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Mental health conditions and adherence to direct oral anticoagulants in patients with incident atrial fibrillation: A nationwide cohort study

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ABSTRACT

Objective: Medication adherence is essential for effective stroke prevention in patients with atrial fibrillation (AF). We aimed to assess whether adherence to direct oral anticoagulants (DOACs) in AF patients is affected by the presence of mental health conditions (MHCs).

Methods: The nationwide FinACAF cohort covered 74,222 AF patients from all levels of care receiving DOACs during 2011–2018 in Finland. Medication possession ratio (MPR) was used to quantify adherence. Patients with MPR ≥0.90 were defined adherent. MHCs of interest were depression, bipolar disorder, anxiety disorder and schizophrenia.

Results: The patients' (mean age 75.4 ± 9.5 years, 50.8% female) mean MPR was 0.84 (SD 0.22), and 59.5% had MPR ≥0.90. Compared to patients without MHC, the adjusted ORs (95% CI) for adherent DOAC use emerged slightly lower in patients with depression (0.92 (0.84–0.99)) and bipolar disorder (0.77 (0.61–0.97)) and unsignificant in patients with anxiety disorder (1.08 (0.96–1.21)) and schizophrenia (1.13 (0.90–1.43)). However, when only persistent DOAC therapy was analyzed, no MHC was associated with poor adherence, and instead anxiety disorder was associated with adherent DOAC use (1.18 (1.04–1.34)).

Conclusion: Adherence to DOACs in AF patients in Finland was relatively high, and no meaningful differences between patients with and without MHCs were observed.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting up to 4.1% of the adult population and is a major risk factor of ischemic stroke [1–3]. When used adequately, life-long oral anticoagulation (OAC) therapy can effectively decrease the risk of stroke, and current guidelines recommend direct oral anticoagulants (DOACs) as the first line anticoagulant over the older vitamin K antagonists in non-valvular AF (VKAs) [4,5]. In Finland, DOACs are increasingly common accounting for over 90% of OAC initiations during 2018, and while being more expensive than VKAs, 42–65% of their costs have been reimbursed to AF patients with at least intermediate stroke risk since

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2012 [6]. Unlike VKAs, DOACs do not require routine dose monitoring, and due to the lack of these regular control visits, concerns have been expressed about sufficient adherence to DOAC therapy. Medication adherence is essential for effective stroke prevention with DOACs, and poor DOAC adherence has been associated with higher mortality and stroke risk in patients with AF [7–9]. Medication adherence can be divided in three phases: initiation, implementation, and persistence, with implementation referring to how a patient's actual dosing corresponds to the prescribed dosing from treatment initiation until the last dose [10].

Mental health conditions (MHCs) are common in AF patients and have been associated with lower initiation rate of OAC therapy as well as with lower quality of VKA therapy [6,11]. Additionally, AF patients suffering from MHCs have a higher risk of ischemic stroke than patients without MHCs [11]. Previous studies have suggested poor medication adherence in patients with MHCs, but the effect of MHCs on adherence to DOAC therapy in AF patients is currently unknown [12–16].

The aim of the present nationwide retrospective cohort study covering all AF patients in Finland was to determine whether DOAC adherence in terms of implementation is affected by the presence of MHCs.

2. Methods

2.1. Study population

The Finnish Anticoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study covering all AF patients in Finland during 2004–2018 as well as their drug purchases. Data were gathered from three national health care registers (hospitalizations and outpatient specialist visits: Care Register for Health Care (HILMO); primary health care: Register of Primary Health Care Visits (AvoHILMO); and National Reimbursement Register upheld by Social Insurance Institute (KELA)). The inclusion criterion for the cohort was an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code I48 (including atrial fibrillation and atrial flutter, together referred to as AF) recorded during 2004–2018, and cohort entry occurred on the date of the first recorded AF diagnosis. Patients aged <18 years at cohort entry and those permanently migrated abroad before 31st of December 2018 were primarily excluded. This substudy was conducted within a cohort of patients diagnosed with incident AF during 2007–2018, established in a previous study of the FinACAF cohort [6]. The present substudy focused only on patients receiving DOAC therapy during 2011–2018, when DOACs were approved for stroke prevention in patients with AF in Finland. Additionally, patients with only one redeemed DOAC prescription were excluded. The patient selection process is presented in Supplementary Fig. 1.

