test. p-values from Mann-Whitney test are presented which was performed as post-hoc test sequentially for 2 groups and Bonferroni correction was applied. The statistical threshold for significance for the P value was 0.008. Boldface indicates statistical significance. *AIS* Athens Insomnia Scale, *ALAT* alanine transaminase, *BDI* Beck Depression Inventory, *BMI* Body Mass Index, *BNP* brain natriuretic peptide, *CDT* Clock Drawing Test, *CK* creatine kinase, *EF* ejection fraction, *GFR* glomerular filtration rate, *Hct* hematocrit, *HDL* high-density lipoprotein, *Hgb* hemoglobin, *ISI* Insomnia Severity Index, *K* potassium, *LDL* low density lipoprotein, *MI* myocardial infarction, *Na* sodium, *PLT* platelet count, *RBC* red blood cells, *TG* triglycerides, *Tn* troponin, *TSH* thyroid stimulating hormone, *WBC* white blood cells.

Time of assessment	Cognitive status in CDT/ Cognitive status in MMSE	N (%)	Score in CDT Median [IQR]	Score in MMSE Median [IQR]	Neurocognitive domain scores Median [IQR]					
					Orientation	Registration	Attention	Recall	Language	Praxia
MI-related hospitalization	Without CI/without CI	161 (49)	0	29	10	3	5	2	7	2
	Without CI/CI	62 (19)	0	25	9	3	2	2	7	2
	CI/without CI	49 (15)	2	28	10	3	5	2	7	2
	CI/CI	54 (17)	3	25	9	3	1	2	7	2
Follow-up	Without CI/without CI	214 (66)	0	29	10	3	5	3	7	2
	Without CI/CI	36 (11)	0	25	10	3	1	2	7	2
	CI/without CI	53 (16)	1	28	10	3	5	2	7	2
	CI/CI	23 (7)	3	24	9	3	1	2	7	2

Table 5. Comparison of the CDT and the MMSE results during MI-related hospitalization and after 6 months. *CDT* Clock Drawing Test, *CI* cognitive impairment, *MI* myocardial infarction, *MMSE* Mini Mental State Examination.

Age is the strongest risk factor for CI and dementia[15]. It is estimated that among individuals over 60 years of age, 12–18% exhibit mild cognitive impairment (MCI)[16]. MCI is considered to be a transitional stage between normal cognitive functioning and dementia, where deficits are found in at least one cognitive domain, but without interference with daily functioning[13]. In a recent analysis, the prevalence of underestimated CI in a population of asymptomatic middle-aged and older people (median age 62 years) was 23.6%[17]. In our study, CI regardless of the test performed was observed in approximately 40% of patients after MI (median age in groups 58–65), indicating a very high prevalence in this patient population, despite their relatively good general condition and age.

There are data indicating an association between markers of myocardial injury (troponin) and markers of hemodynamic stress (natriuretic peptides) with cognitive functioning in patients with CVD[18–23] Moreover, their role in the early identification of patients at risk of dementia is also emphasized[22]. In the case of troponin playing a key role in the diagnosis of MI, a prospective cohort study involving 5,407 older men and women showed that higher levels are associated with worse cognitive functioning at the beginning of the study, as well as a faster decline in cognitive abilities, independent of CVD or risk factors[20]. In the case of BNP, which is a recognized marker used in the diagnosis of heart failure, its role as a predictor of the development of cognitive dysfunction has also been suggested [21], and large studies have confirmed the association of high BNP levels with a higher risk of dementia of any cause[23]. There is also a growing body of data linking both biomarkers to structural brain damage. Natriuretic peptides appear to have a greater association with neurodegenerative changes such as brain atrophy, whereas troponins are associated with cerebral vascular changes (such as white matter hyperintensities, cortical cerebral microinfarcts). This may suggest their complementary importance in determining the mechanism of CI[22].

Diabetes is considered an independent risk factor for CI increasing the risk of developing dementia by 60%[24,25]. Also in our study, patients with newly developed (group 3) CI assessed by the CDT had a history of diabetes significantly more often. However, we did not observe similar results in the MMSE. The above observation is consistent with the study conducted by Medha Munshi et al., in which the analysis of diabetic patients showed that the MMSE may be less sensitive than other psychometric tests in this patient population, due to the assessment mainly of memory deficits and, to a small extent, executive functions (specific to vascular dementia)[24]. In a review of nine cross-sectional studies in patients with diabetes, deficits were observed in all cognitive domains, particularly in executive and attentional functions mediated by the frontal lobe[26]. Another study of 103,859 patients undergoing PCI showed that diabetes and CAD alone were only moderate risk factors for dementia, whereas their coexistence was associated with the highest risk of dementia, especially vascular dementia. It has been suggested that the risk of diabetes-related dementia is partly related to CVD, especially of atherosclerotic etiology, which is consistent with our results[27].

