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Improving the Prescription of Oral Anticoagulants in Atrial Fibrillation: A Systematic Review

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Abstract

Objective Oral anticoagulant (OAC) prescription for stroke prevention in atrial fibrillation (AF) patients frequently does not follow current guidelines, with underuse in patients at high risk of stroke and substantial overuse in those at low risk. This review aims to systematically evaluate the effectiveness of interventions to improve appropriate OAC prescription in eligible AF patients for stroke prevention.

Methods Systematic review of controlled and uncontrolled studies published up to July 2017 with interventions designed to improve appropriate OAC prescription for stroke prevention in eligible AF patients (according to risk assessment tool or guidelines). Categorization of intervention types was pre-specified. The main outcome was change in proportion of eligible AF patients prescribed OACs for stroke prevention.

Results Twenty studies conducted in 392 settings were included (cluster randomized controlled trials, controlled trials and uncontrolled before-after designs; $n = 29{,}868$ patients at baseline). Fifteen studies reported significant improvements in appropriate prescription of OACs in AF patients. All interventions with a persuasive element (8/8); all studies targeting health care professional (HCP) education or guideline/protocol implementation (7/7); and all medical care programs (4/4) achieved significant increases in appropriate OAC prescription. Computerized decision support interventions (3/5) and reviews of prescribing (2/4) were less likely to report significant improvements in appropriate OAC prescription.

Conclusion Interventions designed to improve appropriate prescription of OACs in eligible AF patients for stroke prevention can be effective. Successful approaches include education of HCPs; implementation of local guidelines; interdisciplinary medical care programs educating both HCPs and patients and persuasive interventions utilizing peer-group experts. Protocol registration: PROSPERO (CRD42016039654).

Keywords
- atrial fibrillation
- oral anticoagulation
- systematic review
- intervention
- stroke prevention

Introduction

Atrial fibrillation (AF) currently affects over 33 million people worldwide with increasing prevalence in the United Kingdom and globally.[1,2] Current national and international guidance recommends that female AF patients with a CHA_2DS_2-VASc score of ≥ 2 and male patients with a score of ≥ 1 should be offered oral anticoagulation (OAC) including vitamin K

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antagonists (VKAs) and non-VKA oral anticoagulants (NOACs) to reduce risk of stroke[3–5] (taking bleeding into account using the HAS-BLED score[6]). Over the last decade, rates of OAC use for stroke prevention in newly diagnosed AF patients have steadily increased to 71% worldwide[7]; reaching around 80% in Europe and the United States.[7,8] However, there is still substantial room for improvement in appropriate, guideline-adherent, OAC prescribing. Worldwide, around half of all newly diagnosed AF patients with a CHA_2DS_2-VASc score of 0 (low risk) are prescribed OACs contrary to guideline advice, putting them at unnecessary risk of haemorrhage.[7] Conversely, of all high-risk U.K. patients with a CHA_2DS_2-VASc score of ≥ 2 only 68% are receiving OACs, falling to 40% in India and 31% in China,[7] exposing many to a risk of stroke. Under-prescription of OACs in patients aged 65 years and above has also been reported across Europe.[9]

Research has explored possible reasons for under-prescription of OACs in AF patients, with general practitioners (GPs) reporting feeling responsible for haemorrhages in anticoagulated patients.[10] Patients' co-morbidities and concerns about their ability to achieve adequate time in therapeutic range may create barriers to the prescription of VKAs.[10] Health care professionals (HCPs) may be especially reluctant to prescribe OACs to older adults due to a perceived increased likelihood of falls and subsequent haemorrhage; however, research suggests that stroke risk is much greater in older adults with AF, making anticoagulation more vital.[10]

Interventions have attempted to improve HCPs' adherence to guidelines in prescribing OACs to AF patients,[11] but there is no clear evidence regarding which intervention design and theoretical framework is most effective. This article presents the first review to systematically evaluate the effectiveness of interventions with any comparator designed to improve appropriate prescription of OACs in eligible AF patients for stroke prevention.

Methods

Protocol and Registration

The systematic methodology of this review was based on the Cochrane Collaboration handbook[12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[13] The review protocol was registered on PROSPERO prior to conducting literature searches (CRD42016039654).

Eligibility Criteria

Quantitative studies reporting interventions designed to increase the rate of prescription of OACs for stroke prevention in AF patients eligible for OAC treatment, or to improve adherence to guidelines, were considered for inclusion. Patients eligible for OAC treatment were defined as CHA_2DS_2-VASc score of ≥ 2 if female, ≥ 1 if male, or equivalent risk stratification tool, or stated as eligible according to guidelines. Eligible study designs included controlled studies (randomized or non-randomized, prospective or retrospective, concomitant or historical control) and uncontrolled before-after studies with any comparator. Studies focusing on any HCP prescriber in any health care setting were eligible. Interventions designed to improve both HCPs' prescription of and patients' uptake/adherence to OACs were eligible provided the rate of OAC prescription was reported. Interventions were categorized as 'Persuasive' and/or 'Educational and informational', and/or 'Action and monitoring', according to Johnson and May's intervention types for behavioural change in HCPs.[14] Studies with an outcome describing change in the proportion of AF patients eligible for OAC treatment who were prescribed OACs by HCPs for stroke prevention were included (or change in the proportion of such patients taking OACs, if the intervention was aimed only at improving HCPs' prescription and not patient uptake).

Studies including patients with a CHA_2DS_2-VASc score of < 2 if female or < 1 if male (or ineligible for OACs on an equivalent risk stratification tool or according to guidelines) were excluded from this review. Interventions focusing only on the patient, or studies whose outcome was the proportion of patients eligible for OACs who were taking OACs, where the intervention was aimed at both the patient and the health professional were excluded. Qualitative studies and case series were also excluded from this review.

Literature Searches

Searches were performed with no language/publication date restrictions from inception to June 2016 in the bibliographic databases, including MEDLINE and MEDLINE in Process, EMBASE, PsycINFO, CINAHL and The Cochrane Library (CDSR, DARE and CENTRAL); Science Citation Index (Web of Science) for citation searching; World Health Organization International Clinical Trials Registry Platform and Clinical Trials.gov for trials in progress; Conference Proceedings Citation Index; Open Gray; and the Health Management Information Consortium for grey literature and bibliographies of relevant articles. A combination of text words and index terms related to the condition (AF), the therapy (OAC) and the intervention (interventions to increase appropriate OAC prescription) were utilized (►**Supplementary Fig. S1**, available in the online version). A search update was performed up to July 2017 using the limits 'therapy' and 'best balance' to concentrate the search on OAC therapy, locating relevant papers while avoiding irrelevant material.

