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Prescribing of low-dose rivaroxaban in patients with atherosclerotic cardiovascular disease in the United Kingdom and the Netherlands

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Aims: Low-dose rivaroxaban has been indicated for the management of atherosclerotic cardiovascular disease (ASCVD) after recent (2019-2020) updates to European guidelines. We aimed to describe prescription trends of low-dose rivaroxaban in ASCVD patients over the period 2015-2022 in two European countries, to compare the trends before and after guideline changes, and to determine the characteristics of users.

Methods: In a cross-sectional interrupted time series analysis, utilization of low-dose rivaroxaban (2.5 mg, twice daily) was measured in Clinical Practice Research Datalink Aurum (United Kingdom [UK]) and the PHARMO Database Network (the Netherlands) from 1 January 2015 to 28 February 2022 in patients with an ASCVD diagnosis. Incidence rates (IRs) and incidence rate ratios (IRRs) of new use (within 182 days) compared to the reference period, 2015-2018, were calculated. Age, sex and comorbidities of users were compared to those of nonusers.

Results: In the UK, from 721 271 eligible subjects the IR of new use of low-dose rivaroxaban in the period 2015-2018, before guideline changes, was 12.4 per 100 000 person-years and after guideline changes in 2020-2022 was 124.0 (IRR 10.0, 95% confidence interval [CI] 8.5, 11.8). In the Netherlands from 394 851 subjects, the IR in 2015-2018 was 2.4 per 100 000 person-years and in 2020 was 16.3 (IRR 6.7, 95% CI 4.0, 11.4). Users were younger (UK mean difference [MD] −6.1 years, Netherlands −2.4 years; P < .05) and more likely to be male (UK difference 11.5%, Netherlands 13.4%; P < .001) than nonusers.

Conclusions: There was a statistically significant increase in the use of low-dose rivaroxaban for the management of ASCVD after guideline changes in the UK and the Netherlands. There were international differences, but low-dose rivaroxaban has not been put into widespread practice.

1 | INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), including myocardial infarction (MI), unstable angina, ischaemic heart disease and peripheral artery disease (PAD), accounts for 31% of global deaths.[1] MI is the most prominent reason for hospitalization and patients remain at high risk of reoccurrence, with around 10% having recurrent events per year.[2,3] There are effective strategies for the secondary prevention of ASCVD, such as the use of low-dose aspirin, but these can prove to be insufficient. Anticoagulation through the use of vitamin K antagonists can provide additional benefit by reducing the risk of reoccurring events, but this has been associated with increased risk of bleeding.[4] The use of the direct factor Xa inhibitor rivaroxaban at a low dose, in addition to aspirin, has been shown to be effective in the secondary prevention of ASCVD events.[5,6] Rivaroxaban is primarily used in higher dosages to prevent systemic embolism and stroke in patients with atrial fibrillation, and to prevent and treat venous thromboembolism.[7,8]

The ATLAS randomized controlled trial (RCT), published in January 2012, compared use of low-dose rivaroxaban versus placebo in patients with acute coronary syndrome.[6] ATLAS demonstrated a reduction in cardiovascular deaths (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.74, 0.96). Essentially, the trial tested a dual anticoagulation strategy since 98.7% were using aspirin as a concomitant medication. In October 2017, COMPASS, a large multinational RCT, compared the use of low-dose (2.5 mg, twice daily) rivaroxaban-plus-aspirin to aspirin alone for superiority in reducing recurrent ASCVD events.[5] Major adverse cardiovascular event (includes cardiovascular death, stroke and MI) occurred less in the treatment group than in the control group (HR 0.76, 95% CI 0.66, 0.86). The superiority of the treatment group halted the trial after a mean follow-up of 23 months.[5] Major bleeding occurred more in the treatment group (HR 1.70, 95% CI 1.40, 2.05), although longer-term use seemed to diminish some of this additional risk.[9]

Recent meta-analyses of relevant RCTs show that although there are benefits of prescribing low-dose rivaroxaban, there is an increased risk of major bleeding.[10–12] Despite this, there have been changes to national and international prescribing guidelines,[13–16] such as the reimbursement guidelines of the Netherlands National Health Care Institute (Zorginstituut Nederland),[16] the European Society of Cardiology (ESC) practice guidelines[14,17] and the United Kingdom (UK) National Institute for Health and Care Excellence (NICE).[13] At present it is the only dual-anticoagulation strategy endorsed by the ESC for patients at a moderate or high-risk of ischemic events and without high bleeding risk (recommendation class IIa-IIb, evidence level B).[14,17,18] It is not yet clear whether these actions have led to changes in the prescribing of low-dose rivaroxaban for patients with ASCVD in practice.

What is already known about this subject

- Low-dose rivaroxaban (2.5 mg, twice daily) with aspirin can prevent recurrence of cardiovascular events but at an additional risk of bleeding.
- European clinical and reimbursement guidelines have incorporated the use of low-dose rivaroxaban for the management of atherosclerotic cardiovascular disease (ASCVD).
- It is not yet known the extent to which low-dose rivaroxaban is being prescribed and for which patient groups.

