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Association of aortic valve calcification and vitamin K antagonist treatment

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Abstract

Aims: Vitamin K antagonists (VKA) are suspected of causing aortic valve calcification (AVC). The objective of this study was to clarify whether patients undergoing VKA treatment have increased AVC scores compared to patients treated with new oral anticoagulants (NOAC) and patients who never have been treated with VKA/NOAC.

Methods and results: We included participants from the population-based DANCAVAS trial (n=15,048). Information on confounders was collected, and the AVC scores were measured on non-contrast CT scans. The participants' medication data, including VKA and NOAC data, were collected from the Danish National Health Service Prescription Database. The final population consisted of 14,604 participants (67.4 years, 95% men) of whom 873 had been treated with VKA and 602 with NOAC. The association between AVC score and duration of anticoagulant use was investigated in an adjusted zero-inflated negative binomial regression model. For every year treated with VKA, the AVC score increased, on average, by 6% (ratio of expected counts (REC) = 1.06; 95% CI 1.02-1.10) compared to non-use. The results were consistent in sensitivity analyses excluding patients with known cardiovascular disease and statin users (REC=1.07; 95% CI 1.02-1.11 and REC=1.10; 95% CI 1.03-1.17, respectively). NOAC treatment was not significantly associated with AVC score in any of the corresponding models (REC=1.03, 1.02 and 0.96, respectively).

Conclusion: Compared to no treatment with anticoagulants, VKA use was associated with increased AVC score, while a similar association could not be established for NOAC.

Keywords: Vitamin K; vitamin K antagonists; new oral anticoagulants; aortic valve calcification; cardiac CT scan; risk factors.

Introduction

Vitamin K Antagonist (VKA) has been the most frequently prescribed anticoagulant worldwide, including Denmark, even after the introduction of new oral anticoagulants (NOAC) (1-4). In addition to prevention of thromboembolisms, VKA is the only anticoagulant approved for patients with a mechanical heart valve or mitral stenosis (5).

Vitamin K is a fat-soluble vitamin consisting of two forms, vitamin K1 (phylloquinone) and vitamin K2 (menaquinone). The synthesis of functional clotting factors II, VII, IX and X is dependent on the activation of vitamin K1, and this activation is inhibited by VKA treatment. However, vitamin K2 is also inhibited by VKA. Vitamin K2 is involved in the inhibition of arterial calcification and is essential for the γ-carboxylation of matrix-Gla proteins (MGP) (6-9). γ-carboxylation of MPG is vital for keeping a normal balance of cellular calcium uptake. Without MGP, the mineralization process in bones and blood vessels is hampered (10). Several animal studies have shown that inhibition of the vitamin K-dependent proteins by VKA results in both arterial and soft tissue calcification (11-15). This was first described in mice in 1997 (16). Other studies have suggested that VKA treatment is associated with increased aortic valve calcification (AVC) and aortic calcification in humans (17-19). As severe AVC is a major risk factor in development of aortic valve stenosis (20-23), this might be a significant problem for patients receiving VKA treatment.

The objective of this study was to clarify if patients on VKA treatment have increased AVC scores compared with patients treated with NOAC and patients who never treated with VKA or NOAC.

Methods

Study design and population

This study is a multicentre, retrospective cross-sectional study based on the DANCAVAS trial (24). In brief, the DANCAVAS trial is a population-based randomized screening trial for cardiovascular disease (CVD). From 2014 until 2017, 10,471 Danish men aged 65–74 years were examined with a non-contrast CT scan (25). Additionally, 745 randomly selected women were included in 2015 (24); during 2017-2019, the screening group was expanded to include men aged 60-64 years. The baseline variables from the DANCAVAS trial were available for this study. All participants with a CT scan were included. Subjects with incorrect or insufficient data, including missing AVC score, or previous heart valve surgery were excluded. We were unable to get prescriptions prior to January 2004 and after December 2018. Therefore, participants included in DANCAVAS after December 2018 were excluded. The Danish National Health Service Prescription Database was used to extract participants' medication data on redemption of prescribed VKA; NOAC; and antihypertensive, lipid lowering, antithrombotic and antidiabetic agents (see below).

The study was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20140028) and the Danish Data Protection Agency. The study was conducted in accordance with the Declaration of Helsinki. Written and verbal informed consent was obtained from each participant.

Aortic valve calcification

The AVC score was measured on the non-contrast CT scans. AVC scoring was performed offline by skilled technicians using in-house created and validated software. The AVC score was defined as calcification within the valve leaflet, in the aortic sinus of Valsalva (starting 6 mm below the ostium of the coronaries) and in the aortic valve annulus (26). Calcifications in the coronaries and mitral

valve annulus were carefully excluded. The score was calculated by adding all the calcifications and was expressed in arbitrary units (AU).

