CARDIOLOGY

FEATURES OF DRUG-DRUG INTERACTIONS RIVAROXABAN AND CALCIUM CHANNEL BLOCKERS DEPENDING ON THE *ABCB1* GENOTYPE (rs1045642 AND rs4148738) IN PATIENTS 80 YEARS OF AGE AND OLDER WITH NON-VALVULAR ATRIAL FIBRILLATION

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Received: 04.06.2023
Accepted: 14.11.2023
Published: 29.12.2023

ABSTRACT

Background. *The use of P-glycoprotein (P-gp) inhibitors and carriage of certain ABCB1 polymorphisms can lead to increased concentrations of rivaroxaban and the development of bleeding.*
The aim. *To study the features of drug-drug interactions (DDI) of rivaroxaban in patients over 80 years of age with non-valvular atrial fibrillation depending on the ABCB1 genotype (rs1045642 and rs4148738) using the example of verapamil (P-gp inhibitor) and amlodipine.*
Materials and methods. *One hundred and twenty-eight patients were examined (median age – 87.5 [83–90] years). Genotyping, determination of the minimum equilibrium concentration of rivaroxaban ($C_{min, ss}$), with standardization for the daily dose ($C_{min, ss/D}$), coagulogram and analysis of medical documentation for the presence of clinically significant non-major bleeding (CSNMB) were carried out. DDI was analyzed according to ABCB1 genotype.*
Results. *The use of rivaroxaban with verapamil in comparison with patients not taking calcium channel blockers (CCBs) leads to high $C_{min, ss}$ values in the CC genotype (rs1045642, rs4148738); $C_{min, ss}$ and $C_{min, ss}$/D in the CT genotype (rs1045642); prothrombin time in the CC genotype (rs1045642), more frequent occurrence of CRNM in the TT genotype (rs1045642, rs4148738). In comparison with patients taking amlodipine, it leads to high $C_{min, ss}$ values in the CT genotype (rs1045642), a more frequent occurrence of CSNMB in the TT genotype (rs1045642, rs4148738). The use of rivaroxaban with amlodipine in comparison with patients not taking CCBs leads to high $C_{min, ss}$ and $C_{min, ss}$/D values in the CC genotype (rs1045642) ($p < 0.017$).*
Conclusion. *The use of verapamil with rivaroxaban in ABCB1 TT carriers (rs4148738 and rs4148738) leads to the development of CSNMB in 75 and 78 % of cases, respectively. In patients taking rivaroxaban, it is advisable to test the ABCB1 genotype (rs4148738 and rs4148738) before adding a P-gp inhibitor to therapy.*

Key words: *drug-drug interactions, rivaroxaban, verapamil, ABCB1 (rs1045642 and rs4148738), therapeutic drug monitoring, older patients*

For citation: Sychev D.A., Mirzaev K.B., Cherniaeva M.S., Shakhgildyan N.V., Abdullaev Sh.P., Denisenko N.P., Sozaeva Zh.A., Kachanova A.A., Shastina V.R., Gorbatenkova S.V. Features of drug-drug interactions rivaroxaban and calcium channel blockers depending on the *ABCB1* genotype (rs1045642 and rs4148738) in patients 80 years of age and older with non-valvular atrial fibrillation. *Acta biomedica scientifica*. 2023; 8(6): 51-80. doi: 10.29413/ABS.2023-8.6.6

ОСОБЕННОСТИ МЕЖЛЕКАРСТВЕННОГО ВЗАИМОДЕЙСТВИЯ РИВАРОКСАБАНА И БЛОКАТОРОВ КАЛЬЦИЕВЫХ КАНАЛОВ В ЗАВИСИМОСТИ ОТ ГЕНОТИПА *ABCB1* (rs1045642 И rs4148738) У ПАЦИЕНТОВ 80 ЛЕТ И СТАРШЕ С НЕКЛАПАННОЙ ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

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Статья поступила: 04.06.2023
Статья принята: 14.11.2023
Статья опубликована: 29.12.2023

РЕЗЮМЕ

Обоснование. *Применение ингибиторов гликопротеина P (P-gp) и носительство определённых полиморфизмов ABCB1 могут привести к увеличению концентрации ривароксабана и развитию кровотечений.*
Цель работы. *Изучить особенности межлекарственного взаимодействия (МЛВД) ривароксабана у пациентов старше 80 лет с неклапанной фибрилляцией предсердий в зависимости от генотипа ABCB1 (rs1045642 и rs4148738) на примере верапамила (ингибитор P-gp) и амлодипина.*
Материалы и методы. *Обследовано 128 пациентов (медиана возраста – 87,5 [83–90] лет). Проведены генотипирование, определение минимальной равновесной концентрации ривароксабана ($C_{min, ss}$) со стандартизацией на суточную дозу ($C_{min, ss}/D$), коагулограмма и анализ медицинской документации на наличие клинически значимых небольших кровотечений (КЗНК). Анализ по МЛВД проводился в зависимости от генотипа ABCB1.*
Результаты*. Применение ривароксабана с верапамилом в сравнении с пациентами, не принимающими блокаторы кальциевых каналов (БКК), приводит к высоким значениям $C_{min, ss}$ у генотипа CC (rs1045642, rs4148738); $C_{min, ss}$ и $C_{min, ss}/D$ – у генотипа CT (rs1045642); протромбинового времени – у генотипа CC (rs1045642); более частому возникновению КЗНК у генотипа TT (rs1045642, rs4148738). В сравнении с пациентами, принимающими амлодипин, применение ривароксабана с верапамилом приводит к высоким значениям $C_{min, ss}$ у генотипа CT (rs1045642), более частому возникновению КЗНК у генотипа TT (rs1045642, rs4148738). Применение ривароксабана с амлодипином в сравнении с пациентами, не принимающими БКК, приводит к высоким значениям $C_{min, ss}$ и $C_{min, ss}/D$ у генотипа CC (rs1045642) ($p < 0,017$).*
Заключение*. Применение верапамила с ривароксабаном у носителей генотипа TT ABCB1 (rs4148738 и rs4148738) приводит к развитию КЗНК в 75 % и 78 % случаев соответственно. У пациентов, принимающих ривароксабан, целесообразно исследование генотипа ABCB1 (rs4148738 и rs4148738) перед добавлением к терапии ингибитора P-gp.*

Ключевые слова: *межлекарственные взаимодействия, ривароксабан, верапамил, ABCB1 (rs1045642 и rs4148738), терапевтический лекарственный мониторинг, пожилые пациенты*

Для цитирования: Сычев Д.А., Мирзаев К.Б., Черняева М.С., Шахгильдян Н.В., Абдуллаев Ш.П., Денисенко Н.П., Созаева Ж.А., Качанова А.А., Шастина В.Р., Горбатенкова С.В. Особенности межлекарственного взаимодействия ривароксабана и блокаторов кальциевых каналов в зависимости от генотипа *ABCB1* (rs1045642 и rs4148738) у пациентов 80 лет и старше с неклапанной фибрилляцией предсердий. *Acta biomedica scientifica*. 2023; 8(6): 51-80. doi: 10.29413/ABS.2023-8.6.6

RELEVANCE

Rivaroxaban is a substrate of the glycoprotein P (P-gp) transfer protein encoded by the *ABCB1* gene, which regulates the absorption of rivaroxaban from the lumen of the gastrointestinal tract and is also involved in its excretion through the liver and kidneys. Additionally, rivaroxaban is metabolised by cytochrome P-450 (CYP450), mainly by CYP3A4, with a minor contribution from CYP2J2 [1, 2]. Co-administration of medicinal products (MPs) that inhibit these metabolic pathways may increase rivaroxaban concentrations and increase the risk of adverse reactions (ARs), including bleeding [3]. In our previous study, we observed that co-administration of verapamil (a strong P-gp inhibitor and moderate CYP3A4 inhibitor) in combination with rivaroxaban resulted in a higher minimum equilibrium concentration ($C_{min, ss}$) of rivaroxaban compared with controls (Me, 73.8 [50.6–108.8] vs. 40.5 [25.6–74.3] ng/ml, respectively; $p = 0.003$) and, as a consequence, to more frequent AR in the form of small clinically significant non-major bleeding (CSNMB) (33 % vs. 13 %, respectively; $p = 0.036$) [4].

Genetic factors can also influence P-gp activity. Numerous SNP (single nucleotide polymorphism) have been observed in the *ABCB1* gene encoding P-gp, which may be associated with variations in P-gp expression and activity in humans during *in vitro* cell line studies [5–8]. *ABCB1* polymorphisms and haplotypes have been associated with changes in MP distribution and the development of AR to various MP substrates [9–11], although opinions are still conflicting [12, 13]. Although earlier in our study we did not obtain statistically significant differences in the pharmacokinetic profile in patients 80 years and older with non-valvular atrial fibrillation (AF) caused-specific to *ABCB1* gene polymorphisms (rs1045642 and rs4148738), nevertheless, we showed that AR in the form of clinically significant small hemorrhages was more frequent in patients carrying the homozygous type (TT) of the *ABCB1* gene (rs1045642) compared to patients carrying the wild type (CC) (29.3 % vs. 4.5 % of cases; $p < 0.050$) and prothrombin time (PT) was statistically significantly higher. Patients carrying the homozygous type (TT) of the *ABCB1* (rs4148738) gene were statistically significantly more likely to have clinically significant minor bleeding compared to patients carrying the wild type (CC) (39.3 % vs. 8.1 % of cases; $p < 0.050$) and heterozygous type (CT) (39.3 % vs. 14.3 % of cases; $p < 0.050$) of the *ABCB1* (rs4148738) gene [14].

Therefore, as a continuation of our studies, it was decided to separately analyse the pharmacokinetic profile of patients carrying each of the genotypes (CC, CT and TT) of the *ABCB1* gene (rs1045642 and rs4148738) in relation to concomitant therapy with calcium channel blockers (CCBs), where co-administration of rivaroxaban (P-gp substrate) with amlodipine (dihydropyridine BCA (DCCB)) (P-gp substrate) may lead to drug interaction caused by competition between the substrates for binding sites on cell membranes, and co-administration of rivaroxaban with verapamil (non-DCCB) (strong P-gp inhibitor and moderate CYP3A4 inhibitor) may lead to drug interactions as a result by inhibition of the leading transport and metabolic pathways of rivaroxaban.

THE AIM OF THE STUDY

To study the features of drug interaction between rivaroxaban in patients over 80 years old with non-valvular atrial fibrillation caused-specific to *ABCB1* genotype (rs1045642 and rs4148738) using verapamil (P-gp inhibitor) and amlodipine as an example.

MATERIALS AND METHODS

Study design and ethics

A cross-sectional study of patients 80 years and older with non-valvular AF recruited between January 2019 and February 2020 was conducted. The study was approved by the Ethical Committee of the Russian Medical Academy of Continuous Professional Education (Protocol No. 1 dated January 22, 2019) and was conducted in accordance with the World Medical Association's Declaration of Helsinki in compliance with the rules of good clinical practice. Verbal and written informed consent was obtained from all participants included in the study.

Patients

We examined 128 patients older than 80 years (median age – 87.5 [83–90] years; 75 % women) of Caucasian race with non-valvular AF who were under treatment in a multidisciplinary hospital in Moscow. Patients were consecutively included in the study if they met the inclusion criteria. Inclusion criteria: 1) patients with non-valvular AF of both sexes; 2) age at the time of inclusion in the study – 80 years and older; 3) duration of previous intake of rivaroxaban with verapamil, amlodipine or without CCB – at least 1 year from the time of inclusion in the study; 4) signing a voluntary informed consent for participation in the study. The main exclusion criteria were 1) age less than 80 years; 2) concomitant drug therapy with known drug interactions with rivaroxaban (fluconazole, ketoconazole and other azole antifungal drugs; ritonavir and other human immunodeficiency virus protease inhibitors; amiodarone, clarithromycin, erythromycin; platelet aggregation inhibitors (including acetylsalicylic acid); non-steroidal anti-inflammatory drugs; selective serotonin and norepinephrine reuptake inhibitors; rifampicin, phenytoin, carbamazepine, phenobarbital, *Hypericum perforatum* preparations); 3) patient's violation of the procedures of the examination and treatment plan; 4) refusal to participate in the study.

All patients were taking rivaroxaban (once-daily) for ischemic stroke prophylaxis at a dose of 15 mg/day (86.7 % of patients) and 20 mg/day (13.3 % of patients). Each patient was genotyped for the examined polymorphism and the minimum equilibrium concentration of ri-

varoxaban ($C_{min, ss}$) was determined. An additional standardisation of the minimum equilibrium concentration of rivaroxaban per daily drug dose ($C_{min,ss}$/D) was performed. Furthermore, all patients underwent clinical and biochemical blood tests, urinalysis, coagulogram with determination of PT in plasma. Medical records were analysed for the presence of AR in the form of CSNMB bleeding against the background of rivaroxaban intake during the previous year from the time of inclusion in the study [15, 16].

Genotyping

The material for DNA extraction was venous blood, which was sampled in 4 ml Vacuette® vacuum tubes with K3 EDTA anticoagulant. Genotyping by polymorphisms rs1045642 and rs4148738 of the *ABCB1* gene was performed using real-time polymerase chain reaction on a CFX96 Touch™ Real-Time PCR Detection System DNA amplifier (Bio-Rad Laboratories Inc., USA) at the Research Institute of Molecular and Personalised Medicine, Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia.

Determination of rivaroxaban concentration in plasma

Venous blood was sampled to determine $C_{min, ss}$ of rivaroxaban on day 7 of administering a fixed dose of anticoagulant (at least 5 half-lives) immediately before the next dose of medicinal product. Determination of $C_{min, ss}$ of rivaroxaban in blood was performed by high-performance liquid chromatography with mass spectrometric detection. Samples were analysed on an Agilent 1200 liquid chromatograph (Agilent Technologies, USA) (four-channel pump, mobile phase degasser, chromatographic column thermostat). Agilent Extend-C18 column (Agilent Technologies, USA) (length 100 mm, inner diameter 2.1 mm, grain size 3.5 µm) was used in this study. The methodology is described in more detail in our previous study [14].

Laboratory tests

Venous blood for coagulogram determination, clinical blood count and urinalysis (morning portion) was collected at the same time as blood collection for measurement of $C_{min, ss}$ of rivaroxaban. Coagulogram was determined using an automatic coagulometer ACL Elite Pro (Instrumentation Laboratory, USA); clinical blood analysis was performed on a haematological analyser ADVIA® 2120i (Siemens, USA), biochemical blood analysis was performed using an integrated analyser for biochemical, immunochemical and electrolyte analysis Siemens Dimension X and Plus (Siemens, USA); total urine analysis was performed on an automated urine analyser Aution Max™ AX-4280 Automated Urine Chemistry Analyzer (ARKRAY Factory Inc., Russia). All studies were performed according to the manufacturer's instructions. The glomerular filtration rate was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [17].