What this study adds

- The use of low-dose rivaroxaban for the management of ASCVD increased by seven to 10 times in the first 2 years following guideline changes.
- Incidence of the new use of low-dose rivaroxaban in the first 2 years after guideline changes remains low in the United Kingdom (124.0 per 100 000 person-years) and the Netherlands (16.3 per 100 000 person-years).
- Users of low-dose rivaroxaban are more frequently male, younger and have fewer comorbidities compared to nonusers.

The primary aim of the study was to describe the trends of the utilization of low-dose rivaroxaban for the management of ASCVD over the period January 2015 to February 2022, comparing pre- and postguideline changes in two Western European countries. To understand who were prescribed low-dose rivaroxaban, we aimed to determine the characteristics of those who were prescribed low-dose rivaroxaban in the study period (users) versus nonusers.

2 | METHODS

2.1 | Setting

We analysed data from two Western European healthcare settings: the UK using the Clinical Practice Research Datalink (CPRD) Aurum database and the Netherlands using the PHARMO Database Network:

2.1.1 | CPRD Aurum

The CPRD Aurum database consists of routinely collected electronic healthcare data from primary care practices in the UK, with the vast majority from England and Northern Ireland.[10] It captures diagnoses and symptoms, prescriptions by general practitioners, referrals and laboratory tests. Since the database inception in October 2017, it has accumulated over 41 million patients.[11] The protocol for this research was approved by the CPRD's Research Data Governance Process for MHRA Database Research (protocol number 21_001686).

2.1.2 | PHARMO Database Network

The PHARMO Database Network consists of pharmacy dispensing data which can be linked to data from other healthcare settings. The longitudinal nature of the PHARMO Database Network system enables 7 million active persons (1 January 2018), regardless of age and gender, of a well-defined population in the Netherlands to have a follow-up of 10 to 30 years.[19] In this study, we used pharmacy outpatient data linked to hospital admissions data. The PHARMO Database Network had data availability until December 2020.

2.2 | Design

We measured the utilization of low-dose rivaroxaban (Anatomical Therapeutic Chemical [ATC] code B01AF01, 2.5 mg twice daily) at monthly intervals in the study period January 2015 to February 2022 in the UK or December 2020 in the Netherlands using a cross-sectional time series study design (ENCePP registration EUPAS48079). Through the use of an interrupted time series (ITS) analysis, we estimated the change in drug utilization following national guideline changes for the management of ASCVD.

2.3 | Study population

Adult (≥18 years) patients with any record of ASCVD, defined as an acute MI, unstable angina, ischaemic heart disease or peripheral artery disease, were included in the cohort in the study period January 2015 to February 2022 (December 2020 in the Netherlands, code list given in Supporting Information Appendix S1).[20] Patients were excluded if there was a diagnosis of atrial fibrillation or stroke/ transient ischemic attack in the preceding 365 days prior, or used higher-dose rivaroxaban (>5 mg per day) or other direct oral anticoagulants/vitamin K antagonists 90 days prior, or had less than 1 year of history in the data source before the date of the cross-section for each monthly assessment. The cohort entry date (index date) for each patient was the latest of ASCVD diagnosis, the study start date (01/01/2015) or meeting eligibility criteria (Figure 1). Persons were

censored at the date of death, occurrence of stroke, transient ischaemic attack, major bleeding, atrial fibrillation, a prescription or dispensing of higher-dose rivaroxaban or other anticoagulants, or their end date in the database.

2.4 | Outcomes

For each month of the study period we found the incidence of new use of low-dose rivaroxaban (no prior use within 182 days), allowing incidence rates (IRs) to be calculated. Persons who received a prescription (CPRD Aurum) or dispensing (PHARMO Database Network) of low-dose rivaroxaban (ATC B01AF01, 2.5 mg, twice daily; Supporting Information Appendix S1) in the study period were defined as users and those who did not were defined as nonusers. The 2.5-mg, twice daily product regimen was identified using the handelsproductkenmerken (HPK) code (PHARMO Database Network) and the product code identification (CPRD Aurum). Prescriptions and dispensings with dosing frequency not equal to twice per day were excluded and missing dose frequency information was assumed to be twice daily. Those who are prescribed low-dose rivaroxaban once daily are likely to be patients with add-on dosages to >5 mg per day. The incidence rate of new prescribing or dispensing per 100 000 person-years was defined as the drug utilization outcome measure.

2.5 | Covariates

Patient characteristics were measured in the 365 days prior to cohort entry, including history of diabetes, hypertension, liver disease, chronic kidney disease, hypercholesterolaemia, alcoholism, heart failure and cancer. Age, sex and most recent ASCVD diagnosis were measured at cohort entry (code list given in Supporting Information Appendix S1). Antiplatelet (ATC B01AC) and aspirin (ATC B01AC06) use for users of low-dose rivaroxaban were assessed within any point during the study period.