VKA and NOAC treatment

All prescription data were obtained from the Danish National Health Service Prescription Database. Only prescriptions redeemed before the participants' CT scans were included in the total treatment duration. VKA included warfarin (ATC: B01AA03) and phenprocoumon (B01AA04). NOAC included rivaroxaban (B01AF01+B01AX06), apixaban (B01AF02), edixaban (B01AF03) and dabigatran (B01AE07). Anticoagulants could have been used episodically, which we accounted for in the analysis. The derived treatment episodes were added to find the cumulative treatment duration. Treatment episodes were defined by assigning a usage period to each prescription. An uninterrupted episode was defined as a sequence of prescriptions without gaps between these formal usage periods. VKA and NOAC treatment periods were defined differently. VKA usage period assigned to a prescription was defined as lasting 50 days, starting on the day of dispensing. This period corresponded to two tablets (5 mg warfarin) a day. In a sensitivity analysis, the treatment period was changed from 50 to 100 days, i.e. corresponding to one tablet per day. The NOAC treatment period was dependent on the active ingredient; one tablet a day for rivaroxaban or edoxaban and two tablets a day for apixaban or dabigatran. To account for irregular dispensing due to impaired adherence, a 30-day grace period was added to each period of usage.

Confounders

Potential confounders were defined as follows. Hypertension was defined as measured systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg, antihypertensive treatment within three months prior the CT scan (redeemed prescription with one or more of the following medications: ATC: C02, C03, C07, C08, C09) or disclosed by the participant.

Hypercholesterolemia was defined as total cholesterol ≥5 mmol/L, low-density lipoprotein level (LDL) ≥3 mmol/L, treatment with statins (ATC: C10AA) within three months prior to the CT scan or disclosed by the participant. Diabetes mellitus was defined by HbA1c ≥48.0 mmol/mol, antidiabetic treatment (ATC: A10) within three months prior to the CT scan or disclosed by the participant. Family history of CVD (first-degree relative with a history of CVD: men age <55 years and women age <65 years) and prior CVD (prior stroke, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft) was self-reported by the participants.

Statistics

Participant characteristics were tabulated as four anticoagulation treatment groups: Never users of VKA and NOAC, VKA users (never users of NOAC), NOAC users (never users of VKA) and ever users of both VKA and NOAC. All continuous variables were evaluated from empirical histograms.

Means were compared by one-way ANOVA test, medians by non-parametric K-sample test with continuity correction when available and categorical variables by chi-square test. When two groups were compared, means were compared by Student's T-test and medians by non-parametric K-sample test, whereas categorical variables were compared by chi-square test.

To investigate the association between anticoagulation (VKA and NOAC) usage and AVC score, a zero-inflated negative binomial regression was used. In this model, the AVC score was included as independent count variable (0, 1, 2, 3, …)**.** VKA / NOAC treatment duration and traditional cardiovascular risk factors (gender, age, BMI, diabetes mellitus, hypertension, hypercholesterolemia, smoking status, known CVD, family history of CVD and renal function) were explanatory factors in the model (22). As the AVC score was measured once in this cross-sectional study (and, therefore, does not represent cumulated scores over a specified timeframe), an effect estimate is a ratio of expected counts (REC) – in opposition to a ratio of incidence rates. For

instance, a REC of 1.1 for a continuous variable like age (in years) would mean that an additional life-year increases, on average, the expected count by 10%.

Additionally, ordered logistic regression was performed as supplementary sensitivity analysis for which the AVC score was categorised into the following clinically meaningful classes: 0, 1-300, 300-599, 600-1199 and ≥ 1200 AU. To assess whether age stratification was necessary, a test for interaction effects between age and treatment duration of both VKA and NOAC on AVC score was performed. Furthermore, we examined the data for multicollinearity due to concerns that the variables might be highly correlated. This was done using a variance inflation factor (VIF) test (27).

Analyses were performed using Stata statistical software version 15.0 (StataCorp, College Station, Texas 77845 USA). Two-tailed p-values <0.05 were considered statistically significant.

Results

A total of 15,048 non-contrast cardiac CT scans were collected from the DANCAVAS database. Participants with missing AVC score or previous heart valve surgery (n=314) were excluded. Finally, participants included after 31 December 2018 were excluded (n=160) as medical prescriptions were deficient in this subgroup. A flowchart showing excluded participants is presented in Fig. 1. A total of 14,604 participants were included in the study. Atrial fibrillation was recorded in 1,029 patients. The participants' median age was 67.4 years; 683 had used VKA but never NOAC; 412 had used NOAC but never VKA; and 190 had used both VKA and NOAC. Table 1 describes the participants' baseline characteristics stratified by anticoagulation treatment status.

