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Effect of anticoagulants on kidney function in patients with non-valvular atrial fibrillation

Wpływ antykoagulantów na funkcję nerek u pacjentów z niezastawkowym migotaniem przedsionków

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Lekarz Kamila Cygulska jest absolwentką Wydziału Lekarskiego Uniwersytetu Medycznego w Łodzi. Obecnie odbywa szkolenie specjalizacyjne w zakresie kardiologii w I Klinice Kardiologii Katedry Kardiologii Uniwersytetu Medycznego w Łodzi. Zainteresowania medyczne skupia na prewencji sercowo-naczyniowej oraz echokardiografii. W wolnym czasie realizuje zainteresowania sportowe, między innymi trekking górski, pływanie oraz bieganie długodystansowe.

Abstract

Introduction. Vitamin K antagonists and non-vitamin K antagonist oral anticoagulants (NOAC) are used in the treatment of atrial fibrillation for the prevention of thromboembolic events.

Materials and methods. The authors studied 389 patients (45.8% female) with nonvalvular atrial fibrillation, who have been taking apixaban (12.6%), dabigatran (38.6%), rivaroxaban (26.7%) and acenocoumarol (22.1%). Creatinine levels were controlled after 2, 6 and 12 months. The authors worked out an estimated glomerular filtration rate (eGFR) by means of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Results. The changes in creatinine and eGFR values after 2, 6, 12 months in all 4 subgroups were statistically significant. Post hoc tests showed changes in creatinine and eGFR values after 2, 6, 12 months for apixaban, dabigatran and rivaroxaban compared with acenocoumarol. Three NOACs were associated with ≥ 20% decline in eGFR [hazard ratio (HR): 0.24, 95% confidence interval (CI): 0.16–0.37, $p < 0.001$], ≥ 30% increase in creatinine concentration (HR: 0.19, 95% CI: 0.11–0.32, $p < 0.001$) and eGFR < 44 mL/min/1.73 m^2 (HR: 0.24, 95% CI: 0.11–0.55, $p = 0.002$).

Conclusion. Using of NOACs is connected with more positive effects of renal outcomes than treatment with acenocoumarol.

Key words: nonvalvular atrial fibrillation, acenocoumarol, non-vitamin K antagonist oral anticoagulants (NOACs), estimated glomerular filtration rate (eGFR)

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Introduction

This arrhythmia is widespread cardiac disease. It causes the possibility of morbidity and death rate due to some thromboembolic incidents. The calculations of all the events were based on the CHA_2DS_2-VASc score [1]. Kidney function is significant in the case of people with this arrhythmia, who were given oral anticoagulants since the impairment of their work may contribute to thrombotic diseases and bleeding [2]. Clinical trials have shown that vitamin K

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antagonists strengthened calcification of most vessels and thus have worsened renal function [3]. All non-vitamin K antagonist oral anticoagulants (NOACs) have a beneficial effect on blood vessels and protect the kidney [4, 5].

We were going to compare the results of various anticoagulants on kidneys in patients with with nonvalvular atrial fibrillation (NVAF).

Material and methods

The study was approved by the local ethical committee at the University of Lodz in Poland (number RNN/134/18/KE of 15th May 2018). Some patients were included retrospectively and there was no need for informed consent. The remaining patients agreed to the study and telephone conversations regarding the values of creatinine if they were not hospitalized after the last result.

The authors have included patients with NVAF, who started oral anticoagulation from January 2018 to January 2019 and who have been taking NOACs (apixaban, dabigatran, rivaroxaban) or acenocoumarol since the beginning of their treatment. The patients were observed for one year after starting the therapy. Creatinine levels were controlled after 2, 6 and 12 months. The estimated glomerular filtration rate (eGFR) was worked out through Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. People with chronic kidney disease (CKD) were not excluded. 389 patients (45.8% female) with NVAF took part in the study, who were treated with apixaban (12.6%), dabigatran (38.6%), rivaroxaban (26.7%) and acenocoumarol (22.1%). The research group is presented in Table 1. 3 renal outcomes were assessed: ≥ 20% decline in eGFR, ≥ 30% increase in serum creatinine and eGFR < 44 mL/min/1.73 m^2 (excluding patients with baseline eGFR < 44 mL/min/1.73 m^2).

