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Contemporary Management of Atrial Fibrillation: What Can Clinical Registries Tell Us About Stroke Prevention and Current Therapeutic Approaches?

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Atrial fibrillation (AF) is a global health problem. The condition brings an increased risk of stroke, systemic embolism, and heart failure (HF) and is associated with impaired quality of life, frequent hospitalizations, and mortality.[1] Observational studies have been the main source of information for many years and have defined the clinical presentation, clinical course, and prognosis of AF. Based on key issues identified by observational studies, management of patients with AF has been informed by randomized, controlled trials (RCTs) that provide the main support for guideline recommendations regarding management of patients with AF and prevention of thromboembolic complications. Nevertheless, important questions regarding the clinical course, risks, and management of AF in clinical practice remain unanswered.[1]

Although RCTs provide high-level evidence on the efficacy and safety of therapeutic interventions, they generally involve well-defined study populations that exclude complex patients and have standardized protocols for management with closer monitoring and stricter follow-up than is typical of routine clinical practice. Thus, their results are not always directly applicable to the general population or routine practice.

Traditional observational studies, often limited to small patient populations and performed at a single institution, are giving way to multicenter and national registries, supported by the transfer of information to large databases. Structured data collection can inform the generation of new hypotheses and help to test established ones. Registries are also subject to limitations as well as potential confounding factors related to the population selected, number, and scope of tracked variables and prevailing concepts of the disease under investigation.[2] These difficulties have been highlighted by expert groups that elaborated guidelines for reliable reporting of observational studies.[3]

Study designs vary depending on whether the objectives involve disease definition, diagnostic methodology, occurrence, etiology, prevention, prognosis, and treatment. The information obtained from observational and interventional studies provide different approaches that require integration of a wide array of data to derive a complete perspective on a disease or condition.

This review provides an overview of available registry data on patients with AF and focuses on 3 areas at the heart of AF management: (1) stroke prevention; (2) pharmacological rhythm and rate control; and (3) catheter-based ablation. In addition to cataloging the types of registry data available, we consider how these data contribute to understanding and management of patients with AF and speculate on the future directions of observational research.

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The Search Strategy

Registries or databases reporting on AF management, identified from sources that included CINAHL, Medline, EMBASE, and the Cochrane Database of Systematic Reviews from 2000 to 2012, were selected for closer review, and publications from these registries were tracked. We identified 34 large international or national registries of AF patients, including 17 reporting on thromboprophylaxis and stroke prevention, 8 focused on antiarrhythmic drug (AAD) therapy and cardioversion, 7 studying AF ablation, and 2 detailing left atrial appendage closure (LAAC) registries.

Cataloging AF Registries

Tables 1 through 4 provide overviews of the registries identified, which have been grouped into the following broad categories: (1) those focused on thromboprophylaxis and stroke prevention (Table 1); (2) those on cardioversion and AAD therapy (Table 2); (3) those on ablation (Table 3); and LAAC (Table 4). Several registries address multiple aspects of AF diagnosis and management and could be allocated to more than 1 category. To enable some key findings to be visualized more clearly, registries that provide information on medical treatments for AF (including use of agents for rhythm and rate control, warfarin, aspirin, and new oral anticoagulants [NOACs]) are also shown separately in Table 5.

Thromboprophylaxis and Stroke Prevention Registries

A number of registries provide data on management and prevention of thromboembolism in hospitalized and ambulatory patients with AF, offering insights into the effectiveness of oral anticoagulation (OAC) therapy (Table 1). Several large-scale registries on OAC use have been initiated by the pharmaceutical industry (Table 1) and focus on NOACs. For example, the Global Anticoagulant Registry in the Field (GARFIELD)[7] and Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF),[8] which are observational, global, large-scale prospective registries, assess patterns and outcomes of thromboprophylaxis.

A number of national and regional registries address medication preference by patients. The Adherence eValuation After Ischemic Stroke Longitudinal (AVAIL) registry, for example, expanded on the hospital-based Get with the Guidelines-Stroke quality improvement program and Carotid RX ACCULINK/RX ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE), a prototype registry from the Paul Coverdale National Acute Stroke Registry.[4,5] These evaluate whether patient management accords with practice guidelines and evidence-based research. The Nationwide Danish study,[11] Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)[12] and Prevention of thromboembolic events–European Registry in Atrial Fibrillation (PREFER-AF)[13] registries address this in European and U.S. patient cohorts. Data have been collected from each of these with the exception of CAPTURE, GARFIELD, and ORBIT-AF registries, which are ongoing.

