Cardiology Research and Practice

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Editorial Board

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Editorial

Atrial Fibrillation

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Atrial fibrillation (AF) is the most common clinically important cardiac arrhythmia. The prevalence of AF roughly doubles with each advancing decade of age, from 0.5% at age of 50–59 years to almost 9% at age of 80–89 years [1]. AF is associated with substantial morbidity and mortality. Thus, AF is a significant risk factor for ischemic stroke and accounts for 15–20% of all strokes [2]. Considering the clinical relevance of AF, this journal initiated a special issue dealing with the recent developments in AF over the past few years. This issue contains important work—both review and original articles—addressing the epidemiology, economic impact of AF, and new therapeutic/diagnostic developments and their potential clinical implications.

The general therapeutic strategies in AF include heart rate or rhythm control and anticoagulation. Current drugs used for AF therapy have major limitations, including incomplete efficacy and risks of life-threatening proarrhythmic events and bleeding complications. However, there have been several recent advancements in therapy of AF. They included the availability of new anticoagulants, such as dabigatran, rivaroxaban, and apixaban, as well as guideline changes to incorporate the catheter-based isolation of pulmonary veins (PV) as a class IIa/A indication [3]. Since the first paper evidencing the role of PV as triggers of AF [4], various ablation techniques targeting PV (focal ablation, PV isolation, circumferential antral ablation, cryoballoon) were introduced into clinical practice [5, 6]. Though PV isolation by catheter-based radiofrequency ablation has become an effective treatment option in AF, the studies on long-term outcomes are still limited and less encouraging.

Recently, F. Ouyang et al. examined 5-year outcomes in paroxysmal AF and found that sinus rhythm was present in 46.6% of patients after one procedure [7]. Long-term outcome data after catheter ablation for persistent AF are even less favourable [8]. These data highlight important aspects of catheter ablation, in particular the need for improved tools for patient selection, energy delivery for durable transmural lesions, and more studies on long-term outcomes and the management of very late recurrences as mediators of initial procedural approach refinement. Radiological investigations such as CT scan or cardiac magnetic resonance imaging (cMRI) can demonstrate the complex LA anatomy very well in all three dimensions and should reduce the fluoroscopy times. In this special issue, P. Haemers et al. review the potential application of cMRI in the diagnostic workup and treatment of AF. Besides its value in the guidance of catheter ablation, the authors describe the role of cMRI in identifying the underlying pathophysiological mechanisms of AF and in stroke prevention. cMRI can be used for left atrial scar quantification to assist not only in the procedural approach but also in patient selection.

As mentioned above, stroke is a major critical AF-associated complication. Today, stroke prevention with anticoagulant agents based on the $CHADS_2/CHA_2DS_2$-VASc-Score is the main cornerstone of AF management. However, anticoagulation—even with newly developed oral anticoagulants—has several limitations. In addition to the bleeding risk, anticoagulation is not effectively utilized or contraindicated in significant number of eligible AF patients, often due to the limitations highlighted in the current paper by T. K. Patel et al. While newer oral anticoagulants overcome many of these limitations, all anticoagulants suffer from an unavoidable lifelong commitment to medication and elevated bleeding risk.

The left atrial appendage (LAA) is particularly vulnerable to thrombus formation due to its complex anatomy and low blood flow during AF. Therefore, LAA exclusion may be an especially appealing option for patients with intolerance or contraindications to anticoagulation. The procedure of LAA excision as well as the device characteristics are now highlighted in the current special issue. Indeed, LAA appendage may be a true alternative to anticoagulation in some patients. However, there is a very limited clinical experience with this novel procedure, and it is obvious that further studies are urgently required to clarify the benefits and disadvantages of LAA removal in patients with AF.

In another study of the current issue, C. J. Mercaldi et al. quantified the direct long-term costs, up to 3 years, of both stroke and bleeding events among patients with nonvalvular AF. Health care costs due to AF are enormous; on the basis of current US age- and sex-specific prevalence data, the national incremental AF cost is estimated to range from $6.0 to $26.0 billion [9]. The authors conducted a retrospective cohort study of Medicare beneficiaries newly diagnosed with AF who later developed stroke or hemorrhagic events. The results show that beyond the first year after the event, patients with major bleeding events other than intracranial hemorrhage have significantly higher costs than matched controls, underlying the need for proper cost-effectiveness assessment of the true long-term costs of stroke and major bleeding events. This strategy is particularly required when weighing the risks (bleeding) and benefits (stroke prevention) of anticoagulation in patients with AF.

In summary, we hope that expert contributions to this special issue will improve our understanding of the mechanisms of AF and ultimately result in a better clinical management of AF and long-term outcomes.

Natig Gassanov
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References

[1] W. B. Kannel, P. A. Wolf, E. J. Benjamin, and D. Levy, "Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates," *American Journal of Cardiology*, vol. 82, pp. 2N–9N, 1998.

[2] C. Marini, F. De Santis, S. Sacco et al., "Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: Results from a population-based study," *Stroke*, vol. 36, no. 6, pp. 1115–1119, 2005.

[3] A. J. Camm, G. Y. Lip, R. De Caterina et al., "2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation ∗ Developed with the special contribution of the European Heart Rhythm Association," *European Heart Journal*, vol. 33, no. 21, pp. 2719–2747, 2012.

[4] M. Haïssaguerre, P. Jaïs, D. C. Shah et al., "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins," *The New England Journal of Medicine*, vol. 339, no. 10, pp. 659–666, 1998.

[5] J. G. Andrade, P. Khairy, P. G. Guerra et al., "Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies," *Heart Rhythm*, vol. 8, pp. 1444–1451, 2011.

[6] G. Lee, P. Sanders, and J. M. Kalman, "Catheter ablation of atrial arrhythmias: state of the art," *The Lancet*, vol. 380, pp. 1509–1519, 2012.

[7] F. Ouyang, R. Tilz, J. Chun et al., "Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up," *Circulation*, vol. 122, no. 23, pp. 2368–2377, 2010.

[8] R. R. Tilz, A. Rillig, A. M. Thum et al., "Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the hamburg sequential ablation strategy," *Journal of the American College of Cardiology*, vol. 60, pp. 1921–1929, 2012.

[9] M. H. Kim, S. S. Johnston, B. C. Chu, M. R. Dalal, and K. L. Schulman, "Estimation of total incremental health care costs in patients with atrial fibrillation in the united states," *Circulation: Cardiovascular Quality and Outcomes*, vol. 4, no. 3, pp. 313–320, 2011.

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Clinical Study

Chronobiological Analysis of Blood Pressure in a Patient with Atrial Fibrillation at the Development of Heart Failure and Its Therapeutic and Surgical Treatment

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Dynamics of blood pressure (BP) and heart rate (HR) was traced by automatic monitoring every 30 min uninterruptedly along several months in a patient suffering from combined atrial fibrillation and heart failure during the development of disease and its therapeutic and surgical treatment (pacemaker implanting and atrioventricular ablation). Analyses of spectral components as well as signal's shape revealed instabilities in circadian and semicircadian parameters. A new approach for signal's form description without using cosine approximation is suggested. The meaning that referring a patient as dipper, night peaker, or nondipper might be useful at choosing tactics of his treatment is impugned, because all these "types" can transform themselves in the same person in few days. Optimization timing of treatment provides better results if not the "types" of daily profile would be taken to account but the real form of the BP-signal and timing its first and second derivatives.

1. Introduction

The peculiarity of the case described in the paper was a possibility to trace objectively and in many details the hemodynamic changes continuously at all stages of the development and treatment of the heart disease: from the very beginning of cardiac insufficiency to its culmination, next therapeutic correction and final surgical intervention.

Uninterrupted monitoring of systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) provided recording data, and next applying of specialized chronobiological programs ensured obtaining quantitative information dealing with dynamics of the process.

Before the events described, the patient (GSK, further the patient, P, a man of 82), was suffering for years with essential hypertension. Atrial fibrillation with AV connections dysfunction was registered during the last 6 years, and he had renal failure during the last 3 years.

Cardiovascular functions (SBP, DBP, and HR) are monitored in P uninterruptedly since 1998 (the second continuous monitoring in the world). Every 30 minutes data are automatically registered by TM-2421 recorder (A & D, Japan) and after their cumulation transferred into the computer.

Dynamics of processes was analyzed using specialized software for analyzing trends, global, and gliding spectra [1] and the signal's waveform [2, 3], methods previously described shortly in [4]. For 14 years it provided an opportunity to observe the behavior of cardiovascular functions at many very different changes in environmental conditions and external impacts to the organism [5–8].

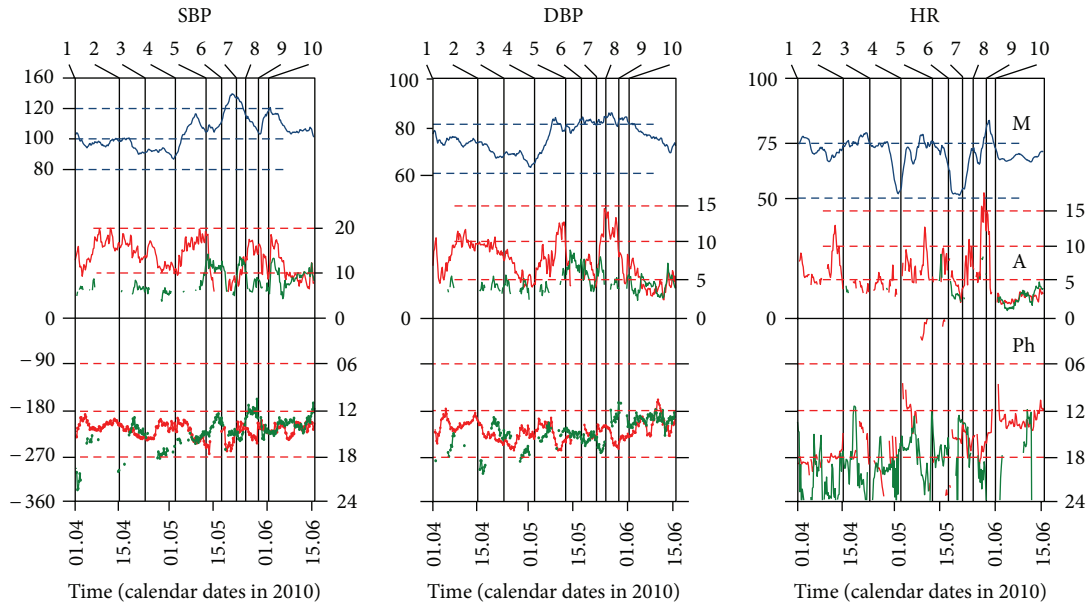


Figure 1: 24- and 12-hour rhythms of cardiovascular functions during heart failure development and treatment. SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate. Blue curves: daily mean values, red: 24-hour rhythm parameters, and green: 12-hour rhythm parameters. Rhythm parameters: M: mesor, A: amplitude, and Ph: acrophase. Abscissae: above: stages of development (according Table 1), below: calendar time (dates in 2010). Ordinates: upper row left: BP or HR values (mmHg, beats/min), upper row right: amplitudes (same units of measurements), lower row left: acrophases (degrees of cycle), and lower row right: acrophases of 24-hour rhythm (clock time).

2. Short History of the Disease

Hypertension was first diagnosed in P in 1959. Its passing was favorable; the subject until 1988 regularly participated in sports with high physical loads and was well tolerated to oxygen deficiency (mountaineering up to 5000 m above the sea level). Manifestations of heart failure were never noted.

In 2005-2006 paroxysms of atrial fibrillation had appeared, with periods of bradycardia when the HR was less than 40 bpm. In process of time the frequencies of paroxysms arise more often. Nevertheless their ECG registering up to 2006 was not done (objectively their presence could be confirmed indirectly by changes of the oscillometric signal's waveforms registered by the recorder during monitoring).

In 2007 appendectomy was implemented using general anesthesia, and in about a week acute renal failure developed. P was turned to the nephrological clinic. During the treatment span the blood pressure often was elevating up to 190 (SBP) and 120 mmHg (DBP). For the first time atrial fibrillation was identified by means of ECG. After 2 months of treatment P was discharged with a diagnosis of chronic kidney disease, stage II. Later the blood pressure was gradually decreasing; regular careful monitoring and periodic adjustment of medication facilitated this process. Nevertheless atrial fibrillation had passed into a permanent form.

3. Methods of Data Analysis

Moving spectra of the whole series for each of variables were computed, as well as the total spectra [2] for different spans of development of the process. Dynamics of the mean value (MESOR), amplitude, and acrophase in the range of 6 to 96 hours were traced. Absence of oscillations (amplitude equal to zero) was accepted as the null hypothesis. The spectral components having probability of the null hypothesis $P < 0.05$ were considered as statistically significant (further for brevity significant). For a more detailed assessment of the circadian signals their real shape (daily profile) was approximated and positions of peak and trough and their quantitative estimation with confidence limits were calculated [2, 3].

The applied methods of analysis allow detecting useful signals among noise and considering the dynamics of parameters as a continuous oscillatory process considering oscillations occurring at different frequencies.

4. Results

The main quantitative characteristics of 24- and 12-hour rhythmic spectral components are presented in Tables 1, 2, and 3 (the higher harmonics of the circadian rhythm were not significant) and in Figure 1. Changes in daily profiles of SBP and HR are shown in Figure 2.

4.1. State before the Acute Disease. During the first quarter of 2010 subjectively the state of the P remained satisfactory. Hemodynamic parameters at this time are shown in Figure 1 (segment 1-2).

All this time P took in beta blockers, calcium channel blockers, and ACE inhibitors. Every few days, the monitor records were analyzed, and dosage, and timing of antihypertensive medications were regularly corrected in accordance

Table 1: Dynamics of the systolic blood pressure in 2010 in the patient GSK.

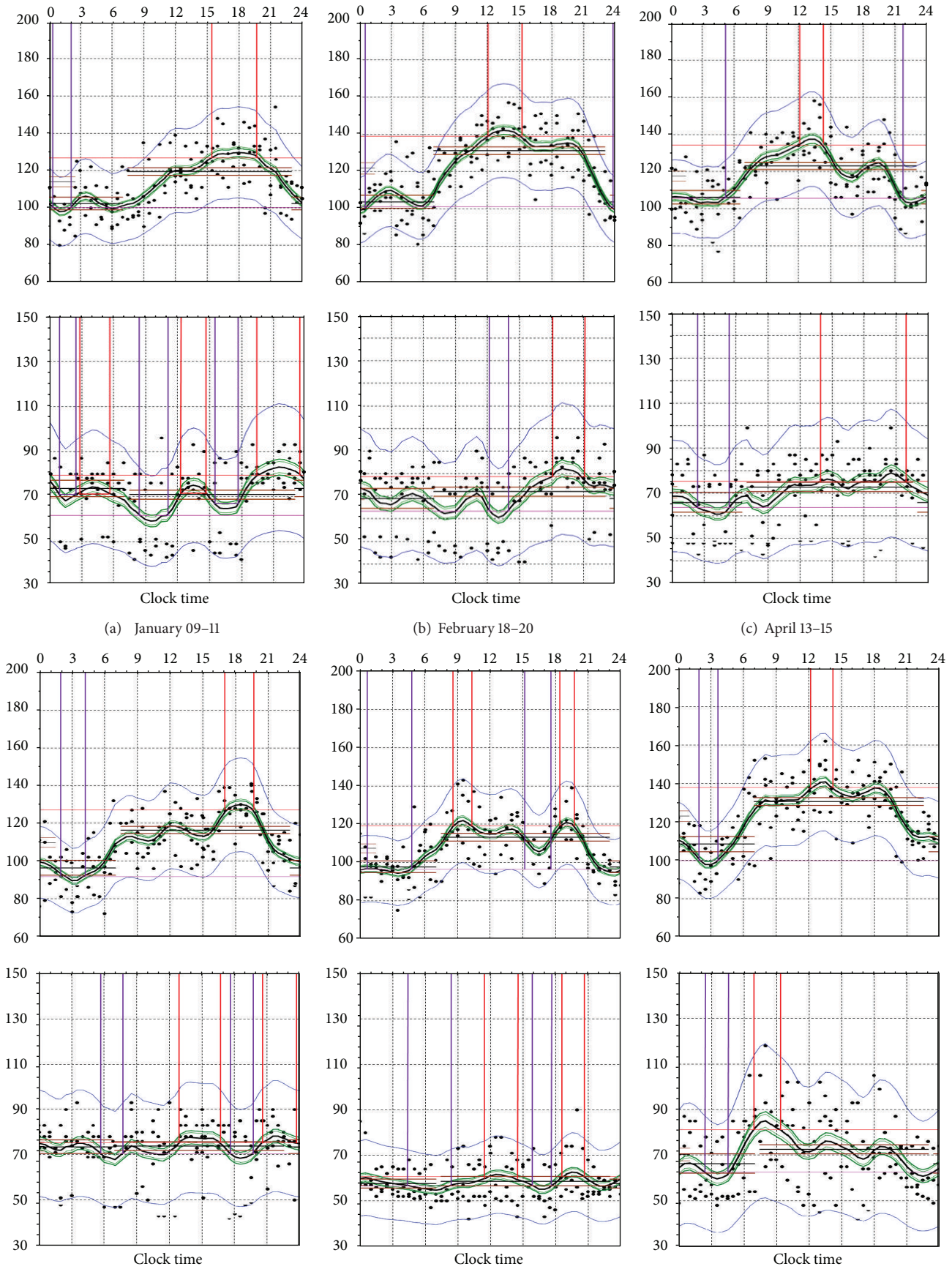
Stage	Time (calendar dates in 2010)	MESOR	24-hour component			12-hour component		
			Amplitude	Acrophase	*P* value	Amplitude	Acrophase	*P* value
1-2	05/01–19/01	117.5 ± 4.4	14.5 ± 3.2	−241 ± 24	<0.0000	2.08 ± 1.7	−219 ± 200	0.5813
1-2	12/02–26/02	121.8 ± 5.4	19.8 ± 2.0	−226 ± 13	<0.0000	2.02 ± 1.7	−256 ± 154	0.6531
1-2	02/04–16/04	115.9 ± 3.7	15.4 ± 5.2	−208 ± 17	<0.0000	4.2 ± 3.9	−259 ± 115	0.2892
2-3	18/04–25/04	111.4 ± 6.2	14.8 ± 3.3	−226 ± 16	<0.0000	5.9 ± 2.9	−223 ± 31	0.0600
3-4	26/04–04/05	109.8 ± 4.8	11.8 ± 3.2	−215 ± 24	<0.0000	3.9 ± 3.1	−254 ± 37	0.1798
4-5	05/05–13/05	126.7 ± 8.8	16.6 ± 3.4	−222 ± 34	<0.0000	6.5 ± 6.2	−233 ± 19	0.0934
5-6	14/05–18/05	127.4 ± 7.4	5.1 ± 6.8	−237 ± 57	0.2261	11.3 ± 1.6	−209 ± 29	<0.0000
6-7	19/05–23/05	144 ± 6.1	7.2 ± 4.1	−240 ± 31	0.0529	7.2 ± 6.2	−225 ± 33	0.0415
7-8	24/05–26/05	136.1 ± 9.3	13.0 ± 5.2	−213 ± 16	<0.0000	10.1 ± 6.1	−226 ± 25	0.0187
8	27/05	129.4 ± 0.4	16.9 ± 0.4	−216 ± 1	<0.0000	5.9 ± 0.3	−191 ± 13	0.0424
8-9	28/05–30/05	124.3 ± 5.0	14.8 ± 3.9	−231 ± 13	<0.0000	7.8 ± 1.9	−179 ± 20	0.0038
9	31/05	131.4 ± 4.9	12.7 ± 5.9	−210 ± 15	0.0001	5.6 ± 2.7	−180 ± 31	0.0754
9-10	01/06-02/06	136.2 ± 4.3	12.0 ± 7.2	−213 ± 18	0.0001	7.3 ± 5.0	−220 ± 33	0.0211
10-11	03/06–08/06	129.6 ± 9.8	6.5 ± 7.2	−216 15	<0.0000	12.5 ± 6.6	−201 ± 17	0.0035
11-12	09/06–17/06	122.9 ± 3.1	12.4 ± 3.3	−216 25	0.0005	12.5 ± 2.3	−204 ± 20	0.0004