Statistical analysis

Statistical calculations were performed using Medcalc software, PQStat v 1.6.8. and Develve. All parameters were shown as average value ± standard deviation (SD). 4 drugs were studied and 6 pairs of comparisons were shown. The authors assumed that changes between the groups were significant when the p-value was < 0.05. The D'Agostino-Pearson test was used to determine the distribution. One-way analysis of variance (ANOVA) Kruskal-Wallis test was applied to test the change between the average differences in creatinine and eGFR values after 2, 6 and 12 months of 4 subgroups (multiple testing), then Dunn Bonferroni post hoc test was used. The minimum sample size for each ANOVA Kruskal-Wallis analysis was estimated using Develve software. Cox proportional hazard regression was calculated to see the differences between the groups for all renal outcomes.

Results

Mean pre-treatment eGFR in the study group was 67.12 ± 20.41 mL/min per 1.73 m^2 and average serum creatinine value was 1.08 ± 0.39 mg/dL. The mean eGFR after 12 months was 67.64 ± 20.59 mL/min per 1.73 m^2, whereas the average serum creatinine was 1.07 ± 0.37 mg/dL. eGFR below 15 mL/min per 1.73 m^2 was found in one patient (Tables 2–4). The changes in the values of creatinine and eGFR were calculated as the creatinine and eGFR levels adjusted for baseline levels after 2, 6, 12 months. The minimum sample size for each ANOVA Kruskal-Wallis analysis was estimated using Develve software (the minimum sample size for creatinine ANOVA Kruskal-Wallis analysis after 2 months equals 49 patients, after 6 months equals 44 patients, after 12 months equals 20 patients; the minimum sample size for eGFR ANOVA Kruskal-Wallis analysis after 2 months equals 26 patients, after 6 months equals 28 patients, after 12 months equals 13 patients).

The percentage of people being treated by means of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diuretics have been shown in Table 1. There hasn't been any significant difference among the number of patients using these drugs and being exposed to the risk of contrast. It was calculated using chi-square for multidimensional contingency tables in PQSTAT software v 1.6.8. (for ACEI or ARB chi-square statistic 0.94, p = 0.82; for diuretics (one or more) chi-square 2.38, p = 0.5; for contrast chi-square 3.77, p = 0.29).

According to Kruskal-Wallis ANOVA analysis, the changes in creatinine values after 2, 6, 12 months in 4 subgroups were statistically significant (after 2 months H test statistic = 71.64, p < 0.001, after 6 months H test statistic = 56.61, p < 0.001 after 12 months H test statistic = 89.73, p < 0.001). Post hoc tests (Dunn Bonferroni) showed important differences in creatinine values after 2 months (for apixaban, dabigatran and rivaroxaban p < 0.001 compared with acenocoumarol), after 6 months (for apixaban p = 0.001, dabigatran and rivaroxaban p < 0.001 compared with acenocoumarol), after 12 months (for apixaban, rivaroxaban and dabigatran p < 0.001). According to Kruskal-Wallis ANOVA analysis, the changes in eGFR values after 2, 6, 12 months in 4 subgroups were statistically significant (after 2 months H statistical test = 76.36, p < 0.001, after 6 months H test statistic = 54.04; p < 0.001, after 12 months H statistical test = 99.00, p < 0.001). *Post hoc* tests (Dunn Bonferroni) showed changes in eGFR values after 2 months (for apixaban, dabigatran and rivaroxaban p < 0.001 compared with acenocoumarol), after 6 months (for apixaban p = 0.003, dabigatran and rivaroxaban p < 0.001 compared with acenocoumarol), after 12 months (for apixaban, rivaroxaban and dabigatran p < 0.001) (Figure 1).