Sleep disorders are widespread in the adult population. Growing evidence links insomnia with an increased risk of future cardiovascular events.To date, few studies have assessed the prevalence of insomnia in patients with MI, but available data indicate a high prevalence of sleep disorders in this population, the presence of which may worsen the course of the disease and complicate further rehabilitation[28] Some researchers point to a higher prevalence of CI among patients with insomnia, as well as poorer attentional function scores among these individuals[29]. This is consistent with our results and requires further research.

As there were no specific clinical differences between the groups, especially 2 and 3, the next stage of the study involved the assessment of the type of cognitive function impaired in the post-MI patient population. Interestingly, we observed that attention is always impaired in the presence of CI. Also, when there is an improvement in mental status, we have a higher score for attention. The homogeneous type of CI and the lack of specific differences between the 4 groups, as well as the occurrence of CI among those with greater myocardial damage and diabetes, allows us to assume a homogeneous aetiology of atherosclerotic cognitive deficits in the study population.

MMSE and CDT are the 2 most commonly used tools to detect CI and dementia, and many studies confirm their strong correlation[30]. The strongest correlation was found between the MMSE and the CDT scoring system according to Schulman, which we used for the analyses[31].

However, what is noteworthy in our study is the fact that there is a group of patients who, despite having a normal result on the MMSE, present CI on the CDT, and vice versa. It should be considered whether this is the result of the adopted cut-off point of the tests and, consequently, their insufficient sensitivity in detecting cognitive deficits, or whether it is a group of patients with other impaired cognitive functions for which a given test is not specific enough to detect. Available literature indicates that the CDT is a tool to assess the functioning of the frontal and temporo-parietal lobes, and therefore, enabling the detection of deficits in visuospatial and executive functions[32], for which the MMSE seems to have limited sensitivity[33]. Hence, the CDT can detect CI even in patients who present high scores on the MMSE. The value of our project is the use of two screening tools, and the results obtained seem to confirm the hypothesis that people with CI on the CDT and a normal MMSE result are probably a group of patients with CI for whom the MMSE is not sensitive enough. Therefore, it seems rational to perform both tests. However, this involves a lot of time. In the daily practice of a cardiologist, a simple tool is needed that will quickly enable the selection of patients most at risk of CI and dementia, in order to be able to further refer them to the appropriate specialist, including a neurologist or psychologist.

