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Heterogeneity after harmonisation: A retrospective cohort study of bleeding and stroke risk after the introduction of direct oral anticoagulants in four Western European countries

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Abstract

Purpose: Database heterogeneity can impact effect estimates. Harmonisation provided by common protocols and common data models (CDMs) can increase the validity of pharmacoepidemiologic research. In a case study measuring the changes in the safety and effectiveness of stroke prevention therapy after the introduction of direct oral anticoagulants (DOACs), we performed an international comparison.

Methods: Using data from Stockholm, Denmark, Scotland and Norway, harmonised with a common protocol and CDM, two calendar-based cohorts were created: 2012 and 2017. Patients with a diagnosis code of atrial fibrillation 5 years preceding the 1-year cohort window were included. DOAC, vitamin K antagonist and aspirin treatment were assessed in the 6 months prior to the start of each year while strokes and bleeds were assessed during the year. A Poisson regression generated incidence rate ratios (IRRs) to compare outcomes from 2017 to 2012 adjusted for changes in individual-level baseline characteristics.

Results: In 280 359 patients in the 2012 cohort and 356 779 in the 2017 cohort, treatment with OACs increased on average from 45% to 65%, while treatment with aspirin decreased from 30% to 10%. In all countries except Scotland, there were decreases in the risk of stroke and no changes in bleeding risk, after adjustment for changes in baseline characteristics. In Scotland, major bleeding (IRR 1.09, 95% confidence interval [CI] [1.00; 1.18]) and intracranial haemorrhage (IRR 1.31, 95% CI [1.13; 1.52]) increased from 2012 to 2017.

Conclusions: Stroke prevention therapy improved from 2012 to 2017 with a corresponding reduction in stroke risk without increasing the risk of bleeding in all countries, except Scotland. The heterogeneity that remains after methodological harmonisation can be informative of the underlying population and database.

J. J. Komen and N. B. Hunt contributed equally to this paper.

KEYWORDS
anti-coagulants, bleeding, heterogeneity, multi-database, stroke, utilisation

Key Points

- Database heterogeneity impacts effect estimates in observational research; data and methodological harmonisation can reduce variation
- In a multi-country cohort study using harmonised data and methods, there was a shift towards direct oral anticoagulants in the period 2012–2017 with a reduction in stroke risk without increasing the risk of bleeding in Stockholm, Denmark and Norway, but not Scotland
- Major bleeding rates (incidence rate ratio [IRR] 1.09, 95% confidence interval [CI] [1.00; 1.18]) driven by intracranial haemorrhage (IRR 1.31, 95% CI [1.13; 1.52]) increased in the period 2012–2017 in Scotland
- Despite improvements in stroke prevention therapy, stroke rates remained unchanged (IRR 0.99, 95% CI [0.9; 1.09]) in Scotland only, in the period 2012–2017
- Multi-database pharmacoepidemiologic studies with heterogeneity that remains after data and methodological harmonisation can be informative of underlying population differences

Plain Language Summary

In this case study, we made an international comparison of the change in the safety and effectiveness of stroke prevention therapy. Using harmonised data from Stockholm (Sweden), Denmark, Scotland and Norway, cohorts were created for 2012 and 2017. Oral anti-coagulant treatment was assessed in the 6 months prior to the start of each year while strokes and bleeds were assessed during the year. Outcomes were compared in 2017–2012, adjusting for changes in baseline characteristics. In 280 359 patients in the 2012 cohort and 356 779 in the 2017 cohort, treatment with OACs increased from 45% to 65%, while treatment with aspirin decreased from 30% to 10%. All countries except Scotland had decreases in the risk of stroke and no changes in bleeding risk, after adjustment for changes in baseline characteristics. In Scotland, major bleeding increased by 9% and intracranial haemorrhage increased by 31% from 2012 to 2017. The variation between the databases that remain after harmonisation methods are applied is informative and by performing observational research in multiple databases, we can increase the validity of the research.

1 | INTRODUCTION

Variability in effect estimates due to variation in methodology and data sources used can influence the results and conclusions in pharmacoepidemiologic research. Despite discussions surrounding specific epidemiological methods, there is seldom a discussion of choices of databases as a potential source of variability. By encompassing multiple databases which span multiple jurisdictions in pharmacoepidemiologic research, more generalisable results can be generated by taking into account such (international) variability. Using harmonisation techniques such as common protocols and common data models (CDMs) or database networks, researchers attempt to standardise the methodology used to generate study results. Prominent examples such as the U.S. Food and Drug Administration's Sentinel initiative, the Canadian Network for Observational Drug Effect Studies, and more recently, the European Health Data & Evidence Network provide harmonisation.[1–4] However, despite these initiatives, researchers still cannot avoid problematic database heterogeneity, as demonstrated even within the same country.[5]