Statistical data processing was performed in the IBM SPSS Statistics 26 software package (IMB Corp., USA). Sample description for non-normally distributed indicators was performed by calculating the median (Me) and interquartile range as the 25th and 75th percentiles (C25 and C75); for normally distributed indicators – by determining the mean (Mean) with standard deviation (SD, standard deviation). The normality of the distribution of the obtained parameters was evaluated using the Shapiro – Wilk criterion. For non-normally distributed indicators, the non-parametric Mann – Whitney U test was applied; categorical data were evaluated using Fisher's exact test, where differences are considered statistically significant at $p < 0.050$. To reduce the probability of occurrence of the first type errors in multiple comparisons, the statistical significance of differences was assessed with the Bonferroni correction, dividing the value of 0.05 by the number of comparisons (3) [18], with $p < 0.017$ considered to be the threshold value of statistical significance of differences.

RESULTS

Peculiarities of drug interaction between rivaroxaban and calcium channel blockers cause-specific to *ABCB1* (rs1045642) genotype

Cause-specific to the *ABCB1* genotype (rs1045642), patients were divided into three groups: group 1 – carriers of the wild-type CC genotype ($n = 22$); group 2 – carriers of the heterozygous CT genotype ($n = 65$); group 3 – carriers of the homozygous TT genotype ($n = 41$). Drug interactions were analysed within each group cause-specific to concomitant therapy: patients taking rivaroxaban without CCB were assumed to have no drug interactions; patients taking rivaroxaban + amlodipine DCCB had a potentially possible drug interaction caused by substrate competition for binding sites on cell membranes; in patients taking rivaroxaban + non-DCCB (verapamil), a strong P-gp inhibitor, these drugs may lead to drug interactions as a result of inhibition of the leading transport and metabolic pathways of rivaroxaban.

Group 1. Wild type (CC) carriers of the *ABCB1* gene (rs1045642)

We divided group 1 patients ($n = 22$) into subgroups cause-specific to concomitant therapy. Subgroup 1 – 7 patients taking rivaroxaban without CCB (median age – 91 [81.0–91.0] years; 71.4 % women); subgroup 2 – 11 patients taking rivaroxaban + amlodipine (median age – 89.0 [81.0–90.0] years; 90.9 % women); subgroup 3 – 4 patients taking rivaroxaban + verapamil (median age – 90.5 [85.3–93.5] years; 100 % women). The baseline characteristics of the patients included in the subgroups are presented in Table 1. Patients in subgroup 3 (rivaroxaban + verapamil) were more likely to have a history of stroke than patients in subgroup 1 (rivaroxaban without CCB). In other parameters, patients in the subgroups studied were comparable.

In patients carrying the wild-type (WS) *ABCB1* gene (rs1045642), the $C_{min, ss}$ levels of rivaroxaban were statistically significantly higher in subgroup 3 (rivaroxaban + verapamil) compared with subgroup 1 (rivaroxaban without CCB) ($p = 0.014$) and statistically significantly higher in subgroup 2 (rivaroxaban + amlodipine) compared with subgroup 1 ($p = 0.002$).

In subgroup 2 (rivaroxaban + amlodipine), the $C_{min, ss}$/D levels of rivaroxaban were statistically significantly higher than in subgroup 1 (rivaroxaban without CCB) ($p = 0.023$).

PT levels in subgroup 3 (rivaroxaban + verapamil) were higher than in subgroup 1, (rivaroxaban without CCB) and subgroup 2 (rivaroxaban + amlodipine), but without reaching statistical significance of differences $p = 0.059$ and $p = 0.358$, respectively) (Table 2).

Group 2. Heterozygous type (CT) carriers of the *ABCB1* gene (rs1045642)

We divided group 2 patients ($n = 65$) into 3 subgroups cause-specific to concomitant therapy. Subgroup 1 – 28 patients taking rivaroxaban without CCB (median age – 88.0 [84.0–90.0] years; 71.4 % women); subgroup 2 – 23 patients taking rivaroxaban + amlodipine (median age – 85.0 [83.0–88.0] years; 82.6 % of women); subgroup 3 – 14 patients taking rivaroxaban + verapamil (median age – 88.0 [81.0–89.3] years; 64.3 % of women). The baseline characteristics of the patients included in the subgroups are presented in Table 3. The patients in the study groups were comparable with respect to the main parameters.

Baseline characteristics of patients carrying the CT genotype of the *ABCB1* gene (rs1045642)

In patients carrying the heterozygous type (CT) of the *ABCB1* gene (rs1045642), the $C_{min, ss}$ levels of rivaroxaban were statistically significantly higher in subgroup 3 (rivaroxaban + verapamil) compared to subgroup 1 (rivaroxaban without CCB) ($p = 0.011$) and compared to subgroup 2 (rivaroxaban + amlodipine) ($p = 0.017$). Rivaroxaban $C_{min, ss}$/D levels were statistically significantly higher in subgroup 3 (rivaroxaban + verapamil) compared to subgroup 1 (rivaroxaban without CCB) ($p = 0.014$) (Table 4).

No differences in PT and the number of patients who experienced AR in the form of clinically significant minor

TABLE 1

BASELINE CHARACTERISTICS OF PATIENTS CARRYING THE CC GENOTYPE OF *ABCB1* GENE (rs1045642)

Indicators	CC genotype ($n = 22$) of the *ABCB1* gene (rs1045642)					
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	Rivaroxaban without CCB and rivaroxaban + amlodipine	Rivaroxaban and amlodipine and rivaroxaban + verapamil	*p* value
Number of patients, abs. (%)	7/22 (31.8)	11/22 (50)	4/22 (18.2)	18/22 (81.8)	15/22 (68.2)	–
Age (years), Me [C25–C75]	91.0 [81.0–91.0]	89.0 [81.0–90.0]	90.5 [85.3–93.5]	89.5 [81.0–91.0]	89.0 [84.0–91.0]	$p_4 = 0.596$ $p_5 = 0.315$ $p_6 = 0.280$ $p_7 = 0.262$ $p_8 = 1.000$
Women, abs. (%)	5/7 (71.4)	10/11 (90.9)	4/4 (100)	18/18 (100)	14/15 (93.3)	$p_4 = 0.280$ $p_5 = 0.237$ $p_6 = 0.533$ $p_7 = 0.380$ $p_8 = 0.163$
BMI (kg/m^2), Me [C25–C75]	27.2 [24.1–30.3]	25.6 [24.2–29.8]	29.3 [22.1–33.1]	25.6 [24.3–29.5]	26.5 [24.2–31.4]	$p_4 = 0.792$ $p_5 = 0.762$ $p_6 = 0.539$ $p_7 = 0.554$ $p_8 = 1.000$
Scale CHA_2DS_2-VASc (scores), Me [C25–C75]	5.0 [3.0–6.0]	6.0 [5.3–6.0]	7.0 [4.5–8.8]	6.0 [5.0–6.0]	6.0 [5.3–6.0]	$p_4 = 0.282$ $p_5 = 0.257$ $p_6 = 0.461$ $p_7 = 0.277$ $p_8 = 0.180$
HAS-BLED (scores), Me [C25–C75]	4.5 [3.0–6.0]	3.0 [3.0–3.8]	4.5 [3.0–5.0]	3.0 [3.0–6.0]	3.0 [3.0–4.0]	$p_4 = 0.081$ $p_5 = 0.762$ $p_6 = 0.073$ $p_7 = 0.382$ $p_8 = 0.151$

TABLE 1 (*continued*)

Number of MPs (scores), Me [C25–C75]	6.0 [5.0–8.0]	6.0 [5.0–9.0]	6.0 [5.3–7.5]	6.0 [5.0–8.3]	6.0 [5.0–8.0]	$p_4 = 1.000$ $p_5 = 1.000$ $p_6 = 0.851$ $p_7 = 0.837$ $p_8 = 1.000$
Number of MPs ≥ 5, abs. (%)	6/7 (85.7)	11/11 (100)	4/4 (100)	17/18 (94.4)	15/15 (100)	$p_4 = 0.197$ $p_5 = 0.428$ $p_6 = –$ $p_7 = 0.629$ $p_8 = 0.134$
Dose of rivaroxaban 15 mg, abs. (%)	6/7 (85.7)	9/11 (81.8)	3/4 (75)	15/18 (83.3)	12/15 (80)	$p_4 = 0.829$ $p_5 = 0.658$ $p_6 = 0.770$ $p_7 = 0.696$ $p_8 = 0.746$
Dose of rivaroxaban 20 mg, abs. (%)	1/7 (14.3)	2/11 (18.2)	1/4 (25)	3/18 (16.7)	3/15 (20)	$p_4 = 0.829$ $p_5 = 0.658$ $p_6 = 0.770$ $p_7 = 0.696$ $p_8 = 0.746$
Creatinine (μmol/L), Me [C25–C75]	96.8 [79.4–104.0]	97.4 [82.8–129.5]	91.8 [58.9–106.9]	97.3 [82.3–109.0]	96.4 [82.8–111.8]	$p_4 = 0.497$ $p_5 = 0.648$ $p_6 = 0.343$ $p_7 = 0.386$ $p_8 = 0.856$
Hemoglobin (g/L), Me [C25–C75]	116.0 [112.0–147.0]	118.0 [112.0–126.0]	120.5 [108.0–132.3]	117.0 [112.0–131.3]	118.0 [112.0–127.0]	$p_4 = 0.536$ $p_5 = 0.648$ $p_6 = 0.753$ $p_7 = 1.000$ $p_8 = 0.490$
Platelets (10^9/L), Me [C25–C75]	248.0 [191.0–263.0]	245.0 [192.0–305.0]	164.5 [156.0–254.8]	246.5 [191.8–271.5]	245.0 [188.0–283.0]	$p_4 = 0.536$ $p_5 = 0.527$ $p_6 = 0.078$ $p_7 = 0.141$ $p_8 = 0.837$
Comorbidities						
CHD, abs. (%)	7/7 (100)	11/11 (100)	4/4 (100)	18/18 (100)	15/15 (100)	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$
Effort-induced angina pectoris, abs. (%)	6/7 (85.7)	10/11 (90.9)	4/4 (100)	16/18 (88.9)	14/15 (93.3)	$p_4 = 0.732$ $p_5 = 0.428$ $p_6 = 0.360$ $p_7 = 0.533$ $p_8 = 1.000$
Heart failure, abs. (%)	7/7 (100)	11/11 (100)	4/4 (100)	18/18 (100)	15/15 (100)	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$
Arterial hypertension, abs. (%)	6/7 (85.7)	9/11 (81.8)	4/4 (100)	15/18 (83.3)	13/15 (86.7)	$p_4 = 0.829$ $p_5 = 0.428$ $p_6 = 0.360$ $p_7 = 0.380$ $p_8 = 0.952$
History of previous myocardial infarction, abs. (%)	2/7 (28.6)	9/11 (81.8)	2/4 (50)	8/18 (44.4)	8/15 (53.3)	$p_4 = 0.280$ $p_5 = 0.477$ $p_6 = 0.876$ $p_7 = 0.840$ $p_8 = 0.277$

TABLE 1 (*continued*)

ACVA (acute cerebrovascular accident) in past medical history, abs. (%)	0/7 (0)	2/11 (18.2)	3/4 (75)	2/18 (11.1)	5/15 (33.3)	$p_4 = 0.231$ $p_5 = 0.007$ $p_6 = 0.039$ $p_7 = 0.006$ $p_8 = 0.082$
Bronchial asthma, abs. (%)	0/7 (0)	0/11 (0)	1/4 (25)	0/18 (0)	1/15 (6.7)	$p_4 = –$ $p_5 = 0.165$ $p_6 = 0.086$ $p_7 = 0.030$ $p_8 = 0.484$
Lower extremity atherosclerosis, abs. (%)	0/7 (0)	0/11 (0)	1/4 (25)	0/18 (0)	1/15 (6.7)	$p_4 = –$ $p_5 = 0.165$ $p_6 = 0.086$ $p_7 = 0.030$ $p_8 = 0.484$
Chronic bronchitis, abs. (%)	3/7 (42.9)	4/11 (36.4)	0/4 (0)	7/18 (38.9)	4/15 (26.7)	$p_4 = 0.783$ $p_5 = 0.125$ $p_6 = 0.159$ $p_7 = 0.131$ $p_8 = 0.448$
Type 2 diabetes mellitus, abs. (%)	3/7 (42.9)	3/11 (27.3)	0/4 (0)	6/18 (33.3)	3/15 (20)	$p_4 = 0.494$ $p_5 = 0.125$ $p_6 = 0.243$ $p_7 = 0.176$ $p_8 = 0.262$
Charlson's comorbidity index (abs.), Me [C25–C75]	11.0 [9.0–12.0]	10.0 [9.0–12.0]	11.0 [10.3–14.0]	10 [9–12]	10.0 [9.0–12.0]	$p_4 = 0.860$ $p_5 = 0.527$ $p_6 = 0.280$ $p_7 = 0.300$ $p_8 = 0.945$
GFR (glomerular filtration rate) (CKD-EPI) (ml/min/1.73 m^2), Me [C25–C75]	45.8 [41.9–59.9]	44.1 [32.9–55.3]	47.2 [38.2–76.6]	44.1 [41.2–56.1]	44.8 [36.7–55.3]	$p_4 = 0.246$ $p_5 = 1.000$ $p_6 = 0.412$ $p_7 = 0.594$ $p_8 = 0.488$
CKD Stage 4 (GFR < 30 ml/min/1.73 m^2), abs. (%)	0/7 (0)	2/11 (18.2)	0	2/18 (11.1)	2/15 (13.3)	$p_4 = 0.231$ $p_5 = –$ $p_6 = 0.360$ $p_7 = 0.484$ $p_8 = 0.293$
GFR in CKD Stage 4 (ml/min/1.73 m^2), Me [C25–C75]	–	20.5 [19.5–20.5]	–	20.5 [19.5–20.5]	20.4 [19.5–20.4]	–
CKD Stage 3B (GFR = 30–44 ml/min/1.73 m^2), abs. (%)	3/7 (42.9)	5/11 (45.5)	1/4 (25)	8/18 (44.4)	5/15 (33.3)	$p_4 = 0.914$ $p_5 = 0.554$ $p_6 = 0.475$ $p_7 = 0.474$ $p_8 = 0.751$
GFR in CKD Stage 3B (ml/min/1.73 m^2), Me [C25–C75]	41.9 [40.4–41.9]	42.8 [37.9–44.1]	36.59	42.3 [39.4–44.1]	42.7 [36.6–44.1]	$p_4 = 1.000$ $p_5 = 0.500$ $p_6 = 0.333$ $p_7 = 0.222$ $p_8 = 1.000$
CKD Stage 3A (GFR = 45–59 ml/min/1.73 m^2), abs. (%)	2/7 (28.6)	3/11 (27.3)	2/4 (50)	5/18 (27.8)	5/15 (33.3)	$p_4 = 0.952$ $p_5 = 0.477$ $p_6 = 0.409$ $p_7 = 0.388$ $p_8 = 0.751$

TABLE 1 (*continued*)

GFR in CKD Stage 3A (ml/min/1.73 m^2), Me [C25–C75]	50.6 [45.8–50.6]	54.8 [45.5–54.8]	47.2 [45.9–47.2]	54.8 [45.6–56.1]	48.5 [45.7–55.8]	$p_4 = 1.000$ $p_5 = 1.000$ $p_6 = 1.000$ $p_7 = 0.857$ $p_8 = 0.293$
CKD Stage 2 (GFR = 60–89 ml/min/1.73 m^2), abs. (%)	1/7 (14.3)	1/11 (9.1)	1/4 (25)	2/18 (11.1)	2/15 (13.3)	$p_4 = 0.732$ $p_5 = 0.658$ $p_6 = 0.432$ $p_7 = 0.464$ $p_8 = 0.571$
GFR in CKD Stage 2 (ml/min/1.73 m^2), Me [C25–C75]	59.87	81.1	85.97	70.5 [59.9–70.5]	83.5 [81.1–83.5]	$p_4 = 1.000$ $p_5 = 1.000$ $p_6 = 1.000$ $p_7 = 1.000$ $p_8 = 1.000$
CKD Stage 1 (GFR ≥ 90 ml/min/1.73 m^2), abs. (%)	1/7 (14.3)	–	–	1/18 (5.6)	0/15 (0)	$p_4 = 0.197$ $p_5 = 0.428$ $p_6 = –$ $p_7 = 0.629$ $p_8 = 0.147$
GFR in CKD Stage 1 (ml/min/1.73 m^2), Me [C25–C75]	96.96	–	–	96.96	–	–

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_7 – differences between the group of patients taking rivaroxaban without CCBs + patients taking rivaroxaban in combination with DCCBs (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCBs (verapamil); p_8 – differences between the group of patients taking rivaroxaban without CCBs and the group of patients taking rivaroxaban in combination with all CCBs (amlodipine + verapamil); BMI – body mass index; CHA_2DS_2-VASc – scale for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65–74 years; Sex Category); HAS-BLED – scale for assessing the risk of bleeding in atrial fibrillation (Hypertension; Abnormal renal-liver function; Stroke; Bleeding history or predisposition; Labile international normalised ratio; Elderly (65 years); Drugs or alcohol concomitantly); CHD – coronary heart disease; ACVA – acute cerebrovascular accident.