2.6 | Statistical methods

An ITS analysis was used to determine whether the introduction of the Netherlands National Health Care Institute (Zorginstituut Nederland, 29 January 2019)[16] and the UK NICE (17 October 2019)[13] recommendations had an impact on utilization. The primary analysis compared the periods pre- (from 1 January 2015 until the national guideline change intervention) and postintervention (from intervention until the end of data collection) using a segmented Poisson regression analysis per database. We censored data points 3 months prior to and 3 months following the date of intervention. For the estimates of the effects of intervention, 95% CIs and Wald P values were estimated. The ITS model was specified as follows:
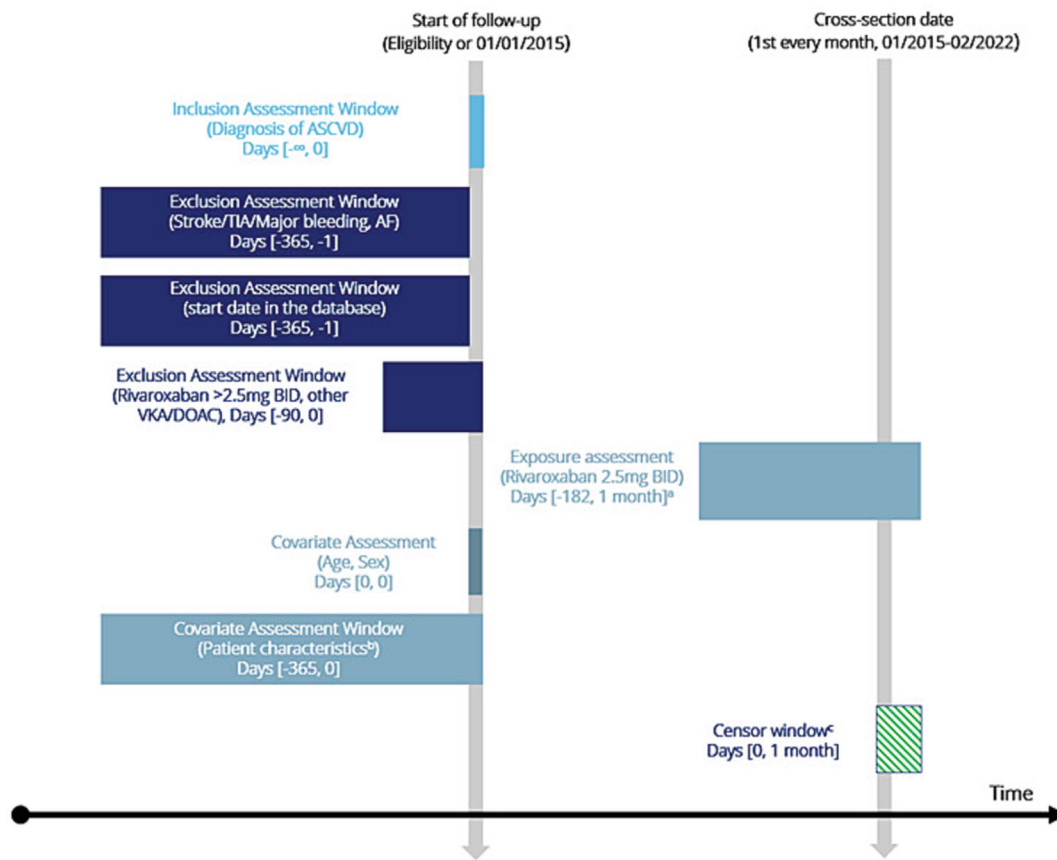
FIGURE 1 A graphical depiction of the study design and patient inclusion.[34] (A) Exposure assessment: prescribing or dispensing of low-dose rivaroxaban was assessed in the month proceeding the cross-section date. The new users were those who did not receive a prescription or dispensing in the preceding 182 days to the cross-section date. (B) Patient characteristics: comorbidities (hypertension, hypercholesterolaemia, alcoholism, diabetes, liver disease, chronic kidney disease, cancer). (C) Censor window: persons are censored at date of death, occurrence of stroke, TIA, major bleeding, atrial fibrillation, prescription or dispensing of higher-dose rivaroxaban or other anticoagulants or end date in the database. ASCVD, atherosclerotic cardiovascular disease; TIA, transient ischaemic attack; AF, atrial fibrillation; BID, bis in die (twice per day).

$$\text{outcome}_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{int}_t + \beta_3 \times \text{time since int}_t + e$$

where outcome_t is the outcome measure incidence at time t, time is the time elapsed since the start of the study as the month number (starting with 1 January 2015 as month 1), int is the variable representing the pre-intervention period (coded 0) or the post-intervention period (coded 1), time since int is the time elapsed since the intervention, β_0 is the y-intercept, β_1 is the slope indicating overall low-dose rivaroxaban use over time, β_2 estimates the step change after the intervention and β_3 estimates the slope change after the intervention.

To capture the changes in drug utilization, we calculated incidence rate ratios (IRRs) for the periods 2020-2022 in the UK or 2020 only in the Netherlands, using incidence in the period 2015-2018 as the reference. Chi-square and t-tests were used to evaluate differences in patient characteristics for the users versus nonusers. Associations between the covariates (age at cohort entry, sex, history of diabetes, hypertension, liver disease, chronic kidney disease, hypercholesterolaemia, alcoholism, heart failure, cancer) and the odds of low-dose rivaroxaban use were examined using a logistic regression model

to estimate the odds ratio (OR) and corresponding 95% CI. The adjusted model included the measured covariates.