Registries Reporting on AAD Therapy and Cardioversion

Pharmacological and direct-current cardioversion of AF has been charted by a number of registries to provide information on global treatment patterns (Table 2). The global Registry on Cardiac rhythm disorders assessing the control of Atrial Fibrillation (RECORD-AF)[25] was one of the first world-wide observational surveys of the management of patients with newly diagnosed paroxysmal or persistent AF, and the Real Life Global Survey Evaluating Patients with Atrial Fibrillation (REALISE-AF)[24] cross-sectional study captured data in 26 participating countries on AF management and cardiovascular (CV) risk profiles. RECORD-AF has also been extended to cover the Asia-Pacific region (RECORD-AF Asia Pacific).[28] In addition, RHYTHM-AF is an international prospective study aimed at determining regional variability, outcomes, and cost-effectiveness among patients with recent-onset AF considered for cardioversion in 10 countries of antiarrhythmic and antithrombotic treatment.[29] As shown in Table 2, other smaller, national registries assessing AAD use and cardioversion include US Atrial Fibrillation Focus on Effective Clinical Treatment Strategies (AFFECTS),[18] the German Outpatient Registry Upon Morbidity of Atrial Fibrillation (ATRIUM) registry,[20] and the Canadian Registry of Atrial Fibrillation (CARAF).[21]

Registries Reporting on AF Ablation and LAAC

Table 3 details registries assessing ablation therapy for AF. The Atrial Fibrillation Ablation Pilot Study, a prospective, multinational registry conducted by the European Heart Rhythm Association of the European Society of Cardiology,[31] was undertaken preceding a long-term Atrial Fibrillation Ablation pan-European Registry by the Euro-observational Research Programme, which opened in 2012 and invited participation from clinical sites in 54 countries. To date, some 875 patients have been enrolled from 61 or 137 registered centers in 19 or 29 registered nations. Table 3 describes other registries on AF ablation, such as the Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI),[36]organized by the US Cardiac Safety Research Consortium (CSRC),[39] and

Table 1. Registries With a Focus on Thromboprophylaxis and Stroke Prevention

Registry (Sponsor)	Country	Years	Setting	Study Aim	Patient Characteristics	No. of AF Patients	Female (%)	Mean Age (±SD)	Paroxysmal AF (%)	$CHADS_2$ (CHA_2DS_2VASC)
AFNET[1] (German Competence Network)	Germany	2010	Inpatients/ outpatients	Personalized management	AF	9558	—	—	—	1.6 to 1.9
AVAIL[4]	USA	July 2006–Sept 2009	Inpatients	Long-term use of antithrombotic therapies	Patients with ischemic stroke/TIA and AF post discharge	291	51.6	76	—	2 to 6
CAPTURE[5]	USA (Illinois)	Nov 2002–March 2003	Inpatients	Comparison of quality indicators	Stroke/TIA	1953	53.2/ 57.1	66.7/67.5	—	—
Euro Heart Survey[6]	35 countries Europe	Sep 2003–Jul 2004	Inpatients/ outpatients	Management against European guidelines	AF confirmed by ECG or Holter recording	3890	43.5	66.4±12.2	30.1	0 to 6
GARFIELD (Bayer)[7]	50 countries worldwide	Ongoing (2009–2015)	Inpatients/ outpatients	Evaluate management and outcomes	Newly diagnosed nonvalvular AF with additional risk factor for stroke	Aiming for 55 000	—	—	—	—
GLORIA-AF (Boehringer Ingelheim)[8]	Global (62 centers)	May 2011–Jan 2013	Inpatients	Characteristics influencing choice of therapy	Newly diagnosed nonvalvular AF patients at risk for stroke	Aiming for 55 000	—	—	—	—
J-RHYTHM[9]	Japan	Jan 2009–July 2009	Outpatients	Regional use of anticoagulation therapy	AF	7937	31.1	69.7±9.9	37.1	1.7±1.2
National Cardiovascular Data Registry's ACTION Registry–Get With the Guidelines[10]	USA	July 2008–Sept 2009		Outcomes of patients with acute myocardial infarction and AF	Myocardial infarction with AF	4947	42.4	Median 78	—	0: 3.7% 1: 12.9% ≥2: 80.9%
Nationwide Danish study[11]	Denmark	Patient registry data from 1997–2008	Inpatients/ outpatients	Net clinical benefit of OACs	Non-valvular AF	141 500	47.2	72.6 ±12.9	—	0 to 6 (0 to 9)
ORBIT-AF[12]	USA	June 2010–Nov 2014	Outpatients	Characterize treatment and outcomes	Incident or prevalent AF	10 126	43	75	46	75% ≥2 (85% ≥2)
PINNACLE-AF (http://www.ncdr.com/webncdr/pinnacle) (National Cardiovascular Data Registry)	USA	Ongoing	Outpatients	Monitoring practise pattern changes over time	AF	100 000+	–	—	—	—