The uptake of direct oral anticoagulants (DOACs) for the prevention of stroke in atrial fibrillation (AF) patients has been driven by guidelines favouring their use over vitamin K antagonists (VKAs),[6,7] and has increased the proportion of AF patients treated with an oral anticoagulant (OAC).[8,9] It was shown in Stockholm that this improvement in stroke prevention therapy was accompanied by a reduction in stroke, while bleeding rates remained unchanged.[10] However, there is a greater risk of bleeding and stroke with DOAC use in the United Kingdom (UK) compared to other countries. In a pan-European cohort study, the risk of major bleeding with all DOACs (Hazard ratio, HR 1.13, 95% confidence interval [CI] [1.02; 1.13]) and, in particular, intracranial bleeding with rivaroxaban use (HR 2.38, 95% CI [1.20; 4.72]) compared to VKAs was greater in UK primary care data than in the other international databanks included,[11,12] which is also reflected elsewhere.[13–17]

With a harmonised approach to the conduct of a multi-database pharmacoepidemiologic study, heterogeneity originating from methodological differences can be decreased and we can better reveal genuine international differences in effect estimates. Inter-database differences in data completeness and quality may persist. Here, in this retrospective

cohort case study, we applied database harmonisation methods to allow for a valid international comparison. Since the introduction of DOACs onto the European market in the early 2010s, evidence from Stockholm has shown the uptake has been great and stroke prevention has improved.[10] Evidence would be improved by using data from more countries to account for international differences and to improve generalisability. In this multi-database case study, we aimed to assess and compare how stroke prevention therapy, stroke, and bleeding rates have changed in 2017 compared to 2012 among AF patients compared between four western European databases.

2 | METHODS

2.1 | Databases

Data from four Western European healthcare settings: Stockholm (Sweden), Denmark, Scotland and Norway were included. All databases are described in detail elsewhere and an overview is provided in Table S1.[18–23] Each database contains dispensing data from community pharmacies and diagnoses recorded in secondary care (admissions, discharge and outpatient consultations). Diagnostic data from primary care was only available for the Stockholm healthcare region. Each data access provider (DAP) extracted the necessary data for the study with patients selected according to the participation criteria and their associated relevant clinical information according to the code lists provided. To harmonise the cohort creation, data processing, variable creation and analytics, all data underwent the extract, transform, load (ETL) process into a CDM. The data was analysed locally according to a common protocol and using a common code list and analytical programme (R script).

The CDM was developed for this study-specific data and it provided only syntactic harmonisation, that is, the data structures and formats are changed but the meanings (exposure and event codes) are maintained. This allowed for a large degree of flexibility so that the source-specific variability remained low and DAPs could contribute fully to the study. All sources use the same medical ontology. In this distributed analysis, the data remained local and only the final analytical results are transferred externally. Similar analyses have previously been published based on data from the Stockholm region,[10] but due to methodological differences in the present analyses, those data were re-analysed to be included in the present study to allow for cross-country comparisons.

2.2 | Patient selection

Two cohorts of AF patients, the 2012 and 2017 cohort, were created (see Figure S1 for a graphical study presentation). In these time periods, the uptake of DOACs is expected to be great since their introduction into the market in the early 2010s, as already seen in data from Stockholm.[10] For the 2012 cohort, all patients with a recorded AF diagnosis from January 2007 (January 2008 for Norway due to data availability) until December 2011 were included. Patients had to be alive on 1 January 2012 and were excluded if they entered or exited the data source in the study period. Patients were also excluded if they had mechanical valves or mitral stenosis in the five-year prior to inclusion. Antithrombotic treatment was defined on 1 January 2012 by searching for a prescription claim of a VKA, a DOAC or aspirin from July to December 2011. Patients without any of those treatments were defined as untreated. For the 2017 cohort, the same criteria were employed, but for an AF diagnosis from January 2012 until December 2016, patients had to be alive on 1 January 2017, and treatment by prescriptions claims was identified in the period July–December 2016.

Patients were exclusively assigned to one of the four treatment groups: DOAC, VKA, aspirin or no treatment. For those who filled both an aspirin and an OAC prescription (either VKA or DOAC) during the six-month, the patient was assigned to the VKA or DOAC group. For those who filled both a VKA and a DOAC prescription, the patient was assigned to the drug they filled last in the treatment-assessment period.

2.3 | Baseline characteristics

For baseline comorbidities, both CHA_2Ds_2-VASc and a modified HAS-BLED score, that is, a stroke risk and a bleeding risk predictor score, were calculated.[24,25] Components of both scores were identified in the 5 years prior to 2012 and 2017 (see Table S2 for ICD-10 codes). Besides age and sex, the components of the CHA_2DS_2-VASc score are heart failure, hypertension, stroke/transient ischemic attack (TIA)/systemic embolism, vascular disease and diabetes. The components of the modified HAS-BLED score are hypertension, renal disease, liver disease, stroke, prior bleeding and medication usage predisposing to bleeding (i.e., non-steroidal anti-inflammatory drugs [NSAIDs], $P2Y_{12}$-inhibitors or oral corticosteroids). HAS-BLED score was developed prior to the introduction of DOACs, but it has been found to be non-inferior for predicting bleeding risk to other comparable risk scores, regardless of the type of OAC used.[26]

For baseline medications, prescription claims were assessed in the 6 months prior to January 2012 and January 2017 (see Table S2 for ATC codes). Co-medication included NSAIDs, $P2Y_{12}$-inhibitors, oral corticosteroids, diuretics, beta-blockers, calcium-channel blockers, renin-angiotensin-aldosterone system (RAAS)-inhibitors, statins, oral antidiabetic drugs, insulin, proton pump inhibitors and antidepressants.