Comments
Stages of developing process:
(1) out of disease (before April 18),
(2) beginning of acute respiratory illness (April 18),
(3) ankle oedema joints (April 26),
(4) dyspnoea joints (May 5),
(5) admission to the therapeutic clinic (May 14),
(6) copping heart failure (May 19),
(7) transferring to the surgical clinic (May 24),
(8) pacemaker transplanted (May 27),
(9) atrio-ventricular ablation performed (May 31),
(10) discharge (June 2),
(11) weekly rehabilitation at home (up to June 9),
(12) stabile state at home (after June 9).
After symbol "±" 95% confidence limits of values are shown.
Patient GSK, a man of 84.

Table 2: Dynamics of the diastolic blood pressure in 2010.

Stage	Time (calendar dates in 2010)	Mesor	24-hour component			12-hour component		
			Amplitude	Acrophase	*P* value	Amplitude	Acrophase	*P* value
1-2	05/01–19/01	75.8 ± 2.8	9.1 ± 2.6	−239 ± 30	<0.0000	1.8 ± 1.6	−196 ± 237	0.5044
1-2	12/02–26/02	78.4 ± 3.8	13.7 ± 2.1	−223 ± 22	<0.0000	1.3 ± 1.3	−235 ± 188	0.7178
1-2	02/04–16/04	74.5 ± 2.2	9.3 ± 3.9	−210 ± 26	0.0003	2.9 ± 2.4	−248 ± 158	0.2602
2-3	18/04–25/04	69.6 ± 3.3	9.4 ± 1.7	−237 ± 25	<0.0000	4.2 ± 2.1	−229 ± 73	0.0586
3-4	26/04–04/05	67.6 ± 4.1	6.0 ± 2.4	−229 ± 35	9.44*E*−05	2.9 ± 2.7	−271 ± 70	0.1838
4-5	05/05–13/05	77.4 ± 10.0	9.5 ± 4.5	−225 ± 150	<0.0000	3.9 ± 2.4	−222 ± 26	0.0829
5-6	14/05–18/05	80.4 ± 3.2	3.6 ± 5.8	−150 ± 156	0.3468	7.6 ± 2.0	−225 ± 27	0.0001
6-7	19/05–23/05	82.5 ± 1.8	6.0 ± 5.0	−214 ± 78	0.0847	5.7 ± 2.6	−235 ± 26	0.0012
7-8	24/05–26/05	82.8 ± 2.3	11.0 ± 6.3	−213 ± 36	<0.0000	6.4 ± 3.3	−252 ± 67	0.0184
8	27/05	84.7 ± 2.4	13.8 ± 2.8	−213 ± 30	<0.0000	3.3 ± 1.8	−223 ± 55	0.1898
8-9	28/05–30/05	83.5 ± 4.3	11.8 ± 2.4	−242 ± 19	<0.0000	4.6 ± 1.6	−191 ± 34	0.0283
9	31/05	83.5 ± 0.6	8.8 ± 0.7	−236 ± 42	<0.0000	3.4 ± 1.7	−170 ± 39	0.0649
9-10	01/06-02/06	83.7 ± 1.5	6.3 ± 3.4	−232 ± 51	0.0002	3.4 ± 2.4	−197 ± 21	0.0757
10-11	03/06–08/06	79.6 ± 3.6	6.17 ± 2.9	−211 ± 28	<0.0000	4.7 ± 2.1	−200 ± 17	0.0041
11-12	09/06–17/06	74.3 ± 4.4	4.4 ± 2.0	−202 ± 44	0.0027	4.6 ± 2.2	−195 ± 21	0.0019

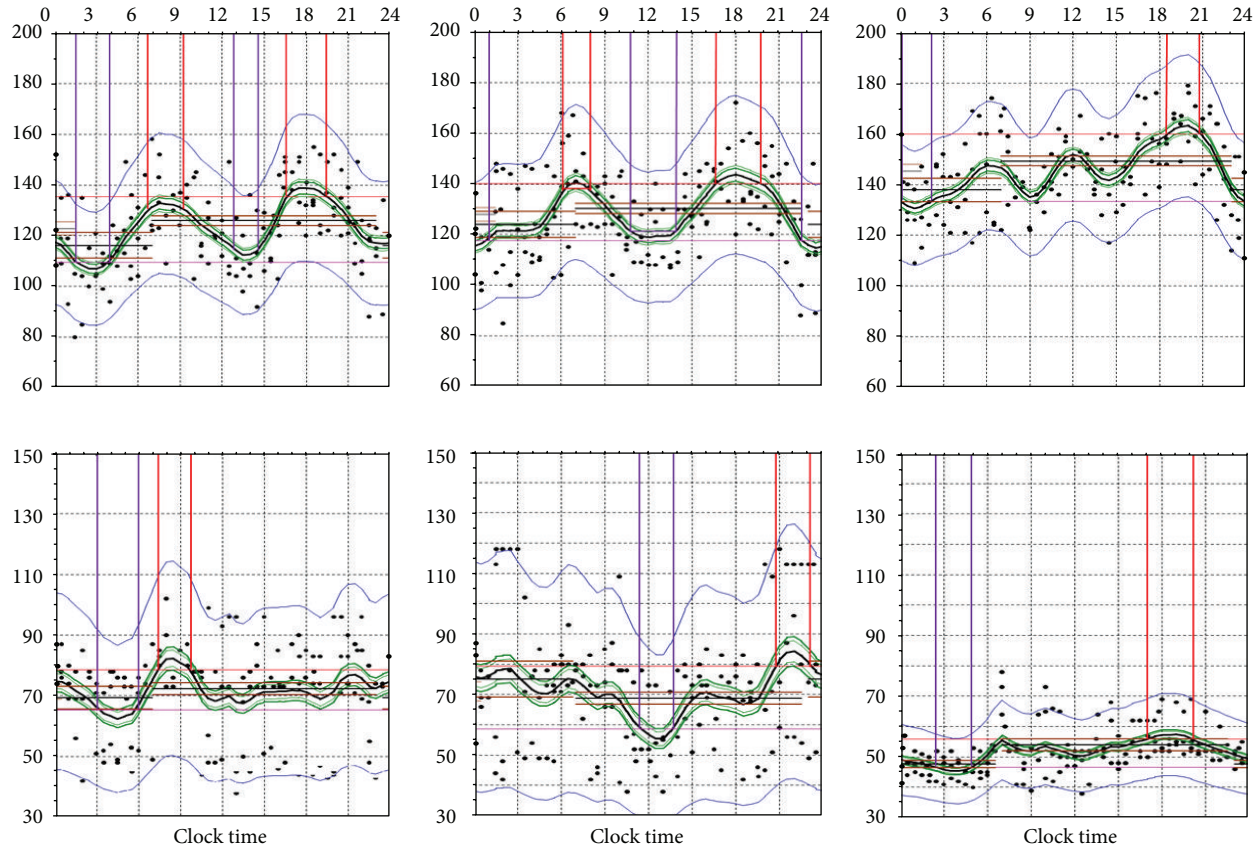
Comments are the same as in Table 1.



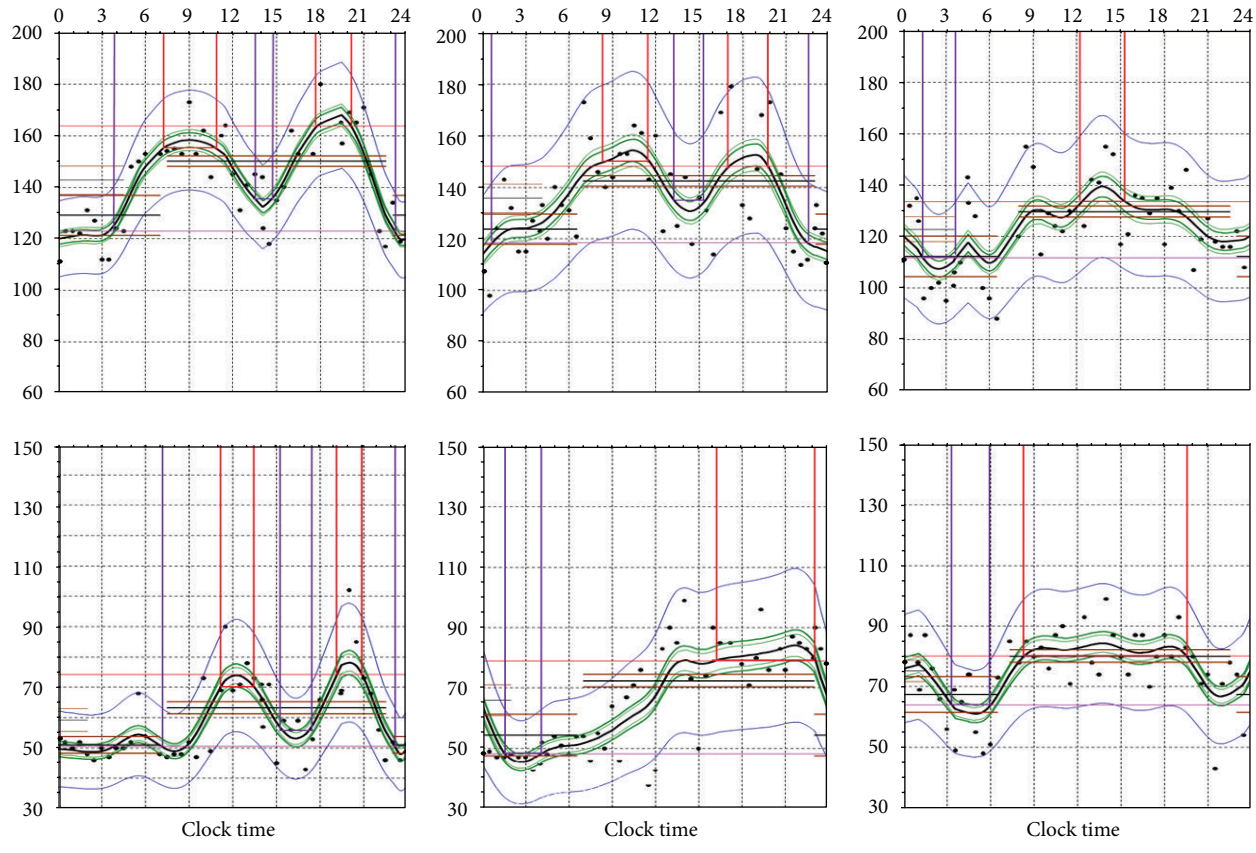
(a) January 09–11 (b) February 18–20 (c) April 13–15

(d) April 22–24 (e) Apr 30–May 02 (f) May 05–07

Figure 2: Continued.



(g) May14–16 (h) May 18-19 (i) May 21–23



(j) May 24 (k) May 25 (l) May 26

Figure 2: Continued.

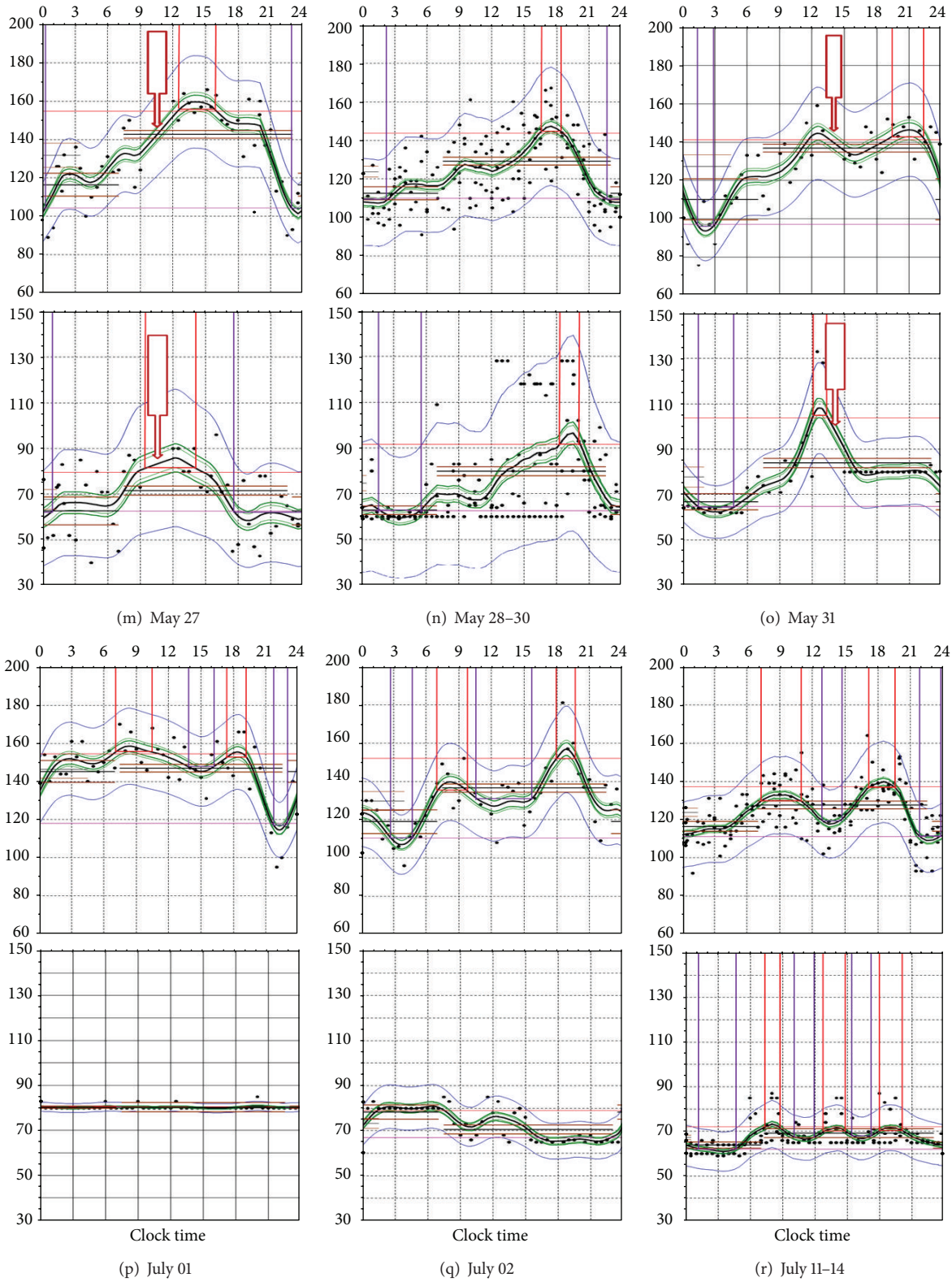


Figure 2: Daily profiles of systolic blood pressure (SBP), and heart rate (HR) before heart failure and during its treatment. ((a)–(r)): Subsequent stages of development. Upper row: SBP; lower row: HR. Abscissa: clock time; ordinates: variable's value (SBP: mmHg; HR: beats/min). Black dots: separate records, Black curve: approximation of the process, Green lines: 95% confidence limits (CL) of approximation, blue lines: 95%CL of records population, Horizontal brown lines: middle night-time and middle day-time variable levels and Vertical red lines: positions of top and statistically significant elevations during the 24-hour span (99%CL-s). Vertical violet lines: positions of bottom and statistically significant decreases during the 24-hour span and their (99%CL-s).

Table 3: Dynamics of the heart rate in 2010.