Study Selection Process

Search results were exported to EndNote V.X7.4 (Thomson Reuters, New York, New York, United States) and duplicates removed. Titles and abstracts were read for relevance and full-text versions of potentially eligible publications obtained. Non-English language articles were translated. A standardized, pre-determined, study criteria form was applied to all full-text documents, with ineligible publications and reasons for ineligibility recorded (►**Supplementary Table S1**, available in the online version).

Data Extraction and Quality Assessment

Data were extracted using a standardized, piloted data extraction form. Discrepancies were compared with original data.

Information on following characteristics was extracted: study design, health care setting, AF type and risk stratification, intervention/comparator arms, intervention-deliverer, target population and findings. The theoretical focus of the intervention was determined based on the categories suggested by Johnson and May: persuasive interventions (marketing, mass media, local consensus processes, local opinion leaders); educational and informational interventions (educational materials and meetings); and action and monitoring interventions (audit and feedback, reminders).[14]

Risk of bias assessment was tailored to different study designs. The Cochrane Collaboration's risk of bias tool was used to quality assess randomized controlled studies[15] (►**Supplementary Fig. S2**, available in the online version); an adjusted version was used for non-randomized controlled studies (►**Supplementary Fig. S3**, available in the online version). The National Institutes of Health (NIH) Regional Heart, Lung and Blood Institute Quality Assessment Tool for observational, cohort and cross-sectional studies was used to assess risk of bias in cross-sectional studies[16] (►**Supplementary Fig. S4**, available in the online version); and an adapted version of the NIH Quality Assessment Tool for before-after studies with no control group was used to assess risk of bias in uncontrolled before-after studies[16] (►**Supplementary Fig. S5**, available in the online version).

All study selection, data extraction and quality assessment processes were conducted independently and in duplicate; discrepancies were resolved by an additional reviewer.

Data Synthesis

As study designs were heterogeneous, a narrative synthesis was conducted. Tables of characteristics were created for eligible controlled and uncontrolled studies (►**Tables 1** and **2**; further details in ►**Supplementary Table S2**, available in the online version). To facilitate comparison, data were summarized in a standardized way. Results were considered by different characteristics and risk of bias to elicit systematic differences (►**Table 3**). It was not possible to formally assess possible publication bias.

Results

This review identified 12,807 records, of which 72 were assessed for full eligibility; of these, 52 did not meet eligibility criteria (►**Supplementary Table S1**, available in the online version). Twenty studies were included in this review and informed the analysis (►**Fig. 1**). Protocol papers of four on-going studies were located.[17–20]

Study Characteristics

The 20 included studies were conducted at 392 individual health care settings (including GP surgeries and secondary/tertiary care hospitals) (►**Tables 1** and **2**). At baseline, 29,868 patients were included; 11,105 in controlled and 18,763 in uncontrolled studies. Study designs included 3 cluster randomized controlled trials (RCTs),[21–23] 5 controlled studies,[24–28] 1 cross-sectional study[29] and 11 uncontrolled before-after studies.[30–40]

Intervention Design

Of the 20 studies, one provided an educational intervention with an expert panel,[40] three were based on implementation of local or national clinical guidelines,[28,32,34] two implemented a clinical protocol[35,37] and one comprised a multicomponent intervention (education, decision support tool, performance feedback).[38] Three were based on a review of current prescribing,[25,33,36] and one incorporated a review of prescribing and the introduction of a clinical protocol.[31] Five integrated computerized decision support or risk assessment tools into their systems[21–23,27,30] and four were based on medical care programs offering HCP training and HCP–patient consultations.[24,26,29,39] To improve OAC prescription, six interventions used action and monitoring techniques,[21–24,26,30] six combined education and interventional techniques with action and monitoring,[25,27,32,33,37,39] four attempted to use persuasion plus educational and interventional techniques,[28,35,36,40] one used persuasion plus action and monitoring[31] and three were multifaceted, using persuasive, educational and interventional and action and monitoring techniques.[29,34,38]

Interventions were delivered by a range of professionals, with eight delivered by either researchers or a combination of researchers and HCPs such as primary, secondary and tertiary care clinicians, nurses, pharmacists, allied HCPs and software suppliers.[21–23,25,27,28,33,37] Ten interventions were delivered by HCPs only, including secondary care clinicians, GPs, primary care teams, clinical pharmacists, allied and nursing HCPs and local clinical stakeholders. Two interventions had unspecified deliverers.[24,32] Five interventions were aimed at improving OAC prescribing among GPs,[21–23,28,38] three at hospital physicians,[24,25,27] one at cardiologists,[26] four at interdisciplinary primary care teams,[29,31,37,39] one at an interdisciplinary hospital team,[40] two at hospital prescribers[30,32] and four at hospital clinicians and GPs.[33–36]

Follow-Up

Of the 12 uncontrolled studies, only Bajorek et al provided follow-up beyond the post-intervention data (3- and 6-month follow-up).[33] Of the three RCTs, one provided a maximum follow-up of 11 months[22] and two provided data at 12 months.[21,23] Four of the five controlled trials provided data from historical control groups that commenced 4 months,[25] 1[27,28] year and 3 years[26] before the intervention cohorts, respectively. The final controlled study reported an average follow-up length of 25 months[24] (►**Supplementary Table S2**, available in the online version).