2.2. Adherence to DOAC therapy

The present study focused on the implementation of initiated DOAC therapy. The commonly used medication possession ratio (MPR) method was chosen to quantify adherence since it inherently accounts for stockpiling and is suitable for comparison of adherence between two groups on monotherapy [17,18]. The MPR of each patient was calculated by dividing the number of days covered with the sum of purchased daily doses during follow-up by the number of days between the first and the last DOAC purchase dates added with the days covered with the dose of the last purchase:

$$MPR = \frac{Days\ covered\ with\ the\ sum\ of\ daily\ doses\ during\ follow-up}{Days\ between\ first\ and\ last\ DOAC\ purchase\ plus\ the\ days\ covered\ with\ the\ daily\ dose\ from\ last\ DOAC\ purchase}$$

MPR values were capped to a maximum of 1.0 and patients with MPR $\geq$ 0.90 were defined adherent. The cut-off of 0.90 was chosen, as MPR <0.90 has been associated with reduced efficacy of stroke prevention with DOACs [7,19]. Since we assessed adherence between therapy initiation and discontinuation, long temporary discontinuations in DOAC therapy may cause significant downward bias in the results. Therefore, a sensitivity analysis was conducted by including only persistent DOAC use, i.e., purchases prior to first therapy discontinuation. Discontinuation was defined as the first 135-day gap in DOAC redemptions, since in Finland it is possible to purchase drugs with reimbursement for a maximum of 90 days and an additional 45-day grace period was allowed.

2.3. Mental health conditions

MHCs of interest were depression, anxiety disorder, bipolar disorder, and schizophrenia, chosen due to their high prevalence and burden in the aging population of patients with AF [20]. Patients were classified into these groups if they were recorded with the International Classification of Diseases, 10th revision (ICD-10) diagnosis code or International Classification of Primary Care, Second Edition (ICPC-2) entry of the condition prior to cohort entry (depression (ICD-10: F32, F33, F34.1; ICPC-2: P76), anxiety disorder (ICD-10: F40-F42, F43.1; ICPC-2: P74), bipolar disorder (ICD-10: F31; ICPC-2: P73), schizophrenia (ICD-10: F20; ICPC-2: P72)). Patients with more than one of these conditions were classified into each diagnostic category separately. Additionally, patients were classified into psychiatric medication group if they had fulfilled a prescription of an antidepressant, antipsychotic, or mood stabilizing medication within the year before the first AF diagnosis (ATC: N05A, N05BE01, N06A) irrespective of whether they had a previous specific psychiatric diagnosis. Medication data were not utilized to classify patients into specific MHC categories. Patients without diagnostic codes of psychiatric conditions or psychiatric medications were classified as patients without MHC.

2.4. Study ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (nr. 15/2017) and granted research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019–3 and Tax Register VH/874/07.01.03/2019)). The patients' identification numbers were pseudonymized, and the research group received individualized, but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2002.

2.5. Statistical analysis

The chi-square test was used to compare differences between proportions, and the independent samples *t*-test was used to analyze normally distributed continuous variables. MPR was non-normally distributed, and therefore, mean MPR between patients with and without MHCs were compared using the Mann-Whitney *U* test. Unadjusted and adjusted odds ratios (ORs) of adherence to DOAC therapy (MPR $\geq$0.90) for each MHC category were calculated using the binary logistic regression. Adjustments were made for age, sex and calendar year of DOAC initiation, and additionally for stroke and bleeding risk factors (heart failure, hypertension, diabetes, prior stroke, vascular

disease, prior bleeding, alcohol use disorder, renal failure and liver cirrhosis or failure), dementia, income (highest annual income during follow-up divided in quintiles), dosage of the first purchased DOAC (once or twice daily), previous use of VKAs and polypharmacy (>5 different medications during the year preceding DOAC initiation), since these have been shown to affect medication adherence in previous studies [21–24]. The definitions of the comorbidities and risk scores are displayed in Supplementary Table 1. Statistical analyses were performed with the IBM SPSS Statistics software (version 27.0, SPSS, Inc., Chicago, Illinois) and R (version 4.0.5, https://www.R-project.org).