Table 1. Baseline characteristics of the study group (N = 389)

Parameter	Apixaban (N = 49)	Rivaroxaban (N = 104)	Acenocoumarol (N = 86)	Dabigatran (N = 150)
Age, years	69.6 ± 10.3	69.54 ± 10.8	67.33 ± 9.31	67.87 ± 10.3
eGFR [mL/min/1,73 m^2]	61.83 ± 22.64	64.84 ± 22.78	74.89 ± 17.24	65.97 ± 18.27
CHA_2DS_2-VASc	3.6 ± 1.8	3.3 ± 1.6	3.2 ± 1.3	3.2 ± 1.5
Creatinine concentration	1.22 ± 0.48	1.14 ± 0.46	0.95 ± 0.25	1.08 ± 0.34
HAS-BLED	1.9 ± 1.1	1.7 ± 0.9	1.8 ± 1.0	1.6 ± 0.9
Female (N = 178)	21	44	40	73
Medical history				
Acetylsalicylic acid treatment	10.2%	10.6%	7.0%	8.7%
Clopidogrel treatment	12.2%	9.6%	4.7%	7.3%
Pulmonary hypertension	8.2%	5.8%	5.8%	3.3%
Hypertension	85.7%	86.5%	75.6%	82.7%
Hyperlipidemia	75.5%	60.6%	48.8%	59.3%
PCI	26.5%	23.1%	12.8%	22.7%
Heart failure	55.1%	49.0%	48.8%	46.0%
Diabetes mellitus	28.6%	36.5%	27.9%	27.3%
Thromboembolism	4.1%	7.7%	16.3%	10.7%
Myocardial infarction	18.4%	18.3%	11.6%	13.3%
Anaemia	14.3%	6.7%	8.1%	4.0%
Kidney disease	36.7%	18.3%	8.1%	10.7%
Obesity	30.6%	26.92%	30.23%	26.67%
Alcoholism	2.0%	1.0%	1.2%	0.7%
Smoking	10.2%	5.8%	4.7%	11.3%
Cardioversion	55.1%	58.7%	41.9%	60.7%
Hyperthyroidism	14.3%	6.7%	8.1%	6.0%
Hypothyroidism	6.1%	9.6%	10.5%	10.7%
Cancer	6.1%	5.7%	4.7%	7.3%
Depression	2.0%	1.9%	0.0%	2.7%
Ablation	26.5%	16.4%	7.0%	30.0%
Pacemaker/ICD	10.2%	22.1%	26.7%	12.7%
Liver disease	4.1%	1.0%	0.0%	1.3%
Peripheral artery disease	0.0%	2.9%	2.3%	0.0%
ACEI or ARB	83.6%	78.9%	83.7%	82.0%
Diuretics (one or more)	65.3%	54.8%	62.8%	56.7%
Contrast	16.3%	6.73%	9.3%	8.7%

Values are mean ± standard deviation or %. Thromboembolism includes ischemic stroke, systemic embolism and transient ischemic attack; eGFR — estimated glomerular rate; CHA_2DS_2-VASc — congestive heart failure, hypertension, age ≥ 75 years, age 65 to 74 years, stroke or transient ischemic attack or thromboembolism, vascular disease, diabetes, sex category (female); HAS-BLED — hypertension, abnormal kidney and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; PCI — percutaneous coronary intervention; ICD — implantable cardioverter-defibrillator; ACEI —angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers

3 NOACs were connected with limited risks of ≥ 20% decrease in eGFR [hazard ratio (HR): 0.24; 95% confidence interval (CI) 0.16–0.37, p < 0.001], ≥ 30% increase in creatinine concentration (HR: 0.19, 95% CI: 0.11–0.32, p < 0.001) and eGFR < 44 mL/min/1.73 m^2 (HR: 0.24, 95% CI: 0.11–0.55, p = 0.002) with the correction of p-values by Dunn Bonferroni tests. Every NOAC and acenocoumarol was analysed, NOACs showed smaller risks of ≥ 20% decrease in eGFR, ≥ 30% increase in creatinine concentration and eGFR < 44 mL/min/1.73 m^2 except apixaban (Tables 5–7).