Fidelity

Measures assessing the fidelity of the interventions to the intended method were provided by four studies.[22–24,40] Hsieh et al reported that the proportion of HCPs completing five stroke quality measures increased from 75% before the intervention to 86% during the intervention.[40] Arts et al monitored the triggers for notifications and the usage of their notification system, reporting 3,848 notifications, of which 188 (5%) were clicked on for further information, 76 were

Table 1 Study characteristics of all included controlled studies

Author/Year/ Country/Study design/Data collection	Setting/patients	Type of AF (risk stratification)	Intervention	Intervention focus (type)[14]	Deliverer/Target population	Comparator/control	Outcome relevant to this review	Effect
Bajorek et al[21] Australia, 2016 Cluster RCT Trial conducted 01/ 2012–06/ 2013	Primary care practices $n = 48$ Patients $n = 393$ (intervention: 206; control 187)	Unspecified AF (age ≥65 years: moderate or higher risk of stroke)	CARAT: Computerized risk assessment tool	Action & Monitoring (reminder, reason for not following recommendation)	Deliverer: Researchers and GPs Target: GPs	Usual care in control general practices (own clinical judgement, processes and resources)	Use of OAC	Baseline Intervention a. (total $n = 206$): 89.3% (184) Follow-up Intervention a. (total $n = 206$): 92.2% (190) $p = 0.02$
Arts et al[22] The Netherlands, 2017 Cluster-RCT Trial conducted 10/2013 to 09/2013	Primary care practices $n = 19$ Patients baseline: $n = 731$ (intervention: 496; control 235) Follow-up: $n = 781$ (intervention: 522; control: 259)	All AF patients: incident and pre-existing AF	Computerized decision support system with pop ups Intervention Group 1: could decline pop ups Group 2: could decline pop ups with justification	Action & Monitoring (reminder, reason for not following recommendation)	Deliverer: Researchers and GPs Target: GPs	Usual care in control general practices (no pop ups received)	Proportion of patients treated according to the Dutch guidelines	Follow-up Control a. (total $n = 259$): 50% (130) Follow-up Intervention a. (total $n = 522$): 55% (287) Chi-square between-group difference at follow-up: $p = 0.23$
Holt et al[23] UK, 2017 Cluster-RCT 06/2014	Primary care practices $n = 47$ Patients $n = 5,339$ (patients eligible for OAC at 6 mo in the 23 intervention practices: median (IQR): 108 (74, 212); in the 23 control practices: 106 (44,162))	Unspecified AF ($CHADS_2 \geq 2$)	Computerized risk assessment tool AURAS-AF: (AUtomated Risk Assessment for Stroke in Atrial Fibrillation)	Action & Monitoring (reminder, reason for no treatment initiation)	Deliverer: Researchers in collaboration with a leading primary care software supplier Target: GPs	Usual care in control general practices, including the requirements of the QOF funding system	Proportion of patients eligible for OAC who were currently prescribed an OAC ($CHADS_2 \geq 2$)	Mean difference in OAC prescribing between intervention and control adjusting for baseline 1.21% 95% CI [−0.72 to 3.13] $p = 0.213$
Jackson et al[28] Australia, 2004 Controlled before-after (historical control) Pre-intervention sample: 02/2001–01/2002; Post-intervention sample: 02/2002–01/2003	Primary care practices (n = not reported) Patients pre-intervention: 245; post-intervention: 157 control region, n = unknown	Unspecified AF, some with chronic AF (stroke risk assessment using Australian endorsed guidelines[46])	Educational program promoting regional guidelines Research pharmacists visited GPs to discuss rationale for OAC prescription and safe OAC use	Persuasive (guidelines developed in consultation with local specialists) Educational & Informational (educational visit, distribution of educational material and RHH guidelines)	Deliverer: Research pharmacist Target: GPs	Usual practice in the pre-intervention period/ North of the state as a control area	Percentage of eligible patients receiving warfarin upon hospital discharge	Pre-intervention on discharge total 39% Post-intervention on discharge total 51% $p < 0.05$
Touchette et al[25] USA, 2008 Controlled cohort (historical control) Patient enrolment 09/ 2001–02/2002	Secondary care – Urban teaching hospital, $n = 1$ Patients, $n = 252$ (intervention: 154; historical control: 98)	New onset, chronic or unspecified AF (high risk according to Chest 2004 guidelines[47])	Pharmacist review and assessment of prescribing (inpatients) One training session on identifying NVAF and guideline use in NVAF management	Educational & Informational Action & monitoring (recommended antithrombotic plan)	Deliverer: Researchers and Clinical pharmacists Target: Hospital physicians	Routine medical care/ historical control group from the 3-mo period (05–07/2001) prior to the intervention	Percentage of patients receiving warfarin in-hospital at discharge	Control 41.8% ($n = 41/98$) Intervention 45.5% ($n = 70/154$) Between-group difference 3.7% $p = 0.60$

(*Continued*)

Table 1 (*Continued*)

Author/Year/ Country/Study design/Data collection	Setting/patients	Type of AF (risk stratification)	Intervention	Intervention focus (type)[14]	Deliverer/Target population	Comparator/control	Outcome relevant to this review	Effect
Hendriks et al[26] Netherlands, 2010 Controlled cohort (historical control) Patient referred to clinic between 06/ 2006 and 04/2007	Secondary care – Outpatient clinic of a University hospital, $n = 1$ Patients, $n = 213$ (intervention: 111; historical control: 102)	Paroxysmal, persistent, permanent or unspecified AF ($CHADS_2$ 0, 1 or > 1)	Integrated chronic care program Nurse-led assessment, computerized decision support tool (cardio-consult AF), consult with cardiologist	Action & Monitoring (dedicated software program, supervising cardiologist confirming treatment)	Deliverer: Nurse specialist Target: Supervising cardiologist	Usual care without the support of a specialist nurse/ historical control group (Euro Heart survey 2003–2004)	Percentage of patients receiving VKA treatment (according to the ACC/AHA/ESC AF guidelines)	Control $CHADS_2 > 1$, 80% ($n = 42/52$) Intervention $CHADS_2 > 1$, 90% ($n = 34/38$) $p < 0.001$
Boriani et al[24] Italy, 2012 Controlled cohort Date of data collection not reported	Secondary care –Cardiology clinics, $n = 50$ Patients, $n = 3,438$ (intervention: 1,961; control: 1,447)	Unspecified AF ($CHADS_2 \geq 1$; patients with ICDs)	Medical care program, ANGELS of AF: (Anticoagulation Use Evaluation and Life Threatening Events Sentinels) Information from implantable cardiac defibrillators passed to HCGs	Action & Monitoring (automatic algorithm and report to physician)	Deliverer: Unspecified Target: Hospital physicians	Cardiology clinics following centre's standard clinical practice without reports	Percentage of patients on OAC therapy at the end of the observational period ($\leq$ 48 mo) ($CHADS_2 \geq 1$)	Between-group difference, 15.8% $p < 0.001$
Cook et al[27] USA, 2015 Controlled cohort (historical control, Notifications triggered in the period 12/2009–02/2010)	Tertiary care hospital, $n = 1$ Patients = 494 newly diagnosed with AF (intervention: 268; historical control: 226)	Unspecified AF ($CHADS_2 \geq 2$)	Computerized decision support tool and clinical alert system embedded in the hospital systems Answers to FAQs and a directory of experts provided	Educational and Informational (link for additional information) Action and Monitoring (decision rule)	Deliverer: Researchers in collaboration with board-certified cardiologists Target: Hospital physicians	Usual care/historical control from the corresponding 3-mo period 1 year prior (12/2008–02/2009)	Prescription of warfarin in all eligible patients within 30 d of AF diagnosis ($CHADS_2 \geq 2$)	Between-group difference Adjusted OR 0.91 [95% CI, 0.60–1.38] $p = 0.65$