Stage	Time (calendar dates in 2010)	Mesor	24-hour component			12-hour component		
			Amplitude	Acrophase	*P* value	Amplitude	Acrophase	*P* value
1-2	05/01–19/01	71.7 ± 5.0	7.1 ± 3.6	−325 ± 24	0.0073	3.1 ± 2.2	−319 ± 202	0.2962
1-2	12/02–26/02	73.3 ± 3.0	7.3 ± 2.6	−283 ± 31	0.0004	2.4 ± 2.3	−327 ± 175	0.4040
1-2	02/04–16/04	71.1 ± 5.8	6.1 ± 5.0	−270 ± 62	0.0422	2.3 ± 2.1	−331 ± 106	0.4741
2-3	18/04–25/04	74.6 ± 4.2	3.9 ± 2.3	−260 ± 65	0.0918	1.7 ± 1.5	−316 ± 151	0.5135
3-4	26/04–04/05	65.6 ± 16	3.9 ± 4.0	−276 ± 115	0.1508	2.7 ± 2.9	−286 ± 66	0.2693
4-5	05/05–13/05	71.8 ± 7.0	6.8 ± 5.1	−156 ± 221	0.0613	3.2 ± 3.1	−271 ± 102	0.3629
5-6	14/05–18/05	70.5 ± 5.4	5.0 ± 6.7	−208 ± 289	0.2876	4.2 ± 3.7	−268 ± 33	0.2581
6-7	19/05–23/05	54.2 ± 6.6	4.9 ± 3.4	−232 ± 122	0.0294	3.0 ± 2.2	−243 ± 136	0.1125
7-8	24/05–26/05	64.5 ± 13.2	8.0 ± 4.2	−246 ± 34	0.0022	3.1 ± 2.4	−311 ± 60	0.2628
8	27/05	69.9 ± 3.6	5.2 ± 4.2	−234 ± 12	0.0514	2.6 ± 1.9	−311 ± 116	0.4111
8-9	28/05–30/05	70.3 ± 10.4	11.2 ± 10.7	−262 ± 34	0.0079	5.9 ± 8.0	−246 ± 201	0.1206
9	31/05	81.5 ± 3.5	13.4 ± 4.4	−229 ± 10	<0.0000	5.0 ± 2.6	−150 ± 61	0.0780
9-10	01/06-02/06	76.5 ± 8.1	3.9 ± 8.24	−169 ± 160	0.1519	1.9 ± 2.9	−354 ± 228	0.3926
10-11	03/06–08/06	67.3 ± 2.7	2.4 ± 1.2	−198 ± 45	0.0516	2.0 ± 1.4	−254 ± 22	0.0514
11-12	09/06–17/06	67.9 ± 2.4	3.2 ± 1.0	−201 ± 30	0.0008	3.4 ± 1.7	−241 ± 10	0.0008

Comments are the same as in Table 1.

to their changes. As a result of such adjustment rates of BP exceeded the commonly accepted target values only rarely (10% of all measurements); see Figures 2(a)–2(c).

The daily mean SBP value changed slightly, rising from 114–121 in January to 118–126mmHg, in the middle of February, and then dropped again to 112–116mmHg in the middle of April (expression of the seasonal changes?).

The amplitude of the 24-hour rhythm component (A-24) at 10–20 mm. 12-hour component (A-12) was expressed rarely, and when it was statistically significant, its amplitude varied from 5 to 10 mmHg. Presence of this ultradian component was manifested by additional waves of the daily profile (see Figures 2(b)-2(c)).

24-hour rhythm acrophase (AF-24) fluctuated around 225° in the range from −187 up to 262°, that is, about 15 hours (from 12 : 30 to 17 : 30). AF-12 (when this rhythmic component was significant) varied around 240° (−30 to −360°).

Dynamics of DBP repeated in the main features the dynamics of SBP. Peaks and troughs of DBP were coinciding, and dynamics of daily mean values, amplitude of oscillation and their acrophases were similar (synchronous).

The daily mean level of HR ranged around 75 bpm, its A-24 ranged from 5 to 12, and A-12 (when it was statistically significant) was less than 5 bpm. AF-24 was not synchronized with that of systolic and diastolic blood pressure; most often it fell to 18–21 hours. AF-12 was very unstable, varying from −180 to −360°.

4.2. Changes in the Profile of Hemodynamic Parameters during Progression of the Disease, after Joining of Heart Failure and at Medication and Surgical Treatment. On April 18, 2010 the patient developed acute respiratory illness that lasted about a week and manifested as a poor health, a runny nose, and eye-watering (see Figure 1, Sections 2-3); the temperature was not overdue 37°. The daily mean of BP becomes decreased if compared with the previous few weeks; A-24 was progressively decreasing, especially in DBP. A-12 has not changed. HR daily mean decreased, but the A-24 and A-12 did not change. In the SBP profile circadian rhythm dominated, and small 6–8-hour variations were superimposed to it (see Figure 2(d)). Circadian rhythm of HR was not regular, and when he nonetheless appeared his A-24 was reduced, and acrophase unstable (see Figures 1 and 2(d)).

On April 26 oedema of feet and ankles appeared. BP was decreasing in combination with low A-24 and bradycardia (see Figure 1, Sections 3-4 and Figure 2(e)). The P appealed to the physician. Following his advice, timing adjustment of regular P was canceled and changed to the standard procedure taking medicine in the morning and in the evening; the preparations were also changed.

On May 5 dyspnoea joined, which occurred even at low physical activity (see Figure 1, Sections 4-5). The level of blood pressure as well as A-24 and A-12 began to grow. BP values became above 140 mmHg in 19% of measurements; sometimes they exceeded 160 mmHg. The mean heart rate returned to normal, but, because of tachycardia affiliation, amplitude of oscillations increased (see Figure 2(f)).

On May 11 diuretics medication began. On May 14 because of progressing heart failure the P was admitted to a therapeutic cardiology clinic. During his stay in the hospital P had the opportunity to continue the continuous BP and HR monitoring but analysis of its results was carried out retrospectively.

After May 14, due to intensive diuretic therapy (both medicamentous and drip feeds), the phenomenon of heart failure has been copped, but BP had not decreased (see Figure 1, Sections 5-6). Circadian rhythm has stopped: A-24

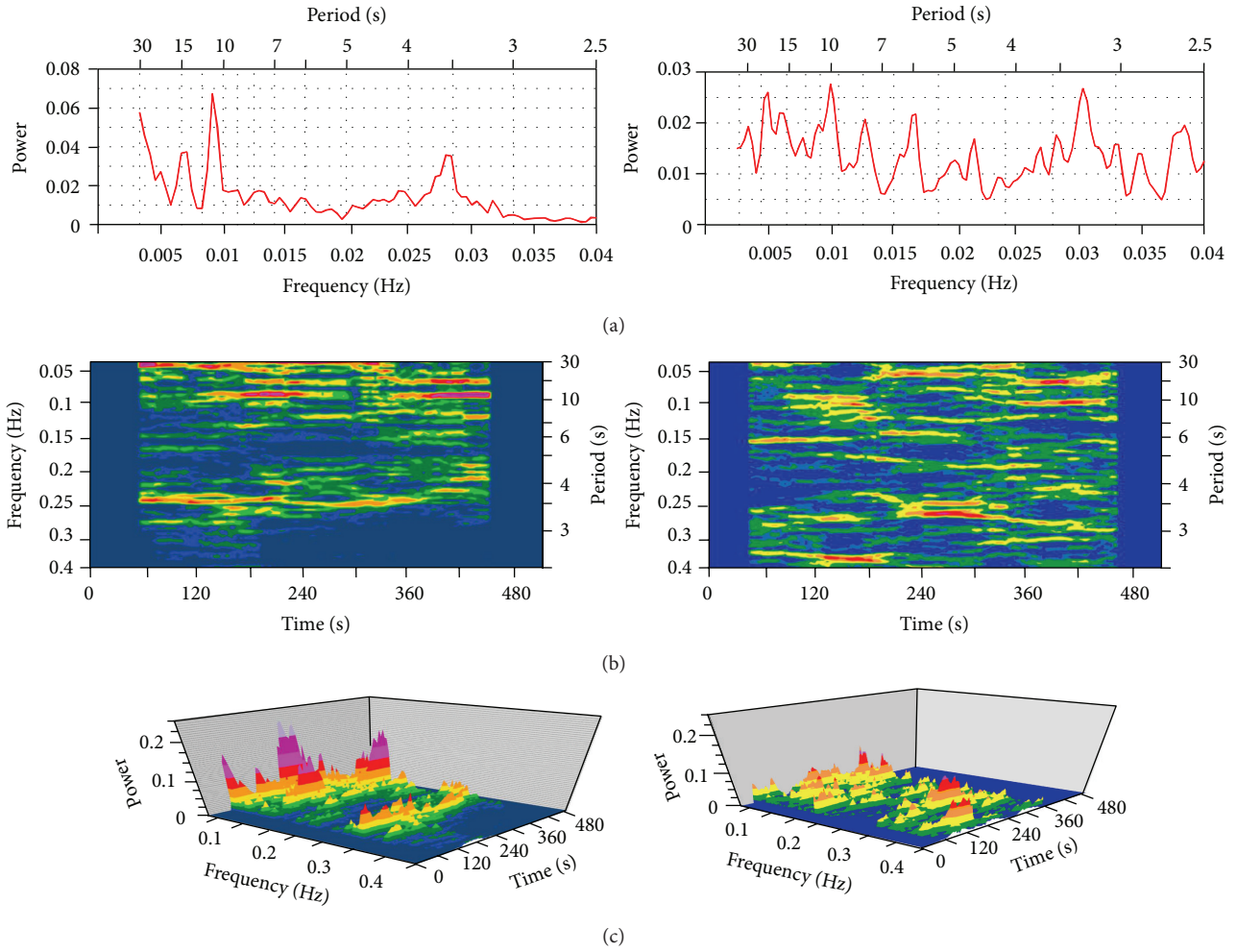


Figure 3: Spectra of electrocardiograms (ECG) in two persons. Left fragment: sinus rhythm in patient B; right one: atrial fibrillation in patient GSK. (a): global spectra of 9 minutes record. Abscissas: spectral components, below: frequency (Hz), and above: period length of oscillations (sec); ordinate: power (η^2) of spectral components (η^2 = ratio of described and general variances). ((b) and (c)); 3D gliding spectra of the same records. and (b): view from above (elevation = 90°); (c): view from aside (elevation, rotation, and perspective = 30°). Abscissa: time from starting records (sec), ordinate: frequency (Hz), and applicate: spectral power marked by different colors; blue: statistically not significant values, green components significant at $0.05 > P > 0.01$, yellow: at $0.01 > P > 0.001$, orange: at $0.001 > P > 0.0001$, and red: at $0.0001 > P > 0.00001$.

abruptly decreased and ceased to be significant (note to break the red curve, reflecting the A-24 in Figure 1 on the fragments of SBP and DBP). At the same time the 12-hour rhythm became intensified; its amplitude increased more than twice (green curve on the same fragment). HR began to decline, but its A-24 has doubled and A-12 has become more significant.

As a result, BP has become bimodal with the largest rises in 6–9 and 16–20 and downturns in 0–4 and 11–16 h (see Figures 2(g)-2(h)). 12-hour and even shorter oscillations dominated in HR, combining with apparently circadian profile but with the inverted phase.

During indwelling in the clinic Holter ECG monitoring was carried out, and pauses of more than 2.5 sec were revealed. The necessity of pacemaker implantation become obvious. Retrospective analysis of the ECG spectrum is shown in Figure 3.

To May 19 edema disappeared, shortness of breath decreased, and drop-feed injections were stopped. BP (particularly SBP) remained high exceeding in 69% of the measurements 140 mmHg (see Figure 2(i)). A-24 restored, but does not exceed the A-12 one. Bradycardia restored too (see Figure 1, Sections 6-7). Circadian rhythm of HR heart rate appeared again, but its A-24 was very low (see Figure 2(i)). According to Holter monitoring HR during the day span often happened to be rarer than 40 bpm, and it was considered as a sign for surgical intervention.

On May 24 the P was transferred to the surgical department. BP remained high, A-24 increased, especially in DBP even surpassing that of the SAD (see Figure 1, Sections 7-8). BP profile was unstable, varying from one day to another, and the ratio of 24- and 12-hour rhythm components varied greatly too (see Figures 2(j)–2(l)). In HR A-24 was

predominant, but the phase of the HR rhythm was unstable (see Figures 2(j)–2(l)).

On May 27 the dual chamber pacemaker was implanted (see Figure 1, event 8). SBP began to decline, but the level of DBP did not change. 24-hour component of rhythm clearly dominated; 12-hour one was weak. HR did not fall below 65 bpm; there was a tendency to tachycardia. A-24 increased drastically (see Figure 1, Sections 8-9, and Figures 2(m) and 2(n)). ECG recording demonstrated necessity of interruption of the atrioventricular conduction pathways. Next observation had shown that ventricular tachisystolia could not be copped by usual therapeutic treatment. Cardioversion was not acceptable because of patient's age and heart chambers size.

On May 31 at 1-2 PM atrioventricular node ablation had been performed (see Figure 1, event 9, and Figure 2(o)). The HR level was established by means of pacemaker tuning, but the mean BP remained high (83% of measurements exceeded 140 mmHg). No any daily or ultradian fluctuations of BP were checked after surgery during the next 30 hours (up to the evening of the following day). BP began decreasing only after 9 PM, June 1 (see Figures 2(p)-2(q)).

On June 2 the P was discharged from the hospital (Figure 1, event 10, and Figure 2(q)). The manifestations of arrhythmia did not disturb him anymore. The possibility to make regular analyses of the monitor records and to perform according timing corrections of antihypertensive drugs became renewed.

The BP mean began decreasing and stabilized in 1 week (since June 9). Excesses of SBP over 140 mmHg occurred only in 16% of records. A-24 also declined and stabilized at values which were lower than ones in the beginning of the year. A-12 remained significant and was equal to A-24. Because of it the circadian profile remained bimodal, although bimodality was not as strong as during May 14–20 (see Figure 2(r)). The HR profile was keeping pacemaker's setting—60 bpm at night and not less than 65 during the day time (see Figure 2(r)).

5. Discussion

5.1. Methods for Detection Rhythms and Estimating Their Parameters. In this paper all computing was made by means of original program complex, elaborated especially for unequidistant data, which are most often used in medicobiological research.

In the standard software elaborated for technical purposes the warranty for precision of results is equidistance of data; the main components of rhythm (24- and 12-hourly) are often evaluated in those programs after their approximation by means of cosine function—the method named "single cosinor" [9]. It is widely used to analyze the results of BP and HR monitoring [10], although in the standard software usually neither cosine parameters nor their statistical significance is estimated.

The first program used during our research (KEKS 2 [2]) permits doing calculations in unequidistant series (having gaps in data). It detects the whole spectrum of periodic oscillations within the user-defined band of frequencies and evaluates mesor, amplitude, and acrophase as well as their statistical significance for every spectral component. A total series is used, thus results of analysis should be called the "global spectrum."

The second program (GLISSER 3) allows to trace dynamics of spectral components and their parameters in the series and provides revealing their amplitude and frequency modulations [2]. Results of analyses are called "gliding spectrum." Specialized version of this program (GLIRR) is adapted for the gliding spectral analysis of electrocardiogram and creates 3D visualization of the process [2]. Well-known method of time serial sections [11] is reproduced in GLISSER as one of the possibilities among many others.

Because all three programs use trigonometric approximation, they smooth the real form of signals too much; they detect periodical signals and reveal their modulations, but too many cosine harmonics should be used for detailed description signal's real shape; in particular, the straight parts of the profiles are reproduced as curved.

For reproducing those parts of oscillations which allow to judge the true state of peaks and troughs of the process, and the steepness of its ups and downs, and time of their distribution the program "FORM" was elaborated.

Accuracy of shape description is determined by user by means of setting initial parameters. The program FORM [2] provides those calculations. It is based on the modification of Sawitsky-Goley filter and does not use sinusoidal transformations. The program is able to detect in unequidistal and noisy series even such difficult for description signals as having saw shaped or rectangular cycles.

5.2. The Behavior of 24- and 12-Hour Oscillators under Extreme Conditions. Results of computing time series by gliding spectral programs might be visualized in 3D graph. Coordinates of its base are frequencies (ordinate) and time (abscissa). Values of spectral parameter (e.g., power or amplitude) are presented. Constant (stationary) rhythm looks in 3D representation like a mountain crest going parallel to abscissa and having everywhere equal heath proportional to the spectrum parameter. If amplitude (or power) is changing in time it reflects in the height of the crest. If frequency of rhythmic oscillations is modulated position of crest is moving along the ordinate axis. When looking at such graph from above (elevation of viewer as 90°) the crest looks likes a stripe.

Different values of parameter might be expressed by different shading or colors (like it is usually made in geographical maps to show relief of the earth surface).

Unlike the serial sections method gliding spectra permit demonstrating the simultaneous development of several spectral components.

The application of this method demonstrates in Figure 4 the simultaneous development of 24- and 12-hour spectral components.

24-hour spectral component (24-sc) looks like the band within the boundaries of statistical significance. Interruption of the band means the disappearance of oscillations at this frequency. 12-hour spectral component (12-sc) looks less constant as 24-h one.

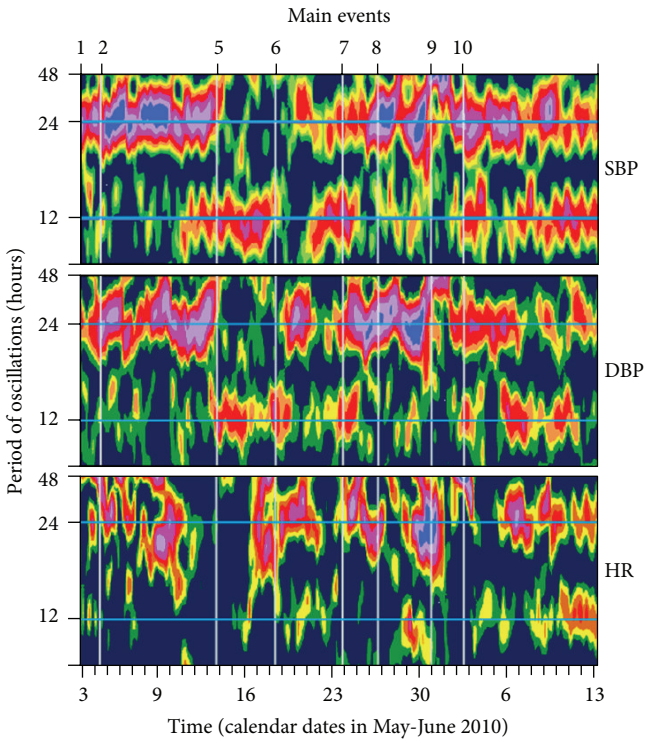


Figure 4: Gliding spectra of systolic and diastolic blood pressure and heart rate during treatment of heart failure and cardiac surgery. Abscissa: time (calendar dates in 2010), ordinates: period length (hours), and applicate: areas corresponding to oscillations of equal power (η^2); blue: $\eta^2 < 0.05$, green: $0.05 > \eta^2 > 0.10$, yellow: $0.10 > \eta^2 > 0.15$, orange: $0.15 > \eta^2 > 0.20$, red: $0.20 > \eta^2 > 0.25$, and other colors: $\eta^2 > 0.25$. Main events: 1-2: healthy, 2–5: increasing heart failure, at the therapeutic clinic, 5-6: intensive therapeutic treatment, 6: finish intensive therapeutic treatment, 7: transferring to the surgical clinic, 8: pacemaker implanting, 9: atrium-ventricular ablation, and 10: discharge for home rehabilitation (numbers are the same as in Table 1).