Table 2. Mean creatinine values and standard deviations after 2, 6, 12 months

Drug	Initial creatinine concentration	Creatinine concentration after 2 months	Creatinine concentration after 6 months	Creatinine concentration after 12 months
Apixaban	1.22 ± 0.48	1.15 ± 0.46	1.2 ± 0.48	1.19 ± 0.49
Rivaroxaban	1.14 ± 0.46	1.04 ± 0.33	1.07 ± 0.37	1.08 ± 0.43
Acenocumarol	0.95 ± 0.25	1.03 ± 0.26	1.06 ± 0.3	1.16 ± 0.37
Dabigatran	1.08 ± 0.34	0.99 ± 0.25	0.99 ± 0.24	0.97 ± 0.24

Table 3. Chronic kidney disease stages before oral anticoagulation

Stage of renal failure (acc. to GFR value)	Apixaban N	Rivaroxaban N	Acenocoumarol N	Dabigatran N
G1	7	20	17	19
G2	18	39	52	70
G3a	9	25	13	41
G3b	12	13	4	16
G4	3	6	0	4
G5	0	1	0	0

GFR – glomerular filtration rate

Table 4. Chronic kidney disease stages after 12 months of oral anticoagulation

Stage of renal failure (acc. to GFR value)	Apixaban N	Rivaroxaban N	Acenocoumarol N	Dabigatran N
G1	4	20	6	30
G2	22	46	44	80
G3a	10	19	19	28
G3b	10	17	15	10
G4	3	2	1	2
G5	0	0	1	0

GFR – glomerular filtration rate

Discussion

This research proved that NOACs have a less pronounced effect on kidney function compared to VKA. While comparing acenocoumarol with NOACs, new drugs were associated with a smaller risk of ≥ 20% decrease in eGFR, ≥ 30% increase in creatinine concentration and eGFR < 44 mL/min/1.73 m^2.

Vitamin K antagonists inhibit the synthesis of active clotting factors related to vitamin K (II, VII, IX, X). VKAs increase vascular calcifications strengthened by inhibition of the vitamin K-dependent protein matrix gamma-carboxyglutamic acid and activation of the vascular bone morphogenetic protein (BMP) signalling pathway [6–8]. An increase of osteogenesis and calcium accumulation results from increased activation of BMP, their receptors and inhibitor (MPG) [9, 10]. Factor Xa and thrombin contributed to increased risk of vascular inflammation through thrombin receptor – protease-activated receptor (PAR2) [6]. PAR2 signalling is important in the control of kidney haemodynamics, perfusion and rapid vasoconstriction. PAR2 stimulation can cause the growth of renal renin activation. PAR2 inhibition may cause decrease activation of interleukin 6 and 8 and leukocytes. PAR antagonists nephron cells can cause decreased giving off molecules such as transforming growth factor β (TGF-β), which may lead to the increase of kidney fibrosis and nephritis [11].

Yao et al. [12] assessed four renal outcomes in 2 years: ≥ 30% decline in eGFR, doubling of the serum creatinine value, acute kidney injury and kidney failure (eGFR < 15 mL/min/1,73 m^2) and showed that 3 NOACs were connected with a lower risk of these four endpoints in comparison with