Abbreviations: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association Task Force on Practice Guidelines; ANGELS, the anticoagulation use evaluation and life threatening events sentinels; AURAS-AF, automated risk assessment for stroke in atrial fibrillation; $CHADS_2$, scoring scheme for stroke risk assessment; CI, confidence interval; EHR, electronic health record; EMR, electronic medical record; ESC, European Society of Cardiology Committee for Practice Guidelines; FAQ, frequently asked question; GPs, general practitioners; HCG, human chorionic gonadotrophin; ICDs, implantable cardioverter-defibrillators; IQR, interquartile range; NPSG, National Patient Safety Goals; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; OAT, oral anticoagulant therapy; OR, odds ratio; QOF, Quality and Outcomes Framework; RCT, randomized controlled trial; RHH, Royal Hobart Hospital; VKA, vitamin K antagonist.

Table 2 Study characteristics of all included observational studies without a control group

Author/Year/Country/ Study design	Setting	Type of AF (risk stratification)	Intervention	Intervention focus (type)[14]	Deliverer/ Target population	Comparator	Outcome relevant to this review	Effect
Sobrequés et al[31] Spain, 2002 Before-after Pre-intervention: 09/2001; Post-intervention: 03/2002	Primary care centre, $n = 1$ Patients pre- and post-intervention: 53	Chronic AF (age $\geq$ 75 years high risk of stroke)	Review of current prescribing Introduction of a clinical protocol	Persuasive (local consensus process, expert opinion, clinical guidelines) Action & Monitoring (audit & feedback)	*Deliverer:* Hospital cardiologist in collaboration with the primary care centre team *Target:* Interdisciplinary primary care team	Audit prior to intervention	Percentage of eligible patients taking acenocumarol	Pre-intervention 70.5% (total $n = 53$) Post-intervention 88.6% (total $n = 53$) *Between-group difference* 18.1% $p < 0.01$
Lowdon et al[32] UK, 2004 Before-after Audit 1: 01/2001–04/2002; Audit 2: 05–12/ 2002	Secondary care – Elderly Medicine Unit, $n = 1$ Patients pre-intervention: 87; post-intervention: 33	NVAF (risk factors were identified in medical notes to stratify individuals' stroke risk, eligible at risk patients identified separately)	Audit prior to and after the introduction of evidence-based guidelines	Educational and Informational (introduction of SIGN evidence-based guidelines[48]) Action & Monitoring (audit & feedback)	*Deliverer:* Unspecified *Target:* Hospital prescribers	Audit prior to intervention	Percentage of eligible patients prescribed OACs	Pre-intervention eligible patients only (no contraindications) 43.7% ($n = 38/87$); Post-intervention 90.9% ($n = 30/33$); *Between-group difference* eligible patients only (no contraindications) 47.2% $p < 0.001$
Bajorek et al[33] Australia, 2005 Before-after Date of data collection not reported (recruitment over a 6-mo period)	Secondary care (Aged Care) – Teaching hospital, $n = 1$ Patients pre-intervention: 218; post-intervention: 200	Pre-existing or new-onset AF (risk of stroke based on key universal, international[49] and local consensus guidelines,[50] age $\geq$ 65 years (moderate or higher risk of stroke)	Pharmacist-led review of prescribing, liaising with and educating health care professionals Discussion of recommendations at clinical rounds	Educational and Informational (an education session) Action & Monitoring (algorithms and a review process, follow-up in the community setting)	*Deliverer:* Project pharmacist in collaboration with HCPs and consumers *Target:* Hospital-based clinicians, GPs, patients	Usual practice in the pre-intervention period	Percentage of patients receiving warfarin ($\pm$ aspirin)	*On admission (pre-intervention)* 20.7% ($n = 45/218$) *At discharge* 17.4% ($n = 38/218$) *Between-group difference* 3.3% $p = 0.39$
Bo et al[34] Italy, 2007 Before-after Pre-implementation: 01–06/2000; Post-implementation: 01–06/2004 Guideline adopted in June 2003	Tertiary care teaching hospital ($n = 1$) Patients pre-intervention: 106, post-intervention: 105	Chronic NVAF as secondary diagnosis (risk stratification model developed, risk of stroke separated into low, moderate, high and very high)	Development and implementation of locally adapted guidelines Meetings of the multidisciplinary team (content not discussed)	Persuasive (clinical guidelines and local medical journal adverts) Educational & Informational (ad hoc meetings, distribution of educational material) Action & Monitoring (audit report, contact with GP)	*Deliverer:* Large multidisciplinary group *Target:* Hospital physicians and family practitioners	Usual practice in the pre-implementation period	Increase in strongly recommended OAC prescription at discharge	*Pre-intervention* 56.6% with OAC ($n = 60/106$) Post-intervention 81.9% ($n = 86/105$) *Between-group absolute difference* 25.3% (95% CI: 15%, 35%)
Coll-Vinent et al[35] Spain, 2007 Before-after Pre-intervention: 14 d in 06/2004; Post-intervention: 14 d in 06/2005	Tertiary care hospital, $n = 1$, & primary care clinic, $n = 1$ Patients pre-intervention: 293; post-intervention: 267	Paroxysmal, persistent or permanent AF (risk stratification not reported)	Development and dissemination of a clinical protocol based on current clinical guidelines Educational sessions on AF treatment, discussion of the	Persuasive (local consensus process) Educational & Informational (protocol distribution, clinical sessions)	*Deliverer:* Representative physicians from all the health care settings involved *Target:* Hospital physicians and GPs	Usual practice in the pre-intervention period	Percentage of patients receiving OAC treatment	*After visit in the pre-intervention period:* 52% ($n = 151/293$) *After visit in the post-intervention period:* 62% ($n = 163/267$) *Between-group difference:* After visit