Continued

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Table 1. Continued

Registry (Sponsor)	Country	Years	Setting	Study Aim	Patient Characteristics	No. of AF Patients	Female (%)	Mean Age (±SD)	Paroxysmal AF (%)	$CHADS_2$ (CHA_2DS_2VASC)
PREFER-AF (Daiichi-Sankyo)[13]	7 countries Europe	2012	Inpatients/ outpatients	Management of patients under 2010 guidelines	History of AF	7243	40	71.5±11	30	(3.4)
REACH[14]	44 countries		Outpatients	Implications of AF	PAD patients at risk of AF	6814	35.6	72.8±9.2	—	2.8±1.3
RE-LY[15]	47 countries	Nov 2005–April 2009	Inpatients/ outpatients	Comparison of warfarin and dabigatran	AF with an additional risk factor for stroke	13 507	45.4	66.2	—	—
REVERSE[16] (Sociedad Española de Cardiología)	Spain	Feb–June 2004	Inpatients (cardioversion)	Comparison of treatment and clinical characteristics	Persistent AF referred for cardioversion	1515	37	63±11	0	—
Swedish AF Cohort[17]	Sweden	July 2005–Dec 2008	Inpatients/ outpatients	Investigate risk factors in AF	AF	182 678	47%	76.2	—	0 to 6

ACTION indicates Acute Coronary Treatment and Intervention Outcomes Network; AF, atrial fibrillation; OAC, oral anticoagulation; PAD, peripheral artery disease; TIA, transient ischemic attack.

the CARAF program in Canada.[21] In addition to AF ablation, LAAC is under investigation as a potential alternative to anticoagulation for patients at high risk of stroke in the Amplatzer cardiac plug (ACP)[37] and ASA Plavix Feasibility Study With Watchman LAAC (ASAP)[38] registries (Table 4).

Insights From Registries

Registries on Thromboprophylaxis and Stroke Prevention

Stroke epidemiology and risk factors

Patients with AF are at risk of stroke and twice as likely to die within 1 year as those without AF.[40] The Euro Heart survey, in which patients with AF (new in 18%, paroxysmal in 28%, persistent in 22%, and permanent in 29%) had a mean age of 67 years and 26% older than 75 years, found that 86% were at high risk for stroke.[6]

Data from the Nationwide Danish study highlight that chronic kidney disease (CKD) in patients with AF is associated with even greater risk of stroke or systemic embolism. In this cohort, the risk of stroke or thromboembolism in patients with CKD (hazard ratio, 1.49) was significantly lower in patients treated with warfarin.[41] Reports from this registry also note higher risk of bleeding among patients with CKD treated with warfarin, aspirin, or both.[42] Bleeding risks associated with OACs are a potential disadvantage of therapy, but data from registries help identify patients most likely to encounter bleeding complications. The concept of "net clinical benefit" aims to balance the risks of ischemic stroke and bleeding on OAC therapy[43] and was originally tested using U.S. registry data. This concept, used to compare NOACs and warfarin, have been facilitated by registry data.[11,44] Banerjee et al. used "real-world" data on net clinical benefit of warfarin from the Danish National Patient Registry and modeled the expected net clinical benefit for NOACs (dabigatran, rivaroxaban, and apixaban) on the basis of recent clinical trial outcomes.[11] The findings indicated that when there is a high risk of both ischemic stroke and intracranial hemorrhage, all 3 of the new agents have a greater net clinical benefit, compared to warfarin (Figure).[45,46]

Registry findings, such as those from Denmark and Sweden (Table 1), have helped develop and refine risk-scoring systems for stroke and bleeding in AF patient cohorts.[17,41] Scoring systems such as $CHADS_2$ and CHA_2DS_2-VASc have changed the approach to risk stratification of AF patients and guide judicious use of OAC in patients at greatest risk.[47,48] Registry data have been crucial in deriving risk stratification schemes and validating the utility in clinical practice.[48–50] Both the $CHADS_2$ and CHA_2D_2-VASC scores were found, by examination of registry data, to underestimate the risk of

Table 2. Registries Reporting on Antiarrhythmic Drug Therapy and Cardioversion in AF

Registry	Country	Years	Setting	Study Aim	Patient Characteristics	No. of AF Patients	Female (%)	Mean Age (±SD)	Paroxysmal AF (%)	$CHADS_2$ (CHA_2DS_2VASC)
AFFECTS[18,19]	USA	Mar 2005–Dec 2007	Outpatients	Clinical practice patterns in management	AF with increased risk of stroke	1461	46.3	66.2±13.3	79.7	—
ATRIUM[20]	Germany	2009	Outpatients	Management of AF in Germany	All stages of AF	3667	42.0	72.0±9.0	27.1	2.2±1.3 (3.8±1.7)
CARAF I and II[21]	Canada	1991–2007	Outpatients	Use of AADs in Canada from 1991 to 2007	New-onset paroxysmal AF	1400	—	—	100	—
GULF-SAFE[22] (Gulf Heart Association)	6 Middle Eastern countries	Oct 2009–July 2010	Emergency department	AF management in the Gulf	AF	2043	48.0	57.0±16.0	17.0	2.1±0.5
MADRE[23]	Germany	2010–2012	Outpatients	Efficacy and tolerance of dronedarone in clinical practice	Paroxysmal or persistent AF	191	44.5	63±9.9	62.5	—
REALISE-AF[24]	26 countries worldwide	Nov 2009–June 2010	Outpatients	World-wide management	At least 1 AF episode in the last 12 months	10 523	44	66.6±12.2	24.8	—
RECORDAF[25–27]	21 countries worldwide	May 2007–Apr 2008	Inpatients/ outpatients	World-wide management	Recent-onset AF	5604	42.8	66±11.9	45.6	—
RECORDAF-Asia Pacific[28]	8 countries Asia/Pacific	Apr 2009–July 2010	Outpatients	Management across Asia-Pacific	Recently diagnosed AF	2629	40	64±13	49	—
RHYTHM-AF[29,30]	10 countries worldwide	May 2010–Feb 2013	Inpatients (cardioversion)	Antithrombotic therapy in relation to stroke risk and AF duration	AF patients suitable for cardioversion	3940	38	66±12	—	3±2*