Despite of growing heart failure, the power of 24-sc remained high. Its colors were changing from orange to purple, it means the amplitude of this component was modulated, and the distance between equal colors in the graph demonstrated regularity of modulation with a period of about a week (circaseptan).

At start of observations circadian component was dominating, and the 12-hour one was represented only like small not continuous islands.

After the heart failure began developing, 12-sc remained weak, but after the start of intensive diuretics medication the 24-sc disappeared, and 12-sc immediately becomes dominant (in daily profile of blood pressure was manifested as bimodality of approximating curve, see Figures 2(f) and 2(g)). After completion of intensive therapy 12-hour component was again lost, and the leading position returned to 24-hour one. Inhibition of 24-sc in the rhythm of blood pressure with the replacement of them by 12-sc has been noted also previously in the same person after a sudden increase in the dosage of antihypertensive drugs [6].

Spectral characteristics of the rhythm occurred changes also under conditions of both surgical procedures, but they were not similar.

Implanting pacemaker on May 27 included several stages: (1) skin incision and entry into the vein, (2) passaging a probe through the veins and penetrating into the heart cavities, (3) fixing electrodes, and (4) removing the probe and suturing the incision. Interrupting atrio-ventricular conduction pathways on May 31 differed fundamentally from that described manipulations mainly at the third stage, when destruction of the anatomical integrity of the organ was performed (which was not done at the first intervention).

The main difference in the rhythms behavior of BP (see Figure 4) was strengthening the 24-sc in the first case but its disappearance in the second one. Its "silence" lasted about 30 hours, after which the oscillations were restored with the same phase relationship as before. 12-sc was depressed immediately after the first operation and reappeared simultaneously with the 24-sc.

Earlier sudden stop of a 24-ch and his subsequent sharp recovery has been observed during rapid transmeridian flights across 9 time zones [12]. Such behavior of the oscillator, from physical point of view, corresponds to the passage by its so-called singular point, when drastic changes of conditions compel oscillations to stop, for choosing new oscillatory parameters adequate to those new conditions.

First of all, it refers to the phase of fluctuations. They are usually defined by any external synchronizer. During and after flights phase light regimen and social environment routine are inherent for different time zone and serve as pacemakers.

Moment of ablation was that shock which plunged 24-sc to the singularity, but after surgery lightening and social environment remained the same, thus when a new switch on the oscillator got restored the previous phase of oscillations restored too (see Figure 1).

The circadian rhythm of HR before the operation was unstable: arrhythmia, immanent for the P; its period length was not strongly equal to 24, but varied within the whole circadian range of 20–28 h; its amplitude and phase were also not constant (see Figure 1) as well as its power (see Figure 4). The first surgery has caused strong increase of the power (see Figure 4), which was manifested as tachycardia (see Figure 2(o)). The following ablation stopped the circadian HR oscillator (as well as in BP), but later the natural circadian variations of HR could not be restored independently and recovered in a week after setting pacemaker which was tuned up to different frequencies for the night and day spans (see Figure 4).

Such behavior of HR rhythmicity supports the previously stated assumption that behavior of 24- and 12-hourly oscillators at various drastic modifications of the organism's activity might be independent [8, 13]. The genes that specify the 24-hour rhythm are now actively studied [14–17]. There are also data that the more frequent (ultradian) oscillations (with periods multiple to 24 hours) might be determined by the combined activity of different 24-hour genes [18–20]. Phenotypically these oscillations are manifested themselves as usually in the activities of peripheral organs [21–23], and

their power is increasing during adaptive reorganizations of organism [24, 25]. The observations described in this paper allow assuming that the activity in different peripheral organs has also different anatomical substrates, including specific structures inherent immanently to them.

If our suppositions would be correct we could suggest that the regulatory mechanisms of peripheral circadian and semicircadian heart oscillator include the system of conductive cardiomyocytes. After its mechanical destruction the role of circadian oscillator in relation to the inotropic function is recovered and passes on myocardium of the ventricles, but chronotropic (in terms of circadian and ultradian rhythms) function is not peculiar to ventricles and is lost.

5.3. The Physiological Coordination of Diastolic and Systolic Blood Pressure. The natural oscillatory changes in functional activity provide the opportunity of adjustment to changing environmental conditions and, thus, serve as a means for keeping homeostasis: homeostasis should be understood not as a strictly stable state but as coordinated fluctuations not exceeding any limits. These limits, beyond whose pathological changes appear, serve as the boundaries of the norm.

Fluctuations in the various functional systems do not necessarily occur simultaneously (activity of some of them may not coincide) but they occur in concert, that is, in a certain sequence of time; from physical point of view, they are coherent. A lot of external impacts may violate this time coordination (desynchronization occurs). As the most easily diagnosable signs of desynchronized rhythms are changing the correlation coefficients between the processes (which characterizes the tightness of interrelations) and the regression coefficients between them (quantifying the functional dependence of one process from another one) [26, 27].

Such an approach would require to assess the mutual coordination of the three registered by monitoring functions—SBP, DAD and HR. However, as the heart rate of the P was erratical due to atrial fibrillation, the analysis was possible only for SBP and DBP.

Regression coefficients for SBP versus DBP and DBP versus SBP are not equal (Figure 5). According to their changes in the dynamics of development any two processes are possible to assume, each of them is leading being related to the other one: leader's modification entails the more significant changes in regression coefficient (correlation coefficient at the permutation of regression variables does not change).

Figure 5 shows the change in regression coefficients for SBP and DBP SBP DBP, as well as the correlation coefficients at different stages of development and treatment of disease in P. Changes in correlation coefficients most commonly used in the literature to assess the degree of desynchronization [28–30] almost did not deviate from the values observed in P, during the absence of heart failure symptoms. Changes in the regression coefficient for SBP DBP were expressed much more strongly than those of DBP to SBP.

Taking into account that the value of SBP is largely determined by the state of central regulatory level circulatory system, and diastolic blood pressure—the state of arteriolar level—we can conclude that the consistency of responses in the regulation of the cardiovascular system to the changing conditions of the circulation is the last to take a leadership role. An intensive therapeutic treatment of heart failure, which was accompanied by suppression of the circadian rhythm component, probably temporarily modified the baroreflex (see event markers 5 to 6 in Figure 4). Subsequent reaction proceeded wavelike: increased reflex reactions immediately after the end of intensive therapy replaced by of weakening. Implantation of a pacemaker (see the marker events in Figure 4) was just on the background of a weakening. Immediately after the intervention with the baroreceptor reflex abruptly increased, and the reaction of SBP relative to DBP was inadequately grown up to repeat surgery ablation of conductive paths (see the marker events of 9 in Figure 4). Restoration of normal relations between DBP and SBP occurred after the operation gradually over several weeks after discharge of the patient at home.

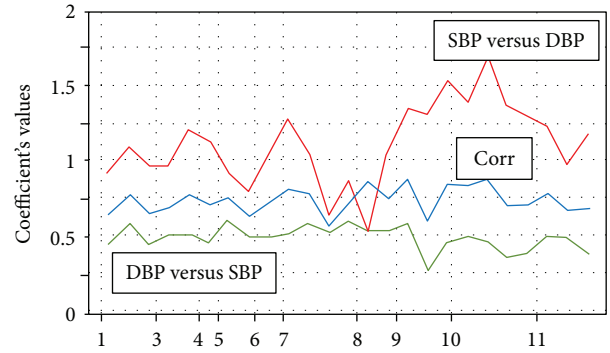


Figure 5: Interdependence of systolic and diastolic blood pressure at different stages of heart failure treatment and cardiac surgery. Abscissa: main events of developing process: 1–3: healthy, 3-4: increasing heart failure, at the therapeutic clinic, 6: finish intensive therapeutic treatment, 7: transferring to the surgical clinic, 8: pacemaker implanting, 9: atrium-ventricular ablation, 10: discharge for home rehabilitation, and 11: after a week at home (numbers are the same as in Table 1). Ordinate: regression coefficients, SBP versus DBP (red), DBP versus SBP (green), and correlation coefficient (blue).

These observations demonstrate that the correlation coefficient which is widely used to assess desynchronoses is not the best tool for this purpose. Regression coefficients are much more informative, and from the possible combinations of the two of them regression SBP versus DBP is more sensitive.

Changes of the SBP versus DBP correlation coefficients and regression ones in subjects with desynchronoses, arisen as a result of chaotic schedule of shift work and regularity of sleep and rest [31–33], confirm our present observations.

5.4. Assessment of the Daily Profile of the Process as a Criterion for Optimal Timing of the Treatment Effects. That fact that the external impacts on the body, applied at different phases of the circadian rhythm, do not entail the same effect, is known for a long time. This phenomenon is universal; it was shown

in relation to light signals, diets, physiotherapy, and many other effects [34–38].

Let us demonstrate some examples from our own observations dealing with experimental surgery. The rate of collagen accumulation of the wound area, the rate of development of the capillary bed in granulation tissue during its healing, and agility of rearrangement peritoneal mesothelium after its injury, as well as other reactions in posttraumatic tissue regeneration are varying depending on whether the injury was inflicted in the morning, afternoon, or evening [39–52].

The main regularities in time dependence of medication effectiveness at their admission at different circadian phase (time of the day) were systematized still about 40 years ago [53]. Taking into account those peculiarities at medical practice was named chronotherapy. Many publications are devoted to optimizing the treatment of hypertensive states by choosing time of the day when the drug should be most effective when using smaller doses.

Such works were usually based on one-day monitoring and the ratio of the averages of daily and nocturnal BP values were calculated (the so-called circadian index). In accordance with the result, the patient is defined as a dipper, nondipper, or nigt-peaker, and antihypertensive medication would be recommended for taking in the morning or in the evening [54–66]. The results were very controversial, and chronotherapy of hypertension began causing skepticism [67].

In 2008, a quite different principle of chronotherapy was proposed—not the simple taking into account only the day time and nocturnal rates, and not the approximation of the 24-hour profile of the circadian curve by the rigid sinusoidal functions: Cosinor method which was proposed a few decades ago [9] does not provide restoration of the real circadian profile because it is able to take into account the ultradian components only of a priori settled periods lengths. This approach makes it possible to determine the rate of change of the process (velocity, the first derivative) throughout the whole circadian cycle as well as the distribution of the accelerations (second derivative). Distribution of accelerations, in turn, makes it possible to decide, when regulatory physiological mechanisms might be included into control of the process [68]. According to results revealed, it should be expedient to use the drug not at the time when BP reaches its maximum values, but when the regulatory mechanisms are just beginning to be switched up: to prevent a fire is easier than to extinguish it only after the flame should be broken out.

Profile of daily course of the process is revealed by means of modified Savitzky and Golay [69] filtering combined with the superposed epochs principle [70]. Revealing profile would be done on the base of three-day monitoring, which makes possible it to calculate all the parameters of the curve with their statistical confidence intervals [3, 71]. Next parameters and their statistical probability might be estimated being appointed by users (Figure 6):

(1) distribution of data recorded according to phases of the cycle,

(2) average of data values (mean level),

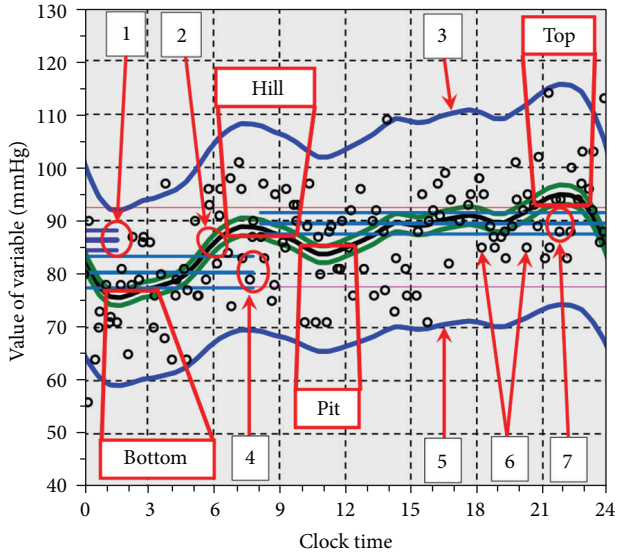


Figure 6: Main features of signal profile. Abscissa: time, ordinate: values of variable. 1: general mean level, 2: approximating curve (profile), 3: upper confidence limit of population, 4: mean level of night values, 5: lower confidence limit of population, 6: separate records, 7: Mean level of night values. Top: highest area of the process, Bottom: lowest area of the process, hill: intermediate elevation, pit: intermediate decrease. Red horizontal bars at those areas: confidence limits of their timing. Hills and tops are shown only if they are statistically significant comparing with the neighboring areas. Ovals include value of parameter and its confidence limits.

(3) approximation of the mid value of the process at various phases of the cycle,

(4) peak (top) value,

(5) peak's phase,

(6) trough (bottom) value,

(7) trough's phase,

(8) values and positions in the cycle of intermediate elevations and decreases of the profile.

Repetitive investigation of BP and HR circadian profile in the same persons revealed that it does not remain constant; even no acute disease takes place (see Figures 2(a), 2(b), and 2(c)). In all cases, the P looked as a dipper, but the wave shape was quite not equal, and timing of medication for preventing excessive leaps of BP at each case should be different.

This approach allowed the P to keep his BP for a long time within acceptable limits. After May 4, 2010 chronobiological approach has been canceled, and drugs were taken after traditional pattern—in the morning and in the evening. After that, BP became gradually increasing, exceeded the permissible limits, and returned to the target values only after discharge, when the opportunity of regular analyzing circadian profile and adjusting timing of treatment in accordance with the acceleration of the process had come back (see Figure 2).

Approach based on the described principle has been applied in dozens of cases at treatment hypertensive patients, and has shown good results [72].

Taking into account that the daily profile of BP and HR rarely remains stable for half a week (especially during development of pathology), monitoring for longer than 3-days span may blur the assessment of the actual parameters of the daily profile. From the other side, to settle any medical conclusion based on only one-day recording means to operate in a deficit of information.

Recommendations made earlier (also with our participation) to carry out continuous monitoring at least one week [73–80] from the point of view of our today experience seem to be informative more scientifically than having actual diagnostic value: the treatment of individual patients is more expedient to carry out for several times three-day ambulatory monitoring at intervals of several days: during treatment of hypertensive states approaching to the target BP values occur gradually, and this mode allows to optimize timing of antihypertensive medications in the better way.

Our observations impugn the meaning that referring a patient as dipper, night-peaker, or non-dipper may be useful at choosing tactics of his treatment: all these types can transform themselves in few days. From the other side, even if BP "type" was not changed the real peak and trough positions in the cycle might be moved, and such circumstance should require new treatment timing.

Natural mobility of circadian BP profile impugns also the prognostic validity of dipper—nondipper classification.

6. Conclusion

Long-term (multiday) BP and HR monitoring provides valuable information of continuous dynamics of the processes at all stages of their development. This is important, since at the "traditional" planning observation are performed only before any event and after it (e.g., transmeridian flight or surgery), but not during the same event. Unfortunately, today such studies can be carried out only for scientific purposes. If they should be available for every patient, their predictive value for the early detection of cardiovascular diseases becomes very valuable.

Such idea was expressed still many years ago [81–84] and lives up to now, but for most of people it seems to be as an utopia.

To reach it, progress on several fronts is necessary: (1) miniaturization of recorders in order to rescue patients from troubles associated with wearing the device, (2) wireless transmission of recorded data to any analytical center, (3) establishment of such centers, equipped with the necessary hard- and software, (4) improvement of existing programs for data processing and development of new ones, and (5) training specialists who would be able to use such sophisticated equipment and interpret the results from the medical point of view.

It is difficult to predict how much time will be spent on such work, but if we would like to be ready to use advantages of the latest future technology, the development of theoretical approaches must begin without delay today.

Progress comes much faster than we can imagine. One of the authors of this paper for the first time used the BP monitor still in 1971. It was a large heavy box, its weight was about 20 kg, and it should be carried on the rolling table behind the patient, being connected with the user by wires and an air-tube; records were registered by an ink device; they should be measured and put into computer manually. Let us look at BP monitoring in 40 years.

References

[1] S. Nintcheu-Fata, G. Cornélissen, G. Katinas et al., "Software for contour maps of moving least-squares spectra," *Scripta Medica*, vol. 76, no. 5, pp. 279–283, 2003.

[2] G. S. Katinas, "Methods of time series analysis," in *Chronobiology and Chronomedicine: A Manual*, S. I. Rapoport, V. A. Frolpv, and L. G. Khetagurova, Eds., pp. 206–251, Medical Informatics Agency, Moscow, Russia, 2012.

[3] G. S. Katinas, "Revealing profile of non-sinusoidal oscillations," in *Adaptational Physiology and Life Quality: Problems of Traditional and Innovative Medicine, Proceedings of the International Symposium*, pp. 14–16, People's Friendship University of Russia, Moscow, Russia, 2008.

[4] V. P. Karp and G. S. Katinas, *Computational Methods of Analysis in Chronobiology and Chronomedicine*, Vostochnaya Corona, St-Petersburg, Russia, 1997.

[5] O. Schwartzkopff, D. Hillman, F. Halberg et al., "Circasemidian and circasemiseptan gauges of vascular adjustment after transmeridian crossing of three time zones," in *Symposium Noninvasive Methods in Cardiology*, F. Halberg, T. Kenner, B. Fišer, and J. Siegelová, Eds., pp. 80–85, Masaric University, Brno, Czech Republic, 2010.