3 | RESULTS

We identified 721 271 eligible patients in the UK (CPRD Aurum), with total follow-up time of 2 240 314 years (median 2.9 years, interquartile range [IQR] 5.0). During the study period, 1151 subjects were prescribed low-dose rivaroxaban (Figure 2, left). In the Netherlands (PHARMO Database Network), we identified 394 851 eligible patients with a total follow-up time of 1 531 223 years (median 4.3 years, IQR 4.0). There were 150 subjects who were dispensed low-dose rivaroxaban in the period of data availability 2015-2020 (Figure 2, right). Dose frequency information was 97.0% missing in the UK and 0.0% in the Netherlands. This was due to an incomplete directory of dosing information in the data delivered by the CPRD, rather than underreporting by the prescriber. However, all persons who were prescribed low-dose rivaroxaban for a different indication and therefore dose frequency were excluded. We validated

FIGURE 2 Flow charts of patient inclusion in the United Kingdom (top) and the Netherlands (bottom).
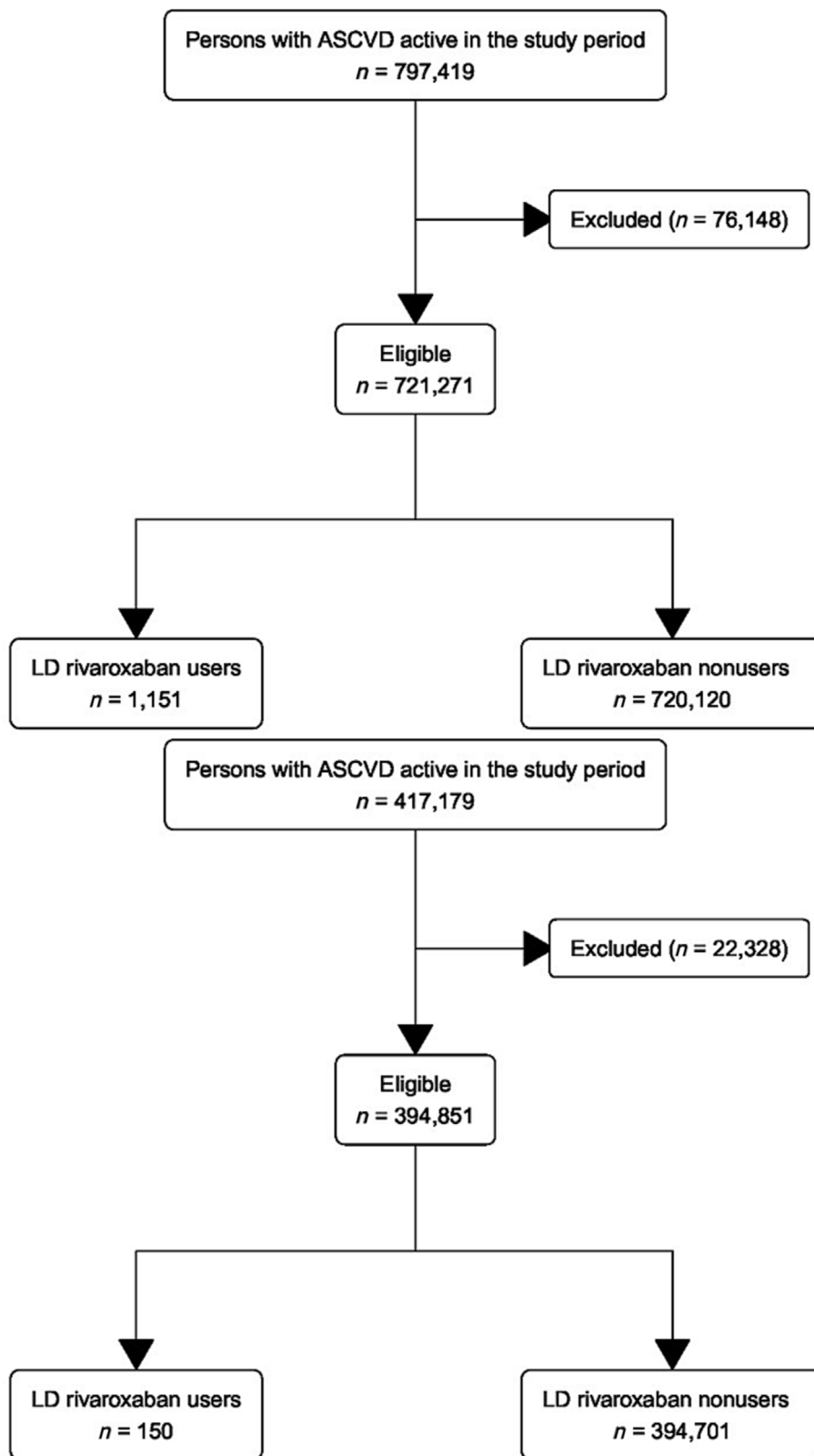
the dosage regime in the UK by dividing the number of tablets prescribed in patients with >1 prescription record by the median time between a person's subsequent prescriptions and found that 79% used two tablets per day.