2.4 | Outcome definitions

For the 2012 cohort, occurrence of the outcome of interest was observed in 2012, and for the 2017 cohort in 2017; identifying both ischemic and haemorrhagic events (see Table S2 for ICD-10 codes). The primary ischemic outcome was the occurrence of an ischemic stroke. The secondary ischemic outcome was a composite of ischemic stroke, unspecified stroke and TIA. The primary haemorrhagic outcome was a composite of any severe bleed. Secondary haemorrhagic outcomes were the occurrence of a gastrointestinal bleed (GIB) or an intracranial haemorrhage (ICH). Registration of the events in

secondary inpatient care was used to only include severe events. Patients were censored at the first occurrence of an outcome of interest, emigration, death or the end of the study period.

2.5 | Statistical analysis

Descriptive statistics were used to describe baseline characteristics and to present incidence rates (IRs) of outcomes per 100 person-years (%/year) in both cohorts. Poisson regression was used to calculate incidence rate ratios (IRRs) to contrast outcomes in 2012 compared to 2017. The analysis was stratified by predefined subgroups according to age groups, CHA_2DS_2-VASc score and HAS-BLED score. Starting with a crude model, first including only outcome and year of inclusion. Age and sex were then added to the model, followed by either the CHA_2DS_2-VASc score for ischemic events, or the HAS-BLED score for haemorrhagic events, to account for potential changes in stroke or bleeding risk that may have acted as the driver for a change in event rates.

2.6 | Supplementary analysis

The Norwegian database only had data available since 2008, and a sensitivity analysis was therefore performed to see how this might affect the results. For all other countries, an analysis was performed where patients were only included from 2008 to 2011 for the 2012 cohort, to mimic the patient selection in Norway.

To assess how treatment and event rates changed over time, an analysis was performed to look at the treatment and event rate per year, starting in 2004 and ending in 2017. For each year, a cohort of patients diagnosed with AF in maximum of 5 years prior to that year was created. For each year-cohort, treatment and outcomes were assessed in the same manner as in the main analysis, looking for treatment in the last year of the AF diagnosis window and outcomes in the year after the AF diagnosis window. Graphs were produced to assess the trends in treatment over time with the proportion of patients treated with an OAC and aspirin monotherapy, and the proportion of patients untreated (no aspirin or OAC). Additional graphs were made to present the trends in outcomes over time with the proportion of patients suffering from a stroke and the proportion of patients suffering from a bleed.

3 | RESULTS

In total, 280 359 patients with AF in the 2012 cohort and 356 779 in the 2017 cohort were included, representing an increase of 27%. Most patients were from Norway ($N = 205\,169$), followed by Denmark ($N = 201\,525$), Scotland ($N = 139\,613$) and Stockholm ($N = 90\,831$). All countries had more patients in their 2017 cohorts than in their 2012 cohorts. Baseline characteristics in terms of age, sex, stroke risk and bleeding risk were similar, both amongst the different countries and when comparing the full 2012 with the 2017 cohort (Tables 1 and Table S3).

TABLE 1 Summary of baseline characteristics per database and per year.

	Stockholm		Denmark		Scotland		Norway	
	2012	2017	2012	2017	2012	2017	2012	2017
n patients	40 898	49 933	87 179	114 346	63 597	76 016	88 685	116 484
Age (mean)	74.54 (12.68)	75.18 (12.04)	72.95 (12.83)	73.93 (12.20)	74.50 (12.24)	75.35 (11.95)	74.35 (13.30)	73.97 (13.36)
Sex (% female)	17 888 (43.7%)	21 003 (42.1%)	37 898 (43.5%)	48 547 (42.5%)	29 377 (46.2%)	34 619 (45.5%)	37 263 (42.0%)	47 818 (41.1%)
CHA_2DS_2-VASc mean, (SD)	3.64 (2.01)	3.62 (1.92)	3.13 (1.84)	3.11 (1.77)	3.38 (1.82)	3.36 (1.76)	3.31 (1.88)	3.21 (1.84)
HAS-BLED mean, (SD)	2.21 (1.30)	2.31 (1.30)	1.93 (1.26)	1.93 (1.23)	2.13 (1.27)	2.23 (1.30)	1.95 (1.25)	2.01 (1.31)

Note: The full baseline characteristics are in Table S3.

TABLE 2 Treatment of AF patients per database and per year.