3. Results

Altogether, 74,222 patients (50.8% female) with incident AF receiving DOAC therapy were identified. The mean age was 75.4 years (SD 9.5) in women and 70.0 years (SD 10.6) in men and the mean duration of DOAC therapy during follow-up was 1.7 years (SD 1.4). Depression was the most common MHC with a prevalence of 4.8% and 13.4% of patients received psychiatric drug therapy. Altogether, 79.4% of the medication group used antidepressants and 36.0% received antipsychotics or mood stabilizers. Patients with MHCs were more often female, had lower income and higher prevalence of cardiovascular risk factors, dementia and alcohol use disorder than patients without MHC history (Table 1).

Overall, mean MPR was 0.84 (SD 0.22), and 44,155 patients (59.5%) were adherent to DOAC therapy with MPR ≥0.90. When compared to patients without MHCs, mean MPR was significantly lower in patients receiving psychiatric medications ($p < 0.05$, Table 2). When each diagnostic MHC category was analyzed separately, we found that MPR in patients with depression or bipolar disorder did not differ from the non-MCH patients, whereas MPR was significantly higher in patients with anxiety disorder or schizophrenia compared to patients without MHCs. Correspondingly, the proportion of adherent patients was higher in patients with anxiety disorder or schizophrenia and lower in patients using psychiatric medication (Table 2). On the other hand, after adjusting for confounding factors, a lower likelihood of adherent DOAC use was observed in patients with depression or bipolar disorder as well as in patients receiving psychiatric medications when compared to patients without MHC, while anxiety disorder and schizophrenia had no effect on DOAC adherence (Table 2). Among the variables included in

Table 1
Descriptive characteristics of the cohort.