In the UK, the IR of the new use of low-dose rivaroxaban in ASCVD patients in the period 2015-2018 was 12.4 per 100 000 person-years and in the period 2020-2022 was 124.0 (IRR 10.0, 95% CI 8.5, 11.8). In the Netherlands, the IR of the new use of low-dose
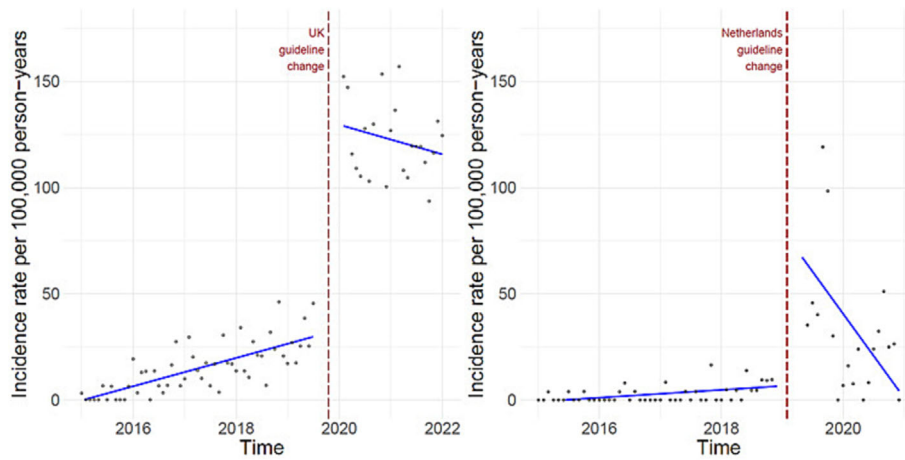
FIGURE 3 The incidence of the new use of low-dose rivaroxaban over the study period 2015-2022 for the secondary prevention of ASCVD events in the United Kingdom (left, until February 2022) and in the Netherlands (right, until December 2020) per 100 000 person-years. An interrupted time-series analysis regression line is fitted, with the date of guideline changes as the intervention.

TABLE 1 Patient characteristics of the cohort measured within 365 days of cohort entry, stratified by users of low-dose rivaroxaban in the study period versus nonusers, those who were eligible but not prescribed low-dose rivaroxaban.

	Country	Users	Nonusers	MD	95% CI	Unadjusted OR	95% CI	Adjusted OR	95% CI
Age at cohort entry (years)	UK	64.4	71.4	−7.0	[−6.2, −7.6]	0.96	[0.96, 0.97]	0.96	[0.96, 0.97]
	NL	66.80	69.20	−2.40	[−1.1, −3.7]				
Under 65 (%)	UK	49.3	30.8	18.5	[15.6, 21.4]	2.19	[1.95, 2.46]	1.86	[1.64, 2.10]
	NL	30.7	36.3	5.4	[−13.3, 2.1]				
Sex (% female)	UK	26.3	37.2	−10.9	[−13.5, −8.3]	0.58	[0.51, 0.66]	0.73	[0.64,0.84]
	NL	28.0	41.4	−13.4	[−20.9, −5.9]				
Hypertension (%)	UK	58.8	54.3	4.5	[1.7, 7.5]	0.83	[0.74, 0.93]	1.11	[0.98, 1.26]
Diabetes mellitus (%)	UK	30.2	25.3	4.9	[2.3, 7.7]	1.28	[1.12, 1.45]	1.39	[1.22, 1.59]
Chronic kidney disease (%)	UK	9.8	21.3	−11.5	[−13.2, −9.7]	0.40	[0.33, 0.49]	0.61	[0.50, 0.75]
Cancer (%)	UK	27.8	31.1	−3.3	[−5.9, −0.7]	0.85	[0.75, 0.96]	1.14	[1.00, 1.30]
Mild liver disease (%)	UK	4.2	2.9	1.3	[0.0, 2.4]	1.44	[1.06, 1.89]	1.15	[0.85, 1.52]
Alcohol abuse (%)	UK	36.2	37.2	−1.0	[−3.8, 1.9]	0.96	[0.85, 1.08]	0.92	[0.81, 1.04]
Hypercholesterolaemia (%)	UK	20.2	20.2	0.0	[−2.3, 2.3]	1.00	[0.86, 1.15]	1.09	[0.94, 1.26]
Heart failure (%)	UK	4.4	8.5	−4.1	[−5.3, −2.8]	0.50	[0.37, 0.65]	0.65	[0.48, 0.85]
Thrombocytopenia (%)	UK	0.6	0.8	−0.2	[−0.7, 0.3]	0.72	[0.31, 1.41]	0.82	[0.35, 1.60]

Note: UK users n = 1151, UK nonusers n = 720 120; NL users n = 150, NL nonusers n = 394 701. MD, mean difference; OR, odds ratio; CI, confidence interval. Emboldened refers to statistically significant adjusted logistic regression. Odds ratios show the association between prescribing and patient characteristics.

rivaroxaban in 2015-2018 was 2.4 per 100 000 person-years and in 2020 was 16.3 (IRR 6.7, 95% CI 4.0, 11.4). In the ITS analysis, we found the estimate of the step change in incidence per 100 000 person-years in the UK to be 88.3 (95% CI 73.3, 103.3), while in the Netherlands it was 55.2 (95% CI 34.1, 76.4; Figure 3).