(*Continued*)

Table 2 (*Continued*)

Author/Year/Country/ Study design	Setting	Type of AF (risk stratification)	Intervention	Intervention focus (type)[14]	Deliverer/ Target population	Comparator	Outcome relevant to this review	Effect
			pre-intervention data, explanation of the protocol					between pre- and post-intervention periods: 10%
Falces et al[29] Spain, 2011 Cross-sectional Conventional care: 01–12/2008; Intervention: 01–12/2009	Primary care centres, $n = 7$, in collaboration with secondary care Patients $n = 3{,}194$ (intervention: 1,622; usual care: 1,572)	Unspecified AF (following ACC/AHA/ESC 2006 guidelines[51])	Integrated care model (hospital cardiologist in primary care clinics, shared clinical history, joint practice guidelines, consultation sessions Theoretical and practical training sessions for continued medical education for primary care and shared care course	Persuasive (clinical guidelines) Educational (training sessions) Action & Monitoring (shared EMR, consultation sessions, follow-up after discharge)	*Deliverer:* Hospital cardiologist and nurse *Target:* Interdisciplinary primary care team	Conventional care in a specialized outpatient clinic	Percentage prescription of OAC therapy (ACC/AHA/ESC AF guidelines)	Usual care: 69.3% ($n = 201/290$) (univariate analysis) Integrated care: 94.6% ($n = 211/223$) (univariate analysis) Logistic regression model: adjusted OR 7.1 [95% CI, 3.8–13.5] $p < 0.001$
Jackson and Peterson[36] Australia, 2011 Before-after Pre-intervention: 02–09/2004; Post-intervention: 10/2004–02/2006	Secondary care – Teaching and research hospital, $n = 1$ Patients pre-intervention: 339; post-intervention: 131	Mainly chronic AF (stroke risk assessment using Australian endorsed guidelines[46])	Pharmacist-led stroke risk assessment program Locally produced guidelines on mouse mats and project information disseminated to HCPs	Persuasive (local consensus processes and opinion leaders) Educational & Informational (guideline dissemination)	*Deliverer:* Clinical pharmacist in collaboration with clinical haematologist, geriatrician, cardiologists, GP *Target:* Hospital clinicians and GPs	Usual practice in the pre-intervention period	Proportion of eligible high-risk patients receiving warfarin at discharge	Pre-intervention high risk 30% ($n = 76/259$) Post-intervention high risk 57% ($n = 65/115$); *Between study arms at discharge:* high risk, $p < 0.0001$
Oliveira et al[37] Portugal, 2014 Before-after Pre-intervention: 05/2012; Post-intervention: 09/2012	Primary care – Family Health Unit, $n = 1$ Patients pre-intervention: 97; post-intervention: 87	Unspecified AF (CHA_2DS_2-VASc ≥ 2 for OAC therapy)	Educational intervention with audit and feedback Results of an OAC therapy adequacy evaluation discussed with HCPs A presentation on guideline-based OAC therapy	Educational & Informational (oral presentation based on guidelines) Action & Monitoring (audit and feedback)	*Deliverer:* Researchers *Target:* Primary care interdisciplinary team	Baseline audit in the pre-intervention period	Percentage of patients prescribed appropriate OAC therapy based on risk scores (94% with CHA_2DS_2-VASc ≥ 2)	Pre-intervention 46.4% ($n = 45/97$) Post-intervention 56.3% ($n = 49/87$) No comparison
Robson et al[38] UK, 2014 Before-after Pre-intervention: 04/2008 to 04/2011; Post-intervention: 04/2011–04/2013	Primary care practice, $n = 139$ Patients pre-intervention: 3,964; post-intervention: 4,168	Unspecified AF ($CHADS_2$ and CHA_2DS_2-VASc ≥ 1)	Local guideline sent to HCPs, multidisciplinary meetings and evidence-based implementation of OAC treatment A computerized decision support tool, feedback of performance compared with other practices The Anticoagulation	Persuasive (summary clinical guidelines and publication) Educational & Informational (guideline dissemination) Action & Monitoring (audit and feedback)	*Deliverer:* Local clinical stakeholders in collaboration with a multidisciplinary primary care team *Target:* GPs	Baseline audit in the pre-intervention period	Percentage of patients with AF and CHA_2DS_2-VASc ≥ 1 on OACs	*Pre-intervention:* 04/2011 52.6% ($n = 2{,}085/3{,}964$) *Post-intervention:* (04/2013) 59.8% ($n = 2{,}492/4{,}168$) *Immediately pre-intervention to post-intervention* 2011 versus 2013: 7.2%

Table 2 (*Continued*)