When comparing participants treated with either VKA or NOAC, participants in the VKA group (N=683) had a significantly higher creatinine level than participants in the NOAC group (N= 412). However, the NOAC-treated group counted significantly fewer participants with diabetes and

known CVD than the VKA-treated groups. The groups did not differ significantly in any other parameters (Table 1). The median treatment duration for VKA was 2.5 years (25% quartile: 0.7, 75%; 6.6), while it was 1.0 years for NOAC (25% quartile: 0.3, 75%; 2.1) (Figure 2).

Figure 3 shows the distribution of the different AVC score categories in patients with various treatment durations of VKA treatment. We found a significant association between VKA treatment duration and increasing AVC score category ($p<0.001$). This association remained significant when patients were stratified into the two age groups, ≤67 years ($p<0.001$) and >67 years ($p<0.001$).

VKA treatment duration was associated with AVC score in the zero-inflated negative binomial regression model (Table 2). For every year in treatment with VKA, the AVC score increased by 6% (REC=1.06, 95% CI=1.02-1.10). When excluding participants with known CVD or participants undergoing lipid-lowering treatment, we observed no substantial changes in the rates (REC=1.07, 95% CI=1.02-1.11 and REC=1.10, 95% CI=1.03-1.17, respectively). Other traditional risk factors such as age, male gender, smoking, BMI, diabetes, hypertension, dyslipidaemia, family history of CVD and known CVD were also found to be associated with a higher AVC score. NOAC treatment was not significantly associated with AVC score in any of these models (REC=1.03, 95% CI=0.95-1.13, REC=1.02, 95% CI=0.92-1.13 and REC=0.96, 95% CI=0.84-1.09, respectively). In the sensitivity analysis with a VKA treatment period of 100 days per prescription (see appendix Table S1), VKA remained positively associated with AVC score (REC=1.04, 95% CI=1.02-1.08). When performing an ordered logistic regression, we found that VKA still had a significant effect on AVC score. The risk of being in a higher AVC class increased by 3% for every year treated with VKA. NOAC treatment remained without significant association (see appendix, Table S1 and S2). In further sensitivity analyses, we excluded patients with atrial fibrillation and patients who had other indications for OAC than atrial fibrillation, respectively. The results were consistent with the above analyses.

No significant interaction effect of VKA on AVC score was observed when testing the interaction between age and duration of VKA (see appendix, Table S3). When testing the interaction between age and NOAC treatment, we found a significant interaction. This was also true for participants who had been treated with both VKA and NOAC at some point. However, the test showed a protective effect of NOAC on participants in the age group 60-68 year (OR=0.69, p=0.04), but a harmful effect on the age group 68-75 years (OR=1.60, p=0.027) (see appendix, Table S3).

When performing the VIF test to test for multicollinearity, the mean VIF was 1.05. The highest VIF score found was hypertension and Body Mass Index (BMI) both with a VIF of 1.14 (see appendix, Table S4). We therefore conclude that no significant correlation exists between the different variables.

Discussion

In this multicentre, retrospective case-control study, we found that the duration of VKA treatment was significantly associated with an increased AVC score. This association was robust to adjustment for known risk factors for calcific aortic valve stenosis. We found no significant association between NOAC treatment and AVC score. These findings indicate that prolonged VKA treatment may accelerate calcification of the aortic valve, and this may be of significance as AVC potentially leads to aortic stenosis. With a growing elderly population and an increased use of anticoagulation medication, the findings in this study may have important ramifications for clinical practice in the future.

Our findings are in accordance with two previous studies. A smaller cross-sectional, observational study compared the AVC score in patients with atrial fibrillations treated with warfarin, NOAC or non-users, finding a trend leaning towards a higher AVC score in patients treated with warfarin

(28). A retrospective, longitudinal observational study compared AVC presence in patients with atrial fibrillations and chronic kidney disease treated with either warfarin or rivaroxaban. This study showed a slower progression of AVC in patients treated with rivaroxaban (29).

Our results should be discussed in the light of the pathophysiology of AVC, which encompasses two different phases – the initiation and the propagation phase. The initiation phase is typically caused by endothelial damage due to mechanical stress on the valve. This damage starts a cascade of inflammation with infiltration of lipids and immune cells and, eventually, the microcalcification process starts (20, 30). The propagation phase is defined by fibrosis and increased calcification, which, in turn, increase the mechanical stress and valvular dysfunction, creating a vicious cycle with increased calcification. Several regulatory pathways are involved in the calcification pathways including bone morphogenetic proteins (21). MGP inhibits calcium crystal formation via regulation of bone morphogenetic proteins 2 and 4 (31-33), but vitamin K2 is required to introduce gamma-carboxylation of MGP (6-9). VKA inhibits the recycling of vitamin K, and the vitamin-K-dependent proteins are therefore left inactive. VKA treatment is thought to promote calcification of the aortic valve through this mechanism (11, 34).