AADs indicates antiarrhythmic drugs; ACTION, Acute Coronary Treatment and Intervention Outcomes Network; AF, atrial fibrillation.
*Mean±SD.

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Table 3. Registries Providing Information on AF Ablation

Registry	Country	Years	Setting	Study Aim	Patient Characteristics	No. of AF Patients	Female (%)	Mean Age (±SD)	Paroxysmal AF (%)	$CHADS_2$ (CHA_2DS_2VASC)
AF ablation pilot study of European Heart Rhythm Association[31]	10 countries Europe	Oct 2010–May 2011	Inpatients	Clinical epidemiology and therapy of European ablation patients	Undergoing AF ablation	1410	28	60	62	0 to 5; ≥1 in 57.8% (0 to 7; ≥1 in 78.9%)
AF ablation Long-term Registry of EURObservational Research Programme[32]	54 countries invited (29 participating so far)	Ongoing	Inpatients	Long-term study of the above	Undergoing AF ablation	875 so far	41.02%	71.16±11.3	19.04	—
AF-Intermountain hospitals[33]	USA	Ongoing	Inpatients	Long-term impact of ablation	Undergoing AF ablation	21 060 (4212 underwent AF ablation)	39.2	66±13.3	—	—
CARAF[21]	Canada	1990–1996	Inpatients	Gender-related differences in AF	AF	1097	38	Women 65.4±0.7 Men 60.5±0.6	100	—
National Multicenter Registry on Procedural Safety of Catheter Ablation for AF[34]	Italy	Jan–Dec 2011	Inpatients	Safety of catheter ablation for AF	Patients who underwent AF catheter ablation	2323	28	60	54	1
Prospective registry[35]	USA	Jan 2010–July 2011	Ablation in high-volume centers	Feasibility and safety of dabigatran in ablation	Undergoing AF ablation	290	21	60	57	30% ≥2 (1.6)
SAFARI[36]	USA	Planned	Inpatients	Safety and efficacy of catheter ablation	Undergoing AF ablation	5000 (aim)	—	—	—	—

AF indicates atrial fibrillation.

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Table 4. Registries Reporting on LAAC

Registry	Country	Years	Setting	Study Aim	Patient Characteristics	No. of AF Patients	Female (%)	Mean Age (±SD)	Paroxysmal AF (%)	$CHADS_2$ (CHA_2DS_2VASC)
ACP[37]	Europe	May 2010–June 2017	Patients with AF at a high risk of stroke	Initial experience with ACP in European patients	On warfarin or dabigatran therapy, $CHADS_2$ score ≥2	143	—	—	—	—
ASAP[38]	Europe	Jan 2009–Dec 2013	Patients contraindicated for long-term warfarin therapy	Safety and efficacy of LAAC in patients	AF contraindicated for warfarin	150	—	73 (±7.4)	—	2.8 (4.4)

ACP indicates Amplatzer cardiac plug; AF, atrial fibrillation; ASA, acetylsalicylic acid; LAAC, left atrial appendage closure.

thromboembolism associated with previous ischemic events.[51] Another scoring system, developed from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study, identified risk stratification schemes for bleeding and thromboembolism to develop a simple method for quantifying the risk of warfarin-associated hemorrhage based on 5 clinical variables with performance comparable to the $CHADS_2$ index.[52]

Registry data show that the CHA_2DS_2VASc score performed better than $CHADS_2$ in identifying patients at high or low risk of thromboembolism. In general, risk stratification systems should be reassessed, given that new data are developed from independent sources. A recent analysis of the ROCKET-AF clinical trial and ATRIA cohort suggested that renal impairment could be added to the $CHADS_2$ score to improve predictive value for identifying "high-risk" patients at risk of stroke.[53] Because all patients in these cohorts were at high risk of stroke and were treated with OACs, the full range and impact of renal function was not investigated. In another analysis of patients across a wide spectrum of renal impairment who were not anticoagulated, renal impairment added little to the predictive value of the $CHADS_2$ and CHA_2DS_2-VASc scores for stratification of thromboembolic risk.[54,55] On the other hand, renal failure patients do have a higher risk of hemorrhagic complications,[56,57] making the net risk-benefit ratio difficult to establish. This is an area where further clinical trials are needed.