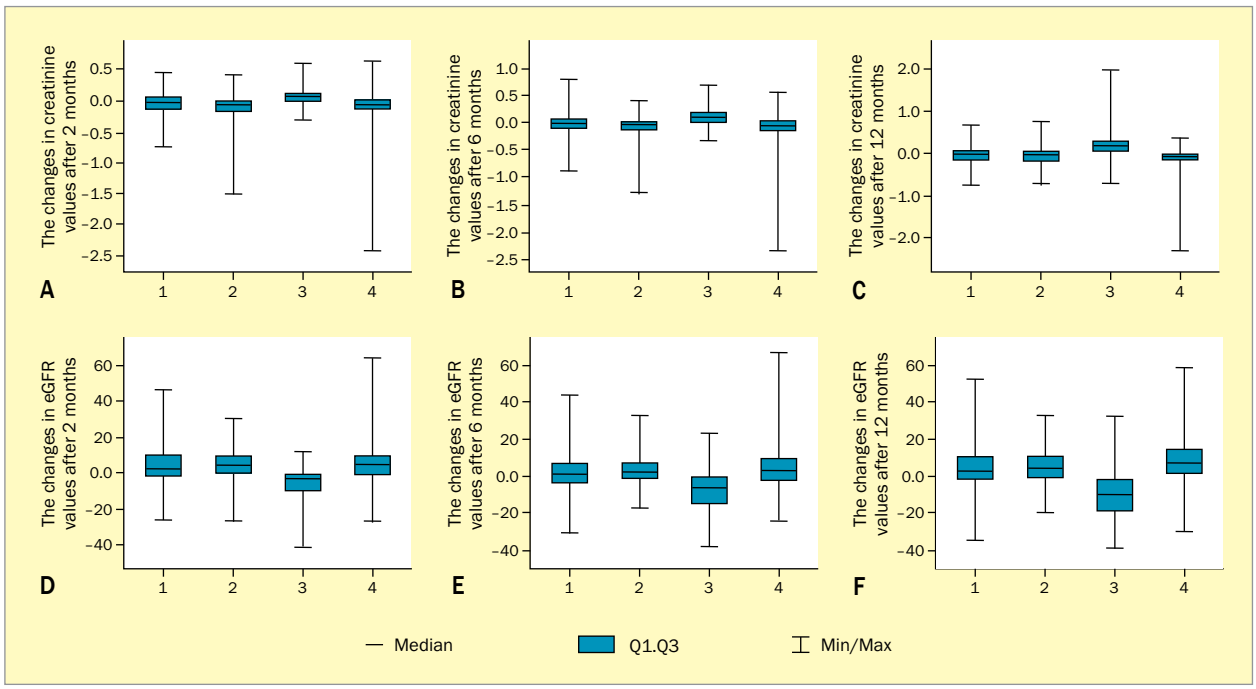

Figure 1. The changes in creatinine and estimated glomerular filtration rate (eGFR) values: **A.** The changes in creatinine values after 2 months in 4 subgroups (1 — apixaban, 2 — rivaroxaban, 3 — acenocoumarol, 4 — dabigatran); **B.** The changes in creatinine values after 6 months in 4 subgroups; **C.** The changes in creatinine values after 12 months in 4 subgroups; **D.** The changes in eGFR values after 2 months in 4 subgroups; **E.** The changes in eGFR values after 6 months in 4 subgroups; **F.** The changes in eGFR values after 12 months in 4 subgroups

Table 5. Hazard ratios (HR) with 95% confidence interval (CI) with the correction of p values by Bonferroni statistics for risk of ≥ 20% decline in estimated glomerular filtration rate (eGFR)

Drug	Number of incidences	HR	95% CI	p
Apixaban	11	0.40	0.21–0.79	0.018
Rivaroxaban	12	0.24	0.11–0.38	< 0.001
Dabigatran	18	0.21	0.12–0.37	< 0.001
Acenocoumarol	43	Reference	Reference	Reference

Table 6. Hazard ratios (HR) with 95% confidence interval (CI) for risk of ≥ 30% increase in creatinine concentration with the correction of p values by Bonferroni statistics

Drug	Number of incidences	HR	95% CI	p
Apixaban	7	0.27	0.16–0.82	0.028
Rivaroxaban	5	0.13	0.05–0.30	< 0.001
Dabigatran	11	0.14	0.09–0.36	< 0.001
Acenocoumarol	32	Reference	Reference	Reference

Table 7. Hazard ratios (HR) with 95% confidence interval (CI) for risk of estimated glomerular filtration rate (eGFR) < 44 mL/min/1.73 m^2 with the correction of p values by Bonferroni statistics

Drug	Number of incidences	HR	95% CI	p
Apixaban	6	0.51	0.2–1.3	0.6
Rivaroxaban	5	0.2	0.07–0.52	0.004
Dabigatran	9	0.24	0.11–0.55	0.002
Acenocoumarol	20	Reference	Reference	Reference

warfarin. During this study, the treatment with NOACs showed benefits, but they were weaker, which may be related to the fact that this study lasted for a year [12]. An interesting analysis by Zhang et al. showed a decreased risk of kidney deterioration for NOACs in juxtaposition with VKAs or acetylsalicylic acid [13].