	Stockholm		Denmark		Scotland		Norway	
	2012	2017	2012	2017	2012	2017	2012	2017
OAC	19 590 (47.9%)	34 385 (68.9%)	43 726 (50.2%)	83 665 (73.2%)	26 702 (42%)	45 163 (59.4%)	44 717 (50.4%)	75 061 (64.4%)
VKA	19 430 (47.5%)	18 449 (36.9%)	40 633 (46.6%)	37 100 (32.4%)	26 657 (41.9%)	25 444 (33.5%)	43 953 (49.6%)	26 728 (22.9%)
DOAC	160 (0.4%)	15 936 (31.9%)	3093 (3.5%)	46 565 (40.7%)	45 (0.1%)	19 719 (25.9%)	764 (0.9%)	48 333 (41.5%)
Aspirin	11 582 (28.3%)	3980 (8%)	22 869 (26.2%)	7645 (6.7%)	23 933 (37.6%)	12 068 (15.9%)	22 565 (25.4%)	14 289 (12.3%)
None	9726 (23.8%)	11 568 (23.2%)	20 584 (23.6%)	23 036 (20.1%)	12 962 (20.4%)	18 785 (24.7%)	21 403 (24.1%)	27 134 (23.3%)

Abbreviations: DOAC, direct oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist.

In all countries, the proportion of AF patients on OAC treatment increased substantially from 2012 to 2017, mainly driven by patients increasingly being treated with a DOAC (Table 2). In Stockholm, OAC use increased from 48% in 2012 to 69% in 2017, in Denmark from 50% to 73%, in Scotland from 42% to 59% and in Norway from 50% to 64%. The proportion of patients receiving aspirin alone decreased from approximately 30% to 10% in all countries. The proportion of patients that were untreated remained almost unchanged at approximately 22% in all countries. Stratifying treatment by age groups showed that in the very old (age of 85 years or above), treatment changed the most from 2012 to 2017 in all countries; more patients received an OAC and the proportion on aspirin monotherapy was more than halved in this age group (see Table S4).

In Stockholm, Denmark and Norway, the crude ischemic stroke rates decreased from 2012 to 2017 (Table 3). The largest relative decreases were found in Stockholm and Norway, in which the crude rates were approximately 40% lower in 2017. The decrease was smaller in Denmark and in Scotland the stroke rate remained unchanged. However, the stroke rates in Scotland and Denmark were already the lowest of the four countries in 2012, at 1.21 events/100 person-years (%/year). The crude bleeding rates, including the rates of GIB and of ICH, were approximately the same in 2017 as in 2012 in all countries.

The results from the Poisson regression show that the crude stroke rates were significantly lower in 2017 than in 2012 in all countries but Scotland (Table 4). They remained significantly lower after adjusting for age and sex and after adjusting for the CHA_2DS_2-VASc score. When stratifying the stroke rates by CHA_2DS_2-VASC score, there were higher stroke rates in patients with higher scores in each country (Figures 1 and 3). In Stockholm and Norway, the stroke rates were most markedly reduced at higher CHA_2DS_2-VASc scores (both score-adjusted, SA IRR 0.63, 95% CI respectively [0.57; 0.70], [0.59; 0.68]) while this was less pronounced in Denmark (SA IRR 0.86, 95% CI [0.79; 0.93]) and not seen in Scotland (SA IRR 0.99, 95% CI [0.90; 1.09]).

The bleeding rates were not statistically different in 2012 compared to 2017 in any country except Scotland. In Scotland, the bleeding rates were significantly increased in 2017 compared to 2012, mainly driven by a higher ICH rate in 2017 (SA IRR 1.31, 95% CI: 1.13; 1.52). Stratifying the bleeding rates by the HAS-BLED scores, higher bleeding risks at higher HAS-BLED scores were observed. The bleeding rates were mostly similar in 2012 and 2017 when stratified by each HAS-BLED score in all countries (Figures 2 and 3). Stratifying by age group showed similar results as stratifying by stroke and bleeding risk scores, both for strokes and bleeds (Figure S3).

3.1 | Sensitivity analyses

When data from 2007 was removed to mimic the Norwegian setting, fewer patients were included in the other countries. However, patient characteristics as well as stroke and bleeding rates remained unchanged (see Table S5).

The proportion of patients receiving an OAC increased gradually between 2012 and 2017 (see Figure S4). The trend of patients

TABLE 3 Number of events and incidence rate per 100 person-years for each outcome per database and year.