Several imaging modalities are available for assessing the development of AVC. These modalities include echocardiography, positron emission tomography (PET) and cardiac CT. We assessed AVC with cardiac CT, which is commonly used and recommended in the European Society of Cardiology (ESC) guidelines for measuring the presence and extent of AVC (35).

Currently, no guideline-recommended pharmacological intervention to halt AVC progression exists. Treatment of hypertension is recommended, as hypertension is known to affect the stenotic aortic valve and accelerate left ventricular hypertrophy. Furthermore, left ventricular hypertrophy is associated with increased cardiovascular morbidity and mortality in patients with aortic valve stenosis (36, 37). Observational retrospective studies have investigated the effect of angiotensin-

converting enzyme (ACE) inhibitors and have found that ACE treatment was associated with less AVC but did not slow the haemodynamic progression (38, 39). Angiotensin receptor blockers may have an effect on both valve fibrosis and calcification (40). However, neither treatment has been investigated in prospective randomized controlled trials (RCT). Lipid-lowering drugs have been suggested to be beneficial in aortic valve stenosis because they lower the level of inflammation and atherosclerosis. However, a subsequent meta-analysis failed to confirm this effect (41). Bisphosphonate or denosumab, which are usually used to maintain bone health, have been suggested to decrease the progression of aortic valve stenosis. However, studies have shown conflicting results (42, 43). Both bisphosphonate and denosumab are being further investigated in the RCT trial SALTIRE 2 (Clinicaltrials.gov: NCT02132026).

Several RCTs are currently investigating the effect of vitamin K supplementation on the progression of calcification. A 12-month prospective, open-label intervention trial randomized patients with asymptomatic or mildly symptomatic AVC 1:1 to either 2 mg vitamin K1 or placebo. The study found a significant deceleration of AVC progression in patients treated with vitamin K1 supplementation (23). Another similar on-going double-blinded, placebo-controlled RCT is investigating whether 720 µg/day vitamin K2 supplementation can reduce the rate of calcification in patients a significant AVC burden (300 AU or higher) (44). The findings in these studies will contribute to our understanding of the role of vitamin K in AVC. More RCTs with a broad range of patients would clarify whether vitamin K supplementation is effective in decreasing or slowing down AVC.

Strengths and limitations

The study is limited by its observational design. Any cause and effect relationship between VKA and AVC score is therefore open to interpretation. However, the study population is large and we were able to adjust statistically for a large number of risk factors. However, residual confounding

may exist as we did not have information on, e.g., presence of bicuspid aortic valve and duration of hypertension.

As the Danish National Health Service Prescription Database does not contain data on medication prior to 2004, we were not able to obtain a life-long record of VKA usage. However, use of this database ensured a minimum of information bias regarding the participants' medical treatment. The DANCAVAS trial mainly included male participants in the age group 60-75. The results from this study are not representative for the entire population, and selection bias must be considered when interpreting and applying the results. Recall bias might be an issue when considering that the participants reported their own illnesses and any illnesses in their family.

As the number of NOAC users was relatively small and NOAC treatment duration was shorter than VKA treatment, the power is small. Therefore, we cannot be certain if there are any real advantages concerning VKA compared to NOAC. However, this is the first study to assess the effect of both VKA and NOAC on AVC score.

Conclusion

We found that adjusted for risk factors, the duration of VKA treatment was associated with AVC score. The increased calcification of the aortic valve is consistent with earlier findings from imaging studies. These results may fuel existing concerns; but before strict conclusion can be drawn, we need prospective studies with patients treated long-term with VKA or NOAC and, finally, RCTs with vitamin K supplementation should be performed.

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Conflict of Interest

None declared.

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Figure legends

Figure 1: Selection of study population

Figure 2: Treatment duration of VKA and NOAC.

Figure 3: Distribution of aortic valve calcification (AVC) score categories in participants with various durations of VKA treatment according to: (A) all subjects; (B) age <67 years; (C) age ≥67 years.