	No MHC	Depression	Bipolar disorder	Anxiety disorder	Schizophrenia	Psychiatric medication
	$n = 61,171$	$n = 3556$	$n = 372$	$n = 1485$	$n = 368$	$n = 9831$
Demographics						
Mean age, years	72.8 (10.3)	70.8 (11.3)*	65.9 (10.4)*	70.2 (11.7)*	69.0 (9.5)*	73.3 (11.0)*
Female sex	29,657 (48.5%)	2233 (62.8%)*	184 (49.3%)	1004 (67.6%)*	198 (53.8%)*	6116 (62.2%)*
Income quintiles		*	*	*	*	*
1st	11,040 (18.1%)	814 (22.9%)	106 (28.4%)	360 (24.2%)	200 (54.3%)	2483 (25.3%)
2nd	12,993 (21.2%)	925 (26.0%)	106 (28.4%)	419 (28.2%)	109 (29.6%)	2512 (25.6%)
3rd	11,516 (18.8%)	734 (20.6%)	61 (16.4%)	297 (20.0%)	37 (10.1%)	1798 (18.3%)
4th	12,655 (20.7%)	655 (18.4%)	53 (14.2%)	249 (16.8%)	12 (3.3%)	1627 (16.5%)
5th	12,957 (21.2%)	428 (12.0%)	47 (12.6%)	160 (10.8%)	10 (2.7%)	1411 (14.4%)
Comorbidities and medications						
Alcohol use disorder	1241 (2.0%)	509 (14.3%)*	103 (27.6%)*	195 (13.1%)*	40 (10.9%)*	873 (8.9%)*
Dementia	2760 (4.5%)	391 (11.0%)*	30 (8.0%)*	126 (8.5%)*	33 (9.0%)*	1228 (12.5%)*
Diabetes	14,169 (23.2%)	1085 (30.5%)*	148 (39.7%)*	406 (27.3%)*	152 (41.3%)*	2834 (28.8%)*
Dyslipidemia	33,984 (55.6%)	2207 (62.1%)*	223 (62.5%)*	899 (60.5%)*	183 (49.7%)*	6107 (62.1%)*
Heart failure	7255 (11.9%)	549 (15.4%)*	60 (16.1%)*	210 (14.1%)*	86 (23.4%)*	1566 (15.9%)*
Hypertension	50,694 (82.9%)	3115 (87.6%)*	314 (84.2%)	1301 (87.6%)*	296(80.4%)	8649 (88.0%)*
Liver cirrhosis or failure	188 (0.3%)	13 (0.4%)	3 (0.8%)	5 (0.3%)	2 (0.5%)	54 (0.5%)*
CHA_2DS_2-VASc score	3.4 (1.6)	3.7 (1.7)*	3.2 (1.7)*	3.7 (1.7)*	3.4 (1.6)	3.9 (1.7)*
Modified HAS-BLED score (max 7)	2.0 (0.9)	2.2 (1.0)*	2.1 (1.1)*	2.2 (0.9)*	2.0 (0.9)	2.2 (1.0)*
Prior bleeding	6543 (10.7%)	566 (15.9%)*	58 (15.5%)*	252 (15.8%)*	51 (13.9%)	1478 (15.0%)*
Prior stroke	8647 (14.1%)	656 (18.4%)*	65 (17.4%)*	278 (18.7%)*	55 (14.9%)	1795 (18.3%)*
Polypharmacy (>5 drugs)	41,397 (67.7%)	3042 (85.5%)*	339 (90.1%)*	1269 (85.5%)*	317 (86.1%)*	8802 (89.5%)*
Renal failure or dialysis	850 (1.4%)	70 (2.0%)*	4 (1.1%)	29 (2.0%)	6 (1.6%)	194 (2.0%)*
Vascular disease	14,716 (24.1%)	971 (27.3%)*	88 (23.6%)	359 (24.2%)	57 (15.5%)*	2700 (27.5%)*
VKA therapy before DOAC	20,409 (33.4%)	1045 (29.4%)*	129 (34.6%)	424 (28.6%)*	93 (25.3%)*	3309 (33.7%)*

Values denote n (%) or mean (standard deviation). Abbreviations: CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, history of stroke or TIA, vascular disease, age 65–74 years, sex category (female); DOAC, direct oral anticoagulant; MHC, mental health condition; modified HAS-BLED, hypertension, abnormal renal or liver function, prior stroke, bleeding history, age > 65 years, alcohol use disorder(no labile INR or concomitant antiplatelet/non-steroidal anti-inflammatory drug use); VKA, vitamin K antagonist. * $p < 0.05$ when compared to patients without MHC

Table 2
Adherence to DOAC therapy according to the presence of MHCs including all DOAC purchases.

Clinical condition	Mean MPR	Proportion of adherent patients (MPR ≥ 0.90)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No MHC	0.843	60.0%	(Reference)	(Reference)
Depression	0.841	59.5%	0.97 (0.91–1.04)	0.92 (0.84–0.99)
Bipolar disorder	0.857	60.1%	0.99 (0.80–1.22)	0.77 (0.61–0.97)
Anxiety disorder	0.857*	63.8%*	1.17 (1.05–1.31)	1.08 (0.96–1.21)
Schizophrenia	0.879*	67.9%*	1.38 (1.11–1.72)	1.13 (0.90–1.43)
Psychiatric medication	0.836*	57.8%*	0.90 (0.86–0.94)	0.94 (0.90–0.99)

Abbreviations: CI, confidence interval; MHC, mental health condition; MPR, medication possession ratio; OR, odds ratio. ORs estimated with binary logistic regression with the following variables included in adjusted analyses: age, sex, calendar year of DOAC initiation, heart failure, hypertension, diabetes, prior stroke, vascular disease, prior bleeding, alcohol use disorder, renal failure and liver cirrhosis or failure, dementia, income, dosage of DOAC, prior VKA use, and polypharmacy. *$p < 0.05$

Table 3
Sensitivity analysis of the adherence to DOAC therapy according to the presence of MHCs including only persistent DOAC therapy.