Author/Year/Country/ Study design	Setting	Type of AF (risk stratification)	Intervention	Intervention focus (type)[14]	Deliverer/ Target population	Comparator	Outcome relevant to this review	Effect
			Program East London (APEL)					*Pre-intervention to post-intervention:* 2011 versus 2013: < 0.001
Das et al[39] UK, 2015 Before-after Service delivered between 06/2012 and 06/2014	Primary care practice, $n = 56$ Patients pre-intervention: 547; post-intervention: 5,471	Unspecified AF ($CHADS_2$ or CHA_2DS_2-VASc score ≥ 1)	The Primary Care Atrial Fibrillation (PCAF) service Database search for eligible AF patients Primary care HCPs take part in consultant cardiologist/ stroke physician led AF clinics, including shared learning and case discussions. A consultant led educational program (no details)	Educational & Informational (consultant-led educational program and clinics) Action & Monitoring (automated electronic tools, follow-up)	*Deliverer:* Local hospital consultant cardiologist & stroke Physicians supported by nursing or allied HCPs *Target:* Primary care interdisciplinary team	Usual care prior to intervention	Overall proportion of eligible patients receiving OACs ($CHADS_2$ or CHA_2DS_2-VASc ≥ 1)	Pre-intervention 77% ($n = 4,187/5,471$) Post-intervention 95% ($n = 5,207/5.471$) *Between-group difference* 18% $p < 0.0001$
Hsieh et al[40] Taiwan, 2016 Before-after Pre-intervention: 05/ 2006–07/2008; During intervention: 08/2010–07/2011	Secondary care – medical centres ($n = 7$) and regional hospital, $n = 7$ Patients pre-intervention: 9,612; during intervention: 7,492	Unspecified AF but all patients with acute ischaemic stroke (risk stratification not reported)	Learning sessions for staff and a summative meeting Multidisciplinary teams met with experts to discuss experiences and barriers to OAC prescription Breakthrough Series (BTS)-stroke activity	Persuasive (expert panel developed quality measures) Educational & Informational (learning sessions and a summative meeting)	*Deliverer:* An expert panel of neurologists, neurosurgeons, emergency medicine specialists and stroke nurses *Target:* Hospital interdisciplinary team	Pre-BTS-stroke activity period	Percentage of discharge prescription of OACs for eligible AF	Pre-intervention 32.1% (total $n = 9,612$) During- intervention 64.1% (total $n = 7,492$) *Between-group difference* 32% $p < 0.001$
Wang and Bajorek[30] Australia, 2017 Before-after Conducted August 2015– October 2015	Tertiary care teaching hospital, $n = 1$ Patients pre-intervention: 253; post-intervention: 251	Principal diagnosis of non-valvular AF/secondary diagnosis of AF contributing to admission (age ≥ 65 years: moderate or higher risk of stroke)	Risk assessment tool (populated by researchers and the treatment recommendations presented to the HCP in person, by phone or in the patients clinical notes)	Action and monitoring (reminders)	*Deliverer:* The principal researcher – a medical doctor *Target:* Hospital prescribers	Audit prior to intervention	Proportion of participants receiving OACs (Warfarin and NOACs)	Pre-intervention a. Total $n = 251$ Warfarin 30.3% (76) NOAC 20.0% (50) Post-intervention a. Total $n = 251$ Warfarin 40.0% (76) NOAC 30.0% (54) Change in Warfarin use, $p < 0.001$ a. Change in NOAC use, $p < 0.001$

Abbreviations: ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association Task Force on Practice Guidelines; $CHADS_2$ and CHA_2DS_2-VASc, scoring schemes for stroke risk assessment; CI, confidence interval; ED, emergency department; EMR, electronic medical record; ESC, European Society of Cardiology Committee for Practice Guidelines; GPs, general practitioners; ; HCP, health care professional; NOAC, non-VKA oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulants; OR, odds ratio

Table 3 Effectiveness of interventions by study characteristics

Characteristic	Category	Change in appropriate OAC prescription/ use (total $n = 20$ studies)	
		Significant increase	No significant change
Date published	Pre-2010	5/7	2/7
	2010 and after	10/13	3/13
Country	EU	10/12	2/12
	Non-EU	5/8	3/8
Study design	Uncontrolled or historical control	13/16	3/16
	Concurrent control	2/4	2/4
Setting	Primary care	7/9	2/9
	Secondary care	5/7	2/7
	Tertiary care	3/4	1/4
Date of data collection	Commenced pre-2010	10/12	2/12
	Commenced 2010 and after	4/6	2/6
	Unknown	1/2	1/2
Type of AF	All/unspecified	10/15	5/15
	Chronic	3/3	0/3
	Non-valvular	2/2	0/2
Severity of AF	$CHADS_2$ or CHA_2DS_2-VASc $\geq$2 or $\geq$75 years old or high-risk according to guidelines	5/8	3/8
	$CHADS_2$ and CHA_2DS_2-VASc $\geq$1 or $\geq$65 years old, or moderate- and high-risk according to guidelines	6/7	1/7
	Unknown/any severity	4/5	1/5
Intervention	Computerized risk assessment tool	2/5	3/5
	Education/guidelines/protocol	7/7	0/7
	Medical care program	4/4	0/4
	Review of prescribing	2/4	2/4
Intervention focus	Action and monitoring	4/6	2/6
	Educational and interventional; Action and monitoring	3/6	3/6
	Educational and interventional; Persuasive	4/4	0/4
	Persuasive; Action and monitoring	1/1	0/1
	Educational and interventional; Persuasive; Action and monitoring	3/3	0/3
Intervention deliverer	Health care professional (HCP)	9/10	1/10
	Researchers (and/or HCPs)	4/8	4/8
	Unspecified	2/2	0/2
Target population	GPs	3/5	2/5
	Primary care interdisciplinary team	4/4	0/4
	Secondary care/Secondary and primary care/ Secondary care interdisciplinary team	8/11	3/11
Comparator	Control health care settings (usual care)	3/5	2/5
	Usual care at the same site prior to the intervention or a historical control	12/15	3/15

Abbreviations: AF, atrial fibrillation; EU, European Union; GP, general practitioner; OAC, oral anticoagulant.