Table 1 – Baseline characteristics

	All participants (N=14,604)	Never users of VKA + NOAC (N=13,319)	VKA users, never users of NOAC (N=683)	NOAC users, never users of VKA (N=412)	Ever user of both VKA + NOAC (N=190)	p-value[a]	p-value[b]
Male	13,859 (95)	12,601 (95)	663 (97)	407 (99)	188 (99)	<0.0001	0.10
Age, years	67.4 (65, 70)	67.3 (64, 70)	68.8 (66, 72)	68.3 (66, 71)	68.4 (66, 71)	<0.0001	0.07
Body mass index, kg/m^2	28.0 (±4.4) 14,576	27.9 (±4.3) 13,296	29.4 (±5.1) 681	29.5 (±5.0)	28.7 (±4.6)	<0.0001	0.64
Diabetes	1,891 (13)	1,656 (12)	143 (21)	65 (16)	20 (11)	<0.0001	0.04
Hypertension	9,134 (63)	8,100 (61)	553 (81)	329 (80)	152 (80)	<0.0001	0.65
Dyslipidemia	11,862 (81)	10,816 (81)	585 (86)	311 (75)	130 (68)	<0.0001	0.08
Smoking status						<0.0001	0.88
Never smokers	4,933 (34)	4,514 (34)	229 (34)	139 (34)	51 (27)		
Former smokers	7,276 (50)	6,572 (49)	370 (54)	216 (52)	118 (62)		
Active smokers	2,331 (16)	2,177 (16)	81 (12)	52 (13)	21 (11)		
Family history of CVD	2,067 (14) 14,558	1,850 (14) 13,275	113 (17) 681	71 (17)	33 (17)	0.08	0.94
Known atrial fibrillation	1,029 (7)	213 (2)	405 (59)	263 (64)	148 (78)	<0.0001	0.16
Known CVD	1,667 (12)	1,393 (10)	166 (24)	78 (19)	30 (16)	<0.0001	0.04
HDL, mmol/L	1.4 (1.1, 1.7) 14,520	1.4 (1.1, 1.7) 13,243	1.3 (1.0, 1.6) 674	1.4 (1.1, 1.6)	1.4 (1.1, 1.6)	<0.0001	0.08
LDL, mmol/L	2.9 (2.2, 3.6) 14,487	2.9 (2.2, 3.6) 13,213	2.6 (1.8, 3.3) 675	2.7 (2.0, 3.4) 411	2.6 (2.0, 3.2) 189	<0.0001	0.17
Total cholesterol, mmol/L	5.0 (±1.1) 14,524	5.1 (±1.1) 13,247	4.7 (±1.1) 675	4.7 (±1.1)	4.6 (±1.0)	<0.0001	0.43
Creatinine, µmol/L	88 (±23) 14,520	87 (±22) 13,243	95 (±44) 675	91 (±19)	92 (±20)	<0.0001	0.049
eGFR, mL/min	78 (±14) 14,511	79 (±13) 13,235	74 (±16) 675	76 (±15) 411	75 (±15)	<0.0001	0.047
Systolic blood pressure, mmHg	149 (±19) 14,507	150 (±19) 13,233	146 (±18) 676	145 (±19) 408	147 (±19)	<0.0001	0.14
Diastolic blood pressure, mmHg	82 (±10) 14,505	82 (±10) 13,232	83 (±10) 675	82 (±10) 408	84 (±10)	0.06	0.37
AVC score, AU	107 (0, 79)	100 (0, 74)	213 (0, 199)	148 (0, 119)	164 (0, 162)	<0.0001	0.27
AVC score categories:							
0	5,915 (41)	5,492 (41)	210 (31)	148 (36)	65 (34)	<0.0001	0.54
1-300	7,406 (51)	6,737 (51)	365 (53)	209 (51)	95 (50)		
301-599	704 (5)	611 (5)	50 (7)	28 (7)	15 (8)		
600-1199	364 (2)	304 (2)	33 (5)	16 (4)	11 (6)		
≥ 1200	215 (1)	175 (1)	25 (4)	11 (3)	4 (2)		

Abbreviations: VKA, vitamin K antagonists; NOAC, new oral anticoagulants; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; AVC, aortic valve calcification; AU, Arbitrary Units.

[a]p-value for difference between all treatment groups.[b]p-value for difference between ever users of VKA alone and ever users of NOAC alone. Two-sided p-values are shown for categorical data compared by chi-square tests; means were compared by one-way ANOVA tests, medians by nonparametric k-sample tests.

Values are n (%), mean (±SD), median (quartile 1, quartile 3) and in case of missing observations total number of patients.

Table 2: Zero-inflated negative binominal regression model of the association between duration of VKA treatment and aortic valve calcification.