	Stockholm		Denmark		Scotland		Norway	
	2012	2017	2012	2017	2012	2017	2012	2017
Ischemic stroke	812 (2.11)	619 (1.32)	987 (1.21)	1099 (1.02)	712 (1.21)	829 (1.19)	1476 (1.79)	1195 (1.09)
Stroke/TIA	1106 (2.88)	876 (1.86)	1930 (2.36)	2061 (1.92)	1480 (2.52)	1595 (2.29)	2194 (2.66)	1863 (1.7)
Major bleed	829 (2.16)	1025 (2.18)	1758 (2.15)	2197 (2.05)	1060 (1.81)	1424 (2.04)	2230 (2.7)	2973 (2.72)
GIB	407 (1.06)	466 (0.99)	1066 (1.3)	1272 (1.19)	725 (1.23)	852 (1.22)	907 (1.1)	1166 (1.07)
ICH	277 (0.72)	366 (0.78)	435 (0.53)	647 (0.6)	277 (0.47)	446 (0.64)	499 (0.61)	625 (0.57)

Note: The stroke/transient ischemic attack (TIA) outcome consists of ischemic stroke, unspecified stroke, and TIA.
Abbreviations: GIB, gastrointestinal bleed; ICH, intracranial haemorrhage.

TABLE 4 Incidence rate ratios (IRRs) per outcome and database, contrasting 2017–2012.

		Crude IRR	Age sex IRR	Score IRR
Stockholm	Ischemic stroke	0.62 (0.56–0.69)	0.61 (0.55–0.68)	0.63 (0.57–0.7)
	Stroke/TIA	0.65 (0.59–0.71)	0.64 (0.58–0.69)	0.66 (0.6–0.72)
	Major bleed	1.01 (0.92–1.11)	0.99 (0.9–1.08)	0.96 (0.88–1.06)
	GIB	0.94 (0.82–1.07)	0.91 (0.8–1.04)	0.89 (0.78–1.01)
	ICH	1.08 (0.92–1.26)	1.05 (0.9–1.23)	1.04 (0.89–1.22)
Denmark	Ischemic stroke	0.85 (0.78–0.92)	0.82 (0.75–0.89)	0.86 (0.79–0.93)
	Stroke/TIA	0.81 (0.76–0.87)	0.79 (0.74–0.84)	0.82 (0.77–0.88)
	Major bleed	0.95 (0.89–1.01)	0.92 (0.86–0.98)	0.95 (0.9–1.02)
	GIB	0.91 (0.84–0.99)	0.88 (0.81–0.95)	0.91 (0.84–0.99)
	ICH	1.13 (1–1.28)	1.09 (0.96–1.23)	1.13 (1–1.28)
Scotland	Ischemic stroke	0.98 (0.89–1.08)	0.95 (0.86–1.05)	0.99 (0.9–1.09)
	Stroke/TIA	0.91 (0.85–0.97)	0.88 (0.82–0.94)	0.92 (0.86–0.99)
	Major bleed	1.13 (1.04–1.23)	1.1 (1.02–1.19)	1.09 (1–1.18)
	GIB	0.99 (0.9–1.09)	0.97 (0.88–1.07)	0.95 (0.86–1.05)
	ICH	1.36 (1.17–1.58)	1.31 (1.13–1.52)	1.31 (1.13–1.52)
Norway	Ischemic stroke	0.61 (0.57–0.66)	0.62 (0.57–0.67)	0.63 (0.59–0.68)
	Stroke/TIA	0.64 (0.6–0.68)	0.65 (0.61–0.69)	0.66 (0.62–0.71)
	Major bleed	1.01 (0.95–1.06)	1.02 (0.97–1.08)	0.97 (0.92–1.02)
	GIB	0.97 (0.89–1.06)	0.98 (0.9–1.07)	0.92 (0.85–1.01)
	ICH	0.94 (0.84–1.06)	0.95 (0.85–1.07)	0.92 (0.82–1.04)

Note: IRRs were crude, adjusted for age and sex and adjusted for risk score. The ischemic outcomes were adjusted for the CHA_2DS_2-VASc score and the bleeding outcomes for the HAS-BLED score.
Abbreviations: GIB, gastrointestinal bleed; ICH, intracranial haemorrhage; TIA, transient ischemic attack.

receiving aspirin monotherapy was stable before 2012 and decreased gradually thereafter, while the untreated group remained at approximately 20% over time (see Figure S5 and S6). The stroke rates declined already before 2012 and continued to decline throughout the study period, while the bleeding rates remained stable over time (see Figures S7 and S8).

4 | DISCUSSION

We found that the number of AF patients as well as the proportion treated with OACs has increased from 2012 to 2017 in Stockholm, Denmark, Norway and Scotland, while the proportion treated with aspirin monotherapy decreased. In all countries but Scotland, ischemic stroke rates were significantly lower in 2017 compared to 2012, after adjustment for the CHA_2DS_2-VASC score. The bleeding rates were unchanged in all countries but Scotland, in which the rate increased by approximately 9% with a 31% increase in ICH.