OACs and stroke prevention

Multiple clinical trials established the effectiveness of the vitamin K antagonists, compared to placebo, aspirin, other antiplatelet agents, or no antithrombotic therapy in patients with AF.[58–61] Nevertheless, the 2006 Euro Heart Survey noted that AF management can be inadequate, with wide variations in physician adherence to evidence-based recommendations for anticoagulation.[6] In 2013, the EORP-AF General Registry Pilot program showed improved uptake of OACs by European cardiologists, with OACs prescribed for 80% of patients with AF.[32] Registry data have provided information regarding patterns of OACs across various health systems at the primary care,[20,60] hospital,[8] network,[62] national,[63,64] and international[21,58] hospital,[7] network,[59] national,[60,61] and international[6,24] levels. Treatment trends over time can be used to project resource utilization and facilitate planning of health services and resources.

National prescribing registries suggest systematic underuse of warfarin,[65] and data from national registries of AF patients, such as the Japanese J-RHYTHM registry, indicate warfarin underutilization in patients at high stroke risk, as well as overuse of warfarin in patients at low risk.[9] In contrast, the Euro Heart Survey found that OAC prescribing for AF was relatively

Table 5. Registries Providing Information on Medical Treatment of AF

Registry	Rate-Control Treatment (%)	Rhythm-Control Treatment (%)	Warfarin (%)	NOACs (%)	Aspirin (%)
AVAIL[4]	—	—	49.1	—	5.5
CAPTURE[5]	—	—	4.73	—	—
J-RHYTHM[9]	—	—	87.3	—	22.3
Nationwide Danish study[11]	—	—	17.6	—	—
ORBIT-AF[12]	—	—	—	—	35
PREFER AF (Daiichi-Sankyo)[13]	—	59.8	34.1	6.1	19.8
REACH[14]	—	—	36.2	—	42.6
RE-LY[15]	—	—	32	—	—
Swedish AF Cohort[17]	—	—	40	—	—
Euro Heart Survey[6]	—	—	60.9	—	30.5
National Cardiovascular Data Registry's ACTION Registry–Get With the Guidelines[10]	—	—	32.5 on admission (41 at discharge)	—	51.5 on admission (95 at discharge)
AFFECTS[18,19]	36	64	58.7 at enrollment (63.7 at follow-up)	—	27.2 at enrollment (31.8 at follow-up)
ATRIUM[20]	75	16	93.0	—	—
MADRE[23]	—	100	—	—	71
REALISE-AF[24]	32.7	57.5	42	—	—
RECORDAF[25–27]	45.1	54.9	—	—	43
Prospective registry[35]	—	—	50	50 (dabigatran)	44

ACTION indicates Acute Coronary Treatment and Intervention Outcomes Network; AF, atrial fibrillation; NOAC, new oral anticoagulant.

high throughout all risk categories and noted that this placed a large proportion of patients with low risk of thromboembolism at higher risk of bleeding complications.[6] Frequent OAC prescribing may relate to the relatively high proportion of academic and specialized centers participating in this study. Registry data from the National Cardiovascular Data Registry's Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get with the Guidelines program also suggest that the patients at highest risk of ischemic stroke are least likely to take OAC medication,[4] again highlighting the need for practice improvement and compliance to ensure the best outcomes among patients with AF. These data on utilization could be gleaned only from registries. Data from a number of registries providing information on the use of warfarin, NOACs, and aspirin are shown in Table 5.

The PREFER-AF Registry found that OACs are now much more widely used than was reported in the German AFNET and the Euro Heart Survey registries on AF, and that NOACs are used by 6.1% of patients with AF.[13]

The increasing number of registries established in recent years to follow trends and outcomes linked to the NOACs—such as GARFIELD, GLORIA-AF, PREFER-AF, and Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)—will continue to highlight practice variations in diverse healthcare settings and patient populations. For example, in the RE-LY trial, dabigatran at 150 mg (but not 110 mg) twice-daily was associated with lower rates of stroke, compared to warfarin.[66] These variations may provide targets for improvement of OAC uptake and optimize available treatment options according to patient profiles. In addition to generating pharmacoepidemiological data on OAC use, these registries capture and assess treatment outcomes, specifically the incidence of bleeding and persistence of therapy (including discontinuation, interruption, and changes of therapy regimen).