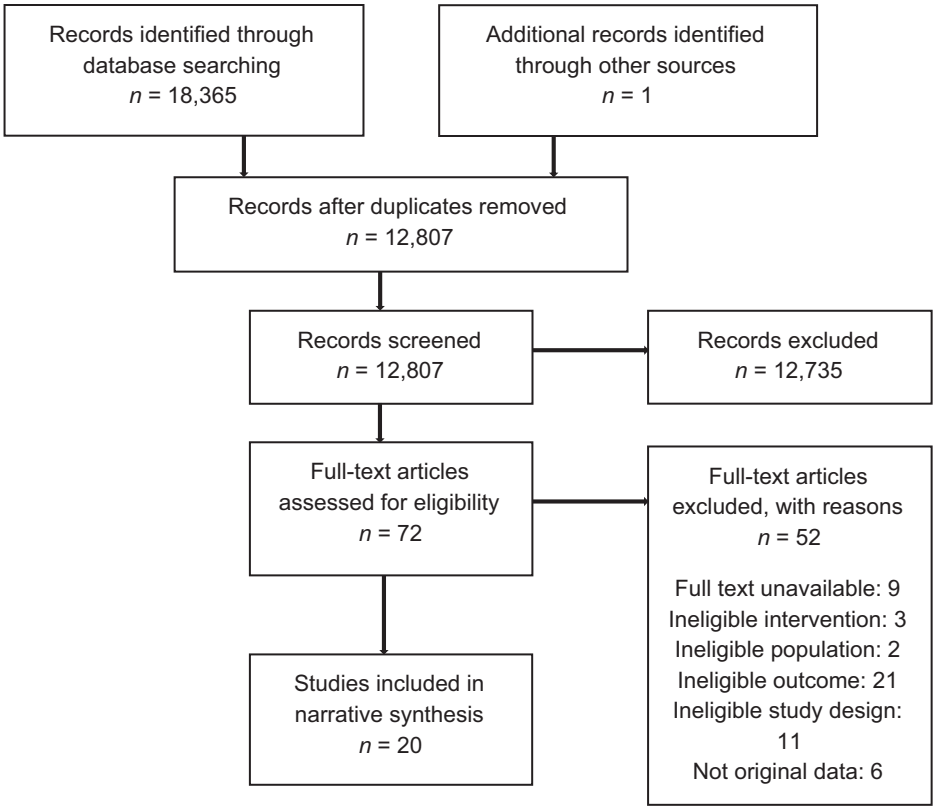

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement flowchart.

actively responded to, of which 44 (58%) were dismissed, and 32 (42%) were accepted, indicating the advice would be followed.[22] Boriani et al reported that the ANGELS of AF reports were the specific trigger for prescribing OACs to 22 (10.5%) patients of the 209 not already receiving OACs.[24] Holt et al obtained data from 12/23 intervention practices on HCPs' responses to screen prompts and their invitations to patients to discuss OAC prescription[23]; 466 patients were identified by the system as eligible at baseline, 159 (34%) of these were confirmed as eligible by HCPs and 35 (22%) of these were prescribed OACs.[23] The mean proportion of those originally identified as eligible who converted to OACs was 4.2%.[23]

Study Quality

The three cluster RCTs[21–23] were at low risk of many sources of bias; however, one RCT did not report control group data at follow-up.[21] One common potential source of performance bias was HCPs being aware of their group allocation. Of the five non-randomized controlled studies,[24–28] three used historical controls[25–27] introducing a risk of bias due to changes in guidance and prescribing behaviours over time. In controlled studies, sample size calculations were either absent[26,28] or their suitability unclear,[24,25,27] raising the possibility of non-significant results due to insufficient sample sizes (ranging from 213 to 5,339 patients); blinding of outcome assessments was also poorly described in three studies.[24,26,28] The cross-sectional study also lacked a sample size calculation.[29] The before-after studies[30–40] were generally at low risk of bias according to the adapted version of the NIH assessment tool used[16] however, in 7 of the 11 studies the population may not have been representative of those who would be eligible for the intervention[30,33,34,36–38,40] due to differences between the study population and the general population in characteristics such as age, ethnicity, deprivation level or co-morbidities (►**Supplementary Figs. S2–S5**, available in the online version).

Effectiveness

Of the 20 studies, 13 reported a significant increase in appropriate OAC prescription/use post-intervention[21,24,26,28–32 34,36,38–40]; two reported an increase, though significance was unclear,[35,37] and five reported no significant effect on appropriate OAC prescription/use[22,23,25,27,33] (►**Tables 1** and **2**, further details in ►**Supplementary Table S2**, available in the online version).

A greater proportion of non-significant results were reported among more effectively controlled study designs, such as cluster RCTs and studies with a concurrent comparator (2/4), than uncontrolled studies or those with historical controls (3/16). Studies conducted with high stroke-risk patients were less likely to report significant findings (5/8) than those with patients at moderate-to-high (6/7) or unknown risk of stroke (4/5). Non-significant results were more frequently reported by studies with interventions based on computerized decision support

tools (3/5) and reviews of prescribing (2/4); with all studies based on the education of HCPs or guideline/protocol implementation (7/7) and medical care programs offering training to the HCP and HCP–patient consultations (4/4) reporting significant improvements in appropriate OAC prescription. Those interventions based on action and monitoring techniques or both action and monitoring and education and intervention (of which 5/12 were computerized decision support tools) were the least likely to report significant improvements in appropriate OAC prescription (7/12). Interventions with a persuasive element were the most likely to report significant improvements in appropriate OAC prescription: 8/8 versus 7/12 studies with no persuasive element.

Interventions partly delivered by researchers, were less likely to report significant improvements in OAC prescription (4/8) than those delivered by HCPs (9/10); however, 5/8 of the researcher-delivered interventions were based on computerized decision support models, the majority of which reported non-significant results (3/5). None of the interventions delivered by researchers contained a persuasive element—a noteworthy characteristic of effective studies—with 8/8 interventions with a persuasive element reporting significant improvements in appropriate OAC prescription (►**Table 3**).

Clinical Outcomes

Clinical outcomes such as the rates of stroke, transient ischaemic attack (TIA), embolism and haemorrhage following the intervention were only provided by two studies.[24,41] Boriani et al reported no difference in the annual embolic event rate in the intervention compared with control group patients ($p = 0.64$).[24] Holt et al reported a significantly higher median (interquartile range) incidence of thromboembolic events per 1,000 patients at 6 months in the intervention compared with the control group (10.3 [0, 16.3 vs. 0 [0, 7.75]]) ($p = 0.03$); there was no difference at 12-month follow-up.[23] Haemorrhagic events were non-significantly higher in the control group compared with the intervention group at 6 and 12 months.[23]

Discussion

This review examined the effectiveness and characteristics of studies designed to increase appropriate OAC prescription in eligible AF patients for stroke prevention. Despite published reviews focusing on improving patient uptake of OACs,[42,43] this review represents the first rigorously conducted systematic evaluation of interventions to improve HCPs' prescribing behaviours in this field. Research published to date represents a wide variety of study designs, settings, interventions and theoretical approaches. This heterogeneity, the substantial proportion of uncontrolled studies and the relatively small number of studies overall, should be borne in mind when considering our findings.