TABLE 2

PECULIARITIES OF DRUG INTERACTION IN PATIENTS CARRYING THE CC GENOTYPE OF THE *ABCB1* GENE (rs1045642)

Indicators	CC genotype ($n = 22$) of the *ABCB1* gene (rs1045642)			*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	
Number of patients, abs. (%)	7/22 (31.8)	11/22 (50)	4/22 (18.2)	–
$C_{min, ss}$ of rivaroxaban (ng/ml), Me [C25–C75]	15.3 [12.0–28.4]	69.4 [45.6–100.8]	67.8 [45.0–76.9]	$p_4 = 0.002$ $p_5 = 0.014$ $p_6 = 0.602$
$C_{min, ss}$/D of rivaroxaban (ng/ml/mg), Me [C25–C75]	1.0 [0.8–1.9]	4.6 [3.0–6.4]	4.0 [2.8–5.1]	$p_4 = 0.003$ $p_5 = 0.023$ $p_6 = 0.647$
Prothrombin time (s), Me [C25–C75]	12.6 [12.3–13.8]	13.4 [12.3–14.5]	14.2 [12.9–18.3]	$p_4 = 0.388$ $p_5 = 0.059$ $p_6 = 0.358$
Data on all clinically significant minor bleeding in response to rivaroxaban by history, abs. (%)	1/7 (14.3)	0/11 (0)	0/4 (0)	$p_4 = 0.197$ $p_5 = 0.428$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil).

bleeding were observed between the compared subgroups ($p > 0.017$) (Table 4).

Group 3. Homozygous type (TT) carriers of the *ABCB1* gene (rs1045642)

We divided patients in group 3 ($n = 41$) into 3 subgroups cause-specific to concomitant therapy. Subgroup 1 – 12 patients taking rivaroxaban without CCB (median age – 88.0 [83.0–88.8] years; 75 % women); subgroup 2 – 17 patients taking rivaroxaban + amlodipine (median age – 86.0 [82.0–88.0] years; 88.2 % women); subgroup 3 – 12 patients taking rivaroxaban + verapamil (median age – 89.5 [85.5–92.0] years; 41.7 % women). The baseline characteristics of the patients inclu-

TABLE 3

BASELINE CHARACTERISTICS OF PATIENTS CARRYING THE CT GENOTYPE OF THE *ABCB1* GENE (rs1045642)

Indicators	CT genotype ($n = 65$) of the *ABCB1* gene (rs1045642)					
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	Rivaroxaban without CCB and rivaroxaban + amlodipine	Rivaroxaban and amlodipine and rivaroxaban + verapamil	*p* value
Number of patients, abs. (%)	28/65 (43.1)	23/65 (35.4)	14/65 (21.5)	51/65 (78.5)	37/65 (56.9)	–
Age (years), Me [C25–C75]	88.0 [84.0–90.0]	85.0 [83.0–88.0]	88.0 [81.0–89.3]	87 [83–90]	86.0 [82.0–89.0]	$p_4 = 0.243$ $p_5 = 0.308$ $p_6 = 0.865$ $p_7 = 0.481$ $p_8 = 0.184$
Women, abs. (%)	20/28 (71.4)	19/23 (82.6)	9/14 (64.3)	39/51 (76.5)	28/37 (75.7)	$p_4 = 0.349$ $p_5 = 0.637$ $p_6 = 0.208$ $p_7 = 0.358$ $p_8 = 0.700$
BMI (kg/m^2), Me [C25–C75]	28.5 [26.0–31.1]	30.5 [26.9–32.3]	30.0 [25.4–32.0]	30.1 [26.2–31.2]	30.5 [26.6–32.1]	$p_4 = 0.271$ $p_5 = 0.424$ $p_6 = 0.624$ $p_7 = 0.805$ $p_8 = 0.237$
Scale CHA_2DS_2-VASc (scores), Me [C25–C75]	6.0 [5.0–7.0]	6.0 [5.0–7.3]	7.0 [5.0–8.0]	6 [5–7]	8.0 [5.0–8.0]	$p_4 = 0.321$ $p_5 = 0.145$ $p_6 = 0.531$ $p_7 = 0.244$ $p_8 = 0.157$
HAS-BLED (scores), Me [C25–C75]	3.0 [2.0–4.0]	3.0 [3.0–3.5]	3.0 [2.0–4.0]	3 [2–4]	3.0 [2.5–4.0]	$p_4 = 0.812$ $p_5 = 0.945$ $p_6 = 0.932$ $p_7 = 0.923$ $p_8 = 0.866$
Number of MPs (scores), Me [C25–C75]	6.0 [5.0–7.0]	8.0 [6.0–9.0]	6.0 [5.8–7.0]	6 [5–8]	7.0 [6.0–8.0]	$p_4 = 0.03$ $p_5 = 0.452$ $p_6 = 0.028$ $p_7 = 0.506$ $p_8 = 0.012$
Number of MPs ≥ 5, abs. (%)	23/28 (82.1)	22/23 (95.7)	12/14 (85.7)	45/51 (88.2)	34/37 (91.9)	$p_4 = 0.136$ $p_5 = 0.770$ $p_6 = 0.283$ $p_7 = 0.799$ $p_8 = 0.124$
Dose of rivaroxaban 15 mg, abs. (%)	25/28 (89.3)	19/23 (82.6)	13/14 (92.9)	44/51 (86.3)	32/37 (86.5)	$p_4 = 0.491$ $p_5 = 0.710$ $p_6 = 0.377$ $p_7 = 0.507$ $p_8 = 0.734$
Dose of rivaroxaban 20 mg, abs. (%)	3/28 (10.7)	4/23 (17.4)	1/14 (7.1)	7/51 (13.7)	4/37 (10.8)	$p_4 = 0.491$ $p_5 = 0.710$ $p_6 = 0.377$ $p_7 = 0.507$ $p_8 = 0.990$

TABLE 3 (*continued*)

Creatinine (μmol/L), Me [C25–C75]	108.0 [92.9–130.8]	94.8 [86.0–110.0]	99.6 [83.4–117.5]	101 [90.3–123]	97.0 [85.8–113.5]	$p_4 = 0.065$ $p_5 = 0.249$ $p_6 = 0.963$ $p_7 = 0.503$ $p_8 = 0.061$
Hemoglobin (g/L), Me [C25–C75]	123.0 [112.5–135.3]	125.0 [11.0–132.0]	127.0 [116.5–134.3]	125 [112–133]	125.0 [112.0–133.0]	$p_4 = 0.726$ $p_5 = 0.823$ $p_6 = 0.506$ $p_7 = 0.626$ $p_8 = 0.895$
Platelets (10^9/L), Me [C25–C75]	222.0 [165.3–260.3]	217.0 [190.0–293.0]	203.0 [169.5–257.5]	219 [175–264]	215.0 [176.0–274.0]	$p_4 = 0.449$ $p_5 = 0.947$ $p_6 = 0.546$ $p_7 = 0.714$ $p_8 = 0.624$
Comorbidities						
CHD, abs. (%)	28/28 (100)	23/23 (100)	14/14 (100)	51/51 (100)	37/37 (100)	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$
Effort-induced angina pectoris, abs. (%)	24/28 (85.7)	20/23 (87.0)	12/14 (85.7)	44/51 (86.3)	32/37 (86.5)	$p_4 = 0.898$ $p_5 = 1.000$ $p_6 = 0.915$ $p_7 = 0.957$ $p_8 = 0.929$
Heart failure, abs. (%)	27/28 (96.4)	21/23 (91.3)	12/14 (85.7)	48/51 (94.1)	33/37 (89.2)	$p_4 = 0.439$ $p_5 = 0.204$ $p_6 = 0.595$ $p_7 = 0.296$ $p_8 = 0.278$
Arterial hypertension, abs. (%)	27/28 (96.4)	22/23 (95.7)	13/14 (92.9)	49/51 (96.1)	35/37 (94.6)	$p_4 = 0.887$ $p_5 = 0.608$ $p_6 = 0.715$ $p_7 = 0.611$ $p_8 = 0.727$
History of previous myocardial infarction, abs. (%)	5/28 (17.9)	4/23 (17.4)	2/14 (14.3)	9/51 (17.6)	6/37 (16.2)	$p_4 = 0.965$ $p_5 = 0.770$ $p_6 = 0.804$ $p_7 = 0.766$ $p_8 = 0.861$
ACVA (acute cerebrovascular accident) in past medical history, abs. (%)	6/28 (21.4)	5/23 (21.7)	3/14 (21.4)	11/51 (21.6)	8/37 (21.6)	$p_4 = 0.979$ $p_5 = 1.000$ $p_6 = 0.982$ $p_7 = 0.991$ $p_8 = 0.985$
Bronchial asthma, abs. (%)	0/28 (0)	1/23 (4.3)	2/14 (14.3)	1/51 (2)	3/37 (8.1)	$p_4 = 0.265$ $p_5 = 0.040$ $p_6 = 0.283$ $p_7 = 0.052$ $p_8 = 0.123$
Lower extremity atherosclerosis, abs. (%)	3/28 (10.7)	5/23 (21.7)	3/14 (21.4)	8/51 (15.7)	8/37 (21.6)	$p_4 = 0.281$ $p_5 = 0.350$ $p_6 = 0.982$ $p_7 = 0.612$ $p_8 = 0.246$
Chronic bronchitis, abs. (%)	10/28 (35.7)	8/23 (34.8)	6/14 (42.9)	18/51 (35.3)	14/37 (37.8)	$p_4 = 0.045$ $p_5 = 0.653$ $p_6 = 0.623$ $p_7 = 0.603$ $p_8 = 0.861$
Type 2 diabetes mellitus, abs. (%)	8/28 (28.6)	7/23 (30.4)	4/14 (28.6)	15/51 (29.4)	11/37 (29.7)	$p_4 = 0.884$ $p_5 = 1.000$ $p_6 = 0.904$ $p_7 = 0.951$ $p_8 = 0.919$

TABLE 3 (*continued*)

Charlson's comorbidity index (abs.), Me [C25–C75]	10.0 [9.0–11.0]	10.0 [9.0–12.0]	10.0 [9.0–12.0]	10 [9–11]	10.0 [9.0–12.0]	$p_4 = 0.869$ $p_5 = 0.927$ $p_6 = 0.841$ $p_7 = 0.864$ $p_8 = 0.946$
GFR (glomerular filtration rate) (CKD-EPI) (ml/min/1.73 m^2), Me [C25–C75]	42.8 [36.0–49.8]	46.5 [40.5–54.2]	51.7 [36.8–56.1]	48.0 [37.1–57.6]	47.8 [38.9–54.4]	$p_4 = 0.153$ $p_5 = 0.119$ $p_6 = 0.632$ $p_7 = 0.231$ $p_8 = 0.075$
CKD Stage 4 (GFR < 30 ml/min/1.73 m^2), abs. (%)	2/28 (7.1)	2/23 (8.7)	1/14 (7.1)	4/51 (7.8)	4/37 (10.8)	$p_4 = 0.837$ $p_5 = 1.000$ $p_6 = 0.867$ $p_7 = 0.931$ $p_8 = 0.990$
GFR in CKD Stage 4 (ml/min/1.73 m^2), Me [C25–C75]	24.3 [19.3–24.3]	27.0 [24.6–27.0]	26.4	26.9 [20.7–29.4]	27.8 [25.0–29.6]	$p_4 = 0.667$ $p_5 = 1.000$ $p_6 = 1.000$ $p_7 = 1.000$ $p_8 = 0.857$
CKD Stage 3B (GFR = 30–44 ml/min/1.73 m^2), abs. (%)	13/28 (46.4)	7/23 (30.4)	4/14 (64.3)	20/51 (39.2)	10/37 (27.0)	$p_4 = 0.244$ $p_5 = 0.116$ $p_6 = 0.550$ $p_7 = 0.218$ $p_8 = 0.182$
GFR in CKD Stage 3B (ml/min/1.73 m^2), Me [C25–C75]	37.8 [32.5–39.1]	40.5 [33.2–41.9]	36.12 [34.3–42.8]	37.8 [32.9–41.6]	38.9 [34.6–42.1]	$p_4 = 0.485$ $p_5 = 0.521$ $p_6 = 0.517$ $p_7 = 0.457$ $p_8 = 0.497$
CKD Stage 3A (GFR = 45–59 ml/min/1.73 m^2), abs. (%)	12/28 (42.9)	11/23 (47.8)	9/14 (64.3)	23/51 (45.1)	19/37 (51.4)	$p_4 = 0.723$ $p_5 = 0.190$ $p_6 = 0.330$ $p_7 = 0.203$ $p_8 = 0.497$
GFR in CKD Stage 3A (ml/min/1.73 m^2), Me [C25–C75]	49.3 [46.4–53.1]	50.5 [46.6–54.2]	53.9 [47.9–56.4]	50.3 [46.6–53.7]	52.6 [47.8–54.9]	$p_4 = 0.525$ $p_5 = 0.247$ $p_6 = 0.412$ $p_7 = 0.246$ $p_8 = 0.177$
CKD Stage 2 (GFR = 60–89 ml/min/1.73 m^2), abs. (%)	1/28 (3.6)	3/23 (13)	1/14 (7.1)	4/51 (7.8)	4/37 (10.8)	$p_4 = 0.211$ $p_5 = 0.608$ $p_6 = 0.575$ $p_7 = 0.931$ $p_8 = 0.278$
GFR in CKD Stage 2 (ml/min/1.73 m^2), Me [C25–C75]	62.37	68.0 [63.3–68.0]	66.76	65.6 [62.6–71.7]	67.4 [64.1–71.7]	$p_4 = 0.500$ $p_5 = 1.000$ $p_6 = 1.000$ $p_7 = 1.000$ $p_8 = 0.400$
CKD Stage 1 (GFR ≥ 90 ml/min/1.73 m^2), abs. (%)	0/28 (100)	0/23 (0)	0/14 (0)	0/51 (0)	0/37 (0)	–
GFR in CKD Stage 1 (ml/min/1.73 m^2), Me [C25–C75]	–	–	–	–		–

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_7 – differences between the group of patients taking rivaroxaban without CCBs + patients taking rivaroxaban in combination with DCCBs (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCBs (verapamil); p_8 – differences between the group of patients taking rivaroxaban without CCBs and the group of patients taking rivaroxaban in combination with all CCBs (amlodipine + verapamil); BMI – body mass index; CHA_2DS_2-VASc – scale for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65–74 years; Sex Category); HAS-BLED – scale for assessing the risk of bleeding in atrial fibrillation (Hypertension; Abnormal renal-liver function; Stroke; Bleeding history or predisposition; Labile international normalised ratio; Elderly (65 years); Drugs or alcohol concomitantly); CHD – coronary heart disease; ACVA – acute cerebrovascular accident.

ded in the subgroups are presented in Table 5. Patients in subgroup 3 (rivaroxaban + verapamil) had more men than patients in subgroup 2 (rivaroxaban + amlodipine); they were also more likely than patients in subgroup 1 (rivaroxaban without CCB) to have lower extremity atherosclerosis and had a higher Charlson comorbidity index. In other parameters, patients in the subgroups studied were comparable.