Registries may offer insights into the off-label use of OAC drugs. The safety and efficacy of periprocedural dabigatran in patients undergoing AF ablation was evaluated in a multicenter registry[35] (Table 3), in which dabigatran was associated with a significant increase in the risk of bleeding and thromboembolism compared to uninterrupted warfarin therapy, although different lengths of time on treatment confounds interpretation of these observations. Two other systematic reviews showed no differences in bleeding or thromboembolism with periprocedural dabigatran versus warfarin in patients undergoing ablation.[67,68] Given these

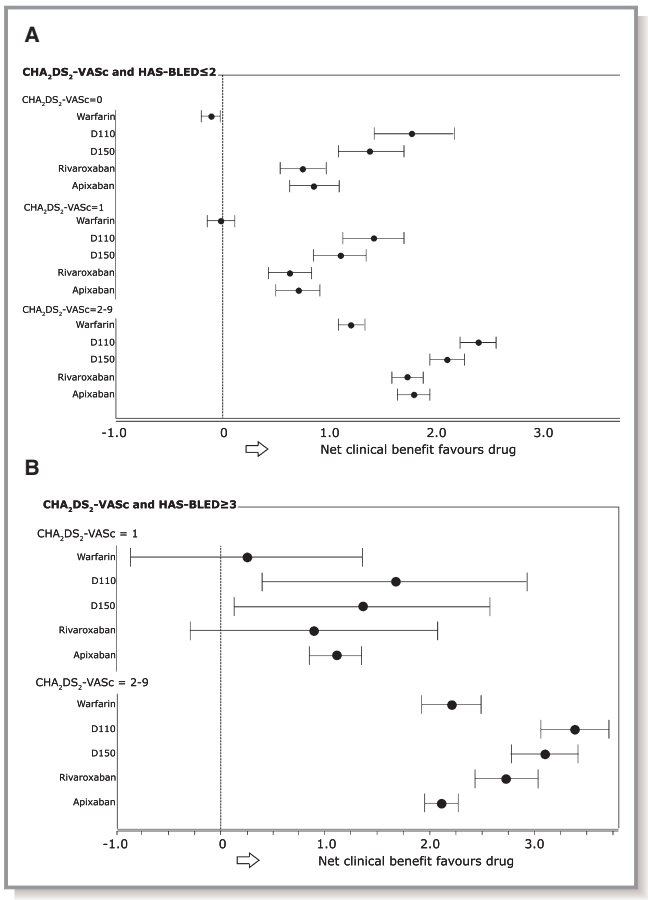

Figure. Net clinical benefit of warfarin and new oral anticoagulants dabigatran, apixaban, rivaroxaban by CHA_2DS_2-VASC and HAS-BLED scores. A, HAS-BLED ≤2. B, HAS-BLED ≤3. For HAS-BLED ≥3, there were no data with CHA_2DS_2-VASC score=0. D110, dabigatran 110 mg (twice-daily; BID); D150, dabigatran 150 mg BID. Modeling was based on recent clinical trial outcome data for the new oral anticoagulants and "real-world" data from the Danish National Patient Registry, collected from patients with nonvalvular AF between 1997 and 2008 to predict the net clinical benefit of new oral anticoagulants, compared to warfarin. Reproduced with permission from Banerjee et al.[11] AF indicates atrial fibrillation.

contradictory results, more data are needed. Whereas registry data can point to potential new approaches to management, investigation in a controlled trial is the preferred way to compare therapeutic strategies and provide robust, reliable evidence with which to inform practice.

Registries on AAD Therapy and Cardioversion

Among the registries listed in Table 2, the RECORD-AF registry involving 21 countries worldwide provides insight into the use of AADs, factors affecting progression from paroxysmal to persistent or permanent AF, and reveals the extent to which clinical practice follows practice guidelines.[26,27,69] RECORD-AF reported an overall success rate of 54% for antiarrhythmic therapy, 60% success for maintenance of sinus rhythm, and 47% for maintaining the heart rate at or below 80 beats per minute at 1 year.[25] Key clinical outcomes reported for rate control and rhythm control strategies at 1 year are shown in Table 6. The data suggest that clinical outcomes of AF are driven by arrhythmia-related hospitalization, rather than rate or rhythm management strategy,[25] but in patients assigned to rate control, there was relatively rapid progression from paroxysmal to persistent AF. In RECORD-AF, use of digoxin in patients without HF was uncommon, especially in North America, and amiodarone was used infrequently, except in patients with HF. One-year findings from the related RECORD-AF Asia Pacific registry showed that rhythm control strategies were often applied to patients with persistent AF and a history of HF or valvular heart disease (37% of patients), and rate-control strategies to patients with recently identified, paroxysmal AF (63%).[28] Patients in the rhythm-control group were prescribed class Ic (39%) or III (49%) AADs, with lower use of β-blockers in this group in the Asia Pacific registry (35%) compared with the global RECORD-AF registry (51%).