Clinical condition	Mean MPR	Proportion of adherent patients (MPR ≥ 0.90)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No MHC	0.888	67.7%	(Reference)	(Reference)
Depression	0.889	67.9%	1.01 (0.94–1.08)	0.97 (0.90–1.05)
Bipolar disorder	0.902	69.2%	1.08 (0.87–1.35)	0.80 (0.63–1.02)
Anxiety disorder	0.906*	71.8%*	1.23 (1.10–1.38)	1.18 (1.04–1.34)
Schizophrenia	0.920*	74.7%*	1.41 (1.11–1.78)	1.14 (0.90–1.47)
Psychiatric medication	0.880*	65.0%*	0.89 (0.85–0.93)	0.98 (0.94–1.04)

Abbreviations: CI, confidence interval; MHC, mental health condition; MPR, medication possession ratio; OR, odds ratio. ORs estimated with binary logistic regression with the following variables included in adjusted analyses: age, sex, calendar year of DOAC initiation, heart failure, hypertension, diabetes, prior stroke, vascular disease, prior bleeding, alcohol use disorder, renal failure and liver cirrhosis or failure, dementia, income, dosage of DOAC, prior VKA use, and polypharmacy. *$p < 0.05$.

the adjusted analyses, twice a day dosing and alcohol use disorder were the strongest predictors for non-adherence (Supplementary Table 2). In the sensitivity analysis including only persistent DOAC use, anxiety disorder was associated with better DOAC adherence, whereas all the other MHC categories had no effect on DOAC adherence, when compared to patients without MHCs (Table 3).

4. Discussion

In this nationwide retrospective cohort study using pharmacy claims data, AF patients with and without MHCs had only marginal differences in their adherence to DOAC therapy. Overall, the crude adherence estimates showed slightly better medication adherence in patients with anxiety disorder and schizophrenia. In the main analysis including all DOAC purchases, depression, bipolar disorder and use of psychotropic medications seemed to associate with poor adherence after adjusting for confounding factors. However, in the sensitivity analysis covering only persistent DOAC therapy, none of the categories were associated with poor adherence, and instead an association between anxiety disorder and adherent DOAC use was observed. Considering this variance in the results of only marginal statistical significance, no robust associations between any of the MHCs and DOAC adherence can be observed.

There are no previous studies investigating the relationship between MHCs and adherence to DOAC therapy in patients with AF. However, there are several studies reporting poor adherence to medical therapy in other chronic conditions in MHC patients [12–16,25] In this respect our results are somewhat contradictory. Nevertheless, observations of non-inferior medication adherence in patients with MHCs can also be found in previous literature [26,27]. Publication bias may contribute to the lack of studies with “null results” in line with our findings of similar medication adherence in patients with and without MHCs.

Previous studies have reported that AF patients suffering from MHCs are less likely to initiate OAC therapy than patients without MHC, and poor OAC coverage may be underlying the observed higher risk of ischemic stroke in AF patients with MHCs [6,11]. However, according to our results, non-adherence to DOAC therapy is unlikely to contribute substantially to the excess stroke risk in these patients. Importantly, unfounded prejudices on insufficient medication adherence due to mental illness should not deem AF patients unsuitable to receive stroke prevention with DOACs.

A recent systematic review and meta-analysis on DOAC adherence in AF patients reported a pooled mean MPR of 0.77 and a proportion of patients with good adherence of 66%, defined as MPR ≥ 0.80 [9]. Therefore, in comparison, the observed mean MPR of 0.84 and 59.5% of patients with MPR ≥ 0.90 in our study reflect overall a relatively high DOAC adherence in Finland. The observed small differences in DOAC adherence between MHC groups in our study are likely multifactorial, including possible differences in medication behavior and self-care resources as well as in the prevalence of social support and institutionalization.

The main strengths of our study are the nationwide nature of the data and the large sample size. The FinACAF cohort covers all AF patients in Finland, gathered from all available national registries from all levels of care, including uniquely also primary care. These registries are well-validated and have high diagnostic accuracy [28–30]. Use of DOACs is based on comprehensive data of redeemed prescriptions, and includes all DOAC purchases, since DOACs are not sold over the counter without prescription.