Patients carrying homozygous type (TT) of *ABCB1* gene (rs1045642) had baseline higher values of $C_{min, ss}$ of rivaroxaban, $C_{min, ss}$/D of rivaroxaban and PT, and no differences were found between the compared subgroups in these parameters ($p > 0.017$) (Table 6).

Along with this AR in the form of clinically significant minor bleeding occurred in 75 % (!) of cases in subgroup 3 (rivaroxaban + verapamil), and this rate was statistically significantly higher in comparison with subgroup 1 (rivaroxaban without CCB) ($p = 0.001$), and in comparison with subgroup 2 (rivaroxaban + amlodipine) ($p = 0.001$) (Table 6).

Peculiarities of drug interaction between rivaroxaban and calcium channel blockers cause-specific to *ABCB1* (rs4148738) genotype

Cause-specific to the *ABCB1* genotype (rs4148738), patients were divided into three groups: group 1 – carriers of the wild-type CC genotype ($n = 37$); group 2 – carriers of the heterozygous ST genotype ($n = 63$); group 3 – carriers of the homozygous TT genotype ($n = 28$). Drug interaction analyses were performed within each group cause-specific to concomitant therapy, in the same manner as for the previous polymorphism.

TABLE 4

PECULIARITIES OF DRUG INTERACTION IN PATIENTS CARRYING THE CT GENOTYPE OF THE *ABCB1* GENE (rs1045642)

Indicators	CT genotype ($n = 65$) of the *ABCB1* gene (rs1045642)			*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	
Number of patients, abs. (%)	28/65 (43.1)	23/65 (35.4)	14/65 (21.5)	–
$C_{min, ss}$ of rivaroxaban (ng/ml), Me [C25–C75]	41.7 [25.7–70.7]	48.6 [28.2–65.5]	90.7 [51.7–140.8]	$p_4 = 0.910$ $p_5 = 0.011$ $p_6 = 0.017$
$C_{min, ss}$/D of rivaroxaban (ng/ml/mg), Me [C25–C75]	2.7 [1.7–4.0]	3.2 [1.9–4.0]	6.1 [3.2–9.4]	$p_4 = 1.000$ $p_5 = 0.014$ $p_6 = 0.020$
Prothrombin time (s), Me [C25–C75]	14.0 [12.6–14.6]	13.2 [12.6–14.3]	14.6 [13.2–16.1]	$p_4 = 0.602$ $p_5 = 0.157$ $p_6 = 0.121$
Data on all clinically significant minor bleeding in response to rivaroxaban by history, abs. (%)	4/28 (14.3)	5/23 (21.7)	1/14 (7.1)	$p_4 = 0.487$ $p_5 = 0.500$ $p_6 = 0.243$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil).

TABLE 5

BASELINE CHARACTERISTICS OF PATIENTS CARRYING THE TT GENOTYPE OF *ABCB1* GENE (rs1045642)

Indicators	TT genotype ($n = 41$) of the *ABCB1* gene (rs1045642)					*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	Rivaroxaban without CCB and rivaroxaban + amlodipine	Rivaroxaban and amlodipine and rivaroxaban + verapamil	
Number of patients, abs. (%)	12/41 (29.3)	17/41 (41.4)	12/41 (29.3)	29/41 (70.7)	29/41 (70.7)	–
Age (years), Me [C25–C75]	88.0 [83.0–88.8]	86.0 [82.0–88.0]	89.5 [85.5–92.0]	87 [82–88]	87.0 [83.0–90.0]	$p_4 = 0.394$ $p_5 = 0.319$ $p_6 = 0.08$ $p_7 = 0.106$ $p_8 = 0.944$

TABLE 5 (*continued*)

Women, abs. (%)	9/12 (75)	15/17 (88.2)	5/12 (41.7)	24/29 (82.8)	20/29 (69.0)	$p_4 = 0.353$ $p_5 = 0.098$ $p_6 = 0.008$ $p_7 = 0.009$ $p_8 = 0.699$
BMI (kg/m^2), Me [C25–C75]	26.6 [23.5–33.0]	27.5 [24.3–31.6]	25.6 [24.2–29.4]	27.4 [24.3–31.9]	26.9 [24.3–30.9]	$p_4 = 0.909$ $p_5 = 0.630$ $p_6 = 0.260$ $p_7 = 0.328$ $p_8 = 0.873$
Scale CHA_2DS_2-VASc (scores), Me [C25–C75]	6.0 [5.0–7.0]	6.0 [5.3–7.5]	6.0 [5.0–6.0]	6 [5–7]	6.0 [5.0–6.0]	$p_4 = 0.762$ $p_5 = 0.863$ $p_6 = 0.657$ $p_7 = 0.707$ $p_8 = 0.946$
HAS-BLED (scores), Me [C25–C75]	3.0 [2.0–4.0]	3.0 [3.0–4.0]	3.0 [2.0–4.0]	3 [2.5–4]	3.0 [3.0–4.0]	$p_4 = 0.606$ $p_5 = 0.941$ $p_6 = 0.442$ $p_7 = 0.611$ $p_8 = 0.847$
Number of MPs (scores), Me [C25–C75]	6.0 [4.3–7.0]	7.0 [5.5–8.5]	7.0 [4.0–8.8]	6.0 [5.0–8.0]	7.0 [5.0–8.5]	$p_4 = 0.166$ $p_5 = 0.755$ $p_6 = 0.444$ $p_7 = 0.724$ $p_8 = –$
Number of MPs ≥ 5, abs. (%)	9/12 (75)	16/17 (94.1)	7/12 (58.3)	25/29 (86.2)	23/29 (79.3)	$p_4 = 0.141$ $p_5 = 0.386$ $p_6 = 0.019$ $p_7 = 0.05$ $p_8 = 0.762$
Dose of rivaroxaban 15 mg, abs. (%)	9/12 (75)	16/17 (94.1)	11/12 (91.7)	25/29 (86.2)	27/29 (93.1)	$p_4 = 0.141$ $p_5 = 0.273$ $p_6 = 0.798$ $p_7 = 0.627$ $p_8 = 0.107$
Dose of rivaroxaban 20 mg, abs. (%)	3/12 (25)	1/17 (5.9)	1/12 (8.3)	4/29 (13.8)	2/29 (6.9)	$p_4 = 0.141$ $p_5 = 0.273$ $p_6 = 0.798$ $p_7 = 0.627$ $p_8 = 0.107$
Creatinine (μmol/l), Me [C25–C75]	97.4 [80.5–121.8]	92.7 [79.7–120.5]	107 [94–137]	97.0 [79.7–121.5]	97.9 [87.9–120.5]	$p_4 = 0.744$ $p_5 = 0.378$ $p_6 = 0.097$ $p_7 = 0.127$ $p_8 = 0.810$
Hemoglobin (g/l), Me [C25–C75]	133.0 [94.0–138.0]	127.0 [119.5–132.0]	111 [106–119]	128.0 [119.0–133.8]	121.0 [111.0–130.0]	$p_4 = 0.547$ $p_5 = 0.211$ $p_6 = 0.007$ $p_7 = 0.016$ $p_8 = 0.308$
Platelets (10^9/l), Me [C25–C75]	239.0 [198.0–293.0]	239.0 [190.0–313.5]	221.0 [177.3–279.0]	239.0 [194.3–297.5]	226.0 [180.5–291.5]	$p_4 = 0.926$ $p_5 = 0.413$ $p_6 = 0.444$ $p_7 = 0.358$ $p_8 = 0.654$
Comorbidities						
CHD, abs. (%)	11/12 (91.7)	17/17 (100)	12/12 (100)	28/29 (96.6)	29/29 (100)	$p_4 = 0.226$ $p_5 = 0.307$ $p_6 = –$ $p_7 = 0.515$ $p_8 = 0.116$
Effort-induced angina pectoris, abs. (%)	8/12 (66.7)	10/17 (58.8)	9/12 (75)	18/29 (62.1)	19/29 (65.5)	$p_4 = 0.668$ $p_5 = 0.653$ $p_5 = 0.367$ $p_7 = 0.427$ $p_8 = 0.944$

TABLE 5 (*continued*)

Heart failure, abs. (%)	11/12 (91.7)	16/17 (94.1)	11/12 (91.7)	27/29 (93.1)	27/29 (93.1)	$p_4 = 0.798$ $p_5 = 1.000$ $p_6 = 0.798$ $p_7 = 0.872$ $p_8 = 0.872$
Arterial hypertension, abs. (%)	12/12 (100)	17/17 (100)	10/12 (83.3)	29/29 (100)	27/29 (93.1)	$p_4 = –$ $p_5 = 0.140$ $p_6 = 0.081$ $p_7 = 0.024$ $p_8 = 0.351$
History of previous myocardial infarction, abs. (%)	5/12 (41.7)	4/17 (23.5)	5/12 (41.7)	9/29 (31)	9/29 (31)	$p_4 = 0.298$ $p_5 = 1.000$ $p_6 = 0.298$ $p_7 = 0.514$ $p_8 = 0.514$
ACVA (acute cerebrovascular accident) in past medical history, abs. (%)	0/12 (0)	6/17 (35.3)	3/12 (25)	6/29 (20.7)	9/29 (31)	$p_4 = 0.021$ $p_5 = 0.064$ $p_6 = 0.555$ $p_7 = 0.762$ $p_8 = 0.029$
Bronchial asthma, abs. (%)	1/12 (8.3)	1/17 (5.9)	3/12 (25)	2/29 (6.9)	4/29 (13.8)	$p_4 = 0.798$ $p_5 = 0.273$ $p_6 = 0.141$ $p_7 = 0.107$ $p_8 = 0.627$
Lower extremity atherosclerosis, abs. (%)	0/12 (0)	6/17 (35.3)	5/12 (41.7)	6/29 (20.7)	11/29 (37.9)	$p_4 = 0.021$ $p_5 = 0.012$ $p_6 = 0.728$ $p_7 = 0.168$ $p_8 = 0.013$
Chronic bronchitis, abs. (%)	5/12 (41.7)	3/17 (17.6)	3/12 (25)	8/29 (27.6)	6/29 (20.7)	$p_4 = 0.154$ $p_5 = 0.386$ $p_6 = 0.630$ $p_7 = 0.865$ $p_8 = 0.168$
Type 2 diabetes mellitus, abs. (%)	1/12 (8.3)	5/17 (29.4)	2/12 (16.7)	6/29 (20.7)	7/29 (24.1)	$p_4 = 0.168$ $p_5 = 0.537$ $p_6 = 0.430$ $p_7 = 0.767$ $p_8 = 0.245$
Charlson's comorbidity index (abs.), Me [C25-C75]	9.0 [9.0–10.0]	10.0 [9.0–11.5]	11.5 [10.0–13.8]	9 [9–11]	10.0 [9.0–12.0]	$p_4 = 0.471$ $p_5 = 0.008$ $p_5 = 0.048$ $p_7 = 0.01$ $p_8 = 0.083$
GFR (glomerular filtration rate) (CKD-EPI) (ml/min/1.73 m^2), Me [C25-C75]	47.9 [39.0–59.4]	49.5 [35.3–55.5]	47.4 [39.3–52.5]	48.0 [37.1–57.6]	47.9 [37.4–53.7]	$p_4 = 1.000$ $p_5 = 0.843$ $p_6 = 0.948$ $p_7 = 0.877$ $p_8 = 0.899$
CKD Stage 4 (GFR < 30 ml/min/1.73 m^2), abs. (%)	0/12 (0)	1/17 (5.9)	1/12 (8.3)	1/29 (3.4)	2/29 (6.9)	$p_4 = 0.393$ $p_5 = 0.328$ $p_6 = 0.798$ $p_7 = 0.509$ $p_8 = 0.351$
GFR in CKD Stage 4 (ml/min/1.73 m^2), Me [C25–C75]	–	28.6	26.8	28.6	27.7 [26.8–27.7]	$p_4 = –$ $p_5 = –$ $p_6 = 1.000$ $p_7 = 1.000$ $p_8 = 0.351$
CKD Stage 3B (GFR = 30–44 ml/min/1.73 m^2), abs. (%)	5/12 (41.7)	5/17 (29.4)	3/12 (25)	10/29 (34.5)	8/29 (27.6)	$p_4 = 0.494$ $p_5 = 0.304$ $p_6 = 0.793$ $p_7 = 0.553$ $p_8 = 0.378$

TABLE 5 (*continued*)

GFR in CKD Stage 3B (ml/min/1.73 m^2), Me [C25–C75]	38.6 [34.5–41.7]	35.1 [33.1–38.3]	38.4 [36.4–38.4]	35.3 [34.5–40.5]	35.9 [34.7–40.4]	$p_4 = 0.548$ $p_5 = 1.000$ $p_6 = 0.143$ $p_7 = 0.371$ $p_8 = 0.378$
CKD Stage 3A (GFR = 45–59 ml/min/1.73 m^2), abs. (%)	5/12 (41.7)	9/17 (52.9)	7/12 (58.3)	14/29 (48.3)	16/29 (55.2)	$p_4 = 0.550$ $p_5 = 0.292$ $p_6 = 0.774$ $p_7 = 0.558$ $p_8 = 0.431$
GFR in CKD Stage 3A (ml/min/1.73 ^{2}), Me [C25–C75]	48.2 [47.9–59.3]	51.3 [47.9–54.1]	51.9 [46.8–52.5]	51.2 [47.9–55.5]	51.5 [47.5–54.3]	$p_4 = 0.833$ $p_5 = 0.530$ $p_5 = 1.000$ $p_7 = 0.699$ $p_8 = 0.431$
CKD Stage 2 (GFR = 60–89 ml/min/1.73 m^2), abs. (%)	2/12 (16.7)	2/17 (11.8)	1/12 (8.3)	4/29 (13.8)	3/29 (10.3)	$p_4 = 0.706$ $p_5 = 0.484$ $p_6 = 0.765$ $p_7 = 0.627$ $p_8 = 0.574$
GFR in CKD Stage 2 (ml/min/1.73 m^2), Me [C25–C75]	61.6 [61.1–61.6]	65.1 [59.7–65.1]	64.19	62.1 [60.4–65.3]	65.1 [64.2–65.1]	$p_4 = 0.800$ $p_5 = 0.667$ $p_6 = 1.000$ $p_7 = 1.000$ $p_8 = 0.574$
CKD Stage 1 (GFR ≥ 90 ml/min/1.73 m^2), abs. (%)	–	–	–	–	–	–
GFR in CKD Stage 1 (ml/min/1.73 m^2), Me [C25–C75]	–	–	–	–	–	–

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_7 – differences between the group of patients taking rivaroxaban without CCBs + patients taking rivaroxaban in combination with DCCBs (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCBs (verapamil); p_8 – differences between the group of patients taking rivaroxaban without CCBs and the group of patients taking rivaroxaban in combination with all CCBs (amlodipine + verapamil); BMI – body mass index; CHA_2DS_2-VASc – scale for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65–74 years; Sex Category); HAS-BLED – scale for assessing the risk of bleeding in atrial fibrillation (Hypertension; Abnormal renal-liver function; Stroke; Bleeding history or predisposition; Labile international normalised ratio; Elderly (65 years); Drugs or alcohol concomitantly); CHD – coronary heart disease; ACVA – acute cerebrovascular accident.