A number of registries provide insight into changing AF management practices that reflect the availability of new agents and updated practice guidelines. For example, CARAF charted the use of antiarrhythmic and atrioventricular-nodal blocking drugs from 1991 to 2007 and showed a peak in AAD use in 1994 (42.5%), followed by a gradual decline, whereas use of rate-controlling medications, particularly β-blockers, increased (52.5% in 2007).[21] Data from a number of registries providing information on the use of rhythm- and rate-control treatments are shown in Table 5. The AFFECTS registry assessing patterns of care in the United States showed that most first-line therapies were aligned with the 2006 American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology guidelines.[18,19] In AFFECTS, rhythm-control treatment was prescribed for 67% of patients with paroxysmal AF and 55% of patients with persistent AF and was more often the initial treatment strategy for older patients. The ATRIUM registry suggested that AF therapies used by primary care providers in Germany did not stabilize patients enough to avoid hospitalization.[20] Rhythm control was used in approximately one third of patients, often in combination with rate control, and almost all patients received antithrombotic therapy. A comparison of the costs associated with rhythm- versus rate-control strategies in Quebec, Canada, found no significant differences overall.[70]

The most commonly used AADs have limited efficacy to restore sinus rhythm and carry the risk of proarrhythmic toxicity, especially in elderly patients with structural heart disease. Registries provide information on outcomes associated with AAD use in clinical practice. The Nationwide Danish study examined the mortality rate associated with AAD

Table 6. Key Clinical Outcomes Reported in the RECORD-AF Registry at 1 Year[25]

Clinical Events	Rhythm Control (%)	Rate Control (%)	*P* Value
Any clinical event	483/2809 (17.2)	405/2225 (18.2)	0.352
Cardiovascular death	24/2804 (0.9)	61/2213 (2.8)	<0.001
Myocardial infarction	14/2785 (0.5)	20/2175 (0.9)	0.078
Stroke or transient ischemic attack	46/2784 (1.7)	60/2179 (2.8)	0.008
Hospitalization for cardiovascular event	465/2793 (16.6)	366/2195 (16.7)	0.891
Hospitalization or increased duration of hospital stay			
Due to arrythmia or proarrhythmia	314/2790 (11.3)	159/2179 (7.3)	<0.001
Due to other cardiovascular events or interventions	190/2791 (6.8)	204/2182 (9.3)	0.001
Due to major complications of ablative procedure	15/2786 (0.5)	14/2171 (0.6)	0.626

Occurrence of clinical outcomes was counted between baseline and 12 months in patients with AF or a history of AF, excluding permanent AF or transient/reversible causes of AF. Cardiovascular death recorded at 12 months includes any events reported until the end of the 15th month after baseline. AF indicates atrial fibrillation; RECORD-AF, The global Registry on Cardiac rhythm disorders assessing the control of Atrial Fibrillation.

therapy in patients with AF hospitalized between 1995 and 2004.[71] In this unselected cohort, treatment with flecainide, propafenone, sotalol, or amiodarone was not associated with increased risk of death, compared to treatment without AADs, even during the first 30 days when risk is usually highest.

Registries assembled by regulatory agencies, such as the U.S. Food and Drug Administration (FDA) Mini-Sentinel program and the U.S. Department of Defense database, reported lower all-cause mortality with dronedarone than with other AADs.[72] Population-based administrative databases are able to provide information from a large general population of patients with AF, with longer follow-up than is possible in most RCTs. The FDA Mini-Sentinel program aims to detect and refine safety signals for marketed medical products and additionally identify algorithms used within administrative databases to detect and analyze health outcomes for patients with AF.[73] This registry suggests that a substantial proportion of the variation in AF prevalence across studies may be the result of the choice of different criteria for confirming AF. A systematic literature review was performed to characterize the validity of algorithms to identify patients with AF from electronic health data.[74] Use of nonrepresentative populations, a paucity of recent data, and a disproportionate focus on data from inpatients hindered conclusions about algorithm validity, and the researchers advised that additional research is needed in contemporary representative populations.

Follow-up of patients in registries can track AF recurrence, although inferences require confirmatory evidence from clinical trials. In the MADRE registry, dronedarone was administered for rhythm control in a small cohort of patients followed for 300 days. AF recurrence was common (66.5%), suggesting that dronedarone may not be superior to other AADs in maintaining sinus rhythm.[23] Outcomes among ambulatory patients, drawn from the cross-sectional REALISE-AF survey, showed that the target heart rate was not achieved in 71% of the cases in which a rate-control strategy was chosen, whereas 26% of those selected for a rhythm-control strategy found that AADs failed to maintain sinus rhythm.[6] Overall, 44% of patients with controlled AF were asymptomatic. Results from REALISE-AF highlight that guidelines for use of AADs are not closely followed, and alternative therapies are needed to improve CV outcomes in patients with AF.

Table 2 highlights country-to-country differences in electrical versus pharmacological cardioversion practice, with RHYTHM-AF showing a preference for direct-current cardioversion at academic centers in Germany, where there is ease of access and a generally high primary success rate.[30] Electrical cardioversion is also a common choice in Sweden, whereas pharmacological cardioversion is more often chosen in Spain.