[6] G. S. Katinas, G. Cornélissen, K. Otsuka, E. Haus, E. E. Bakken, and F. Halberg, "Why continued surveillance? Intermittent blood pressure and heart rate abnormality under treatment," *Biomedicine and Pharmacotherapy*, vol. 59, supplement 1, pp. S141–S151, 2005.

[7] F. Halberg, G. Cornélissen, G. S. Katinas, and S. Sanchez de la Peá, "Continued self-surveillance for treatment a frequent vascular variability syndrome," *International Journal of Geronto-Geriatrics*, vol. 11, no. 14, pp. 147–154, 2008.

[8] G. S. Katinas, S. M. Chibisov, O. Schwartzkopff, G. Cornélissen, and F. Halberg, "~12-hour and ~84-hour oscillations during human adjustments to crossing time zones: more than waveform descriptors," *International Journal of Geronto-Geriatrics*, vol. 13, no. 1, pp. 9–19, 2010.

[9] F. Halberg, R. Engel, R. Swank, G. Seaman, and W. Hissen, "Cosinor-auswertung circadianer rhythmen mit niedriger amplitude im menschlichen blut," *Physical Medicine and Rehabilitation*, vol. 5, pp. 101–107, 1966.

[10] A. N. Rogoza, V. P. Nikolsky, E. V. Oshchepkova, O. N. Epifanova, N. K. Runikhina, and V. V. Dmitriev, "Day-long blood pressure monitoring in hypertension," Russian Cardiology Research and Production Complex, Moscow, Russia, 2002.

[11] F. Halberg, "Chronobiology," *Annual Review of Physiology*, vol. 31, pp. 675–725, 1969.

[12] O. Schwartzkopff, D. Hillman, F. Halberg et al., "Circasemidian and circasemiseptan gauges of vascular adjustment after transmeridian crossing of 3 time zones," in *Proceedings of the 10th International Congress 'Health and Education in 21th Century—Innivation Technology in Biology and Medicine'*, pp. 12–15, People's Friendship University of Russia, Moscow, Russia, December 2009.

[13] G. S. Katinas, S. M. Chibisob, and F. Halberg, "Is the 12-hour oscillator independent in the organism?" in *Proceedings of the 10th International Congress 'Health and Education in XXI Century—Innivation Technology in Biology and Medicine'*, pp. 576–577, People's Friendship University of Russia, Moscow, Russia, December 2009.

[14] S. M. Reppert and D. R. Weaver, "Molecular analysis of mammalian circadian rhythms," *Annual Review of Physiology*, vol. 63, pp. 647–676, 2001.

[15] T. Yamamoto, Y. Nakahata, H. Soma, M. Akashi, T. Mamine, and T. Takumi, "Transcriptional oscillation of canonical clock genes in mouse peripheral tissues," *BMC Molecular Biology*, vol. 5, article 18, 2004.

[16] H. Kobayashi, K. Oishi, S. Hanai, and N. Ishida, "Effect of feeding on peripheral circadian rhythms and behaviour in mammals," *Genes to Cells*, vol. 9, no. 9, pp. 857–864, 2004.

[17] L. Fu, M. S. Patel, A. Bradley, E. F. Wagner, and G. Karsenty, "The molecular clock mediates leptin-regulated bone formation," *Cell*, vol. 122, no. 5, pp. 803–815, 2005.

[18] T. Watanabe, M. Kojima, S. Tomida et al., "Peripheral clock gene expression in CS mice with bimodal locomotor rhythms," *Neuroscience Research*, vol. 54, no. 4, pp. 295–301, 2006.

[19] J. B. Hogenesch, "Harmonics of circadian gene transcription in mammals," *PLoS Genetics*, vol. 5, no. 4, Article ID 1000442, 2009.

[20] M. E. Hughes, L. Di Tacchio, K. R. Hayes et al., "Harmonics of circadian gene transcription in mammals," *PLoS Genetics*, vol. 5, no. 4, Article ID 10004422, 2009.

[21] O. G. Liashko, L. V. Chigrina, Y. O. Kotovoj, M. O. Kotovoj, and G. S. Katinas, "The rhythm of mucus formation in the small intestinal epithelium of rats and mice," *Arkhiv Anatomii, Gistologii i Embriologii*, vol. 69, no. 7, pp. 91–95, 1975.

[22] O. G. Lashko, "Frequency analysis of border enterocytes biorhythms at adequate and inverted feeding," *Arkhiv Anatomii, Gistologii i Embriologii*, vol. 73, no. 10, pp. 86–91, 1977.

[23] G. Cornélissen, C. Bratteli, C. Alinder et al., "About-daily and about-weekly hemodynamic variations, including small- and large-artery compliance," in *Proceedings of the International Conference 'Frontiers of Biomedical Science'*, Chronobiology, pp. 114–118, Chengdu, China, September 2006.

[24] G. S. Katinas, *Die Charakteristik Der Biorhythmen Des Funktionellen ZustanDes Einiger Gewebe Wahrend Adaptiver Reaktionen. Deutsch-Sowjet Symp*, vol. 20, Chronobiologie und Chronomedizin, Halle, Germany, 1978.

[25] G. S. Katinas, "Zur Charakterisierung ultradianer Biorhithmen des Funktionzustandes einiger Gewebe bei adaptiven Reaktionen," in *Chronobiologie-Chronomedizin. Vortr Deutsch-Soviet Symp*, pp. 511–526, Akademie-Verlag, Berlin, Germany, 1981.

[26] L. A. Alexina, M. V. Demetyev, G. S. Katinas, A. V. Sorokin, and S. M. Chibisov, "Methods for complex correlation and regression analysis of organism's functional status," *Saint Petersburg State Medical University Records*, vol. 18, no. 3, pp. 72–75, 2011.

[27] B. Gavish, I. Z. Ben-Dov, and M. Bursztyn, "Linear relationship between systolic and diastolic blood pressure monitored over 24 h: assessment and correlates," *Journal of Hypertension*, vol. 26, no. 2, pp. 182–185, 2008.

[28] M. Yoshizawa, M. Abe, and A. Tanaka, "Comparison of maximum cross-correlation coefficient between blood pressure and heart rate with traditional index associated with baroreflex sensitivity," in *Proceedings of the IEEE Engineering in Medicine and Biology Society*, pp. 2574–2577, 2008.

[29] K. J. Bär, S. Schulz, M. Koschke et al., "Correlations between the autonomic modulation of heart rate, blood pressure and the pupillary light reflex in healthy subjects," *Journal of the Neurological Sciences*, vol. 279, no. 1-2, pp. 9–13, 2009.

[30] C. S. E. Bulte, S. W. M. Keet, C. Boer, and R. A. Bouwman, "Level of agreement between heart rate variability and pulse rate variability in healthy individuals," *European Journal of Anaesthesiology*, vol. 28, no. 1, pp. 34–38, 2011.

[31] G. S. Katinas and A. V. Martynikhin, "Revealing un-stationary in adaptive processes," in *First Russian Congress of Pathophysiology*, p. 225, Moscow, Russia, 1996.

[32] S. M. Chibisov, G. S. Katinas, M. V. Demetyev et al., "Desynchronosis of circadian rhythms in cardio-vascular function at shift work," in *Contemporary Problems of Science and Education, Medical Science*, vol. 5, 2011, http://www.science-education.ru/ .

[33] M. V. Demetyev, A. V. Sorokin, S. M. Chibisov, and G. S. Katinas, "Mutual coordination of blood pressure and heart rate in persons at shift work," in *Proceedings of the 12th International Congress 'Health and Education in XXI cCentury'*, pp. 69–73, People's Friendship University of Russia, Moscow, Russia, December 2011.

[34] J. Aschoff, "Die tagesperiodik licht- und dunkelaktiver tiere," *Revue Suisse de Zoologie*, vol. 71, pp. 528–558, 1964.

[35] J. Aschoff, Ed., *Circadian Clocks*, North Holland Press, Amsterdam, The Netherlands, 1965.

[36] C. Goetz, C. Wildgruber, and R. A. Wever, "Meal timing in humans during isolation without time cues," *Journal of Biological Rhythms*, vol. 1, no. 2, pp. 151–162, 1986.

[37] W. L. Koukkary and R. B. Sothern, *Introducting Biological Rhythms. A Primer on the Temporal Organization of Life, With Implications For Health, Society, Reproduction and the Natural Environment*, Springer, New York, NY, USA, 2006.

[38] G. S. Katinas, G. Cornélissen, and F. Halberg, "Timing availability of food alters functional circadian differences within intracellular morphology of rat enterocytes," in *Proceedings of the International Conference 'Frontiers of Biomedical Science'*, Chronobiology, pp. 96–100, Chengdu, China, September 2006.

[39] G. S. Katinas, L. R. Sapozhnikova, and S. V. Lonshakov, "Impact of time of the day when trauma was inflicted at the mesothelium proliferation," *Arkhiv Anatomii Gistologii i Embriologii*, vol. 74, no. 4, pp. 69–73, 1978.

[40] L. R. Sapozhnikova, "Posttraumatic regeneration of endothelium and mesothelium and the time of trauma infliction," in *74th Versammlung der Anatomischen Gesellschaft*, vol. 76, Regensburg, Germany, 1979.

[41] L. R. Sapozhnikova and G. S. Katinas, "Nucleoli of endothelial cells during regeneration after trauma inflicted at different time of the day," *Arkhiv Anatomii, Gistologii i Embriologii*, vol. 74, no. 4, pp. 69–73, 1980.

[42] G. S. Katinas and L. R. Sapozhnikova, "Posttraumatic regeneration of endothelium and mesothelium and the time of trauma infliction," *Verhandlungen der Anatomischen Gesellschaft*, vol. 74, p. 551, 1980.

[43] L. R. Sapozhnikova, J. M. Aviño Marrades, and G. S. Katinas, "Post-traumatic regeneration and time in the 24-hour cycle," in *Tissue Biology*, vol. 3, pp. 54–56, Tartu, Estonia, 1980.

[44] G. S. Katinas, V. A. Brezhneva, V. L. Bykov, V. G. Gololobov, and O. G. Lyashko, "Rhythmicity of cell proliferation in lymphoid organs and peculiarities of skin graft rejection after surgery performed at different time of the day," in *Tissue Biology*, vol. 3, pp. 131–133, Tartu, Estonia, 1980.

[45] V. G. Gololobov and G. S. Katinas, "Tissue reactions dynamics at skin graft allo-transplantation in mice, epidermis and its derivatives," *Arkhiv Anatomii, Gistologii i embrIologii*, vol. 80, no. 6, pp. 50–58, 1981.

[46] G. S. Katinas and L. R. Sapozhnikova, "Nucleoli of mesothelial cells during regeneration after injuries inflicted at different times of the day," *Arkhiv Anatomii, Gistologii i Embriologii*, vol. 80, no. 3, pp. 58–63, 1981.

[47] G. S. Katinas, J. M. Aviño Marrades, and L. R. Sapozhnikova, "The tissue regeneration after trauma at various time of day," *Verhandlungen der Anatomischen Gesellschaft*, vol. 77, pp. 661–662, 1983.

[48] G. S. Katinas, "Chronobiological problems of tissue regeneration," in *Proceedings of the Constituent Congress of the International Society for Pathophysiology*, vol. 269, Kuopio, Finland, 1991.

[49] D. Weinert, D. E. Korzhevsky, G. S. Katinas et al., "Influence of Lyz-Pro dipeptide applied at various times of the day on granulation tissue development," in *Proceedings of the Constituent Congress of the International Society for Pathophysiology*, vol. 273, Kuopio, Finland, 1991.

[50] D. E. Korzhevsky, G. S. Katinas, D. Weinert, and H. Eimert, "Fibrocites and endotheliocites population density in granulation tissue at pharmacological stimulation depends on time of the day when trauma was inflicted," in *Temporal Organization of Organism's Sensitivity*, pp. 67–68, Sverdlovsk, Russia, 1991.

[51] G. S. Katinas, F. Halberg, G. Cornélissen et al., "About 8- and ~84-h rhythms in endotheliocytes as in endothelin-1 and effect of trauma," *Peptides*, vol. 22, no. 4, pp. 647–659, 2001.

[52] G. Katinas, L. Sapozhnikova, J. Aviño Marrades, O. Schwartzkopff, G. Cornélissen, and F. Halberg, "Circadian time of trauma affects formation of collagen in scar's connective tissue: a chronometaanalysis," in *Proceedings of the 3rd International Conference 'Civilization diseases in the spirit of V.I. Vernadsky'*, pp. 118–120, People's Friendship University of Russia, Moscow, Russia, October 2005.

[53] A. Reinberg and F. Halberg, "Circadian chronopharmacology," *Annual Review of Pharmacology*, vol. 11, pp. 455–492, 1971.

[54] H. G. Guellner, F. C. Bartter, and F. Halberg, "Timing antihypertensive medication," *The Lancet*, vol. 2, no. 8141, p. 527, 1979.

[55] R. M. Zaslavskaja, M. G. Varsickij, and M. M. Tejbljum, "Chronotherapie bei Patienten mit Hypertonie," in *Proceedings of the 3rd DDR-UdSSR Symposium 'Chronobiologie und Chronomedizin'*, pp. 38–39, Martin-Luter University of Halle-Wittenberg, Halle, Germany, Juli 1986.

[56] R. M. Zaslavskaya, *Chronodiagnosis and Chronotherapy of Cardiovascular Diseases*, Medicina, Moscow, Russia, 2nd edition, 1993.

[57] P. Palatini, A. Racioppa, G. Raule, M. Zaninotto, M. Penzo, and A. C. Pessina, "Effect of timing of administration on the plasma ACE inhibitory activity and the antihypertensive effect of quinapril," *Clinical Pharmacology and Therapeutics*, vol. 52, no. 4, pp. 378–383, 1992.

[58] G. Nold, G. Strobel, and B. Lemmer, "Morning versus evening amlodipine treatment: effect on circadian blood pressure profile in essential hypertensive patients," *Blood Pressure Monitoring*, vol. 3, no. 1, pp. 17–25, 1998.

[59] Y. G. Qiu, X. Y. Yao, Q. M. Tao et al., "Profile on circadian blood pressure and the influencing factors in essential hypertensive patients after treatment," *Zhonghua Liu Xing Bing Xue Za Zhi*, vol. 25, no. 8, pp. 710–714, 2004.

[60] C. S. Chu, K. T. Lee, S. H. Chen et al., "Morning versus evening administration of a calcium channel blocker in combination therapy for essential hypertension by ambulatory blood pressure monitoring analysis," *International Heart Journal*, vol. 46, no. 3, pp. 433–442, 2005.

[61] C. Cuspidi, S. Meani, C. Valerio et al., "Reproducibility of dipping/nondipping pattern in untreated essential hypertensive patients: impact of sex and age," *Blood Pressure Monitoring*, vol. 12, no. 2, pp. 101–106, 2007.

[62] Y. Watanabe, G. Cornélissen, F. Halberg et al., ". benefit from losartan with hydrochlorothiazide at different circadian times in MESOR-hypertension or CHAT," in *Symp Noninvasive Methods in Cardiology*, F. Halberg, T. Kenner, B. Fišer, and J. Siegelová, Eds., pp. 149–167, Masaric University, Brno, 2008.

[63] A. Takeda, T. Toda, T. Fujii, and N. Matsui, "Bedtime administration of long-acting antihypertensive drugs restores normal nocturnal blood pressure fall in nondippers with essential hypertension," *Clinical and Experimental Nephrology*, vol. 13, no. 5, pp. 467–472, 2009.

[64] Y. Meng, Z. Zhang, X. Liang, C. Wu, and G. Qi, "Effects of combination therapy with amlodipine and fosinopril administered at different times on blood pressure and circadian blood pressure pattern in patients with essential hypertension," *Acta Cardiologica*, vol. 65, no. 3, pp. 309–314, 2010.

[65] R. C. Hermida, D. E. Ayala, M. J. Fontao, and A. Mojón, "Chronotherapy with valsartan/amlodipine fixed combination: improved blood pressure control of essential hypertension with bedtime dosing," *Chronobiology International*, vol. 27, no. 6, pp. 1287–1303, 2010.

[66] B. Lemmer, "Chronopharmacology—impact of circadian rhythms at medicamentous therapy of cardio-vascular diseases," in *Chronobiology and Chronomedicine: A Manual*, S. I. Rapoport, V. A. Frolpv, and L. G. Khetagurova, Eds., pp. 462–480, Medical Informatics Agency, Moscow, Russia, 2012.

[67] R. M. Zaslavskaya, "Chronopharmacology and chronotherapy," in *Chronobiology and Chronomedicine: A Manual*, F. I. Komarov and S. I. Rapoport, Eds., pp. 197–210, Triada-X, Moscow, Russis, 2000.

[68] G. S. Katinas, "Possibilities of correction the 24-hour profile of arterial blood pressure according to results of monitoring," in *Proceedings of the 1st Russian Congress of Chronobiology and Chronomedicine*, pp. 30–33, IPO SOIGSMI, Vladikavkaz, Russia, 2008.

[69] A. Savitzky and M. J. E. Golay, "Smoothing and differentiation of data by simplified least squares procedures," *Analytical Chemistry*, vol. 36, no. 8, pp. 1627–1639, 1964.

[70] C. Chree and J. M. Stagg, "Recurrence phenomena in terrestrial magnetism," *Philosophical Transactions of the Royal Society of London A*, vol. 227, pp. 21–62, 1928.

[71] G. S. Katinas, G. Cornelissen, O. Schwartzkopff, and F. Halberg, "Visualization of amplitude-phase relationships in entrainment processes," *Bulletin of Peoples' Friendship University of Russia. Series Medical*, no. 2, pp. 13–22, 2012.

[72] G. S. Katinas, O. V. Mamontov, A. O. Konrady et al., "Optimization of chronotherapy of hypertension according to ambulatory blood pressure monitoring (ABPM) after modeling circadian rhythms (CR) by means of Sawittzky-Goley filters," in *Proceedings of the 14th International Society for Holter and Noninvasive Electrocardiology (ISHNE '11)*, vol. 8, Moscow, Russia, April 2011.

[73] F. Halberg, E. Halberg, and K. Shankaraiah, "Circadian monitoring and plexo-serial linear-nonlinear rhythmometry of

systolic and diastolic blood pressure and pulse in the elderly," *Chronobiologia*, vol. 8, article 186, 1981.