Users of low-dose rivaroxaban were younger at the cohort entry (UK mean difference [MD] −6.93 years, P < .001; Netherlands MD −2.40 years, P < .05) and were less likely to be female (UK difference −10.9%; Netherlands difference −13.4%, both P < .001; Table 1) compared to nonusers. In the UK, users suffered less from chronic kidney disease (MD −11.5%, P < .001), cancer (MD −3.3%, P < .05) and heart failure (MD −4.1%, P < .001), but more from diabetes mellitus (MD 4.9%, P < .001) and mild-to-moderate liver disease (MD 1.3%, P < .05) in the year prior to cohort entry. Comparison of comorbidities in users and nonusers was not possible in the Netherlands due to low numbers of users. In the 90 days surrounding the first low-dose rivaroxaban prescription, there was an antiplatelet prescription for 92.7% of low-dose rivaroxaban users in the Netherlands (69.7% for aspirin) and 95.2% in the UK (85.8% for aspirin).

The most recent diagnosis of ASCVD prior to cohort entry for users in the UK (Table 2) was more likely to be peripheral vascular

TABLE 2 Most recent atherosclerotic cardiovascular disease (ASCVD) diagnosis of subjects in the cohort prior to cohort entry, stratified by users of low-dose rivaroxaban in the study period versus nonusers.

ASCVD diagnosis prior to cohort entry	UK users ($n = 1151$)	UK nonusers ($n = 720\ 120$)
Peripheral vascular disease (%)	19.2	5.4
Ischaemic heart disease (%)	16.5	27.8
Acute non-ST segment elevation myocardial infarction (%)	10.9	8.5
Intermittent claudication (%)	11.0	5.4
Angina pectoris (%)	7.3	15.8
Acute ST segment elevation myocardial infarction (%)	7.9	4.8
Coronary artery disease (%)	4.6	4.1
Acute myocardial infarction (%)	9.6	11.2

Note: Prior ASCVD diagnosis χ^2 statistic $= 829.55$, $P < .001$.

disease (MD 13.8%) or intermittent claudication (MD 5.6%) and less likely to be ischaemic heart disease (MD −11.3%) or angina pectoris (MD −8.5%). All group mean differences in initial ASCVD diagnosis were statistically significant ($P < .001$). The median time between first ASCVD diagnosis and first use of low-dose rivaroxaban was 617 days (IQR 2399), while in the Netherlands it was 2729 days (IQR 2898; Supporting Information Table S1).

4 | DISCUSSION

In the UK, we found an association between the implementation of new cardiovascular management guidelines in the wake of the publication of the COMPASS RCT, with an increase in the utilization of low-dose rivaroxaban. There were substantial differences between the UK and the Netherlands. Although Dutch outpatient pharmacy data showed an increase in utilization over the study period, particularly in 2019, the incidence of new low-dose rivaroxaban use remained relatively low after 2019 compared to the UK. In addition, patients in the Netherlands seemed to be prescribed low-dose rivaroxaban at later stages of the disease, as seen with the differences between initial diagnosis and first prescription, perhaps switching at an older age since there is a greater proportion of users over 65 years old in the Netherlands than in the UK.

Users were also more likely to be initially diagnosed with peripheral artery disease and associated symptoms rather than angina pectoris and ischaemic heart disease, as seen in nonusers. Clinical trials have demonstrated that low-dose rivaroxaban reduces the risk of adverse limb and cardiovascular events in patients with PAD, including a lower risk of venous thromboembolism after revascularisation.[21–23] Rivaroxaban could therefore be of additional benefit for these patients, and thus explains the increased use amongst those with a PAD diagnosis. In real-world data, persons with ASCVD who could be prescribed low-dose rivaroxaban as per the

COMPASS eligibility criteria in the international REACH registry database was found to be 52.9%. Those with PAD only were more likely eligible (68.4%), as also seen here.[24]

Users of low-dose rivaroxaban were younger and more likely to be male, although sex differences have not been observed in clinical trials.[5,25] COMPASS demonstrated that rivaroxaban was effective at reducing the risk of major adverse cardiovascular events (MACE) in patients who are younger than 65 years (HR 0.63, 95% CI 0.48, 0.84) but not those older than 75 years (HR 0.89, 95% CI 0.69, 1.14). Our study shows that those younger than 65 are more likely to be prescribed low-dose rivaroxaban in the UK. Patient characteristics and individual benefit-risk assessments will inform the choice of whether to prescribe low-dose rivaroxaban, as many of potential users are also at high risk of bleeding.[26,27]

In the UK, diabetes mellitus was associated with low-dose rivaroxaban use, while hypertension, chronic kidney disease and cancer were associated with nonuse. In general, all anticoagulation strategies increase the risk of bleeding, and this is particularly true with rivaroxaban.[28,29] There is a 70% increased risk of bleeding with low-dose rivaroxaban plus aspirin therapy compared to aspirin monotherapy, lower than with other anticoagulation strategies.[5] The additional risk needs to be balanced against the benefits of the anticoagulants, especially considering the dose-dependent effect of the risk of bleeding. Clinicians may still be wary of prescribing rivaroxaban for the management of ASCVD in patients at a high risk of ischaemic events and prior stroke/transient ischemic attack, including those with prior renal disease, liver disease, cancer or bleeding, as seen in our data.[30] In general, multimorbidity should not necessarily be a reason to not prescribe and discontinuation is associated with an excess risk of stroke, in addition to the loss of cardiovascular benefits.[31,32] Coupled with the ESC level of recommendation (level IIa-IIb, evidence level B),[14,17,18] it is unlikely that the use of low-dose rivaroxaban will be expanded to all patients with ASCVD, explaining the low incidence of use seen in this study.