Registries on AF Ablation

Catheter-based pulmonary vein isolation for AF ablation, introduced more than 2 decades ago, is viewed today as a reasonable therapeutic option to prevent symptomatic AF in patients refractory to, or intolerant of, antiarrhythmic medication.[26] Although several small randomized trials of AF ablation of AF showed significantly higher rates of freedom from AF with ablation, compared to AADs, this reflects outcomes in highly selected patients performed by experienced operators. Some were single-center studies, follow-up was generally limited to 12 months, and monitoring for recurrent AF varied considerably.[25,26,75]

Given the limitation of these trials, registry data offer important insights into the application, success, and limitations of ablation therapy (Table 3). The AF ablation pilot study

of the European Heart Rhythm Association, the first systematic, prospective international study specifically aimed at collecting information on AF ablation practices in Europe, suggests that patients selected for ablation are younger and more symptomatic of the arrhythmia, with up to one third seeking to reduce or eliminate the need for medications.[31] This preliminary study showed that the most commonly employed ablation strategy is electrical isolation of the pulmonary veins and that, at discharge, 91.4% of patients were in sinus rhythm and 88.3% of patients were receiving vitamin K antagonists and 67% AADs. After 1 year, of 944 patients, 73.7% were free of recurrent AF based on periodic ECG monitoring, 56.6% without AADs, and conduction block was present in approximately 60%.[31] The overall complication rate was 7.7%, in the range of other multicenter surveys.[76]

Other insights come from a world-wide survey of catheter ablations that focused on methodology, rather than patient characteristics and outcomes. In this survey, success rates were higher in patients with paroxysmal than persistent and long-standing AF, and 70% of patients did not require further AAD treatment during follow-up.[77] Reports from Canada of the costs, compared to medical therapy, for paroxysmal AF found catheter ablation a fiscally viable alternative, with cost equivalence after 4 years.[78] LAAC devices, such as the ACP and the Watchman device, have been proposed as alternatives to anticoagulation in patients at high risk of stroke (Table 4).

The Future of AF Registries

Currently available registries are providing a wealth of data that will help guide management of AF patients. Trial data have confirmed the effectiveness of novel anticoagulants, including dabigatran, rivaroxaban, apixaban, NOACs and edoxaban,[65,79–81] and other agents may be introduced in the future. Efforts are underway to address the comparative effectiveness of these agents,[11,82,83] but ongoing registry data will establish evolving clinical practices regarding their use relative to warfarin and one another.[4,15] Another important function of longitudinal registries is to identify safety concerns surrounding these agents.

Registry data can have important limitations that should not be overlooked. Among these are data from single centers involving short follow-up in which patient demographics and patterns of AF are not well characterized. Unlike RCTs, which include highly selected patients that limit generalizability, registries are population based and therefore subject to bias. Registries lack controls from which to draw comparative assessments. Furthermore, data are lacking for some regions, and the majority have focused on Europe and the United States, although studies such as RECORD-AF Asia Pacific seek to address this. It has been also suggested, by the 2014 AHA/ACC/Heart Rhythm Society guidelines for management of patients with AF, that comparisons between registries from different sociocultural backgrounds may be obscured by the difficulty to quantify and report individualized antithrombotic therapy based on a shared physician-patient decision.[84] An important factor to consider when studying registry data is whether the registry is sponsored through industry, given that this may introduce the possibility of bias into the outcomes.

Some challenges face those attempting to initiate registries, such as specifying the purpose of the registry early on, how the data will be used, who will analyze it, who will have access to it, and, most important, who will fund it.[36,85] This information can, for example, determine whether patients in the registry are similar to those enrolled in RCTs, generate hypotheses for future clinical trials, and determine the effectiveness of therapy in subpopulations. Obtaining sufficient funding for a registry is also a critical challenge. Previous registries have been either voluntary or linked to reimbursement.[36] Determining the best funding mechanism for a registry early on is one of the most critical first steps to the success of such a registry. Investment in a national registry certainly requires substantial resources. Such investments must be balanced with other important safety and clinical effectiveness studies, such as CABANA and EAST.[36,86]

AF typically coexists with other conditions as both risk factors and complications. Registry data can inform our knowledge of the relationship between AF and other diseases to facilitate tailored, patient-specific approaches.

Conclusions

As highlighted in this review, registries extend knowledge of the natural history, risk factors, treatment practices, and long-term outcomes and risks of management strategies within a truly representative population of AF patients managed in clinical practice. Together with patient database evaluations, these resources can greatly improve understanding of the needs and gaps in care for diverse patient subgroups. Though a comprehensive review of administrative databases was not within the scope of this review, increasingly relevant literature derived from mining of patient data can inform the management of patients with AF in an array of care settings.

Registry data are the means by which to determine whether patients are managed in line with evidence-based guidelines—but they offer more than just a reflection of whether everyday practice adheres to accepted norms or ideals. Follow-up of large numbers of patients allows assessment of long-term outcomes and infrequent complications. There is scope to gather more information on the impact of AF and its management on quality of life as well as to provide

insights into the overall health economic burden of AF. These registries have already helped shape and improve the way we manage patients, and well-designed registries have the potential to yield hypotheses to guide future clinical and basic research.

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