Overall, 15 of the 20 included studies reported improvements in appropriate prescription of OACs in eligible AF patients for stroke prevention, indicating that such interventions can be effective in influencing HCPs' prescribing behaviours. Trials with a concurrent comparator were less likely to report significant improvements, raising questions about the appropriateness of uncontrolled study designs during the last decade, and strongly indicating the need for controlled studies to support appropriate conclusions. Studies with high stroke-risk AF patients (CHA_2DS_2-VASc ≥ 2 or according to guidelines) were less likely to show improvement in appropriate OAC prescription than those with participants at moderate-high or unspecified stroke risk. This finding may reflect the reported reluctance of HCPs to prescribe OACs to patients over 65 years who are likely to be at greater risk of stroke but also of falls and subsequent haemorrhage.[9]

Certain intervention designs appeared to be less effective in modifying HCPs' prescribing behaviours than others, such as computerized decision support tools and reviews of current prescribing. The integration of computerized decision support tools within electronic medical record systems is very common now; however, the greater the number of reminders or alerts a HCP receives the less likely they are to respond.[44] This alert fatigue,[44] may limit effectiveness of such interventions. Reviews of prescribing were often conducted by pharmacists, and it may be that clinicians respond better to interventions conducted by peer clinicians as discussed below.

Interventions based on HCP education, implementing guidelines or protocols and medical care programs were the most effective. The majority of HCP education and guideline/protocol implementation interventions had an element of persuasion in their theoretical focus (often facilitating HCP involvement in local guideline production or comparing HCPs' practice with peers). In contrast, a systematic overview of the theoretical foci of studies in HCP behavioural change reviews indicated that interventions with persuasive elements have proffered inconsistent results. However, some success has been reported by studies using local opinion leaders to promote evidence-based practice in HCPs.[45] Most of the effective medical care programs, and HCP education and guideline/protocol implementation interventions were conducted by clinicians or multidisciplinary groups. It may be that interventions enabling clinicians to seek consensus with, and receive expert opinion from, their peer group are particularly effective in prompting behavioural change. These findings suggest that persuasive interventions based on HCP–peer group interaction, or both HCPs and patients in medical care programs, may be effective models for prompting behavioural change in OAC prescription for stroke prevention in eligible AF patients. These findings may also be useful for intervention design in other fields where HCP behavioural change is sought; however, large-scale cluster RCTs are required to determine the most effective HCP behaviour change interventions with greater certainty.

Strengths

This article represents the first systematic review of interventions to improve appropriate OAC prescription in

eligible AF patients for stroke prevention. Despite the inclusion of only 20 studies, this research was based on 29,868 patients seen in 392 health care setting providing primary, secondary and tertiary care. This review was methodologically robust, with independent, duplicated screening, data extraction and quality assessment processes. Translation of non-English language papers guaranteed the inclusion of appropriate material. The main outcome was change in rate of OAC prescription to eligible AF patients for stroke prevention; rate of OAC use was only considered if the intervention was aimed only at HCPs. This distinction guaranteed that we explored the effect of the interventions directly on the HCP, not the patient. Additionally, the theoretical underpinnings of studies were examined to provide suggestions regarding the most effective elements, as recommended by the Medical Research Council. This approach is unique to a review in this field.

Limitations

Substantial heterogeneity in study design prohibited meta-analysis of individual results, preventing authors from drawing quantifiable conclusions regarding the effectiveness of interventions overall. This heterogeneity limits the certainty of conclusions drawn regarding the effectiveness of different study characteristics. Only 4 of the 20 included studies had concurrent controls, with the majority having either historical control or no control data, introducing a substantial risk of bias. This review included a comparatively small total number of studies ($n = 20$); however, the large total patient population (29,868 patients at baseline) and the consistency of many of the findings adds confidence to our observations. The lack of measures reporting the fidelity of the interventions to the intended method in the included studies creates uncertainty as to the effective elements within interventions, which should be addressed in the design of future studies. It should also be noted that the included studies provided very little consideration of the effect of their interventions on clinical outcomes, such as rates of stroke, haemorrhage and TIA. Future studies should include long-term follow-up of relevant clinical outcomes to improve their clinical relevance for both HCPs and patients.

Conclusion

AF is a growing global issue. Current research suggests that in many countries HCPs are still under-prescribing OACs in high stroke-risk patients and over-prescribing in low-risk patients. Effective interventions are needed to improve appropriate prescription of OACs in eligible AF patients to prevent unnecessary risk of stroke and haemorrhage. This review suggests that effective interventions should include persuasive elements delivered by HCPs to HCPs or multidisciplinary teams. HCP education, implementing guidelines/protocols and medical care programs with education for both HCPs and patients may all be effective interventions. These findings may also inform development of behavioural change interventions for HCPs in other health care fields.

What is known about this topic?

- AF is an increasing international health concern.
  AF affects over 33 million people worldwide with prevalence increasing globally. The growth of the aging population in developed countries is a substantial contributing factor.
- Poor global guideline adherence in OAC prescription.
  Despite recent improvements, greater guideline-adherence is needed worldwide in the prescription of OACs to eligible AF patients for stroke prevention. Under-prescription in higher stroke-risk patients, including those over 65 years, and substantial over-prescription in those at low risk is still reported globally, putting patients at unnecessary risk of stroke and haemorrhage.

What does this paper add?

- The first review of interventions aimed at HCPs.
  This is the first systematic review of interventions specifically designed to improve HCPs' appropriate prescription of OACs in eligible AF patients for stroke prevention.
- Effective interventions could improve guideline adherence, reducing stroke and haemorrhage.
  This review provides an indication of which intervention designs and theoretical foci may be most effective. Effective, practical, behaviour change interventions could be readily integrated into health care systems and have the potential to increase appropriate OAC prescription in eligible AF patients for stroke prevention, reducing rates of avoidable stroke and haemorrhage.

Authors' Contributions

K.J., R.V.P., D.A.L., G.N.T., D.B. and J.L.C. conceived the review and developed the methodological strategy; D.B., N.T., R.V.P. and R.F. performed the study selection; R.V.P., D.B. and G.N.T. performed study selection, data extraction and quality assessment with K.J. and D.A.L. as arbitrators. R.V.P. drafted the paper with input and critical review from all authors.

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Conflict of Interest
K.J. reports grants from National Institute for Health Research (NIHR), outside the submitted work, during the conduct of the study. D.A.L. reports grants from Boehringer Ingelheim and Bristol-Myers-Squibb, and personal fees from Boehringer Ingelheim, Bristol-Myers-Squibb, Bayer, Pfizer and Daiichi-Sankyo, outside the submitted work. R.V.P., G.N.T., D.B., J.L.C. and R.F. report no competing interests.

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