Some other research proved that warfarin may cause an increased risk of decrease of eGFR than dabigatran in the study of RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) [2]. Apixaban similarly contributed to acute renal failure as warfarin in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial [14].

Another study of NOACs and warfarin confirmed better results of therapy for a normal dose of dabigatran in patients with correct renal function, whereas a low dose of apixaban or dabigatran in 150 mg could be applied in nonvascular atrial fibrillation patients with moderate kidney disease [15–17].

The significant changes in kidney function in the ptients treated with apixaban or warfarin were not in a subanalysis ARISTOTLE. The advantages of apixaban versus warfarin on thromboembolic events and serious bleeding were shown in patients with adequate or wrong kidney haemodynamics [14]. RE-LY and ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with VItamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trials confirmed a slower decrease of eGFR with dabigatran and rivaroxaban than with warfarin [6, 18]. The correct renal function is significant for people with atrial fibrillation because it diminishes the cases of thromboembolic events and bleeding [2, 16].

Summing it up, the impact of oral anticoagulants on renal function is essential for the effectiveness of this treatment. Taking into consideration the values of thromboembolic and bleeding cases, one cannot fail to notice that these drugs are a good choice compared to VKAs [19].

Conclusion

Therapy with NOACs carries a smaller risk of adverse renal outcomes than treatment with acenocoumarol. 3 NOACs had decreased risks of ≥ 20% decrease in eGFR, ≥ 30% increase in creatinine concentration and eGFR < 44 mL/ /min/1.73 m^2. When comparing each NOAC with acenocoumarol, all NOACs showed fewer risks of ≥ 20% drop in eGFR and ≥ 30% increase in creatinine concentration and eGFR < 44 mL/min/1.73 m^2 except apixaban.

Limitation of study

The presented study lasted only a year and the observed group was not as large as in multicentre studies.

Funding

None declared.

Conflict(s) of interest

The authors declare no conflicts of interest.

Streszczenie

Wstęp. Antagoniści witaminy K i doustne leki przeciwkrzepliwe niebędące antagonistami witaminy K (NOAC) są wykorzystywane w leczeniu migotania przedsionków w prewencji incydentów zakrzepowo-zatorowych.

Materiał i metody. Do badania włączono 389 pacjentów (45,8% kobiet) z niezastawkowym migotaniem przedsionków (NVAF), którzy przyjmowali apiksaban (12,6%), dabigatran (38,6%), riwaroksaban (26,7%) i acenokumarol (22,1%). Stężenie kreatyniny było kontrolowane po 2, 6 i 12 miesiącach. Oceniono szacowany współczynnik przesączania kłębuszkowego (eGFR) za pomocą wzoru *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI).

Wyniki. Różnice w wartościach kreatyniny i eGFR po 2, 6 i 12 miesiącach w 4 podgrupach były istotne statystycznie. Testy *post hoc* ujawniły różnice w stężeniu kreatyniny i wartości eGFR po 2, 6 i 12 miesiącach w odniesieniu do apiksabanu, dabigatranu i riwaroksabanu w porównaniu z acenokumarolem. Stosowanie trzech NOAC było skojarzone z co najmniej 20-procentowym spadkiem eGFR (współczynnik ryzyka [HR]: 0,24; 95-proc. przedział ufności [CI]: 0,16–0,37; p < 0,001), z co najmniej 30-procentowym wzrostem stężenia kreatyniny (HR: 0,19; 95% CI: 0,11–0,32; p < 0,001) oraz z eGFR poniżej 44 ml/min/1,73 m^2 (HR: 0,24; 95% CI: 0,11–0,55; p = 0,002).

Wnioski. Zastosowanie NOAC wiąże się z korzystniejszym wpływem na funkcję nerek niż leczenie acenokumarolem.

Słowa kluczowe: niezastawkowe migotanie przedsionków, acenokumarol, doustne leki przeciwkrzepliwe niebędące antagonistami witaminy K (NOAC), szacowany współczynnik filtracji kłębuszkowej (eGFR)

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