	All subjects with a full profile (14,301)			**Excluding patients with known CVD (N= 12,682)**			**Excluding patients in treatment with lipid lowering drugs (N=9,435)**		
	REC	95% CI	p-value	REC	95% CI	p-value	REC	95% CI	p-value
VKA, yrs	1.06	1.02-1.10	0.003	1.07	1.02-1.11	0.003	1.10	1.03-1.17	0.003
NOAC, yrs	1.03	0.95-1.13	0.46	1.02	0.92-1.13	0.7	0.96	0.84-1.09	0.51
Age, yrs	1.09	1.08-1.10	<0.0001	1.09	1.08-1.11	<0.0001	1.09	1.07-1.10	<0.0001
Sex									
Male	2.43	2.02-2.91	<0.0001	2.78	2.28-3.39	<0.0001	2.35	1.80-3.04	<0.0001
Smoking status									
Former smoker	1.15	1.05-1.25	0.002	1.11	1.02-1.22	0.02	1.10	0.98-1.23	0.12
Active smoker	1.33	1.19-1.49	<0.0001	1.34	1.19-1.52	<0.0001	1.55	1.33-1.81	<0.0001
BMI, kg/m^2	1.04	1.03-1.05	<0.0001	1.04	1.03-1.05	<0.0001	1.05	1.04-1.06	<0.0001
Diabetes	1.16	1.04-1.30	0.006	1.16	1.03-1.32	0.02	1.24	0.98-1.56	0.07
Hypertension	1.39	1.28-1.51	<0.0001	1.40	1.28-1.53	<0.0001	1.26	1.14-1.41	<0.0001
Dyslipidemia	1.20	1.08-1.34	0.001	1.23	1.09-1.38	<0.0001	1.01	0.89-1.14	0.94
Family history of CVD	1.17	1.05-1.30	0.003	1.22	1.08-1.37	0.001	1.12	0.96-1.31	0.16
Known CVD	1.27	1.14-1.42	<0.0001				1.19	0.90-1.56	0.22
eGFR, mL/min	1.00	1.00-1.00	0.71	1.00	1.00-1.00	0.93	1.00	1.00-1.00	0.81

Abbreviations: VKA, vitamin K antagonists; AVC, aortic valve calcification; REC, ratio of expected counts, CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; NOAC, new oral anticoagulants.

AVC score as a count variable (Arbitrary units, AU)