[74] M. Keenan, W. März, and F. Halberg, "Automatic 7-day monitoring of human blood pressure (BP) in health," *Journal of the Minnesota Academy of Science*, vol. 51, article 14, 1986.

[75] K. T. Borer, G. Cornélissen, and F. Halberg, "Week-long blood pressure monitoring for reference values and diagnosis of disease risk syndromes," in *Proceedings of the 7th Meeting of the Society for Research on Biological Rhythms*, Jacksonville, Fla, USA, May 2000.

[76] F. Halberg, G. Katinas, G. Cornélissen et al., "Ambulatory blood pressure monitoring: the need of 7-day record," *Scripta Medica*, vol. 78, no. 2, pp. 83–88, 2005.

[77] F. Halberg, G. Cornélissen, G. S. Katinas et al., "Need to implement minimal standards in dealing with blood pressure and heart rate for prehabilitation a resolution proposed for a consensus in Moscow," People's Friendship University of Russia, Moscow, Russia, Series Medical Physiology, vol. 6, pp. 40–46, 2007.

[78] S. M. Chibisov and G. S. Katinas, "Circadian rhythms of the heart before and after electric cardioversion," 2008, Contemporary high-tech technologies 6: 40-41 http://www.rae.ru/snt/?section=content&op=show_article&article_id=4843.

[79] S. M. Chibisov, G. S. Katinas, and F. Halberg, "Chronostructure of biorhythms of heart before and after electric cardioversion," in *Proceedings of the 1st Russian Congress of Chronobiology and Chronomedicine*, pp. 55–58, IPO SOIGSMI, Vladikavkaz, Russia, 2008.

[80] S. M. Chibisov, S. I. Rapoport, and G. S. Katinas, "Multy-day arterial blood pressure and heart rate monitoring at paroxysmal atrial fibrillation," *Klin Med (Mosk)*, no. 3, pp. 68–70, 2009.

[81] F. Halberg, T. K. Breus, G. Cornélissen et al., "International womb-to-tomb chronome initiative group. Chronobiology in space. Keynote," in *Proceedings of the 37th Annual Meeting of Japanese Society Aerospace Environmental Medicine*, 1, University Minnesota/Medtronic Chronobiology Seminar, Nagoya, Japan, November 1991.

[82] G. Cornélissen, G. G. Klee, O. Sullivan M et al., "International womb-to-tomb chronome initiative group: toward a chronotherapy of high blood pressure and cancer," University of Minnesota/Medtronic Chronobiology Seminar Series 4, 1991.

[83] F. Halberg, G. Cornélissen, and International Womb-to-Tomb Chronome Initiative Group, "Fairy tale or reality?" in *Resolution from a Meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation)*, vol. 8 of *Medtronic Chronobiology Seminar*, Brussels, Belgium, March 1995.

[84] G. Cornélissen, E. Haus, and F. Halberg, "Chronobiologic blood pressure assessment from womb to tomb," in *Biologic Rhythms in Clinical and Laboratory Med*, Y. Touitou and E. Haus, Eds., pp. 428–452, Springer, Berlin, Germany, 1994.

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Review Article

Comparison of Atrial Fibrillation in the Young versus That in the Elderly: A Review

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The incidence and prevalence of atrial fibrillation (AF) are projected to increase significantly worldwide, imposing a significant burden on healthcare resources. The disease itself is extremely heterogeneous in its epidemiology, pathophysiology, and treatment options based on individual patient characteristics. Whilst ageing is well recognised to be an independent risk factor for the development of AF, this condition also affects the young in whom the condition is frequently symptomatic and troublesome. Traditional thinking suggests that the causal factors and pathogenesis of the condition in the young with structurally normal atria but electrophysiological "triggers" in the form of pulmonary vein ectopics leading to lone AF are in stark contrast to that in the elderly who have AF primarily due to an abnormal substrate consisting of fibrosed and dilated atria acting in concert with the pulmonary vein triggers. However, there can be exceptions to this rule as there is increasing evidence of structural and electrophysiological abnormalities in the atrial substrate in young patients with "lone AF," as well as elderly patients who present with idiopathic AF. These reports seem to be blurring the distinction in the pathophysiology of so-called idiopathic lone AF in the young versus that in the elderly. Moreover with availability of improved and modern investigational and diagnostic techniques, novel causes of AF are being reported thereby seemingly consigning the diagnosis of "lone AF" to a rather mythical existence. We shall also elucidate in this paper the differences seen in the epidemiology, causes, pathogenesis, and clinical features of AF in the young versus that seen in the elderly, thereby requiring clearly defined management strategies to tackle this arrhythmia and its associated consequences.

1. Epidemiology

There has been a worldwide increase in the ageing population, and as age is the most significant risk factor for AF, AF cases are predicted to reach nearly 16 million in the USA and 25 to 30 million in Europe by 2050 [1, 2]. The prevalence of AF shows a strong age dependence varying from 0.5% in patients aged <40 years to 5% in patients aged >65 years and nearly 10% amongst octogenarians [3–6]. Both the Framingham Heart Study and the Rotterdam Study estimated that the lifetime risk for development of AF in adults >40 years and at the age of 55 years respectively to be approximately 1 in 4 [7, 8]. The Cardiovascular Health Study which was a large population study of 5201 elderly adults (age ≥ 65 years) showed an incidence of 17.6 and 42.7 events per 1000 person-years amongst men aged 65 to 74 years and 75 to 84 years, respectively, whereas amongst women in the corresponding age groups, the incidences were 10.1 and 21.6 [9]. The SAFE study which was a UK-based multicentre randomised control trial of elderly (≥65 years) patients with AF showed an overall prevalence of 7.2% and 10.3% in those aged 75 years and older, with a 1.6% yearly incidence of new AF [10].

AF in the young in the absence of identifiable causes can be idiopathic or termed as "lone AF," that is, not associated with comorbidities or obvious cardiac disease. The term "lone AF," itself was first described nearly sixty years back by Evans and Swann [11]. Traditionally the cut-off age of 60 years has also been included in the diagnosis of lone AF as suggested by ACC/AHA/ESC guidelines [12] and

used previously in several landmark epidemiological studies such as the Framingham Heart Study [13] and the Mayo Clinic Study [14]. Old age is indeed one of the strongest risk factors for AF [6] but terming adults over 60 years as "elderly" seems rather controversial in this modern age of improving longevity. The rationale for this "threshold age" therefore has to be questioned [15]. At variance with this age-based definition of lone AF, studies such as that by Kopecky et al. have analysed the outcome of lone AF in patients aged over 61 years, mean age 74 years (range, 61–97 years) [16]. As newer aetiologies are uncovered and the existence of "truly lone AF" becomes increasingly controversial [17–19], the prevalence of "lone AF" also seems to be steadily "decreasing" in modern studies. A recent study of 3978 AF patients from the Euro Heart Survey by Weijs et al. that excluded age or left atrial size from the definition reported a prevalence of idiopathic AF of 3% out of 3978 patients [20]. The mean age of patients with idiopathic AF in this study was 58 (SD 14) years and nearly half of these (48%) were older than 60 years. Similarly a 30-year follow-up study reported by the Mayo Clinic reported that lone AF constituted only 2% of the total proportion of patients with AF [14]. In contrast, earlier studies showed that lone AF occurs in 1.6% to 30% of all cases of AF, depending on the definition of idiopathic AF or inclusion criteria used [13, 21–23].

2. AF Aetiology in the Young

Lone AF is a diagnosis of exclusion for which any clinical features of comorbidities or structural cardiac abnormalities that could cause AF must be ruled out. Novel risk factors for AF are increasingly being discovered such as genetic causes, lifestyle factors (such as alcohol consumption, personality traits, and smoking), body mass index, and physical activity, thereby all refuting the diagnosis of "lone AF." In addition, it can also be argued that occult cardiac pathologies such as hypertension or ischaemic heart disease may well be diagnosed in these patients if they are investigated thoroughly.

2.1. Familial. Nearly seven decades ago, Wolff described a case of familial AF in three brothers [24] and since then studies have found a positive family history of AF in up to a third of AF patients [25, 26]. Having a positive family history especially in younger patients nearly doubles the risk of developing AF [27]. In 1997, Brugada et al. described the first genetic locus on chromosome 10q22-24 in a family with AF segregated as an autosomal dominant trait [28]. In the last few years, genomewide association studies for AF have shown SNPs (small nuclear polymorphisms) at three genetic loci—4q25, 16q22, and 1q21 (reviewed in [29]). Monogenic forms of AF have also been described due to mutations of genes encoding for potassium channels (KCNQI, KCNE2, KCNJ2, and KCNA5), sodium channel gene SCN5A, K(ATP) gene, the ABCC9 gene, and the connexin 40 gene GJA5 [30–36]. Attempts to further unravel the interplay of genomics and AF have shown that the genetic basis of AF is both complex and heterogeneous.

2.2. Alcohol. The "holiday heart syndrome" was described in 1978 by Ettinger to explain the association between supraventricular tachyarrhythmias particularly AF and episodes of increased alcohol consumption during weekends and holiday binge drinking by people without structural heart disease [37]. Overall chronic heavy alcohol consumption (>36 g/day) has been shown to increase risk of AF in several studies including the Framingham cohort (reviewed in [17, 38]). Mechanisms of acute alcohol-induced AF include metabolic acidosis, catecholamine release, and electrolyte disturbances whereas chronic overconsumption leads to myocardial fibrosis, dilatation, and autonomic changes [38]. Binge drinking is particularly prevalent amongst young people and alcohol has been identified to potentiate paroxysmal AF in up to two-thirds of cases [39]. In the elderly, the relationship between AF and alcohol intake is more complex however. The Cardiovascular Health Study showed an inverse association between alcohol consumption and risk of AF in patients over 60 years old, with a 4% lower risk for each additional drink per week [9]. Other studies have also shown a lack of association between risk of developing AF and moderate alcohol consumption [40, 41].

2.3. Obesity. A meta-analysis by Wanahita et al looking at 16 studies that enrolled 123249 individuals (mean age 56 ± 2 years) demonstrated a 49% increased risk of developing AF due to obesity (relative risk 1.49, 95% CI 1.36–1.64) [42]. Obesity-associated left ventricular hypertrophy and left atrial dilation are postulated to be important causes which lead to AF [43, 44]. A 3–8% increased risk of developing AF has been associated with each unit increase in body mass index [45, 46]. Obstructive sleep apnoea which is also associated with obesity has been shown to portend risk of AF development in individuals <65 years of age [47]. The association between obesity and lone AF is not robust however [19] and in fact taller and leaner adults are reported to be more prone to develop lone AF [42, 48].

2.4. Sports and Physical Activity. AF has been recognised to be the commonest cause of palpitations amongst young athletes [49]. Endurance athletes such as marathon runners have been shown to have a greater predisposition to develop AF when compared to nonathletes [48, 50–52]. Karjalainen et al. diagnosed lone AF in 5.3% out of a cohort of 228 male cross-country runners (mean age 47.5 years) [53]. Mont et al. reported a four times higher proportion of sports enthusiasts who had lone AF (aged <65 years) in comparison to controls in a Catalonian population (63% versus 15%) [51]. The same group reported that >1500 lifetime hours is the threshold for increased AF propensity [52]. In more than half of the sportsmen with lone AF, a likely vagal precipitant was identified (postprandial, postexercise or at rest). Interestingly, in the recent GIRAFA study, cumulative work-related moderate-to-heavy physical activity has also been shown to predict risk of developing lone AF in middle aged men aged <65 years [48]. A meta-analysis of six case control studies, including 655 athletes and 895 controls (predominantly men), with a mean age of 51 ± 9 years showed

a significantly higher risk of AF in athletes (OR = 5.29; 3.57–7.85; $P = 0.0001$) [54]. Increased left atrial volume was shown to strongly predict AF in athletes [54]. Mechanisms for sports-induced AF postulated include enlarged left atrium and left ventricular mass [17], increased vagal tone leading to bradycardia as well as shorter atrial refractory period [17] and hypovolemia [55].

2.5. Cardiac Pathologies. There are a variety of cardiac pathologies associated with AF in the young. These include hypertrophic cardiomyopathy which confers a four-to sixfold greater risk of AF [56]. Prevalence of AF in these patients is relatively high at about 22% and incidence is 2% annually [56]. Even in this pathology, prevalence increases with age and is seen predominantly in the elderly (>60 years age) [56]. Congenital Heart Disease is another risk factor for AF and with improved surgical outcomes, increasing numbers of infants and children are surviving into adulthood. A large Quebec-based population study of about 38000 adult congenital heart disease patients, with a median age of 42 years, showed a prevalence of atrial arrhythmias of 15.1% (three times greater than that seen in the general population [57]). Wolff-Parkinson-syndrome, myocarditis, pericarditis, and dilated cardiomyopathy are some of the other causes of AF in the young. Valvular heart disease secondary to rheumatic fever is also a significant cause of AF in the young in the developing world.

2.6. Other Risk Factors. Behavioural or emotional triggers such as Type A personality [58], stress [58], anger, and hostility in men [59] have also been shown to predispose to development of AF. Other risk factors associated with AF include increased coffee and nicotine consumption [17, 58, 60]. The association with caffeine intake is debatable however as a canine study showed inverse association between risk of AF and intravenous caffeine and no causative role was found in the Danish diet, cancer, and health study [61, 62]. Smoking has been shown to lead to atrial fibrosis which is well recognised to portend AF [63]. Endocrine causes of AF in the young include hyperthyroidism and phaeochromocytoma.

3. AF Aetiology in the Elderly

As shown in the Framingham Heart Study, AF is usually secondary to a variety of cardiac pathologies (ischaemic heart disease, heart failure, and valvular heart disease) as well as systemic disorders (hypertension, diabetes, hyperthyroidism) [6, 64]. This is particularly true in the elderly who also have an increased predisposition of these conditions. However even accounting for other comorbidities, ageing is the strongest independent risk factor that predisposes to AF [6, 65]. The Cardiovascular Health Study showed that the prevalence of AF was 9.1% in the subgroup with clinical cardiovascular disease, 4.6% in the subgroup with only subclinical cardiovascular disease, and 1.6% in the absence of clinical or subclinical cardiovascular disease (i.e., lone AF) [22]. Independent risk factors for AF in the elderly included age, treated systemic hypertension, congestive cardiac failure, valvular heart disease, stroke, enlarged left atria size, mitral or aortic valve dysfunction, echocardiographic features of diastolic dysfunction, and raised serum levels of NT-proBNP [22, 66, 67]. Hyperthyroidism is another cause of atrial fibrillation in the elderly and one study reports an AF incidence of 25% amongst hyperthyroid patients older than 60 years in comparison to 5% in those aged less than 60 years [68].

4. Pathophysiology of Lone AF

AF initiation and maintenance is the result of pulmonary vein repetitive activity (triggers), atrial abnormalities (substrate), and remodelling. Lone AF is likely to be initiated and maintained by the interplay of pulmonary vein ectopics and the posterior wall of the left atrium [69, 70]. Any substrate abnormalities noted have previously been attributed to AF-induced structural remodelling rather than deemed to have a causative role in initiating lone AF. There is increasing evidence however of structural as well as electrophysiological abnormalities in the substrate (i.e., atrium) as well in lone AF. For instance, atrial biopsies in such patients have shown fibrotic changes and even other occult pathologies such as myocarditis [71, 72]. More recently, electrophysiological studies in patients with a history of paroxysmal lone AF remote from the arrhythmia have also shown abnormalities strongly suggestive of dysfunctional atrial conduction involved in AF initiation and progression [73]. These include larger atrial volumes, longer effective refractory period, longer conduction time along linear catheters, longer bi-atrial activation time, slower conduction velocity, larger proportion of fractionated electrograms, longer corrected sinus node recover time, and lower mean atrial voltage [73]. Another study of early onset lone AF patients (age less than forty years old) showed a significant difference in P wave morphology thereby implying abnormal interatrial conduction [74]. These findings seem to implicate a causative role for altered atrial electrophysiology in initiating lone AF. However as AF-induced electrical remodelling is well recognised to start early within a few hours of the onset of AF [75], there remains the possibility that these changes could be secondary to very early remodelling. For instance, previous experiments in a goat model of paroxysmal AF by Garratt et al. showed that it takes between 5 days to 4 weeks to develop changes in atrial substrate which then self-perpetuate AF [76, 77]. A variety of studies have also implicated inflammation in having an aetiological role in the initiation and perpetuation of atrial fibrillation due to evidence of raised inflammatory markers such as interleukin-6 and C-reactive protein in AF patients [78, 79]. In view of the multiple confounding factors and comorbidities associated with inflammation, the jury is still out whether it is a cause or consequence of AF [80]. Structural remodelling as a consequence of AF can cause calcium overload and atrial myocyte apoptosis leading to an inflammatory response [81]. In lone AF patients, there have been contradictory results such as from a large study by Ellinor et al. that showed no difference in high sensitive CRP [82] but others have noted high levels of CRP and high sensitive CRP in lone AF patients [83, 84]. Significantly, however, Aviles et al. included patients with hypertension in their

definition of lone AF albeit with overtly structurally normal hearts. This could have been a significant confounding factor as hypertension itself is associated with inflammation [83]. Myocardial perfusion imaging in patients with lone recurrent AF has shown isolated perfusion abnormalities indicative of microvascular dysfunction [85]. Echocardiography has also shown evidence of left ventricular diastolic dysfunction in patients thought to have idiopathic AF [86].

5. Electrophysiological and Structural Alterations in Aged Atria

5.1. Initiation of AF in the Aged Atria. A number of studies (summarised in Table 1) have attempted to unravel the atrial electrophysiological characteristics of aged atria in relation to AF. Whilst most animal and human studies have shown that aged atria have an increased propensity to develop AF [87–93], some studies in elderly AF patients have yielded conflicting results although these could have been influenced by underlying pathology or treatment in patients [94–96]. Increased atrial ERP has been noted in these studies which could be sufficient to overcome any other arrhythmogenic remodelling. There is therefore a need to understand, in the absence of underlying disease, how AF is initiated and maintained in the aged atria.