The uptake of DOACs in clinical practice represents an improvement in stroke prevention in AF occurring between 2012 and 2017. Stockholm data showed comparable rates of OAC use in AF patients in 2010–2012.[18] Through the availability of another, more convenient treatment option more patients were treated with an OAC in 2017. Adjusting for age and sex or the CHA_2DS_2-VASc score did not indicate that the improvements were related to changes in those characteristics. However, other factors may have contributed to the reduced

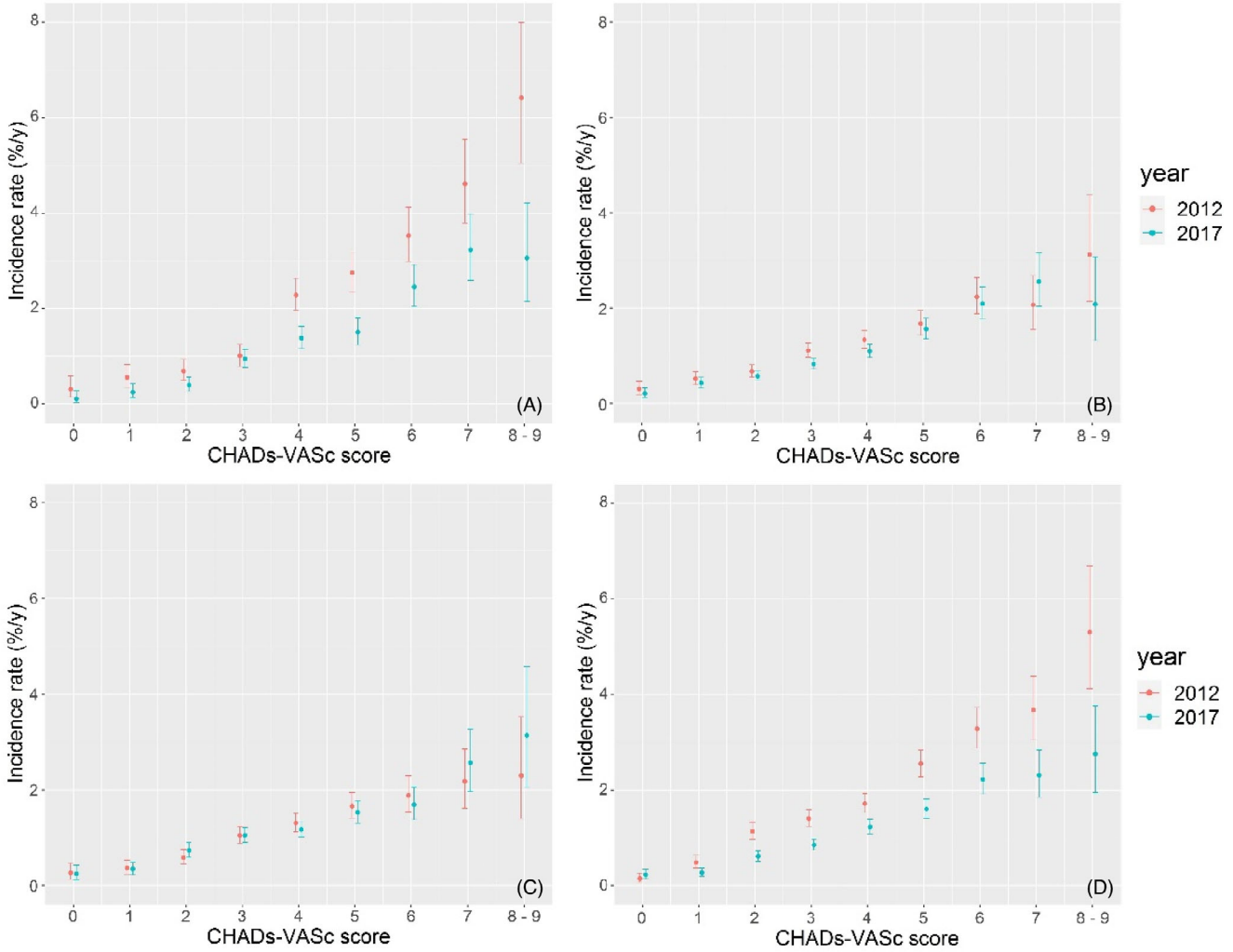

FIGURE 1 Stroke rates per CHA_2DS_2-VASc score for each country. A (top left panel), Stockholm; B, Denmark; C, Scotland; D, Norway.

stroke rates, especially since the stroke rates were already declining in most countries before 2012.[27] The AF population could be healthier in ways not reflected in the databases in 2017, for example with lower blood pressure levels and healthier lifestyles.[28] In addition, the AF patient population increased by 27% so it could be that these were healthier patients now diagnosed with AF, through additional screening.[29] Another factor may have been the introduction of the CHA_2DS_2-VASc score in 2010,[24] after which identification of AF patients with an indication for OAC treatment has become easier, and abandoning aspirin as a stroke-prevention therapy has been recommended in the guidelines from 2012 onwards.[30] In addition, the adherence and persistence to anticoagulant therapy have increased in later years, which likely also improves the effectiveness of the treatment.[31–33]

It was not possible to causally interpret why stroke, bleeding and in particular, ICH rates differed in Scotland, compared to the other countries. Despite a harmonised approach to this multi-database study, with use of a common protocol, code list and syntactic-only CDM filled with study-specific data, heterogeneity can arise from individual coding choices at each local site. For example, the methods and assumptions made by which persons were identified, including the identification of AF from only the secondary healthcare setting. Interrelating with the healthcare system differences is the recording of healthcare data, since all sources use the same medical ontology (ICD-10), but it may differ in how those specific codes are used to define a clinical event and cohort in each country.[34–36]