Figure 1

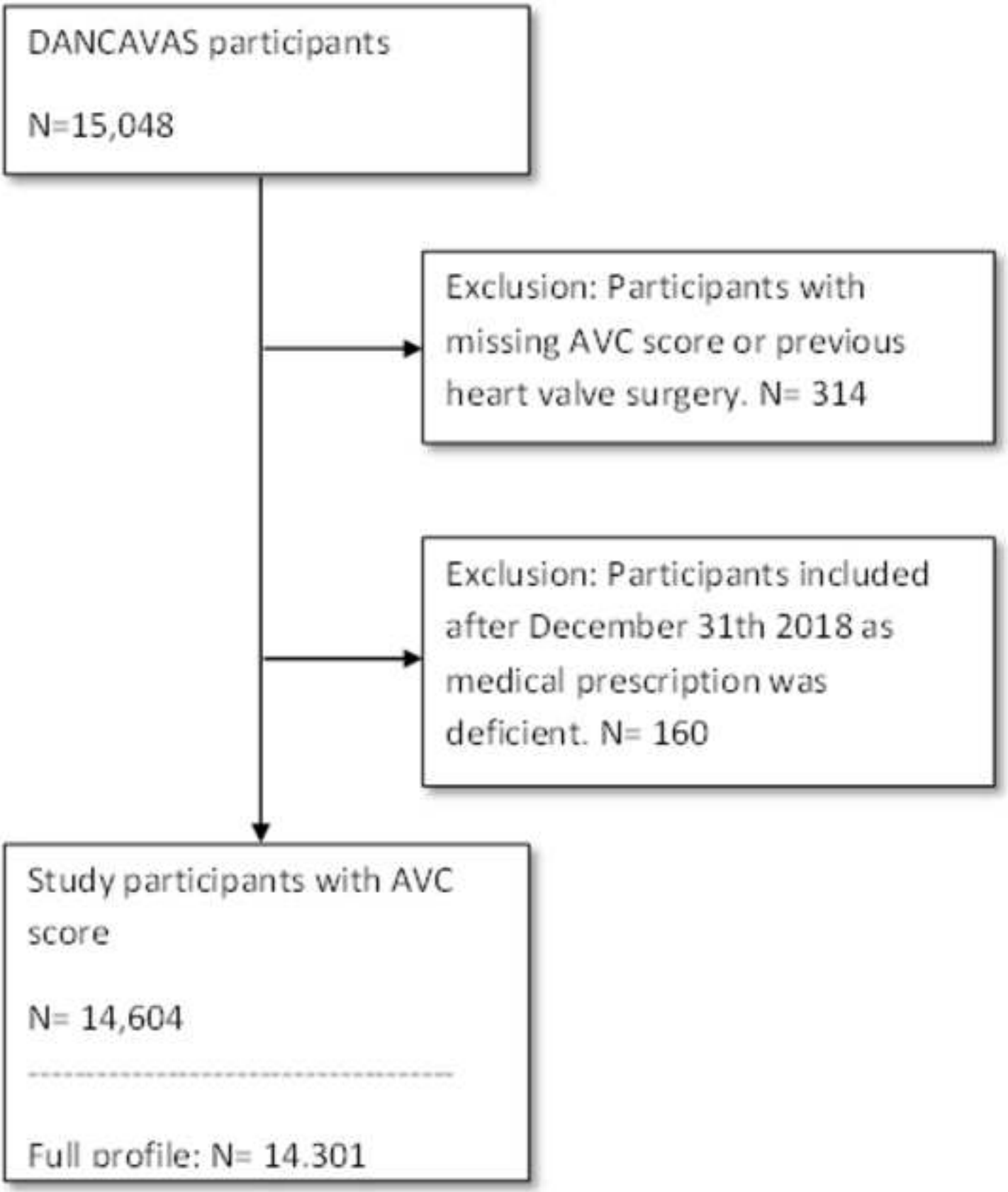


Figure 2

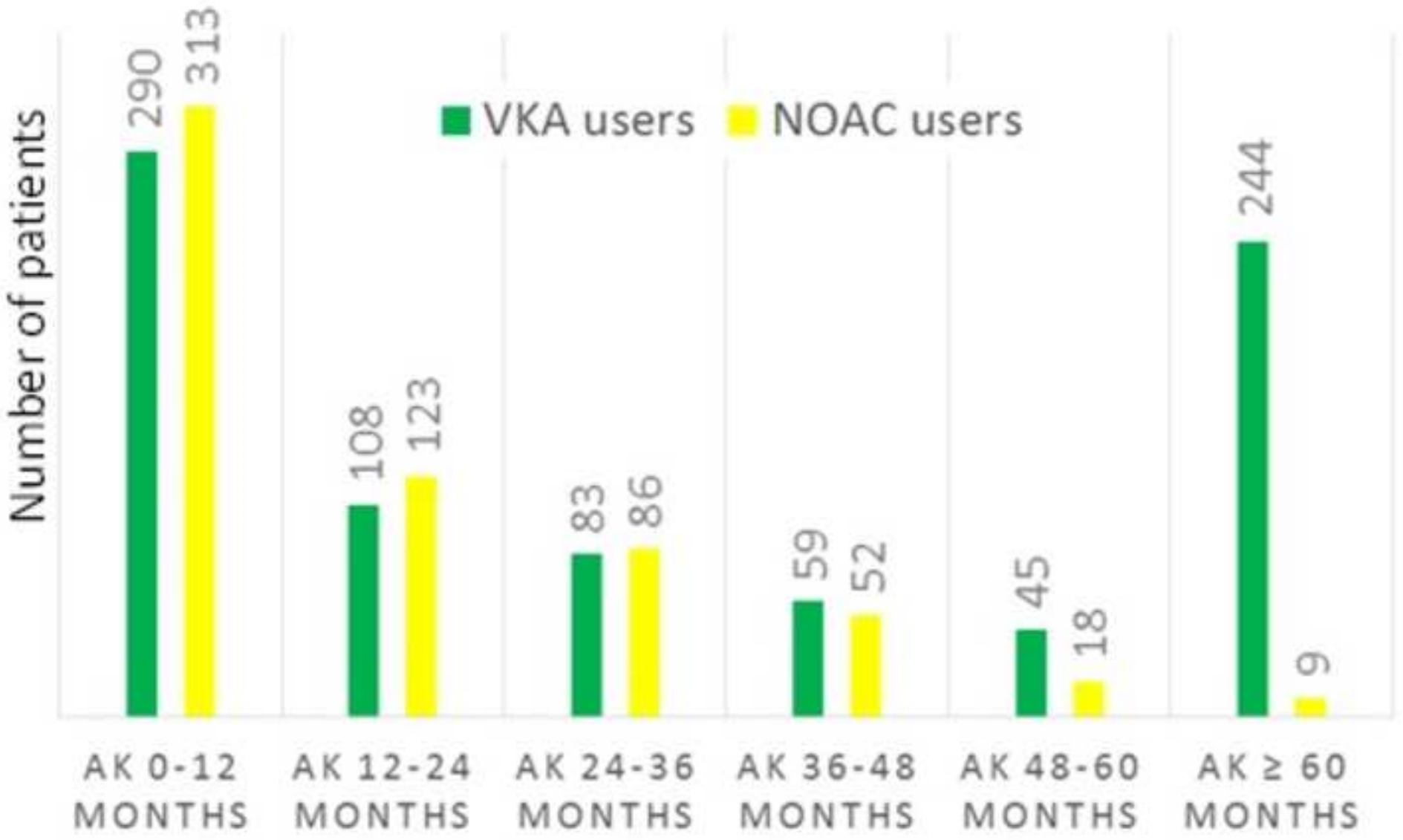
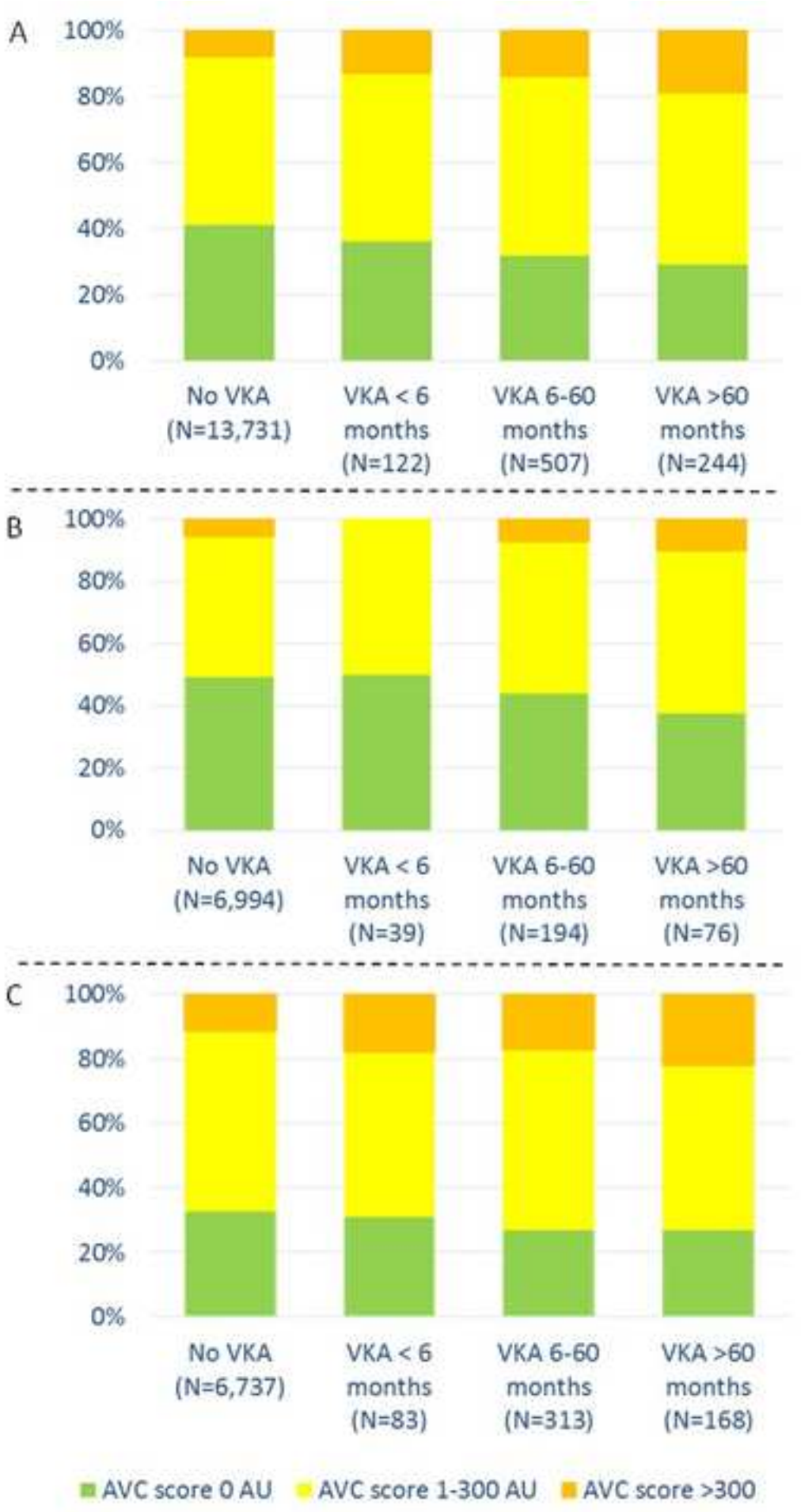


Figure 3

Click here to access/download;Figure;Figure 3.jpg



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