5.2. Initiation of AF. Why the aged atria are more susceptible to the development of AF in the absence of other risk factors remains poorly understood. We shall describe below how ageing may increase the propensity of both (i) triggered activity in the form of DADs and (ii) reentrant circuits.

5.3. Delayed after Depolarizations (DADs) in the Aged Atria. Potential contributory factors that may predispose to DAD formation and indeed the increased incidence of DADs have been demonstrated in some models of ageing [90, 93]. Wongcharoen et al. observed DADs of greater amplitude in aged rabbit LA pulmonary vein sleeve tissue sections associated with an increase in NCX protein which would provide an additional means to facilitate triggered activity as more depolarising current would flow during any spontaneous Ca^{2+} release and therefore, all things being equal, a smaller spontaneous release would produce a bigger DAD [90]. Some other studies have also described evidence of atrial calcium mishandling in AF (Table 1) [97]. This has been attributed to protein kinase A-induced hyperphosphorylation leading to dysfunctional ryanodine receptor [98]. While decreased SERCA and increased RyR protein expression give us clues to SR function, it would also be of interest to understand how SR Ca^{2+} content responds to age in the pulmonary vein. One study using human atrial tissue from elderly patients (mean age 68 years) has suggested that hyperphosphorylation of phospholamban could be contributory to leaky ryanodine receptors and thus abnormal calcium handling in chronic AF patients [99]. Clearly there is a pressing need to understand how Ca^{2+} homeostasis is achieved in the aged atria and how it is subsequently remodelled in the aged atria in AF.

5.4. Reentrant Circuits in the Aged Atria. A reentrant substrate can result from altered functional (electrical) properties or structural changes to the atrium and these are discussed below with reference to ageing.

5.4.1. Effective Refractory Period (ERP). Whilst conflicting results have been noted when analysing the effects of ageing on effective refractory period in both human [95, 96, 100, 101] as well as animal right atria [92, 102, 103], review of various studies indicates that the right atrial ERP is prolonged with ageing [104]. Inconsistency in the literature may relate to variation in anatomical sites studied [105] and, in terms of patient studies, the effects of underlying disease, arrhythmias, drug treatment, or a general lack of studies including very elderly patients as highlighted by Dun and Boyden [104]. The few studies investigating action potential duration (APD) or ERP in aged left atrium also show conflicting results [106, 107]. Furthermore in rabbit pulmonary vein sleeves and left atrial posterior wall APD was prolonged with age [90, 91]. Electrical characteristics and age-associated remodelling of the atrium appear to be region specific [93] and this may underlie differences between the above studies. Interestingly while the prolonged action potential in aged rabbit left atrial posterior wall may be expected to be anti-arrhythmogenic, this gave rise to an increase in APD dispersion (discussed below) which was suggested to potentiate AF [91].

Many ion channels have yet to be studied in the aged atria and work mainly performed in the dog has shown that there is no age-related change in sodium current density [108]. However $I_{Ca\text{-}L}$ is depressed, which would be expected to depress the plateau of the action potential [92], and since repolarising currents activate more strongly at positive potentials, this may slow activation and prolong repolarisation, thus prolonging ERP. Of the repolarising currents only I_{to} has been assessed and peak as well as sustained I_{to} was increased with age in the right atrium [109] but not the left atrium [104]. Indirect evidence suggests I_{KACH} may be enhanced in the right atrium with age [103]; however there are no studies investigating age-associated changes in I_{K1}, I_{Kur}, I_{Kr} and I_{Ks}, in either atria.

5.4.2. Conduction Velocity. A number of studies have reported age-associated general or directional conduction slowing and resultant spiral-reentrant waves in the right atria mainly in tissue strips but also *in vivo* in various species [100, 111]. In the aged dog, conduction of normal beats was unaltered but premature impulses were slowed suggesting a certain amount of depolarizing current is needed to overcome conduction discontinuities in age [92]. By calculating conduction in the direction of the wavefront, Kojodjojo et al. have shown in human atria that increasing age is associated with decreased propagation velocity in both atria during sinus rhythm and also during pacing [107]. In this respect the reduction of I_{Na} noted in AF [112, 113] is potentially significant as it will slow conduction velocity and reduce the excitation wavelength. Based on a very limited number of studies the effects of ageing on peak I_{Na} are inconsistent, showing either no change at low stimulation frequencies but

Table 1: Studies investigating relationship between atrial electrophysiological changes and ageing.

Authors	Species	Characteristics	Key findings
Brembilla-Perrot et al. [96]	Human	Patients aged >70 years versus younger	Decreased AF inducibility due to increased atrial ERP
Centurión et al. [89]	Human	Patients with paroxysmal AF during sinus rhythm aged >60 years versus younger	Greater mean number of abnormal right atrial electrograms defined as ≥100 msec duration and, or showing eight fragmented deflections
Roberts-Thomson et al. [87]	Human	Patients aged >60 years versus younger	Greater number of complex fractionated electrograms
Sakabe et al. [94]	Human	Patients without a history of AF or structural heart disease	No relationship between age and inducibility of AF
		Calcium mishandling	
El-Armouche et al. [99]	Human	Western blotting used to assess phosphorylation levels of Ca handling proteins in right atrial appendage	Hyperphosphorylation of phospholamban could be contributory to leaky ryanodine receptors and thus abnormal calcium handling in chronic AF patients
Hove-Madsen et al. [97]	Human	Age > 66 years	Higher calcium spark frequency and higher incidence of spontaneous calcium waves in comparison to patients with sinus rhythm
Ono et al. [88]	Rats	Old versus young rats	Glycolytic inhibition has been shown to result in spontaneous AF due to calcium mishandling and early after depolarisation-induced triggered activity
Wongcharoen et al. [90]	Rabbits	Responses of pulmonary vein tissues to rapamycin, FK-506, and ouabain in young and aged rabbits	Increased pulmonary vein arrhythmogenesis secondary to ryanodine receptor dysfunction-resultant calcium mis-handling
		Atrial ERP	
Kistler et al. [100]	Human	Electrophysiological and electroanatomical studies in 3 age groups (≥60 years, 31–59 years, and ≤30 years)	Age-associated electrical and structural remodeling (regional conduction slowing, increase in atrial ERP, impaired sinus node function, conduction delay at crista terminalis, and areas of low voltage)
Brembilla-Perot et al. [96]	Human	734 patients (age 16–85 years, mean 61 ± 15 years)	Increased atrial ERP and age >70 years independently predicted reduced AF inducibility
Brorson and Olsson [101]	Human	Right atrial monophasic action potentials recorded in 40 healthy males	No age correlation
Anyukhovsky et al. [92]	Dogs	Young versus old canine atrial	Age-related differences in action potential contour, decreased I_{CaL}, and slower conduction of early premature beats
Huang et al. [106]	Rats	Adult, middle aged versus aged rats	Age-associated prolongation of the monophasic action potential (mAP) and ERP in the right atrium, but a decrease in mAP and ERP in the left atrium, suggesting a potential reentrant mechanism for AF
Kojodjojo et al. [107]	Humans	Most study subjects suffered from atrioventricular reentrant arrhythmias, syncope, or palpitations and hence these atria were not "healthy"	No change in left atrial ERP with ageing
Michelucci et al. [105]	Humans	17 normal subjects (age range 17–78 years)	Age-related increase in right atrial ERP
Su et al. [103]	Rats	Adults versus aged rats	In response to muscarinic stimulation, ageing-related prolongation of atrial maximum diastolic potential but not of APD
Toda [102]	Rabbit	Rabbit ages varied from 2–360 days old	Age-related prolongation of APD

Table 1: Continued.

Authors	Species	Characteristics	Key findings
		Ion channel remodelling in ageing and AF	
I_{CaL} Anyukhovsky et al. [92]	Canine atria		Reduced I_{CaL}
I_{Na} Baba et al. [108]	Canine atria		(i) Peak current unchanged at low stimulation frequencies but reduced at stimulation frequencies relevant to AF
Wu et al. [110]	Rabbit atria		(ii) Decreased in hyperlipidemic aged rabbits
I_{to} Dun et al. [109]	Canine atrium		Increased in the left atrium
I_{KAch} Su et al. [103]	Rat		Indirect evidence of increase [104]

reduced at stimulation frequencies relevant to AF (10 Hz) [108] or a decrease [110].

Changes in connexin expression (especially Cx40 and Cx43) have been noted in AF-related remodelling [114] and are also noted in ageing [115]. A single study has shown an age-associated decrease in connexin 43 in the sinoatrial node but unaltered expression of connexins in the right atria [115]. However a change in the distribution of connexins away from the lateral cell edges to the intercalated discs has also been noted in ageing [116]. This is potentially significant, as it will result in anisotropic propagation of excitation and the formation of reentrant circuits [114, 117].

Increased or heterogeneous fibrosis, often associated with advancing age [92, 111], can disrupt the coupling between individual myocytes and result in non homogenous conduction or conduction slowing which can lead to re-entry (for review see [118]). Recent work has demonstrated increased AF stability in long-term AF in goats due to "microfibrosis" separating myocyte bundles [119]. Conduction abnormalities can occur following redistribution without altered expression [120].

5.4.3. Dispersion of Conduction Velocity and ERP. ERP dispersion and conduction heterogeneity correlate with AF inducibility and both have been shown to increase with ageing [91, 93, 105].

In summary, what induces and sustains AF in the young may be different to that in the old. Anyukhovsky et al. showed in old dogs that atrial tissue was depolarised, with longer APD and a slower max upstroke and greater variability in APD. In chronic AF both young and old, the atrial cell membrane was hyperpolarised, with slowed upstroke and decreased APD. But chronic AF led to an increase of APD dispersion in adults and a decrease in old dogs. Thus, AF was sustained in two different substrates: one with short AP duration and with expanded heterogeneity of AP parameters (adult) and one with short AP duration but limited heterogeneity (old). These data also suggest that the increased dispersion in atrial electrophysiology that occurs in adults may be an important additional contributory factor for AF stabilization at this age, while the occurrence of fibrosis and slowed conduction of premature beats that has been demonstrated previously may be more contributory in the old. Table 2 summarises the atrial electrophysiological differences between the elderly versus the young in relationship to the propensity to develop AF.

Histological changes in healthy elderly patients with AF include increased deposition of collagen, adipose tissue and amyloid, atrophy and vacuolar myocyte degeneration and fibrofatty substitution of the sinoatrial node (reviewed in [118]). Aging-related oxidative damage has been shown to portend atrial fibrillation through mitochondrial bioenergetic dysfunction [121]. Imaging studies have also shown age-related dilatation of the pulmonary veins and the atrium, thereby potentiating pulmonary vein triggers as well as substrate-induced AF maintenance through mechanoelectric feedback [122, 123].

6. Clinical Features

The clinical presentation of AF varies significantly depending on age and comorbidities. In the young, the initial presentation is usually with paroxysmal AF [124]; persistent AF under the age of 50 is often associated with identifiable causes like structural heart disease, hyperthyroidism, or alcohol excess. Whilst the incidence of both paroxysmal and persistent AF increases dramatically over the age of 60, there is a disproportionate increase in chronic forms [125], with the result that 80% of newly diagnosed AF in octogenarians is of a persistent or permanent form, even in the absence of structural heart disease [126]. Moreover, advanced age is a risk factor for early recurrence after first AF presentation and of rapid progression from paroxysmal to persistent AF [125, 127].

AF is classically associated with "typical" symptoms of irregular palpitations, with or without chest pain, breathlessness, or dizziness. Palpitations are reported in 80% of young patients with paroxysmal AF. [128]. In contrast, less than 10% of AF patients over the age of 80 years have palpitations [129] and up to 40% of elderly hospital inpatients found to have AF are entirely asymptomatic [130]. Whilst atypical chest pain is relatively common in young AF patients, in elderly patients anginal chest pain during AF episodes strongly suggests the presence of significant concurrent coronary disease [131] and might be sufficient to warrant investigation for coronary ischaemia even in the absence of typical symptoms of angina.

AF in elderly patients is frequently diagnosed coincidentally during general health assessment, hospital admission for

Table 2: Electrophysiological differences between the elderly and young that can predispose to AF (summarised from human and animal studies in Table 1).

Features	Elderly	Young
Impulse initiation		
(i) Sinus node function	Impaired (leading to longer sinus node recovery times), contributing to abnormal impulse initiation	Generally preserved
(ii) Pulmonary vein ectopic activity	Also contributes to AF pathogenesis although substrate abnormalities have a dominant role in initiation and maintenance	Predominant trigger for AF initiation
Impulse conduction		
(i) P wave morphology and duration (usually signifying interatrial conduction)	Abnormal P wave morphology and prolonged interatrial conduction	Usually normal
(ii) Wavefront propagation	Abnormalities noted such as conduction slowing (particularly of premature impulses) thereby contributing to reentrant waves	Usually normal
Substrate abnormalities		
(i) Complex fractionated atrial electrograms	Greater number	Lesser than in elderly
(ii) Atrial refractoriness—effective Refractory Period (ERP)	ERP prolonged in the right atrium and could contribute to dispersion in refractoriness	Usually not prolonged
(iii) Action potential duration (APD)	Prolonged in the right atrium	Generally within normal limits
(iv) Regional atrial voltage differences	Larger atrial volumes with more number of low voltage areas	Atria usually of normal size and mean voltage within normal limits

nonrelated illnesses, or as a result of its complications [132]. A recent randomized controlled study in primary care suggests that implementing targeted opportunistic screening of over 65-year olds, based on a simple annual pulse assessment, is likely to be cost-effective in improving AF detection [10].

7. Management of AF

7.1. General Principles. The management of AF is concerned with two main aspects; symptom relief (through rate or rhythm control) and prevention of complications. Although certain complications, such as left ventricular dysfunction, may be reduced by these therapies, the prevention of thromboembolic events requires targeted and appropriate antithrombotic therapy. AF management including stroke prevention is dependent on multiple factors including patient age, comorbidities, and disease profile.

7.2. Stroke Risk, Bleeding Complications, and Anticoagulation. AF is associated with a 5-fold increase in the risk of strokes, and strokes due to AF are associated with higher mortality and worse functional outcome [133]. Age has a particularly dramatic impact on the risk of AF-associated stroke: between the ages of 50–59 the average lifetime risk is 5% and 3.9% for men and women, respectively, and this rises exponentially to 22.3% and 23.9% between 80 and 84 [134]. Vitamin K antagonists (usually warfarin) or other oral anticoagulants (see below) reduce the risk of strokes by around 60–70%, albeit at the risk of intracranial haemorrhage and other bleeding-related complications [135, 136].

AF in the context of mitral valve stenosis, or a prosthetic mitral valve, is considered to be extremely high risk, and anticoagulation is mandatory in the absence of clear contraindications [136]. For nonvalvular AF, the CHADS2 score was introduced in 2001 as a simple scoring system to assess the stroke risk (see Table 3) [137]. However, the influence of age is underestimated by the CHADS2 system; recent studies have indicated that, amongst moderate risk patients with a CHADS2 score of 1, individuals over the age of 75 with isolated AF are at a higher risk of stroke than are younger patients with a single additional risk factor [138, 139]. Therefore a more comprehensive scoring system called CHA(2)DS(2)VASc has been recommended in recent guidelines (see Table 4) [140]. By recognizing a spectrum of major and minor risk factors that warrant treatment with anticoagulation, this system more accurately identifies individuals at truly low risk and extends the use of anticoagulation into the previous medium risk category. Notably, using the CHA(2)DS(2)VASc, anticoagulation is considered to be potentially beneficial for all patients aged over 65 years, whilst the decision in younger patients depends on additional risk factors.

Although most AF patients are elderly, until recently these patients have been somewhat underrepresented in clinical trials of anticoagulation. The clinical benefit from

Table 3: CHADS2 scoring system [137].

	Comorbidity	Score
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75 years	1
D	Diabetes mellitus	1
S2	Stroke or TIA	2

CHADS2 score 0; annual stroke risk 1.9%, >1; annual stroke risk 2.8 = 18.2%.

anticoagulation not only persists but potentially increases with advanced age; for example, the recent ATRIA study demonstrated that AF patients aged over 75 years benefit most from warfarin treatment in terms of absolute and relative reduction in stroke rate [141]. Despite this clear evidence of benefit, anticoagulation is considerably underutilised in this age group, typically with only one-third of over 85s receiving appropriate therapy despite an absence of definite contraindications [142].

In physician studies, the most commonly reported concerns with anticoagulation are perceived bleeding risk and a history of falls [143]. Elderly patients certainly do have an increased risk of bleeding complications [144], and whilst all forms of bleed have a potential associated mortality and morbidity, the main concern is intracranial haemorrhage. Although this complication is relatively rare even in the elderly (<1% per year in the BAFTA trial of patients over 75 years old), nevertheless it constitutes 90% of anticoagulation-related deaths [145]. Careful monitoring and control of anticoagulation can improve this balance; the risk of intracranial haemorrhage is only modestly increased with a therapeutic INR between 2-3 but rises sixfold when the INR rises above 3.5. Conversely, targeting a subtherapeutic INR of <1.8 results in a sevenfold reduction in stroke prevention without a reduction in intracranial haemorrhage risk (thus equating to a loss of clinical effectiveness and worse outcomes). "Real-world" studies of anticoagulation in octogenarians, report that the risk of major bleeding (either fatal or requiring transfusion) is 13.1 per 100 patient-years [146]. Whilst this is higher than the rate of 4.7 per 100 patient years seen in younger patients, the highest risk of bleeding was seen in patients with a high CHADS2 score of ≥3. Thus patients who are at highest risk of bleeding are also those who potentially benefit the most in terms of stroke reduction, and the absolute risk reduction in stroke-related mortality exceeds the risk increase of fatal bleeds. The perceived risk of anticoagulation in patients with a history of falls is probably exaggerated; whilst there is a slight excess of nonintracranial bleeds in these individuals, a meta-analysis has calculated that a fall rate of at least 300 per year would be required to negate the stroke-prevention benefit [147].