Differences in the healthcare system can further drive effect estimate heterogeneity and this can sometimes be informative, rather than a hinderance: the DOAC of preferred choice, by greatest use in Scotland and Denmark, is rivaroxaban and this DOAC is associated with an increased risk of bleeding compared to the other DOACs or VKAs.[11] While dabigatran use was associated with slightly lower persistence and adherence compared to apixaban and rivaroxaban.[11,33] Other potential healthcare-specific reasons are that there may have been an initial reluctance to switch to DOACs and previously undertreated AF patients at higher bleeding risks who are now more likely using DOACs. We do not see differences in the effect estimates after adjustment for confounding via age and sex or via risk scores (CHA_2DS_2-VASc or HAS-BLED), but we also do not see vast

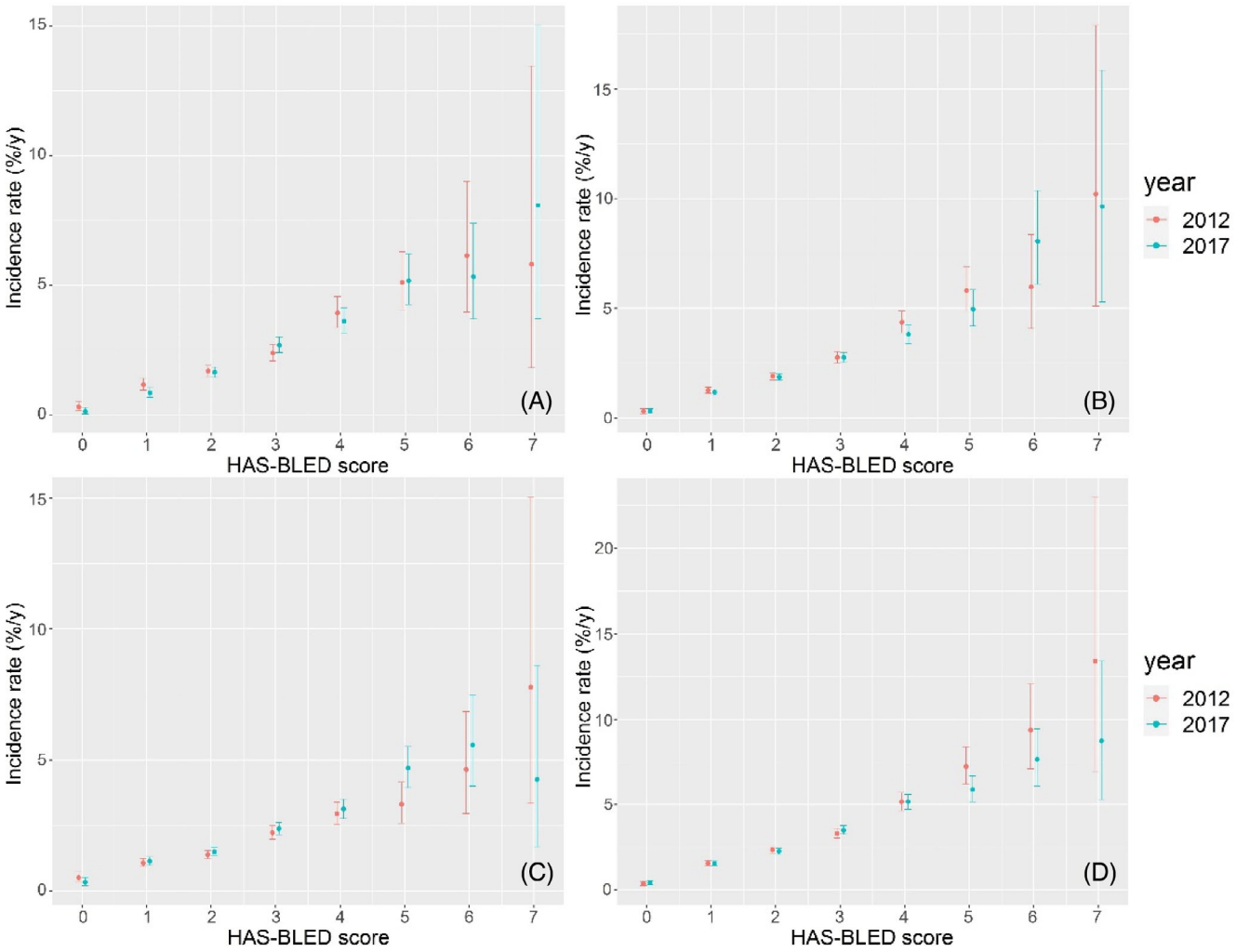

FIGURE 2 Bleeding rate per HAS-BLED score for each country. A (top left panel), Stockholm; B, Denmark; C, Scotland; D, Norway.