TABLE 6

PECULIARITIES OF DRUG INTERACTION IN PATIENTS-CARRIERS OF TT GENOTYPE OF *ABCB1* GENE (rs1045642)

Indicators	TT genotype (n = 41) of the *ABCB1* gene (rs1045642)			*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	
Number of patients, abs. (%)	12/41 (29.3)	17/41 (41.4)	12/41 (29.3)	–
$C_{min, ss}$ of rivaroxaban (ng/ml), Me [C25–C75]	57.5 [36.3–91.2]	63.5 [33.5–114.5]	71.2 [33.7–89.1]	$p_4 = 0.859$ $p_5 = 0.908$ $p_6 = 0.912$
$C_{min, ss}$/D of rivaroxaban (ng/ml/mg), Me [C25–C75]	3.6 [2.2–5.7]	4.2 [2.2–7.1]	4.6 [2.3–5.4]	$p_4 = 0.690$ $p_5 = 0.603$ $p_6 = 0.912$
Prothrombin time (s), Me [C25–C75]	14.1 [13.5–14.5]	14.0 [12.4–15.8]	15.9 [13.4–17.8]	$p_4 = 0.842$ $p_5 = 0.126$ $p_6 = 0.066$
Data on all clinically significant minor bleeding in response to rivaroxaban by history, abs. (%)	1/12 (8.3)	2/17 (11.8)	9/12 (75)	$p_4 = 0.765$ $p_5 = 0.001$ $p_6 = 0.001$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil).

Group 1. Wild-type (CC) carriers of the *ABCB1* gene (rs4148738)

We divided group 1 patients (n = 37) into subgroups cause-specific to concomitant therapy. Subgroup 1 – 14 patients taking rivaroxaban without CCB (median age – 88.0 [83.3–91.0] years; 71.4 % women); subgroup 2 – 14 patients taking rivaroxaban + amlodipine (median age – 88.0 [82.8–90.3] years; 85.7 % women); subgroup 3 – 9 patients taking rivaroxaban + verapamil (median age – 89.0 [81.0–92.0] years; 66.7 % women). The baseline characterization of patients according to rs4148738 (*ABCB1*) genotype is presented in Table 7. The patients in the study groups were comparable with respect to the main parameters.

Among wild-type (CC) carriers of the *ABCB1* gene (rs4148738), the $C_{min, ss}$ level of rivaroxaban was statistically significantly higher in the group of patients taking rivaroxaban + verapamil compared with the group of patients taking rivaroxaban without CCB (Me 77.6 [47.4–115.3] vs. 29.4 [14.5–61.9] ng/ml; $p = 0.014$). The $C_{min, ss}$/D levels of rivaroxaban were higher in the group of patients receiving rivaroxaban + verapamil than in the group of patients not administering CCB in combination with rivaroxaban, but without reaching statistical significance (Me 5.2 [2.3–7.7] vs. 2.0 [1.0–3.8] ng/ml/mg; $p = 0.020$). No statistically significant differences were found in the PT rate and the number of patients who experienced AR in the form of clinically significant small bleedings between the compared groups ($p > 0.017$) (Table 8).

Group 2. Heterozygous type (CT) carriers of the *ABCB1* gene (rs4148738)

We divided group 2 patients (n = 63) into subgroups cause-specific to concomitant therapy. Subgroup 1 – 24 patients taking rivaroxaban without CCB (median age – 88.0 [83.0–91.0] years; 70.8 % women); subgroup 2 – 27 patients taking rivaroxaban + amlodipine (median age – 86.0 [83.0–88.0] years; 81.5 % women); subgroup 3 –

TABLE 7

BASELINE CHARACTERISTICS OF PATIENTS CARRYING THE CC GENOTYPE OF THE *ABCB1* GENE (rs4148738)

Indicators	CC genotype (n = 37) of the *ABCB1* gene (rs4148738)					
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	Rivaroxaban without CCB and rivaroxaban + amlodipine	Rivaroxaban and amlodipine and rivaroxaban + verapamil	p value
Number of patients, abs. (%)	14/37 (37.85)	14/37 (37.85)	9/37 (24.3)	28/37 (75.7)	23/37 (62.2)	–
Age (years), Me [C25–C75]	88.0 [83.3–91.0]	88.0 [82.8–90.3]	89.0 [81.0–92.0]	88.0 [83.3–90.75]	88.0 [82.0–91.0]	$p_4 = 0.982$ $p_5 = 0.975$ $p_6 = 0.926$ $p_7 = 0.931$ $p_8 = 0.963$
Women, abs. (%)	10/14 (71.4)	12/14 (85.7)	6/9 (66.7)	22/28 (78.6)	18/23 (78.3)	$p_4 = 0.357$ $p_5 = 0.809$ $p_6 = 0.280$ $p_7 = 0.469$ $p_8 = 0.639$
BMI (kg/m^2), Me [C25–C75]	29.1 [25.3–30.7]	28.6 [25.6–31.9]	28.6 [23.6–30.9]	29.1 [25.4–31.2]	28.6 [25.6–31.5]	$p_4 = 0.894$ $p_5 = 0.804$ $p_6 = 0.851$ $p_7 = 0.789$ $p_8 = 0.957$
Scale CHA_2DS_2-VASc (scores), Me [C25–C75]	4.5 [3.0–5.8]	6.0 [5.3–6.0]	6.0 [5.0–8.5]	5.0 [4.0–6.0]	6.0 [5.5–6.5]	$p_4 = 0.057$ $p_5 = 0.064$ $p_6 = 0.524$ $p_7 = 0.129$ $p_8 = 0.019$
HAS-BLED (scores), Me [C25–C75]	4.0 [2.3–5.0]	3.0 [3.0–3.0]	4.0 [2.0–5.0]	3.0 [3.0–4.8]	3.0 [3.0–4.0]	$p_4 = 0.208$ $p_5 = 0.799$ $p_6 = 0.284$ $p_7 = 0.767$ $p_8 = 0.295$
Number of MPs (scores), Me [C25–C75]	6.0 [5.0–7.3]	7.0 [5.0–9.0]	6.0 [4.5–8.0]	6.0 [5.0–8.8]	6.0 [5.0–8.0]	$p_4 = 0.285$ $p_5 = 0.877$ $p_6 = 0.277$ $p_7 = 0.614$ $p_8 = 0.429$

TABLE 7 (*continued*)

Number of MPs ≥ 5, abs. (%)	12/14 (85.7)	14/14 (100)	7/9 (77.8)	26/28 (92.9)	21/23 (91.3)	$p_4 = 0.142$ $p_5 = 0.624$ $p_6 = 0.065$ $p_7 = 0.205$ $p_8 = 0.595$
Dose of rivaroxaban 15 mg, abs. (%)	12/14 (85.7)	11/14 (78.6)	8/9 (88.9)	23/28 (82.1)	19/23 (82.6)	$p_4 = 0.622$ $p_5 = 0.825$ $p_6 = 0.524$ $p_7 = 0.633$ $p_8 = 0.804$
Dose of rivaroxaban 20 mg, abs. (%)	2/14 (14.3)	3/14 (21.4)	1/9 (11.1)	5/28 (17.9)	4/23 (17.4)	$p_4 = 0.622$ $p_5 = 0.825$ $p_6 = 0.524$ $p_7 = 0.633$ $p_8 = 0.804$
Creatinine (μmol/l), Me [C25–C75]	106.5 [95.9–127.5]	99.2 [93.6–152.5]	102.0 [92.7–118.0]	121.0 [112.5–129.8]	99.2 [93.6–126.5]	$p_4 = 0.839$ $p_5 = 0.643$ $p_6 = 0.829$ $p_7 = 0.689$ $p_8 = 0.689$
Hemoglobin (g/l), Me [C25–C75]	123.5 [114.8–140.3]	121.0 [104.8–125.5]	127.0 [119.0–133.6]	121.0 [112.5–130.8]	124.0 [112.0–128.0]	$p_4 = 0.246$ $p_5 = 1.000$ $p_6 = 0.159$ $p_7 = 0.453$ $p_8 = 0.411$
Platelets (10^9/l), Me [C25–C75]	247 [188.5–264.5]	239.5 [195.8–328.3]	202.0 [170.0–344.5]	246.0 [193.0–270.5]	220.0 [190.0–328.0]	$p_4 = 0.401$ $p_5 = 0.926$ $p_6 = 0.336$ $p_7 = 0.542$ $p_8 = 0.610$
Comorbidities						
CHD, abs. (%)	14/14 (100)	14/14 (100)	9/9 (100)	28/28 (100)	23/23 (100)	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$
Effort-induced angina pectoris, abs. (%)	12/14 (85.7)	13/14 (92.9)	8/9 (88.9)	25/28 (89.3)	21/23 (91.3)	$p_4 = 0.541$ $p_5 = 0.825$ $p_6 = 0.742$ $p_7 = 0.973$ $p_8 = 0.595$
Heart failure, abs. (%)	14/14 (100)	13/14 (92.9)	8/9 (88.9)	27/28 (96.4)	21/23 (91.3)	$p_4 = 0.309$ $p_5 = 0.202$ $p_6 = 0.742$ $p_7 = 0.384$ $p_8 = 0.257$
Arterial hypertension, abs. (%)	13/14 (92.9)	13/14 (92.9)	8/9 (88.9)	26/28 (92.9)	21/23 (91.3)	$p_4 = 1.000$ $p_5 = 0.742$ $p_6 = 0.742$ $p_7 = 0.704$ $p_8 = 0.867$
History of previous myocardial infarction, abs. (%)	1/14 (7.1)	4/14 (28.6)	3/9 (33.3)	5/28 (17.9)	7/23 (30.4)	$p_4 = 0.139$ $p_5 = 0.106$ $p_6 = 0.809$ $p_7 = 0.327$ $p_8 = 0.095$
ACVA (acute cerebrovascular accident) in past medical history, abs. (%)	0/14 (0)	4/14 (28.6)	3/9 (33.3)	4/28 (14.3)	7/23 (30.4)	$p_4 = 0.031$ $p_5 = 0.021$ $p_6 = 0.809$ $p_7 = 0.204$ $p_8 = 0.022$
Bronchial asthma, abs. (%)	0/14 (0)	1/14 (7.1)	2/9 (22.2)	1/28 (3.6)	3/23 (13)	$p_4 = 0.309$ $p_5 = 0.064$ $p_6 = 0.295$ $p_7 = 0.075$ $p_8 = 0.159$

TABLE 7 (*continued*)

Lower extremity atherosclerosis, abs. (%)	0/14 (0)	2/14 (14.3)	1/9 (11.1)	2/28 (7.1)	3/23 (13)	$p_4 = 0.142$ $p_5 = 0.202$ $p_6 = 0.825$ $p_7 = 0.704$ $p_8 = 0.159$
Chronic bronchitis, abs. (%)	5/14 (35.7)	4/14 (28.6)	4/9 (44.4)	9/28 (32.1)	8/23 (24.8)	$p_4 = 0.686$ $p_5 = 0.675$ $p_6 = 0.435$ $p_7 = 0.501$ $p_8 = 0.954$
Type 2 diabetes mellitus, abs. (%)	5/14 (35.7)	5/14 (35.7)	0/9 (0)	10/28 (35.7)	5/23 (21.7)	$p_4 = 1.000$ $p_5 = 0.043$ $p_6 = 0.043$ $p_7 = 0.036$ $p_8 = 0.353$
Charlson's comorbidity index (abs.), Me [C25-C75]	10.5 [9.0–11.0]	10.0 [9.0–12.0]	11.0 [9.0–12.5]	10.0 [9.0–11.0)]	10.0 [9.0–12.0]	$p_4 = 0.667$ $p_5 = 0.403$ $p_6 = 0.734$ $p_7 = 0.519$ $p_8 = 0.467$
GFR (glomerular filtration rate) (CKD-EPI) (ml/min/1.73 m^2), Me [C25-C75]	41.2 [36.5–49.3]	43.3 [33.1–47.5]	44.6 [35.7–48.2]	42.2 [36.2–45.9]	44.1 [35.7–48.0]	$p_4 = 0.910$ $p_5 = 0.877$ $p_6 = 0.734$ $p_7 = 0.768$ $p_8 = 0.962$
CKD Stage 4 (GFR < 30 ml/min/1.73 m^2), abs. (%)	1/14 (7.1)	3/14 (21.4)	0/9 (0)	4/28 (14.3)	3/23 (13.0)	$p_4 = 0.280$ $p_5 = 0.412$ $p_6 = 0.136$ $p_7 = 0.230$ $p_8 = 0.546$
GFR in CKD Stage 4 (ml/min/1.73 m^2), Me [C25–C75]	29.3	21.4 [19.5–21.4]	0	23.0 [19.9–28.3]	21.4 [19.5–21.4]	$p_4 = 0.500$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = 0.500$
CKD Stage 3B (GFR = 30–44 ml/min/1.73 m^2), abs. (%)	9/14 (64.3)	6/14 (42.9)	4/9 (44.4)	15/28 (53.6)	10/23 (43.5)	$p_4 = 0.256$ $p_5 = 0.349$ $p_6 = 0.940$ $p_7 = 0.634$ $p_8 = 0.270$
GFR in CKD Stage 3B (ml/min/1.73 m^2), Me [C25–C75]	38.7 [36.3–42.7]	40.8 [36.5–44.1]	35.7 [34.3–37.2]	39.0 [36.7–43.5]	37.1 [35.7–44.1]	$p_4 = 0.456$ $p_5 = 0.106$ $p_6 = 0.067$ $p_7 = 0.049$ $p_8 = 1.000$
CKD Stage 3A (GFR = 45–59 ml/min/1.73 m^2), abs. (%)	1/14 (7.1)	3/14 (21.4)	4/9 (44.4)	4/28 (14.3)	7/23 (30.4)	$p_4 = 0.280$ $p_5 = 0.034$ $p_6 = 0.242$ $p_7 = 0.056$ $p_8 = 0.236$
GFR in CKD Stage 3A (ml/min/1.73 m^2), Me [C25–C75]	45.8	46.1 [45.5–46.1]	46.5 [44.7–48.4]	45.9 [45.6–50.3]	47.9 [45.5–51.6]	$p_4 = 1.000$ $p_5 = 1.000$ $p_6 = 0.629$ $p_7 = 0.686$ $p_8 = 0.667$
CKD Stage 2 (GFR = 60–89 ml/min/1.73 m^2), abs. (%)	2/14 (14.3)	2/14 (14.3)	1/9 (11.1)	4/28 (14.3)	2/23 (8.7)	$p_4 = 1.000$ $p_5 = 0.825$ $p_6 = 0.825$ $p_7 = 0.809$ $p_8 = 0.837$
GFR in CKD Stage 2 (ml/min/1.73 ^{2}), Me [C25–C75]	61.1 [59.9–61.1]	70.4 [59.7–70.4]	85.97	61.1 [59.8–76.4]	83.5 [81.1–83.5]	$p_4 = 1.000$ $p_5 = 0.667$ $p_6 = 0.667$ $p_7 = 0.400$ $p_8 = 0.667$