The inherent challenges of real-world retrospective registry studies are our main limitations. Additionally, a gold standard to define medication adherence is lacking and there are numerous methods to measure adherence, which may influence the results considerably [17,31]. Differences in the persistence of DOAC use in patients with and without MHCs seem to affect the results in our main analysis, as the ORs for adherent drug use are overall higher in patients with MHCs in the sensitivity analysis covering only persistent DOAC therapy. Furthermore, our results rely on drug purchases, and data on DOAC prescriptions and the proportion of drugs truly taken are unknown. Clinically indicated treatment gaps are not accounted for in our data, which may cause downward bias on our adherence estimates. Selection bias may be present due to possible differences in DOAC prescription patterns between patients with and without MHCs. Moreover, excluding early discontinuation from the analyses may contribute to bias. However, a study period with less than three drug purchases is unlikely to show true therapy implementation pattern [32,33]. Additionally, information bias may be present in the recording of psychiatric diagnoses, and the psychiatric medications explored in our study are also used in other indications. Our data lacked information on life-style related factors, except for diagnosed alcohol use disorders. Finally, albeit we were able to adjust our findings for multiple factors, residual confounding cannot be excluded.

In conclusion, the present nationwide cohort study demonstrated that no meaningful difference exists in DOAC adherence between AF patients with and without MHCs as measured from pharmacy claims data. DOAC adherence in Finland was relatively high, but interventions are needed to further increase the proportion of patients with sufficient adherence.

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Role of the funder/sponsor

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CRediT authorship contribution statement

Konsta Teppo: Conceptualization, Methodology, Investigation, Data

curation, Formal analysis, Writing – original draft, Visualization. **Jussi Jaakkola:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – review & editing, Visualization, Supervision. **K.E. Juhani Airaksinen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Fausto Biancari:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Olli Halminen:** Data curation, Methodology, Investigation, Writing – review & editing, Project administration. **Jukka Putaala** Conceptualization, Methodology, Writing – review & editing, Supervision. **Pirjo Mustonen:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Jari Haukka:** Conceptualization, Methodology, Data curation, Writing – review & editing, Supervision. **Juha Hartikainen:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Alex Luojus:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Mikko Niemi:** Conceptualization, Methodology, Writing – review & editing. **Miika Linna:** Conceptualization, Methodology, Writing – review & editing. **Mika Lehto:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

Konsta Teppo: none. Jussi Jaakkola: none. Fausto Biancari: none Olli Halminen: none. Jukka Putaala: Dr. Putaala reports personal fees from Boehringer-Ingelheim, personal fees and other from Bayer, grants and personal fees from BMS-Pfizer, personal fees from Portola, other from Amgen, personal fees from Herantis Pharma, personal fees from Terve Media, other from Vital Signum, personal fees from Abbott, outside the submitted work. Pirjo Mustonen: Consultant: Roche, BMS-Pfizer-alliance, Novartis Finland, Boehringer Ingelheim, MSD Finland. Jari Haukka: Consultant: Research Janssen R&D; Speaker: Bayer Finland. Miika Linna: Speaker: BMSPfizer-alliance, Bayer, Boehringer-Ingelheim. Alex Luojus: none. Juha Hartikainen: Research grants: The Finnish Foundation for Cardiovascular Research, EU Horizon 2020, EU FP7. Advisory Board Member: BMS-Pfizer-alliance, Novo Nordisk, Amgen. Speaker: Cardiome, Bayer. K.E. Juhani Airaksinen: Research grants: The Finnish Foundation for Cardiovascular Research; Speaker: Bayer, Pfizer and Boehringer-Ingelheim. Member in the advisory boards: Bayer, Pfizer and AstraZeneca. Mika Lehto: Consultant: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim, and MSD; Speaker: BMS-Pfizer-alliance, Bayer, Boehringer Ingelheim, MSD, Terve Media and Orion Pharma. Research grants: Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund, Boehringer-Ingelheim. Mikko Niemi: None.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

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