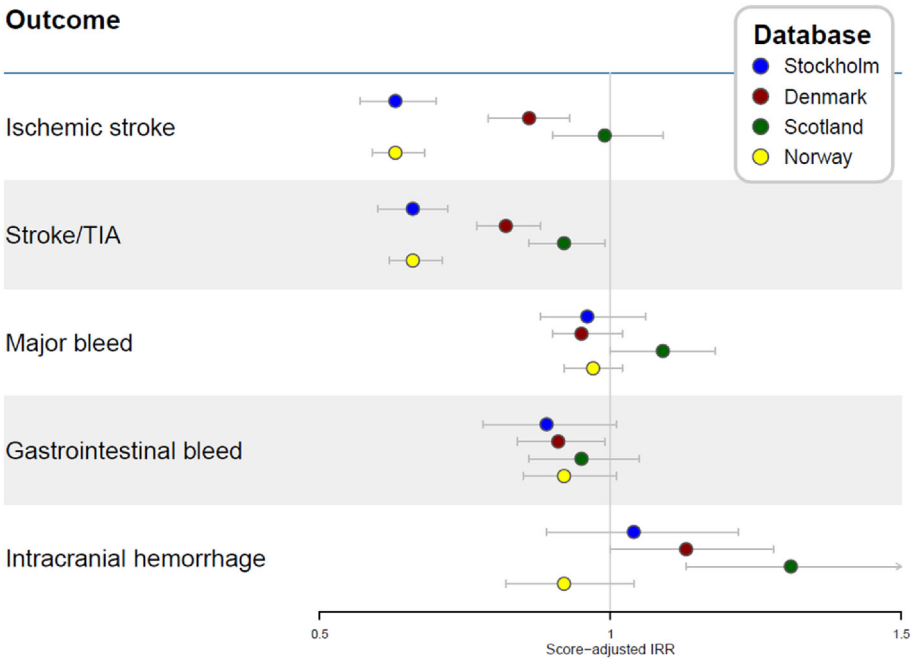

FIGURE 3 Score-adjusted incidence rate ratio of stroke and bleeding in 2017 compared to 2012.

differences in our baseline characteristics (Table 1) per database or calendar cohort.

The Scottish cohort had the lowest stroke and bleeding risks of the other countries in the present study in 2012. The background IR of stroke in Scotland has decreased by 9% in the decade 2011–2020 and more broadly, the UK has comparable rates of stroke mortality to the other countries included in this study.[37–39] Our results, which identified clinical events from secondary healthcare data, are consistent with observational studies investigating the risk of stroke in AF patients identified from primary care using DOACs finding an increased risk of stroke with DOACs compared to VKAs (1.76, 95% CI [1.50; 2.08]).[11] The risk of major bleeding with all DOACs (HR 1.13, 95% CI [1.02; 1.13]) and, in particular, intracranial bleeding with rivaroxaban use (HR 2.38, 95% CI [1.20; 4.72]) compared to VKAs was greater in UK primary care data than in the other international databanks included which could be extrapolated to Scotland,[11,12] and in other studies.[13–17] Conversely, a reduced bleeding risk has also been identified in UK data.[40]

There are several strengths to this study: we used data from four large well-validated databases and included all patients diagnosed with AF in our cohorts, with very limited exclusion criteria. Using syntactically harmonised data through a common protocol, one code list in a single vocabulary (medical ontology) and CDM over the same study period means that much of the heterogeneity due to different methodologies, often seen with cross-national comparisons, is minimised. There are, however, some limitations. First, we were able to show patterns of drug utilisation and outcome rates but without assessment of drug adherence and persistence nor could we draw any causal conclusion what factors were driving the observed changes. Second, we required each patient to have claimed a treatment only at least once in 6 months to be on that treatment. This is a simplified presentation of the treatment of a patient over time, for example, through stopping, switching or combining therapies. This could have led to potential exposure misclassification, however, since we are not comparing outcomes occurring with different treatment strategies, this is of less importance and our approach is sufficient to present changes in treatment practices over time. Third, AF patients are identified from secondary care records, meaning that some patients diagnosed only in primary care will be missing, though this is consistent in all four countries.

5 | CONCLUSIONS

OAC for AF patients increased over the period 2012–2017 characterised by a shift towards DOACs, from 45% use to 65%. In this period, there was a reduction in stroke risk without an increased risk of bleeding in Stockholm, Denmark and Norway, but not in Scotland. Heterogeneity in the methodologies used in multi-database studies can be in part addressed by database harmonisation methods like common protocols and CDMs. The remaining effect estimate heterogeneity can be informative of the potential differences in the underlying population and healthcare system, rather than due to methodological challenges. In performing observational research using data from multiple sources and recognising this heterogeneity we can increase the validity of our effect estimates.

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CONFLICT OF INTEREST STATEMENT

J. J. Komen is currently employed by Daiichi Sankyo, but not during the conduct of the study.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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