TABLE 7 (*continued*)

CKD Stage 1 (GFR ≥ 90 ml/min/1.73 m^2), abs. (%)	1/14 (7.1)	0/14 (0)	0/9 (0)	1/28 (3.6)	–	$p_4 = 0.309$ $p_5 = 0.412$ $p_6 = –$ $p_7 = 0.565$ $p_8 = 0.204$
GFR in CKD Stage 1 (ml/min/1.73 m^2), Me [C25–C75]	96.9	0	0	96.96	–	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_7 – differences between the group of patients taking rivaroxaban without CCBs + patients taking rivaroxaban in combination with DCCBs (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCBs (verapamil); p_8 – differences between the group of patients taking rivaroxaban without CCBs and the group of patients taking rivaroxaban in combination with all CCBs (amlodipine + verapamil); BMI – body mass index; CHA_2DS_2-VASc – scale for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65–74 years; Sex Category); HAS-BLED – scale for assessing the risk of bleeding in atrial fibrillation (Hypertension; Abnormal renal-liver function; Stroke; Bleeding history or predisposition; Labile international normalised ratio; Elderly (65 years); Drugs or alcohol concomitantly); CHD – coronary heart disease; ACVA – acute cerebrovascular accident.

TABLE 8

FEATURES OF DRUG INTERACTION IN PATIENTS CARRYING THE CC GENOTYPE OF THE *ABCB1* GENE (rs4148738)

Indicators	CC genotype (*n* = 37) of the *ABCB1* gene (rs4148738)			*p value*
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	
Number of patients, abs. (%)	14/37 (37.85)	14/37 (37.85)	9/37 (24.3)	–
$C_{min, ss}$ of rivaroxaban (ng/ml), Me [C25–C75]	29.4 [14.5–61.9]	71.2 [28.3–102.8]	77.6 [47.4–115.3]	$p_4 = 0.081$ $p_5 = 0.014$ $p_6 = 0.571$
$C_{min, ss}$/D of rivaroxaban (ng/ml/mg), Me [C25–C75]	2.0 [1.0–3.8]	4.6 [1.9–6.9]	5.2 [2.3–7.7]	$p_4 = 0.098$ $p_5 = 0.020$ $p_6 = 0.378$
Prothrombin time (s), Me [C25–C75]	12.7 [12.3–14.2]	13.3 [12.2–14.7]	13.5 [13.1–15.6]	$p_4 = 0.581$ $p_5 = 0.243$ $p_6 = 0.488$
Data on all clinically significant minor bleeding in response to rivaroxaban by history, abs. (%)	1/14 (7.1)	1/14 (7.1)	1/9 (11.1)	$p_4 = 1.000$ $p_5 = 0.742$ $p_6 = 0.742$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil).

12 patients taking rivaroxaban + verapamil (median age – 88.5 [81.3–90.0] years; 75.0 % women). The baseline characterization of patients according to rs4148738 (*ABCB1*) genotype is presented in Table 9. The patients in the study groups were comparable with respect to the main parameters.

Among carriers of the heterozygous type (CT) of the *ABCB1* gene (rs4148738), the levels of $C_{min, ss}$ of rivaroxaban and $C_{min, ss}$/D of rivaroxaban were higher in the group of patients taking rivaroxaban + verapamil and rivaroxaban + amlodipine than in the group of patients not taking CCB in combination with rivaroxaban, but these differences did not reach statistical significance (Table 10). PT was higher in the group of patients taking rivaroxaban + verapamil than in the group of patients not taking CCB in combination with rivaroxaban, but these differences also did not reach statistical significance (14.6 [13.5–16.8] vs. 14.0 [12.8–14.5] s; $p = 0.083$) (Table 10). No differences in the number of patients who experienced AR in the form of clinically significant small hemorrhages were found between the compared groups ($p > 0.017$) (Table 10).

Group 3. Homozygous type (TT) carriers of the *ABCB1* gene (rs4148738)

We divided patients in group 3 ($n = 28$) into subgroups cause-specific to concomitant therapy. Subgroup 1 – 9 patients taking rivaroxaban without CCB (median age – 88.0 [84.0–89.5] years; 77.8 % women); subgroup 2 – 10 patients taking rivaroxaban + amlodipine (median age – 84.0 [81.8–89.3] years; 100 % women); subgroup 3 – 9 patients taking rivaroxaban + verapamil (median age – 88.0 [86.0–92.0] years; 33.3 % women). The baseline characterization of patients according to rs4148738 *(ABCB1)* gen-

TABLE 9

BASELINE CHARACTERISTICS OF PATIENTS CARRYING THE CT GENOTYPE OF THE *ABCB1* GENE (rs4148738)

Indicators	CT genotype (n = 63) of the *ABCB1* gene (rs4148738)					p value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	Rivaroxaban without CCB and rivaroxaban + amlodipine	Rivaroxaban and amlodipine and rivaroxaban + verapamil	
Number of patients, abs. (%)	24/63 (38.1)	27/63 (42.9)	12/63 (19)	51/63 (81)	39/63 (61.9)	–
Age (years), Me [C25–C75]	88.0 [83.0–91.0]	86.0 [83.0–88.0]	88.5 [81.3–90.0]	87.0 [83.0–90.0]	87.0 [82.0–89.0]	$p_4 = 0.320$ $p_5 = 0.908$ $p_6 = 0.391$ $p_7 = 0.661$ $p_8 = 0.756$
Women, abs. (%)	17/24 (70.8)	22/27 (81.5)	9/12 (75.0)	39/51 (76.5)	31/39 (79.5)	$p_4 = 0.371$ $p_5 = 0.792$ $p_6 = 0.644$ $p_7 = 0.914$ $p_8 = 0.434$
BMI (kg/m^2), Me [C25–C75]	28.5 [25.5–31.1]	30.1 [25.6–31.4]	31.3 [24.1–32.8]	29.0 [25.6–31.2]	30.4 [25.0–31.8]	$p_4 = 0.695$ $p_5 = 0.440$ $p_6 = 0.786$ $p_7 = 0.554$ $p_8 = 0.523$
Scale CHA_2DS_2-VASc (scores), Me [C25–C75]	6 [5–7]	6.0 [5.0–8.0]	5.5 [5.0–8.0]	6.0 [5.0–7.0]	6.0 [5.0–8.0]	$p_4 = 0.669$ $p_5 = 0.914$ $p_6 = 0.603$ $p_7 = 0.715$ $p_8 = 0.789$
HAS-BLED (scores), Me [C25–C75]	3 [2–3]	3.0 [3.0–3.75]	3.0 [2.75–4.0]	3.0 [3.0–3.0]	3.0 [3.0–4.0]	$p_4 = 0.708$ $p_5 = 0.604$ $p_6 = 0.812$ $p_7 = 0.669$ $p_8 = 0.568$
Number of MPs (scores), Me [C25–C75]	6 [5–7]	7.0 [6.0–9.0]	6.0 [5.25–7.0]	6.0 [5.0–8.0]	7.0 [6.0–8.0]	$p_4 = 0.019$ $p_5 = 0.753$ $p_6 = 0.080$ $p_7 = 0.396$ $p_8 = 0.056$
Number of MPs ≥ 5, abs. (%)	20/24 (83.3)	25/27 (92.6)	10/12 (83.3)	45/51 (88.2)	35/39 (89.7)	$p_4 = 0.306$ $p_5 = 1.000$ $p_6 = 0.379$ $p_7 = 0.646$ $p_8 = 0.244$
Dose of rivaroxaban 15 mg, abs. (%)	21/24 (87.5)	24/27 (88.9)	11/12 (91.7)	45/51 (88.2)	35/39 (89.7)	$p_4 = 0.878$ $p_5 = 0.708$ $p_6 = 0.792$ $p_7 = 0.734$ $p_8 = 0.783$
Dose of rivaroxaban 20 mg, abs. (%)	3/24 (12.5)	3/27 (11.1)	1/12 (8.3)	6/51 (11.8)	3/39 (7.7)	$p_4 = 0.878$ $p_5 = 0.708$ $p_6 = 0.792$ $p_7 = 0.734$ $p_8 = 0.783$
Creatinine (μmol/l), Me [C25–C75]	104.0 [89.5–124.3]	97.9 [83.6–122.0]	92.3 [83.6–101.5]	98.1 [86.0–122.0]	94.7 [83.6–110.0]	$p_4 = 0.336$ $p_5 = 0.146$ $p_6 = 0.578$ $p_7 = 0.270$ $p_8 = 0.179$

TABLE 9 (*continued*)

Hemoglobin (g/l), Me [C25–C75]	123.0 [110.3–136.0]	125.0 [113.0–129.0]	124.5 [101.5–132.3]	125.0 [112.0–132.0]	125.0 [112.0–130.0]	$p_4 = 0.799$ $p_5 = 0.497$ $p_6 = 0.869$ $p_7 = 0.649$ $p_8 = 0.630$
Platelets (10^9/l), Me [C25–C75]	215.0 [160.5–259.0]	236.0 [190.0–305.0]	194.5 [161.3–260.5]	224.0 [175.0–276.0]	222.0 [178.0–293.0]	$p_4 = 0.122$ $p_5 = 0.987$ $p_6 = 0.168$ $p_7 = 0.436$ $p_8 = 0.240$
Comorbidities						
CHD, abs. (%)	24/24 (100)	27/27 (100)	12/12 (100)	51/51 (100)	39/39 (100)	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$
Effort-induced angina pectoris, abs. (%)	21/24 (87.5)	20/27 (74.1)	9/12 (75)	41/51 (80.4)	29/39 (74.4)	$p_4 = 0.228$ $p_5 = 0.343$ $p_6 = 0.951$ $p_7 = 0.678$ $p_8 = 0.211$
Heart failure, abs. (%)	23/24 (95.8)	25/27 (92.6)	10/12 (83.3)	48/51 (94.1)	35/39 (89.7)	$p_4 = 0.623$ $p_5 = 0.201$ $p_6 = 0.379$ $p_7 = 0.214$ $p_8 = 0.385$
Arterial hypertension, abs. (%)	23/24 (95.8)	26/27 (96.3)	11/12 (91.7)	49/51 (96.1)	37/39 (94.9)	$p_4 = 0.932$ $p_5 = 0.607$ $p_6 = 0.545$ $p_7 = 0.518$ $p_8 = 0.862$
History of previous myocardial infarction, abs. (%)	9/24 (37.5)	6/27 (22.2)	3/12 (25)	15/51 (29.4)	9/39 (23.1)	$p_4 = 0.232$ $p_5 = 0.453$ $p_6 = 0.849$ $p_7 = 0.761$ $p_8 = 0.218$
ACVA (acute cerebrovascular accident) in past medical history, abs. (%)	6/24 (25.0)	6/27 (22.2)	3/12 (25)	12/51 (23.5)	9/39 (23.1)	$p_4 = 0.815$ $p_5 = 1.000$ $p_6 = 0.849$ $p_7 = 0.914$ $p_8 = 0.862$
Bronchial asthma, abs. (%)	0/24 (0)	0/27 (0)	2/12 (16.7)	0/51 (0)	2/39 (5.1)	$p_4 = –$ $p_5 = 0.040$ $p_6 = 0.029$ $p_7 = 0.003$ $p_8 = 0.260$
Lower extremity atherosclerosis, abs. (%)	3/24 (12.5)	7/27 (25.9)	4/12 (33.3)	10/51 (19.6)	11/39 (28.2)	$p_4 = 0.228$ $p_5 = 0.137$ $p_6 = 0.635$ $p_7 = 0.303$ $p_8 = 0.145$
Chronic bronchitis, abs. (%)	11/24 (45.8)	9/27 (33.3)	5/12 (41.7)	20/51 (39.2)	14/39 (35.9)	$p_4 = 0.361$ $p_5 = 0.813$ $p_6 = 0.617$ $p_7 = 0.876$ $p_8 = 0.434$
Type 2 diabetes mellitus, abs. (%)	7/24 (29.2)	7/27 (25.9)	3/12 (25)	14/51 (27.5)	10/39 (25.6)	$p_4 = 0.796$ $p_5 = 0.792$ $p_6 = 0.951$ $p_7 = 0.863$ $p_8 = 0.759$

TABLE 9 (*continued*)