Further analyses of the type of impaired cognitive domains showed that among patients with a normal CDT score but presenting with CI on the MMSE, attention is impaired. Therefore, performing the CDT and using the MMSE component assessing attention (the patient is requested to subtract 7 from 100, and to keep subtracting 7 from the result) could prove sufficient for initial assessment in this patient population. This simple test may allow a similar effect to be obtained as when both tests are administered in full simultaneously. This observation is important because it saves time during the medical visit.
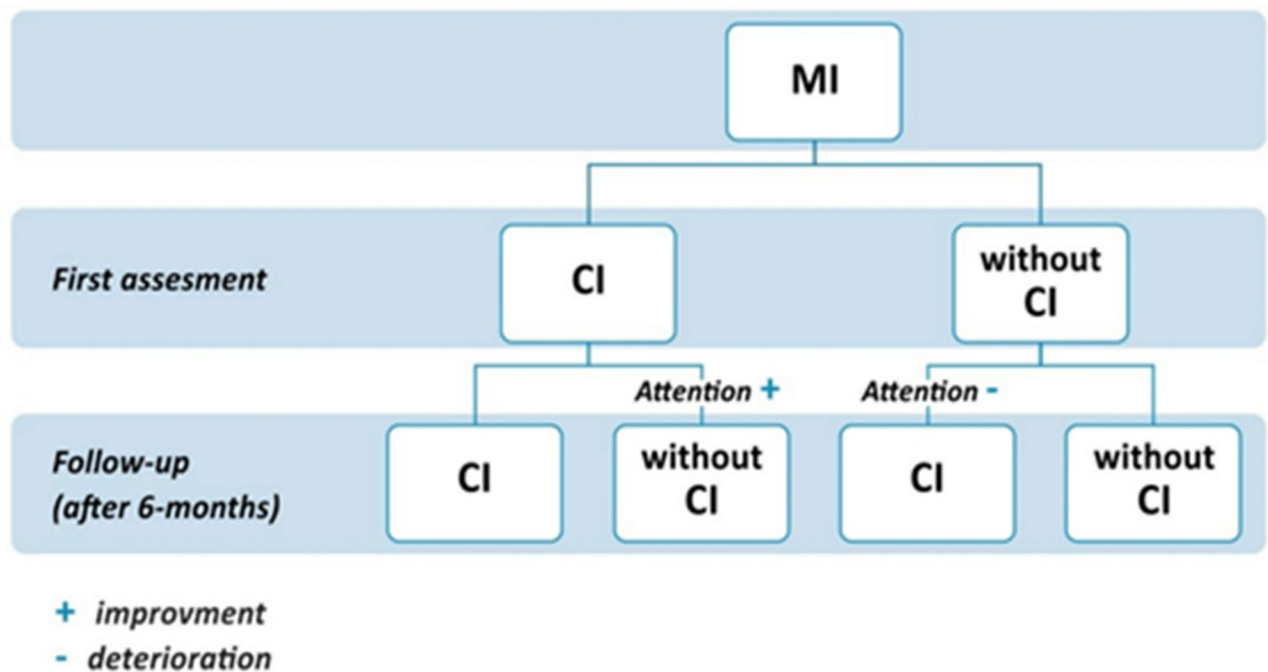
Fig. 2. The schematic representation of the course of the study, including division into 4 groups depending on the cognitive status according to the Mini-Mental State Examination. *CI* cognitive impairment, *MI* myocardial infarction.

The presence of CI significantly impairs the daily functioning of those affected. Impaired attentional function, especially in the post-ACS patient population, associated with difficulties in concentration, can lead to problems in their post-discharge education[34]. The consequence may be poorer adherence to medical recommendations. Unfortunately, it is not common in clinical practice to assess cognitive function after MI, which is due, among other things, to time constraints, but also to the lack of knowledge of simple, rapid and effective screening tools among cardiologists. Taking this into account, the aim of our next study will be precisely to validate a simple screening tool for CI in daily cardiology practice.

Limitations of the study

The study has limitations. Although the study protocol aimed to exclude patients with a documented diagnosis of dementia, there is a possibility that some patients had previously undiagnosed MCI. The study did not include an assessment of pre-infarction cognitive function.

The research was conducted on a Caucasian population and reflects a typical Polish demographic. Further studies are needed to extrapolate the results to the world population.

The study included a relatively young patient population (median age in groups 58–65), due to the refusal of older individuals to complete questionnaires, particularly those unable to follow instructions independently. Therefore, it can be assumed that the prevalence of CI is underestimated, indicating a higher prevalence in clinical practice.

The CDT is a handwriting test. Although the study included patients who were able to perform the tests independently, hand dexterity and handgrip strength were not objectively measured before conducting the test, which may be another limitation of the study.

Despite our attempt to approach the issue of CI as comprehensively as possible, we are aware that there are variables that we did not include in our work that affect cognition, such as peri-infarction arrhythmias, TIA/stroke and drug therapy. In the study, patient complaints were also not taken into account. Our patients had 48 h ECG telemetry monitoring during their stay in the ICU.

An interview was also conducted at that time. Holter ECG was not routinely used, also during follow-up. Therefore, we considered the data on arrhythmias to be biased and were not presented in this study and the same with stroke/TIA. We have not obtained objective confirmation of these episodes in the patients' medical records.

This is why we have decided not to present biased data. These issues are a good prospect for further research, also by our team.

Conclusion

CIs can occur both immediately after MI and during subsequent follow-up. However, as shown in Fig. 2, after 6 months of intensive anti-atherosclerotic treatment (post-MI), cognitive functions improve in some patients, and deteriorate in others. At the same time, the cognitive function that undergoes similar changes in these groups is attention. The uniform type of impaired cognitive function and the lack of specific differences

between the 4 groups allow us to assume a uniform etiology of cognitive deficits. Patients with normal CDT and disorders present in MMSE show deficits in attention functions. Performing CDT and using the MMSE component assessing attention function could prove sufficient for the initial assessment of cognitive functions in the population of patients after MI. The results require confirmation in a larger patient population.

Data availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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Declarations

Competing interests

The authors declare no competing interests.

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