To our knowledge, this is the first drug utilization study for low-dose rivaroxaban for the secondary prevention of cardiovascular disease and this study includes data from two European countries using a study period that included several timepoints where there was a greater potential for changes in utilization to occur. The use of multiple countries provided greater insight into the utilization due to the inclusion of heterogeneous patient populations and healthcare systems.

There are, however, a number of limitations. First, heterogeneity also hampered a clear comparison in actual drug use due to differences in recording information, follow-up time, healthcare settings and clear comparisons of user characteristics. The number of patients with ASCVD is probably underestimated due to the identification of clinical events from different data domains. For example, in CPRD Aurum, primary care historical diagnoses may not be fully captured (as is reflected in a shorter time between first recorded ASCVD diagnosis to first use of low-dose rivaroxaban; Supporting Information Table S1), while in the PHARMO Database Network only hospital admissions were used to capture ASCVD diagnoses. Second, low-dose rivaroxaban is initially prescribed in a secondary care setting so by using CPRD Aurum, we

only find the repeat prescriptions from the primary care physicians in the UK. This would reduce the quantity of prescriptions recorded, misclassify the timing of the first prescription and not capture new users who did not receive a repeat prescription from their primary care practitioner. Third, there was a potential for exposure misclassification: we could only measure counts of aspirin use, which forms part of the dual anticoagulation strategy, although low-dose rivaroxaban monotherapy is not an effective strategy and is unlikely to be prescribed without aspirin in patients with ASCVD.[5] Forth, the start of the SARS-CoV-2 pandemic in 2020 coincided with the period where use was greatest. In the UK, rivaroxaban utilization in general increased at the pandemic's onset, followed by a deceleration.[33]

5 | CONCLUSIONS

We found a statistically significant increase in the prescribing of low-dose rivaroxaban for the management of ASCVD in the UK and in the Netherlands after guideline changes, although its use is still not widespread and there were substantial differences in usage between the two countries. Those who were prescribed the medication were more likely to be younger, male, have fewer comorbidities and were diagnosed with PAD rather than coronary artery disease (CAD).

DATA AVAILABILITY STATEMENT

No data are available. The authors are contractually not allowed to share raw data from CPRD or the PHARMO Database Network in the public domain.

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REFERENCES

1. Cardiovascular diseases (CVDs) [Internet]. [cited 2022 Jun 13]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. 2015;36(19):1163-1170. Available from: https://academic-oup-com.proxy.library.uu.nl/eurheartj/article/36/19/1163/2293202
3. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA*. 2010;304(12):1350-1357. Available from: https://jamanetwork.com/journals/jama/fullarticle/186626
4. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol*. 2003;41(4):S62-S69. doi:10.1016/S0735-1097(02)02776-6
5. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118
6. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366(1):9-19. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1112277
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638
8. The Einstein Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1007903
9. Eikelboom JW, Bosch J, Connolly SJ, et al. Long-term treatment with the combination of rivaroxaban and aspirin in patients with chronic coronary or peripheral artery disease: outcomes during the open label extension of the COMPASS trial. *Eur Hear J - Cardiovasc Pharmacother*. 2022;8:786-795. Available from: https://academic-oup-com.proxy.library.uu.nl/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvac023/6564176
10. Khan SU, Khan MZ, Asad ZUA, et al. Efficacy and safety of low dose rivaroxaban in patients with coronary heart disease: a systematic review and meta-analysis. *J Thromb Thrombolysis*. 2020;50(4):913-920. Available from: 10.1007/s11239-020-02114-7
11. Chen C, Kan Y, Shi Z, et al. Low dose rivaroxaban for atherosclerotic cardiovascular diseases: a systematic review and meta-analysis. *Front Pharmacol*. 2021;11(February):1-12.
12. Galli M, Capodanno D, Benenati S, et al. Efficacy and safety of dual-pathway inhibition in patients with cardiovascular disease: a meta-analysis of 49 802 patients from 7 randomized trials. *Eur Hear J – Cardiovasc Pharmacother*. 2022;8(5):519-528. Available from: https://academic.oup.com/ehjcvp/article/8/5/519/6306410
13. NICE. Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease [Internet]. 2019 [cited 2021 Jul 12]. Available from: https://www.nice.org.uk/guidance/ta607

14. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41(3):407-477. Available from: https://academic.oup.com/eurheartj/article/41/3/407/5556137

15. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42(14):1289-1367. Available from: https://academic.oup.com/eurheartj/article/42/14/1289/5898842

16. Zorginstituut Nederland. rivaroxaban Xarelto® preventie van atherotrombotische complicaties bij volwassen patiënten met CHZ of PAV met een hoog risico op ischemische events. 2019.

17. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018; 39(2):119-177. Available from: https://academic.oup.com/eurheartj/article/39/2/119/4095042

18. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019; 40(2):87-165. Available from: https://pubmed.ncbi.nlm.nih.gov/30165437/

19. PHARMO Database Network [Internet]. [cited 2022 Apr 14]. Available from: http://pharmo.nl/PHARMO-database-network/

20. An J, Zhang Y, Muntner P, Moran AE, Hsu JW, Reynolds K. Recurrent atherosclerotic cardiovascular event rates differ among patients meeting the very high risk definition according to age, sex, race/ethnicity, and socioeconomic status. *J Am Heart Assoc*. 2020;9(23): e017310. doi:10.1161/JAHA.120.017310

21. Hess CN, Szarek M, Anand SS, et al. Rivaroxaban and risk of venous thromboembolism in patients with symptomatic peripheral artery disease after lower extremity revascularization. *JAMA Netw Open*. 2022; 5(6):E2215580 Available from: /pmc/articles/PMC9218845/

22. Kaplovitch E, Eikelboom JW, Dyal L, et al. Rivaroxaban and aspirin in patients with symptomatic lower extremity peripheral artery disease: a subanalysis of the COMPASS randomized clinical trial. *JAMA Cardiol*. 2021;6(1):21-29. Available from: /pmc/articles/PMC7527938/

23. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020; 382(21):1994-2004. Available from: https://www.nejm.org/doi/10.1056/NEJMoa2000052

24. Darmon A, Bhatt DL, Elbez Y, et al. External applicability of the COMPASS trial: an analysis of the reduction of atherothrombosis for continued health (REACH) registry. *Eur Heart J*. 2018;39(9):750-757a. Available from: https://academic.oup.com/eurheartj/article/39/9/750/4656148

25. Hess CN, Baumgartner I, Anand SS, et al. Sex-based differences in outcomes following peripheral artery revascularization: insights from VOYAGER PAD. *J Am Hear Assoc Cardiovasc Cerebrovasc Dis*. 2022; 11(12):e024655 Available from: /pmc/articles/PMC9238670/

26. Bolognese L, Felici M. Chronic ischaemic heart disease and rivaroxaban: which patients derive the greatest benefit? *Eur Hear J Suppl*. 2020;22(Supplement_L):L24-L27. Available from: https://academic-oup-com.proxy.library.uu.nl/eurheartjsupp/article/22/Supplement_L/L24/5989608

27. Khan AA, Lip GYH. Non-vitamin K antagonist oral anticoagulants beyond atrial fibrillation: what did we learn from COMPASS and COMMANDER-HF? *Eur Heart J*. 2019;40(46):3754-3756. Available from: https://academic-oup-com.proxy.library.uu.nl/eurheartj/article/40/46/3754/5298544

28. Souverein P, Van den Ham H, Huerta C, et al. Comparing risk of major bleeding between users of different oral anticoagulants in patients with on valvular atrial fibrillation. *Br J Clin Pharmacol*. 2020;87(3):988-1000. doi:10.1111/bcp.14450

29. Fox KAA, Eikelboom JW, Anand SS, et al. Anti-thrombotic options for secondary prevention in patients with chronic atherosclerotic vascular disease: what does COMPASS add? *Eur Heart J*. 2019;40(18): 1466-1471. Available from: https://academic.oup.com/eurheartj/article/40/18/1466/5045239

30. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronaryintervention: a consensus document from the Academic Research Consortium for High BleedingRisk. *Eur Heart J*. 2019;40(31):2632 Available from: /pmc/articles/PMC6736433/

31. Vanassche T, Verhamme P, Anand SS, et al. Low-dose rivaroxaban plus aspirin in patients with polypharmacy and multimorbidity: an analysis from the COMPASS trial. *Eur Hear J – Cardiovasc Pharmacother*. 2021;8:462-473. Available from: https://academic-oup-com.proxy.library.uu.nl/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvab050/6311809

32. Dagenais GR, Dyal L, Bosch JJ, et al. Cardiovascular consequences of discontinuing low-dose rivaroxaban in people with chronic coronary or peripheral artery disease. *Heart*. 2021;107(14):1130-1137. Available from: https://pubmed.ncbi.nlm.nih.gov/34021038/

33. Alkhameys S, Barrett R. Impact of the COVID-19 pandemic on England's national prescriptions of oral vitamin K antagonist (VKA) and direct-acting oral anticoagulants (DOACs): an interrupted time series analysis (January 2019-February 2021). *Curr Med Res Opin*. 2022;38:1081-1092. Available from: https://www.tandfonline.com/doi/abs/10.1080/03007995.2022.2078100

34. Schneeweiss S, Rassen JA, Brown JS, et al. Graphical depiction of longitudinal study designs in health care databases. *Ann Intern Med*. 2019;170(6):398-406. doi:10.7326/M18-3079

SUPPORTING INFORMATION

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