Charlson's comorbidity index (abs.), Me [C25–C75]	10.0 [9.3–11.0]	10.0 [9.0–11.0]	10.0 [9.0–11.0]	10.0 [9.0–11.0]	10.0 [9.0–11.0]	$p_4 = 0.369$ $p_5 = 0.631$ $p_6 = 0.916$ $p_7 = 0.844$ $p_8 = 0.240$
GFR (glomerular filtration rate) (CKD-EPI) (ml/min/1.73 m^2), Me [C25–C75]	41.2 [36.5–49.3]	43.3 [33.1–47.5]	44.6 [35.7–48.2]	42.2 [36.2–45.9]	51.8 [40.5–56.0]	$p_4 = 0.910$ $p_5 = 0.877$ $p_6 = 0.734$ $p_7 = 0.768$ $p_8 = 0.374$
CKD Stage 4 (GFR < 30 ml/min/1.73 m^2), abs. (%)	2/24 (8.3)	3/27 (11.1)	1/12 (8.3)	5/51 (9.8)	4/39 (10.3)	$p_4 = 0.739$ $p_5 = 1.000$ $p_6 = 0.792$ $p_7 = 0.876$ $p_8 = 0.801$
GFR in CKD Stage 4 (ml/min/1.73 m^2), Me [C25–C75]	29.3	21.4 [19.5–21.4]	0	23.0 [19.9–28.3]	28.9 [26.9–29.5]	$p_4 = 0.500$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = 0.800$
CKD Stage 3B (GFR = 30–44 ml/min/1.73 m^2), abs. (%)	8/24 (33.3)	9/27 (33.3)	1/12 (8.3)	17/51 (33.3)	10/39 (25.6)	$p_4 = 1.000$ $p_5 = 0.102$ $p_6 = 0.099$ $p_7 = 0.085$ $p_8 = 0.512$
GFR in CKD Stage 3B (ml/min/1.73 m^2), Me [C25–C75]	38.7 [36.3–42.7]	40.8 [36.5–44.1]	35.7 [34.3–37.2]	39.0 [36.7–43.5]	38.0 [34.2–41.9]	$p_4 = 0.456$ $p_5 = 0.106$ $p_6 = 0.067$ $p_7 = 0.049$ $p_8 = 0.897$
CKD Stage 3A (GFR = 45–59 ml/min/1.73 m^2), abs. (%)	13/24 (54.2)	11/27 (40.7)	8/12 (66.7)	24/51 (47.1)	19/39 (48.7)	$p_4 = 0.338$ $p_5 = 0.473$ $p_6 = 0.135$ $p_7 = 0.222$ $p_8 = 0.674$
GFR in CKD Stage 3A (ml/min/1.73 m^2), Me [C25–C75]	45.8	46.1 [45.5–46.1]	46.5 [44.7–48.4]	45.9 [45.6–50.3]	53.9 [50.5–55.8]	$p_4 = 1.000$ $p_5 = 1.000$ $p_6 = 0.629$ $p_7 = 0.686$ $p_8 = 0.077$
CKD Stage 2 (GFR = 60–89 ml/min/1.73 m^2), abs. (%)	1/24 (4.2)	4/27 (14.8)	2/12 (16.7)	5/51 (9.8)	6/39 (15.4)	$p_4 = 0.202$ $p_5 = 0.201$ $p_6 = 0.882$ $p_7 = 0.496$ $p_8 = 0.169$
GFR in CKD Stage 2 (ml/min/1.73 m^2), Me [C25–C75]	61.1 [59.9–61.1]	70.4 [59.7–70.4]	85.97	61.1 [59.8–76.4]	66.1 [63.4–69.2]	$p_4 = 1.000$ $p_5 = 0.667$ $p_6 = 0.667$ $p_7 = 0.400$ $p_8 = 0.286$
CKD Stage 1 (GFR ≥ 90 ml/min/1.73 m^2), abs. (%)	–	–	–	–	–	–
GFR in CKD Stage 1 (ml/min/1.73 m^2), Me [C25–C75]	96.6	96.9	0	0		$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_7 – differences between the group of patients taking rivaroxaban without CCBs + patients taking rivaroxaban in combination with DCCBs (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCBs (verapamil); p_8 – differences between the group of patients taking rivaroxaban without CCBs and the group of patients taking rivaroxaban in combination with all CCBs (amlodipine + verapamil); BMI – body mass index; CHA_2DS_2-VASc – scale for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65–74 years; Sex Category); HAS-BLED – scale for assessing the risk of bleeding in atrial fibrillation (Hypertension; Abnormal renal-liver function; Stroke; Bleeding history or predisposition; Labile international normalised ratio; Elderly (65 years); Drugs or alcohol concomitantly); CHD – coronary heart disease; ACVA – acute cerebrovascular accident.

otype is presented in Table 11. Patients in subgroup 3 (rivaroxaban + verapamil) had a higher proportion of women, had higher creatinine levels and lower haemoglobin levels than those in subgroup 2 (rivaroxaban + amlodipine), and had a higher Charlson comorbidity index than patients in subgroup 1 (rivaroxaban without CCB). In other parameters, patients in the studied subgroups were comparable.

Among homozygous type (TT) carriers of the *ABCB1* gene (rs4148738), the levels of $C_{min, ss}$ of rivaroxaban, $C_{min, ss}$/D of rivaroxaban and PT were higher in patients taking rivaroxaban + verapamil compared to all study groups, but without reaching statistical significance of the differences. AR in the form of clinically significant minor bleeding occurred quite frequently – in 77.8 % of cases in the group of patients taking rivaroxaban + verapamil, and this rate was statistically significantly higher in comparison with the group of patients not taking CCB in combination with rivaroxaban (11.1 %; $p = 0.004$), and in comparison with the group of patients taking rivaroxaban + amlodipine, the difference reached statistical significance (30 %; $p = 0.037$) (Table 12).

DISCUSSION

The data obtained reveal that in patients 80 years and older with non-valvular AF and carriers of the wild-type genotype (CC) of the *ABCB1* gene (rs1045642), co-administration of rivaroxaban with CCBs (amlodipine or verapamil), which are capable of drug interaction with rivaroxaban, resulted in higher values of $C_{min, ss}$ of rivaroxaban compared with patients not taking CCBs. In carriers of heterozygous genotype (CT) of *ABCB1* gene (rs1045642), co-

TABLE 10

FEATURES OF DRUG INTERACTION IN PATIENTS CARRYING THE CT GENOTYPE OF THE *ABCB1* GENE (rs4148738)

Indicators	CT genotype ($n = 63$) of the *ABCB1* gene (rs4148738)			*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	
Number of patients, abs. (%)	24/63 (38.1)	27/63 (42.9)	12/63 (19)	–
$C_{min, ss}$ of rivaroxaban (ng/ml), Me [C25–C75]	41.7 [25.4–58.2]	56.4 [29.3–91.3]	56.0 [34.1–114.2]	$p_4 = 0.093$ $p_5 = 0.112$ $p_6 = 0.738$
$C_{min, ss}$/D of rivaroxaban (ng/ml/mg), Me [C25–C75]	2.6 [1.7–3.4]	3.8 [2.0–4.6]	3.7 [2.1–7.6]	$p_4 = 0.093$ $p_5 = 0.131$ $p_6 = 0.715$
Prothrombin time (s), Me [C25–C75]	14.0 [12.7–14.5]	13.3 [12.6–14.6]	14.6 [13.5–16.8]	$p_4 = 0.962$ $p_5 = 0.083$ $p_6 = 0.117$
Data on all clinically significant minor bleeding in response to rivaroxaban by history, abs. (%)	4/24 (16.7)	3/27 (11.1)	2/12 (16.7)	$p_4 = 0.565$ $p_5 = 1.000$ $p_6 = 0.632$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil).

TABLE 11

BASELINE CHARACTERISTICS OF PATIENTS CARRYING THE TT GENOTYPE OF THE *ABCB1* GENE (rs4148738)

Indicators	TT genotype ($n = 28$) of the *ABCB1* gene (rs4148738)					*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	Rivaroxaban without CCB and rivaroxaban + amlodipine	Rivaroxaban and amlodipine and rivaroxaban + verapamil	
Number of patients, abs. (%)	9/28 (32.1)	10/28 (35.8)	9/28 (32.1)	19/28 (67.9)	19/28 (67.9)	–
Age (years), Me [C25–C75]	88.0 [84.0–89.5]	84.0 [81.8–89.3]	88.0 [86.0–92.0]	86.0 [82.0–89.0]	87.0 [83.0–90.0]	$p_4 = 0.400$ $p_5 = 0.666$ $p_6 = 0.113$ $p_7 = 0.243$ $p_8 = 0.809$

TABLE 11 (*continued*)

Women, abs. (%)	7/9 (77.8)	10/10 (100)	3/9 (33.3)	17/19 (89.5)	13/19 (68.4)	$p_4 = 0.115$ $p_5 = 0.058$ $p_6 = 0.002$ $p_7 = 0.002$ $p_8 = 0.609$
BMI (kg/m^2), Me [C25–C75]	25.6 [23.9–32.6]	27.0 [23.8–33.7]	26.8 [25.0–30.1]	26.9 [24.2–33.1]	26.9 [24.7–31.1]	$p_4 = 0.968$ $p_5 = 0.931$ $p_6 = 0.604$ $p_7 = 0.699$ $p_8 = 1.000$
Scale CHA_2DS_2-VASc (scores), Me [C25–C75]	6.0 [5.0–7.0]	6.0 [4.0–6.5]	6.0 [5.3–7.0]	6.0 [5.0–8.0]	6.0 [5.0–7.0]	$p_4 = 0.639$ $p_5 = 0.694$ $p_6 = 0.435$ $p_7 = 0.473$ $p_8 = 1.000$
HAS-BLED (scores), Me [C25–C75]	3.0 [1.75–4.5]	3.0 [3.0–4.5]	3.0 [2.0–4.0]	3.0 [3.0–4.0]	3.0 [5.0–7.0]	$p_4 = 0.429$ $p_5 = 1.000$ $p_6 = 0.222$ $p_7 = 0.442$ $p_8 = 0.765$
Number of MPs (scores), Me [C25–C75]	6.0 [4.0–8.0]	7.0 [6.0–8.0]	6.0 [4.0–9.0]	6.0 [5.0–8.0]	7.0 [6.0–8.0]	$p_4 = 0.243$ $p_5 = 0.666$ $p_6 = 0.842$ $p_7 = 0.923$ $p_8 = 0.332$
Number of MPs ≥ 5, abs. (%)	6/9 (66.7)	10/10 (100)	6/9 (66.7)	16/19 (84.2)	16/19 (84.2)	$p_4 = 0.047$ $p_5 = 1.000$ $p_6 = 0.047$ $p_7 = 0.291$ $p_8 = 0.291$
Dose of rivaroxaban 15 mg, abs. (%)	7/9 (77.8)	9/10 (90)	8/9 (88.9)	16/19 (84.2)	17/19 (89.5)	$p_4 = 0.466$ $p_5 = 0.527$ $p_6 = 0.937$ $p_7 = 0.741$ $p_8 = 0.409$
Dose of rivaroxaban 20 mg, abs. (%)	2/9 (22.2)	1/10 (10)	1/9 (11.1)	3/19 (15.8)	2/19 (10.5)	$p_4 = 0.466$ $p_5 = 0.527$ $p_6 = 0.937$ $p_7 = 0.741$ $p_8 = 0.409$
Creatinine (μmol/l), Me [C25–C75]	97.0 [84.9–117.5]	89.7 [85.0–95.5]	112 [98.6–146.5]	92.9 [85.6–97.7]	94.8 [86.9–112.0]	$p_4 = 0.156$ $p_5 = 0.161$ $p_6 = 0.006$ $p_7 = 0.014$ $p_8 = 0.962$
Hemoglobin (g/l), Me [C25–C75]	132.5 [98.0–144.3]	132.5 [117.8–138.0]	110 [106–117]	132.5 [115.5–138.0]	119.0 [110.0–136.0]	$p_4 = 0.762$ $p_5 = 0.277$ $p_6 = 0.01$ $p_7 = 0.027$ $p_8 = 0.696$
Platelets (10^9/l), Me [C25–C75]	264.5 [201.3–296.8]	208 [172.0–275.0]	216 [165–256]	215.0 [189.3–290.8]	213.0 [175.0–264.0]	$p_4 = 0.146$ $p_5 = 0.093$ $p_6 = 0.905$ $p_7 = 0.322$ $p_8 = 0.066$
Comorbidities						
CHD, abs. (%)	8/9 (88.9)	10/10 (100)	9/9 (100)	18/19 (94.7)	19/19 (100)	$p_4 = 0.279$ $p_5 = 0.303$ $p_6 = –$ $p_7 = 0.483$ $p_8 = 0.139$
Effort-induced angina pectoris, abs. (%)	5/9 (55.6)	7/10 (70)	8/9 (88.9)	12/19 (63.2)	15/19 (78.9)	$p_4 = 0.515$ $p_5 = 0.114$ $p_6 = 0.313$ $p_7 = 0.159$ $p_8 = 0.201$

TABLE 11 (*continued*)

Heart failure, abs. (%)	8/9 (88.9)	10/10 (100)	9/9 (100)	18/19 (94.7)	19/19 (100)	$p_4 = 0.279$ $p_5 = 0.303$ $p_6 = –$ $p_7 = 0.483$ $p_8 = 0.139$
Arterial hypertension, abs. (%)	9/9 (100)	9/10 (90)	8/9 (88.9)	18/19 (94.7)	17/19 (89.5)	$p_4 = 0.330$ $p_5 = 0.303$ $p_6 = 0.937$ $p_7 = 0.575$ $p_8 = 0.312$
History of previous myocardial infarction, abs. (%)	2/9 (22.2)	4/10 (40)	3/9 (33.3)	6/19 (31.6)	7/19 (36.8)	$p_4 = 0.405$ $p_5 = 0.599$ $p_6 = 0.764$ $p_7 = 0.926$ $p_8 = 0.439$
ACVA (acute cerebrovascular accident) in past medical history, abs. (%)	0/9 (0)	3/10 (30)	3/9 (33.3)	3/19 (15.8)	6/19 (31.6)	$p_4 = 0.073$ $p_5 = 0.058$ $p_6 = 0.876$ $p_7 = 0.291$ $p_8 = 0.057$
Bronchial asthma, abs. (%)	1/9 (11.1)	1/10 (10)	2/9 (22.2)	2/19 (10.5)	3/19 (15.8)	$p_4 = 0.937$ $p_5 = 0.527$ $p_6 = 0.466$ $p_7 = 0.409$ $p_8 = 0.741$
Lower extremity atherosclerosis, abs. (%)	0/9 (0)	2/10 (20)	4/9 (44.4)	2/19 (10.5)	6/19 (31.6)	$p_4 = 0.156$ $p_5 = 0.023$ $p_6 = 0.252$ $p_7 = 0.041$ $p_8 = 0.057$
Chronic bronchitis, abs. (%)	2/9 (22.2)	2/10 (20)	0/9 (0)	4/19 (21.1)	2/19 (10.5)	$p_4 = 0.906$ $p_5 = 0.134$ $p_6 = 0.156$ $p_7 = 0.137$ $p_8 = 0.409$
Type 2 diabetes mellitus, abs. (%)	0/9 (0)	3/10 (30)	3/9 (33.3)	3/19 (15.8)	6/19 (31.6)	$p_4 = 0.073$ $p_5 = 0.058$ $p_6 = 0.876$ $p_7 = 0.291$ $p_8 = 0.057$
Charlson's comorbidity index (abs.), Me [C25–C75]	9.0 [9.0–9.5]	10.0 [9.0–12.3]	12.0 [10.0–15.5]	10.0 [9.0–11.0]	12.0 [10.0–13.0]	$p_4 = 0.156$ $p_5 = 0.001$ $p_6 = 0.079$ $p_7 = 0.004$ $p_8 = 0.007$
GFR (glomerular filtration rate) (CKD-EPI) (ml/min/1.73 m^2), Me [C25-C75]	47.9 [39.4–59.3]	50.4 [46.8–54.5]	46.8 [37.5–52.4]	48.0 [45.7–56.7]	49.5 [45.4–52.5]	$p_4 = 0.497$ $p_5 = 0.546$ $p_6 = 0.243$ $p_7 = 0.285$ $p_8 = 0.962$
CKD Stage 4 (GFR < 30 ml/min/1.73 m^2), abs. (%)	0/9 (0)	0/10 (0)	1/9 (11.1)	0/19 (0)	1/19 (5.3)	$p_4 = –$ $p_5 = 0.303$ $p_6 = 0.279$ $p_7 = 0.139$ $p_8 = 0.483$
GFR in CKD Stage 4 (ml/min/1.73 m^2), Me [C25–C75]	0	0	26.8	0	26.81	$p_4 = –$ $p_5 = –$ $p_6 = –$ $p_7 = –$ $p_8 = –$
CKD Stage 3B (GFR = 30–44 ml/min/1.73 m^2), abs. (%)	3/9 (33.3)	1/10 (10)	2/9 (22.2)	4/19 (21.1)	3/19 (15.8)	$p_4 = 0.213$ $p_5 = 0.599$ $p_6 = 0.466$ $p_7 = 0.944$ $p_8 = 0.291$

TABLE 11 (*continued*)

GFR in CKD Stage 3B (ml/min/1.73 m^2), Me [C25–C75]	38.6 [34.4–38.6]	41.1	37.4 [36.4–37.4]	39.4 [35.4–40.9]	38.4 [36.4–38.4]	$p_4 = 0.500$ $p_5 = 1.000$ $p_6 = 1.000$ $p_7 = –$ $p_8 = 1.000$
CKD Stage 3A (GFR = 45–59 ml/min/1.73 m^2), abs. (%)	5/9 (55.6)	8/10 (80)	6/9 (66.7)	13/19 (68.4)	14/19 (73.7)	$p_4 = 0.252$ $p_5 = 0.629$ $p_6 = 0.510$ $p_7 = 0.926$ $p_8 = 0.337$
GFR in CKD Stage 3A (ml/min/1.73 m^2), Me [C25–C75]	48.0 [46.8–59.3]	50.4 [47.1–53.1]	51.6 [46.5–53.2]	49.5 [47.4–55.2]	50.9 [46.9–52.8]	$p_4 = 0.833$ $p_5 = 0.792$ $p_6 = 1.000$ $p_7 = 0.533$ $p_8 = 0.754$
CKD Stage 2 (GFR = 60–89 ml/min/1.73 m^2), abs. (%)	1/9 (11.1)	1/10 (10)	0/9 (0)	2/19 (10.5)	1/19 (5.3)	$p_4 = 0.937$ $p_5 = 0.303$ $p_6 = 0.330$ $p_7 = 0.312$ $p_8 = 0.575$
GFR in CKD Stage 2 (ml/min/1.73 m^2), Me [C25–C75]	61.1	65.1	0	63.1 [61.1–68.1]	65.05	$p_4 = 1.000$ $p_5 = –$ $p_6 = –$ $p_7 = 0.898$ $p_8 = 1.000$
CKD Stage 1 (GFR ≥ 90 ml/min/1.73 m^2), abs. (%)	–	–	––	–	–	–
GFR in CKD Stage 1 (ml/min/1.73 m^2), Me [C25–C75]	–	–	–	–	–	–

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_7 – differences between the group of patients taking rivaroxaban without CCBs + patients taking rivaroxaban in combination with DCCBs (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCBs (verapamil); p_8 – differences between the group of patients taking rivaroxaban without CCBs and the group of patients taking rivaroxaban in combination with all CCBs (amlodipine + verapamil); BMI – body mass index; CHA_2DS_2-VASc – scale for assessing the risk of stroke and systemic thromboembolism in patients with atrial fibrillation (Congestive heart failure; Hypertension; Age ≥ 75 years; Diabetes mellitus; prior Stroke or TIA or thromboembolism; Vascular disease; Age 65–74 years; Sex Category); HAS-BLED – scale for assessing the risk of bleeding in atrial fibrillation (Hypertension; Abnormal renal-liver function; Stroke; Bleeding history or predisposition; Labile international normalised ratio; Elderly (65 years); Drugs or alcohol concomitantly); CHD – coronary heart disease; ACVA – acute cerebrovascular accident.

TABLE 12

PECULIARITIES OF DRUG INTERACTION IN PATIENTS CARRYING TT GENOTYPE OF *ABCB1* GENE (rs4148738)

Indicators	TT genotype (n = 28) of the *ABCB1* gene (rs4148738)			*p* value
	Rivaroxaban without CCBs	Rivaroxaban and amlodipine	Rivaroxaban and verapamil	
Number of patients, abs. (%)	9/28 (32.1)	10/28 (35.8)	9/28 (32.1)	–
$C_{min, ss}$ of rivaroxaban (ng/ml), Me [C25–C75]	66.0 [36.4–103.1]	45.1 [20.1–52.8]	82.2 [49.8–120.95]	$p_4 = 0.165$ $p_5 = 0.508$ $p_6 = 0.022$
$C_{min, ss}$/D of rivaroxaban (ng/ml/mg), Me [C25–C75]	3.8 [2.3–6.9]	3.0 [1.2–3.5]	5.1 [3.3–8.1]	$p_4 = 0.221$ $p_5 = 0.402$ $p_6 = 0.022$
Prothrombin time (s), Me [C25–C75]	14.2 [13.6–14.5]	13.1 [12.3–14.6]	17.4 [13.6–18.5]	$p_4 = 0.252$ $p_5 = 0.046$ $p_6 = 0.027$
Data on all clinically significant minor bleeding in response to rivaroxaban by history, abs. (%)	1/9 (11.1)	3/10 (30)	7/9 (77.8)	$p_4 = 0.313$ $p_5 = 0.004$ $p_6 = 0.037$

Note. abs. – absolute number; p_4 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with DCCB (amlodipine); p_5 – differences between the group of patients taking rivaroxaban without CCB and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil); p_6 – differences between the group of patients taking rivaroxaban in combination with DCCB (amlodipine) and the group of patients taking rivaroxaban in combination with non-DCCB (verapamil).

administration of rivaroxaban with verapamil (strong P-gp inhibitor and moderate CYP3A4 inhibitor) resulted in higher values of $C_{min, ss}$ of rivaroxaban compared to patients, not taking CCBs, and compared to patients taking rivaroxaban and amlodipine (potentially possible drug interactions caused by competition of substrates for binding sites on cell membranes). In carriers of the homozygous genotype (TT) of the *ABCB1* gene (rs1045642), the co-administration of rivaroxaban with verapamil was associated with AR in the majority of cases in the form of clinically significant small bleeds (up to 75 %), and their number was statistically significantly higher in comparison with patients not taking CCB, and in comparison with patients taking rivaroxaban and amlodipine.

In patients 80 years and older with non-valvular AF and patients carrying the wild-type genotype (WS) of the *ABCB1* gene (rs4148738), co-administration of rivaroxaban with verapamil resulted in higher $C_{min, ss}$ values of rivaroxaban compared with patients not taking CCB in combination with rivaroxaban. In carriers of heterozygous genotype (CT) of *ABCB1* gene (rs4148738) co-administration of rivaroxaban with CCB did not lead to statistically significant differences between the studied parameters. In carriers of the homozygous genotype (TT) of the *ABCB1* gene (rs4148738), co-administration of rivaroxaban with verapamil resulted in statistically higher AR in the form of clinically significant minor bleeding compared to the group of patients not taking CCB in combination with rivaroxaban (up to 78 %).

We would like to draw the readers' attention to the fact that earlier in our studies we have already revealed that co-administration of verapamil (a strong P-gp inhibitor and moderate CYP3A4 inhibitor) in combination with rivaroxaban resulted in more frequent AR development (in 33 % of patients) [4], and homozygous type (TT) carriers of *ABCB1* gene (rs1045642 and rs4148738) were associated with more frequent AR development (29.3 % and 39.3 %, respectively) [10]. In this study, it was observed that co-administration of verapamil (a strong P-gp inhibitor and moderate CYP3A4 inhibitor) in combination with rivaroxaban in homozygous type (TT) carriers of the *ABCB1* gene (rs1045642 and rs4148738) resulted in AR in 75 and 78 % of cases, respectively. Consequently, it may be advisable to genotype patients to clarify the carriage of polymorphic variants of *ABCB1* gene (rs1045642 and rs4148738) before the administration of verapamil (a strong P-gp inhibitor and moderate CYP3A4 inhibitor) in combination with rivaroxaban and then decide about the further strategy of patient treatment. This study could prevent the development of AR in the form of clinically significant minor bleeding in patients 80 years and older with non-valvular AF.

The fact that more than half of the patients carrying the TT genotype of the *ABCB1* gene (rs1045642 and rs4148738) in the subgroup of patients taking rivaroxaban + verapamil were men, whereas in the subgroups of patients taking rivaroxaban + amlodipine and rivaroxaban without CCB, women predominated (Tables 5, 11), also requires discussion. In our previous study, we demonstrated that there were 10 cases of CSNMB when taking rivaroxaban with verapamil, 8 of which were haematuria [4]. The resolution of the Eurasian Association of Therapists on the algorithm for assessment and modification of risk factors for minor bleeding in patients with AF treated with direct oral anticoagulants (DOACs) states that the most common causes of haematuria in patients taking rivaroxaban or other DOACs are benign prostatic hyperplasia (BPH) and prostatitis [19]. Consequently, it may be assumed that in patients carrying the TT genotype of the *ABCB1* gene (rs1045642 and rs4148738) the sharply pronounced differences in the CPNA incidence in the three selected subgroups may be explained by the heterogeneity of the subgroups by sex composition. The incidence of BPH, however, increases with age, reaching 88 % after the age of 80 years [20]. Considering the fact that all our patients were over 80 years of age, it can be assumed that of the 25 % (32 patients) of men included in the study, 88 % (28 patients) of the men may have BPH, of which 39 % (11 patients) had haematuria, whereas in the population of men over 75 years of age, haematuria occurs in only 13 % of cases [20]. Alternatively, if we consider haematuria as a complication of BPH, then the cause of its occurrence is not only and not so much the disease of the prostate gland itself, but rather the change in bladder function and, as a consequence, dilated varicose veins of the bladder neck, which can also develop as a result of other (not only BPH) causes, such as bladder 'ageing', changes in neurological status, the presence of comorbidities, and therefore occurs with approximately equal frequency in both older men and older women [20]. Nevertheless, to confirm or refute the assumption that the heterogeneity of subgroups by sex composition influenced the sharply pronounced differences in the CPNA incidence among patients carrying the TT genotype of the *ABCB1* gene (rs1045642 and rs4148738) in the three selected subgroups, it is necessary to conduct an additional study that will include a larger number of participants and homogeneous groups by sex composition.

Our data are comparable with the results of a number of foreign studies. Thus, K. Lorenzini et al. [21] reported a case of bleeding in a 79-year-old patient on taking rivaroxaban 20 mg per day (for 3 months). The authors hypothesised that the presence of homozygous TT genotypes for rs2032582 and rs1045642 of the *ABCB1* gene and decreased CYP3A4/5 activity as a result of drug interaction with simvastatin may have contributed to the increased susceptibility to rivaroxaban in the presented patient.

A. Sennesael et al. [22] prospectively analyzed 10 patients admitted to the emergency department for bleeding against the background of rivaroxaban administration. Among the three patients who experienced severe bleeding associated with $C_{min, ss}$ rivaroxaban > 136 ng/ml, two were heterozygous and one was homozygous (TT) for rs1045642 of the *ABCB1* gene. However, no clear association between *ABCB1* genotype and calculated minimum concentrations was observed ($p > 0.050$). At the same time, however, all three patients were also receiving MPs with potential drug

interactions (diltiazem + clarithromycin, or simvastatin, or amiodarone).

In a study by I. Gouin-Thibault et al. [23], it was revealed that *ABCB1* genotype (rs2032582; c.2677G>A/T; p.Ala893Thr/Ser and rs1045642; c.3435C>T; p.Ile1145Ile) is not a significant determinant of individual variability of rivaroxaban pharmacokinetics in healthy volunteers, whereas co-administration of rivaroxaban with a P-gp/CYP3A4 inhibitor (clarithromycin) may increase the risk of overdose, since it increases rivaroxaban's AUC by 94 % ($p < 0.0001$) and its $C_{max, ss}$ by 92 % ($p < 0.0001$): geometric mean ratios were 1.94 [95% confidence interval (95% CI): 1.42–2.63] and 1.92 [95% CI: 1.60–2.28] for AUC and $C_{max, ss}$, respectively, and this effect was not affected by *ABCB1* genotype.

By contrast, P. Pham et al. [24] assessed the risk of bleeding in patients with AF against the background of administering standard doses of DOACs in combination with verapamil or diltiazem. A total of 1764 patients receiving DOACs with verapamil or diltiazem compared with 3105 patients receiving amlodipine and 1793 patients receiving DOACs with verapamil or diltiazem compared with 3224 patients receiving metoprolol were analysed. Results revealed that rivaroxaban and apixaban were not associated with increased bleeding rates in patients receiving verapamil or diltiazem compared to those receiving amlodipine or metoprolol. Among patients receiving dabigatran etexilate, the overall incidence of bleeding was 52 % higher (hazard ratio (HR) – 1.52; 95% CI: 1.05–2.20) when taking verapamil or diltiazem compared with amlodipine and 43 % higher (HR = 1.43; 95% CI: 1.02–2.20) when compared with metoprolol. The incidence of bleeding during the administration of dabigatran with verapamil or diltiazem was generally higher for other types of bleeding (244.9 vs. 158.4 per 1000 person-years; adjusted risk ratio for total gastrointestinal bleeding – 2.16 (95% CI: 1.30–3.60), minor bleeding – 1.56 (95% CI: 1.07–2.27), minor gastrointestinal bleeding – 2.16 (95% CI: 1.29–3.63). Sensitivity analyses revealed consistent results for dabigatran being used with verapamil and diltiazem with hazard rate increase values ranging from 50 % to 100 % and no statistically significant results for apixaban or rivaroxaban. In contrast to this study, in P. Pham et al. patients had no history of chronic kidney disease (CKD) and also 60 % of patients were younger than 65 years with only about 5.5 % older than 80 years; in this study, only 12 % had no history of CKD and all patients were older than 80 years, which could have affected the difference in the results obtained. The results of our study, however, need to be verified in a prospective study with a larger number of participants.

Study limitations

Our study has several limitations. Firstly, the sample of patients in the groups according to the gene polymorphisms under study was small. Second, the baseline characterization of patients was not comparable in a number of parameters. These limitations may have affected the outcome.

CONCLUSION

This study, in which features of drug interaction between rivaroxaban and CCB in patients 80 years and older with non-valvular AF cause-specific polymorphisms of *ABCB1* gene (rs1045642 and rs4148738) were examined, showed statistically significant changes in the pharmacokinetic profile of certain *ABCB1* gene variants (rs1045642 and rs4148738) and, as a consequence, the occurrence of AR in the form of clinically significant minor bleeding. Therefore, to prevent their occurrence in patients 80 years and older with non-valvular AF, genotyping for variants of the above polymorphisms of the *ABCB1* gene (rs1045642 and rs4148738) may be considered before prescribing verapamil (a strong P-gp inhibitor and a moderate CYP3A4 inhibitor).

Funding

The study was supported by the Russian Science Foundation, project No. 22-15-00251 "Personalised use of direct-acting oral anticoagulants based on a pharmacogenomic approach"; the 2022 competition for grants in the direction of "Conducting basic scientific research and prospecting research by individual scientific groups".

Conflict of interest

The authors of this article declare no conflicts of interest.

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