Recently, guidelines have suggested the use of scoring systems such as HASBLED (see Table 5) in order to better assess bleeding risk prior to commencing anticoagulation. A score of ≥3 is considered to represent high risk of bleeding, and caution and careful monitoring recommended [148]. In view of the complexity of managing anticoagulation in the elderly, there has also been substantial interest in alternatives to oral vitamin K antagonists. However, it is clear that aspirin is significantly less effective than warfarin at preventing strokes, and there appears to be no net benefit over the age of 77 [139]. Recent consensus therefore advises against the use of aspirin for AF thromboprophylaxis [149]. As CHA(2)DS(2)VASc allows identification of patients with an exceedingly low stroke risk, aspirin is now considered to be a nonpreferred alternative for young patients with a single risk factor.

Recently there has been a surge of new anticoagulant alternatives to warfarin. These do not require regular monitoring of clotting profile. Dabigatran is a newly approved oral direct thrombin inhibitor. The RE-LY trial reported that high dose Dabigatran (150 mg b.d.) was more efficacious than warfarin with a similar risk of bleeding complications (intracranial and extracranial), whilst low dose Dabigatran (110 mg b.d.) was noninferior to warfarin with a reduced risk of bleeding [150]. These effects were consistent amongst young and elderly patient subgroups, although there was a slight excess of gastrointestinal bleeds in elderly patients taking higher dose [151]. This drug could therefore provide either improved stroke prevention when used in high doses in young patients or reduced bleeding risk at low doses in the elderly. Rivaroxaban (a factor Xa inhibitor) is another new anticoagulant. The ROCKET-AF trial reported non-inferiority to warfarin in nonvalvular AF, with no significant increase in major bleeding and a lesser incidence of intracranial and fatal bleeding in comparison to warfarin [152]. Of particular relevance to the elderly, the median age in this trial was 73 years (25% were ≥78 years). Apixaban, another factor Xa inhibitor, was reported last year in the Aristotle trial (median age 70 years) to be more efficacious than warfarin and also caused less bleeding [153].

7.3. Rate or Rhythm Control? There are two main strategies of management in AF rate control and rhythm control with either pharmacological or nonpharmacological options.

Pharmacological strategies of rate and rhythm control have been compared in multiple studies. Despite clear theoretical benefits of sinus rhythm in the form of improved atrioventricular dynamics and an improvement in cardiac output, there is no significant benefit of a rhythm control strategy in large randomised population studies. Although there have been few investigations exploring the strategies specifically in different age groups, results of five studies are relevant to a consideration of the elderly and have been included in a meta-analysis [154]; this demonstrates a clear trend towards increased mortality associated with a rhythm control strategy in the elderly. Interestingly, the excess deaths do not appear to relate to proarrhythmic effects or specific side effects of the trial drugs, but rather to other factors such as malignancies or lung disease. This suggests that in elderly frail patients, the use of powerful antiarrhythmic with complex drug interactions may uncover latent comorbidities in a form of nonspecific pharmacotoxicity.

Thus, current guidelines clearly favour a rate-control strategy in the elderly. Initial therapies might include either beta blockers or calcium channel blockers, with digoxin

Table 4: CHADS2VAS2C scoring system [140].

	Comorbidity	Points
C	Congestive heart failure (or left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S2	Prior stroke or TIA or thromboembolism	2
V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e., female gender)	1

Table 5: HASBLED scoring system [148].

Hypertension (BP > 160 without control)	1
Renal disease (dialysis, transplant, Cr > 2.6 mg/dL or >200 μmol/L)	1
Liver disease (cirrhosis, bilirubin > 2x normal, AST/ALT/AP > 3x normal)	1
Stroke	1
Predisposition to bleeding or previous major bleed	1
Labile INR (unstable/high INRs, <60% time in therapeutic range)	1
Age ≥ 65	1
Medications (antiplatelets or NSAIDS)	1
Alcohol excess	1
Risk of spontaneous major bleeding (episodes per 100 patient years)	
Score 0-1	1.02–1.13
Score 2-3	1.88–3.74
Score ≥ 4	≥8.7

added as appropriate where a second agent is necessary. Whilst previous guidelines emphasised the importance of tight control of ventricular rate (resting heart rate below 80 bpm), it has recently been demonstrated that equivalent outcomes are achieved with a less stringent target of 115 bpm [155]. In elderly patients, where issues such as coexisting conduction system disease, polypharmacology, and renal impairment are common, a more relaxed approach to rate control is likely to reduce the complexity of management, including the need for pacemaker implantation [156].

In patients with drug-refractory symptoms due to permanent AF, pacemaker implantation with atrioventricular node ablation results in symptomatic benefit for up to 83% of patients including those over the age of 70 [157]. Many elderly patients with AF have conduction system disease and pacemaker implantation is often indicated for bradycardic indications; AV node ablation in these patients also allows cessation of rate control medications. Moreover, AV node ablation and cardiac resynchronization therapy should also be appropriate where AF coexists with heart failure, with a recent meta-analysis demonstrating significant mortality benefit over pharmacological rate control [158].

Although large clinical studies do not clearly favour either a rate or rhythm control strategy, there are factors that suggest that certain subgroups may benefit from a rhythm control strategy. As older patients with comorbidities demonstrate an excess mortality due to drug-related side effects, so it is arguable that young and otherwise healthy patients should not experience these side effects and therefore experience the full benefits from restoration of sinus rhythm, including improved ventricular function, quality of life, and reduced progression to permanent AF. There is some evidence from studies focusing on younger patients suggesting this to be the case, and a convincing case that where a rhythm control strategy is effective, it is associated with reduced symptoms and improved mortality compared with rate control [159], although the data as yet do not suggest that anticoagulation can safely be withdrawn.

Factors associated with rapid progression of AF (advanced age and structural heart disease) are also associated with a poor response to rhythm control strategy. Recently, the HATCH scoring system (hypertension, age older than 75 years, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and heart failure) has been proposed to identify patients at risk of progression to persistent AF [127]; a HATCH score of ≥2 was associated with a high risk of disease progression despite antiarrhythmic therapy.

Where a rhythm control strategy is considered appropriate, treatment choices are guided by side effects and contraindications rather than expected efficacy. Where there is no underlying structural heart disease, appropriate first line options include dronedarone, flecainide, propafenone, and sotalol [160]. Although amiodarone is a more efficacious antiarrhythmic [161], it is associated with significant pulmonary, liver and thyroid toxicity with a cumulative and

Table 6: Common differences between AF in the young versus elderly.

	AF in the young	AF in elderly patients
Causes	(i) Idiopathic	(i) Ischaemic heart disease
	(ii) Genetic	(ii) Heart failure
	(iii) Alcohol, smoking	(iii) Valvular heart disease
	(iv) Personality traits	(iv) Hypertension
	(v) Body mass index	(v) Cardiomyopathies
	(vi) Endurance sports	(vi) Hyperthyroidism
	(vii) Cardiac pathologies	(vii) Secondary causes such as post operative, infection, pulmonary embolism
	(viii) Endocrine disorders	(viii) Idiopathic
Pathogenesis	Triggers/pulmonary vein Repetitive activity +++ Substrate/atrial abnormalities +	Pulmonary vein repetitive activity ++ Atrial Abnormalities +++
Clinical features	Usually typical symptoms	Atypical symptoms or asymptomatic
Management	Rhythm control preferred Thromboprophylaxis usually not required unless based on CHADS2VASC	Rate control preferred Thromboprophylaxis usually required unless contraindicated

dose-dependent risk; its long-term use in the young therefore requires very cautious consideration.

Dronedarone has recently emerged as an anti-arrhythmic therapy for paroxysmal AF. It appears to be somewhat less efficacious than amiodarone, but associated with less side effects [162]. The recent ATHENA [163] study suggested that dronedarone may impart a benefit in terms of reduced mortality and hospital admission compared to placebo in certain high risk patient groups, but data showing benefit over other anti-arrhythmic therapies are lacking. Importantly, it is also contra-indicated in patients with permanent AF or decompensated heart failure.

In recent years, the major advance in rhythm management has been in nonpharmacological therapy, namely, left atrial ablation. Since the first report by Haissaguerre et al. that pulmonary vein isolation reduced AF recurrence by eliminating spontaneous focal discharges from pulmonary veins that initiated AF, there have been significant advances in ablation techniques [70]. This treatment strategy is particularly efficacious in patients with lone AF and thus the European Society of Cardiology guidelines recommend left atrial ablation (Class IIa recommendation) for symptomatic patients with paroxysmal or persistent AF who have failed to respond to trial of anti-arrhythmic medication [160]. Whilst complications are reported in up to 5% of cases, multiple studies have demonstrated freedom from AF leading to significant improvements in symptoms and quality of life [164, 165]. Results in paroxysmal AF demonstrate that pulmonary vein isolation gives satisfactory symptom control and freedom from AF in around 70 to 80% patients; however, persistent AF generally requires more complicated procedures involving multiple lesions throughout the left atrium (success rates of 65–75%) [166]. Several studies have also demonstrated that catheter ablation is more effective than anti-arrhythmic therapy [167–169] at controlling symptoms as well as restoring sinus rhythm, although there is no firm evidence of benefit in terms of mortality or stroke prevention. Most studies have included patients only under the age of 65, although there have been some small studies suggesting that the procedures can be performed safely in older patients with structurally normal hearts [170].

8. Conclusion

To summarise, AF is a heterogeneous condition, with significant differences in its epidemiology, pathogenesis, clinical presentation and management across age groups (shown in Table 6). Older patients are more likely to have an abnormal substrate and present at an advanced stage with atypical symptoms and associated comorbidities. Whilst there have been a few reports of substrate abnormalities in young patients with idiopathic AF thereby implying a causative role, there is not yet conclusive evidence that these do not simply represent AF-induced atrial remodeling. With increasing recognition of rare aetiologies of what was previously deemed to be "idiopathic AF" and the archaic cut-off age to define "lone AF," the term "lone AF" itself is becoming increasingly obsolete. It is all the more pressing therefore to exclude any occult risk factors for AF as this could influence prognosis and management. The important differences between AF in the young and that in the elderly necessitate clearly defined diagnostic and targeted management strategies to relieve symptoms as well as to prevent complications.

Abbreviations

AF: Atrial fibrillation
APD: Action potential duration
ERP: Effective refractory period.

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References

[1] Y. Miyasaka, M. E. Barnes, B. J. Gersh et al., "Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence," *Circulation*, vol. 114, no. 2, pp. 119–125, 2006.

[2] H. Stefansdottir, T. Aspelund, V. Gudnason et al., "Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections," *Europace*, vol. 13, no. 8, pp. 1110–1117, 2011.

[3] H. Rutzen-Lopez, V. Khanna, and M. R. Reynolds, "Atrial fibrillation: epidemiology, prognosis and therapy," *Minerva Medica*, vol. 102, no. 3, pp. 187–207, 2011.

[4] K. Abusada, S. B. Sharma, R. Jaldai et al., "Epidemiology and management of new-onset atrial fibrillation," *American Journal of Managed Care*, vol. 10, supplement, pp. S50–S57, 2004.

[5] A. S. Go, E. M. Hylek, K. A. Phillips et al., "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study," *Journal of the American Medical Association*, vol. 285, no. 18, pp. 2370–2375, 2001.

[6] E. J. Benjamin, D. Levy, S. M. Vaziri, R. B. D'Agostino, A. J. Belanger, and P. A. Wolf, "Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study," *Journal of the American Medical Association*, vol. 271, no. 11, pp. 840–844, 1994.

[7] D. M. Lloyd-Jones, T. J. Wang, E. P. Leip et al., "Lifetime risk for development of atrial fibrillation: the framingham heart study," *Circulation*, vol. 110, no. 9, pp. 1042–1046, 2004.

[8] J. Heeringa, D. A. M. Van Der Kuip, A. Hofman et al., "Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study," *European Heart Journal*, vol. 27, no. 8, pp. 949–953, 2006.

[9] B. M. Psaty, T. A. Manolio, L. H. Kuller et al., "Incidence of and risk factors for atrial fibrillation in older adults," *Circulation*, vol. 96, no. 7, pp. 2455–2461, 1997.

[10] F. D. R. Hobbs, D. A. Fitzmaurice, J. Mant et al., "A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study," *Health Technology Assessment*, vol. 9, no. 40, pp. 3–5, 2005.

[11] W. Evans and P. Swann, "Lone auricular fibrillation," *British Heart Journal*, vol. 16, pp. 189–194, 1954.

[12] V. Fuster, L. E. Ryden, D. S. Cannom et al., "ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society," *Circulation*, vol. 114, no. 7, pp. e257–e354.

[13] F. N. Brand, R. D. Abbott, W. B. Kannel, and P. A. Wolf, "Characteristics and prognosis of lone atrial fibrillation. 30 year follow-up in the Framingham study," *Journal of the American Medical Association*, vol. 254, no. 24, pp. 3449–3453, 1985.

[14] A. Jahangir, V. Lee, P. A. Friedman et al., "Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study," *Circulation*, vol. 115, no. 24, pp. 3050–3056, 2007.

[15] L. Frost, "Lone atrial fibrillation: good, bad, or ugly?" *Circulation*, vol. 115, no. 24, pp. 3040–3041, 2007.

[16] S. L. Kopecky, B. J. Gersh, M. D. McGoon et al., "Lone atrial fibrillation in elderly persons: a marker for cardiovascular risk," *Archives of Internal Medicine*, vol. 159, no. 10, pp. 1118–1122, 1999.

[17] B. A. Schoonderwoerd, M. D. Smit, L. Pen, and I. C. Van Gelder, "New risk factors for atrial fibrillation: causes of 'not-so-lone atrial fibrillation'," *Europace*, vol. 10, no. 6, pp. 668–673, 2008.

[18] D. G. Wyse, "Idiopathic atrial fibrillation: a rose by any other name?" *Europace*, vol. 14, no. 2, pp. 151–152, 2012.

[19] D. Kozlowski, S. Budrejko, G. Y. H. Lip et al., "Lone atrial fibrillation: what do we know?" *Heart*, vol. 96, no. 7, pp. 498–503, 2010.

[20] B. Weijs, R. Pisters, R. Nieuwlaat et al., "Idiopathic atrial fibrillation revisited in a large longitudinal clinical cohort," *Europace*, vol. 14, no. 2, pp. 184–190, 2012.

[21] S. L. Kopecky, B. J. Gersh, and M. D. McGoon, "The natural history of lone atrial fibrillation. A population-based study over three decades," *New England Journal of Medicine*, vol. 317, no. 11, pp. 669–674, 1987.

[22] C. D. Furberg, B. M. Psaty, T. A. Manolio et al., "Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study)," *American Journal of Cardiology*, vol. 74, no. 3, pp. 236–241, 1994.

[23] S. Lévy, M. Maarek, P. Coumel et al., "Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study," *Circulation*, vol. 99, no. 23, pp. 3028–3035, 1999.

[24] L. Wolff, "Familial auricular fibrillation," *The New England Journal of Medicine*, vol. 229, pp. 396–398, 1943.

[25] D. Darbar, K. J. Herron, J. D. Ballew et al., "Familial atrial fibrillation is a genetically heterogeneous disorder," *Journal of the American College of Cardiology*, vol. 41, no. 12, pp. 2185–2192, 2003.

[26] P. T. Ellinor, D. M. Yoerger, J. N. Ruskin, and C. A. MacRae, "Familial aggregation in lone atrial fibrillation," *Human Genetics*, vol. 118, no. 2, pp. 179–184, 2005.

[27] C. S. Fox, H. Parise, R. B. D'Agostino et al., "Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring," *Journal of the American Medical Association*, vol. 291, no. 23, pp. 2851–2855, 2004.

[28] R. Brugada, T. Tapscott, G. Z. Czernuszewicz et al., "Identification of a genetic locus for familial atrial fibrillation," *New England Journal of Medicine*, vol. 336, no. 13, pp. 905–911, 1997.

[29] M. F. Sinner, P. T. Ellinor, T. Meitinger, E. J. Benjamin, and S. Kääb, "Genome-wide association studies of atrial fibrillation: past, present, and future," *Cardiovascular Research*, vol. 89, no. 4, pp. 701–709, 2011.

[30] Y. H. Chen, S. J. Xu, S. Bendahhou et al., "KCNQ1 gain-of-function mutation in familial atrial fibrillation," *Science*, vol. 299, no. 5604, pp. 251–254, 2003.

[31] Y. Yang, M. Xia, Q. Jin et al., "Identification of a KCNE2 gain-of-function mutation in patients with familial atrial fibrillation," *American Journal of Human Genetics*, vol. 75, no. 5, pp. 899–905, 2004.

[32] M. Xia, Q. Jin, S. Bendahhou et al., "A Kir2.1 gain-of-function mutation underlies familial atrial fibrillation," *Biochemical and Biophysical Research Communications*, vol. 332, no. 4, pp. 1012–1019, 2005.

[33] T. M. Olson, A. E. Alekseev, X. K. Liu et al., "Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation," *Human Molecular Genetics*, vol. 15, no. 14, pp. 2185–2191, 2006.

[34] L. Y. Chen, J. D. Ballew, K. J. Herron, R. J. Rodeheffer, and T. M. Olson, "A common polymorphism in SCN5A is associated with lone atrial fibrillation," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 1, pp. 35–41, 2007.

[35] M. H. Gollob, D. L. Jones, A. D. Krahn et al., "Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation," *New England Journal of Medicine*, vol. 354, no. 25, pp. 2677–2688, 2006.

[36] T. M. Olson, A. E. Alekseev, C. Moreau et al., "KATP channel mutation confers risk for vein of Marshall adrenergic atrial fibrillation," *Nature Clinical Practice Cardiovascular Medicine*, vol. 4, no. 2, pp. 110–116, 2007.

[37] P. O. Ettinger, C. F. Wu, C. De La Cruz Jr., A. B. Weisse, S. S. Ahmed, and T. J. Regan, "Arrhythmias and the 'holiday heart': alcohol associated cardiac rhythm disorders," *American Heart Journal*, vol. 95, no. 5, pp. 555–562, 1978.

[38] C. E. B. Balbão, A. A. V. de Paola, and G. Fenelon, "Effects of alcohol on atrial fibrillation: myths and truths," *Therapeutic Advances in Cardiovascular Disease*, vol. 3, no. 1, pp. 53–63, 2009.

[39] S. R. Lowenstein, P. A. Gabow, and J. Cramer, "The role of alcohol in new-onset atrial fibrillation," *Archives of Internal Medicine*, vol. 143, no. 10, pp. 1882–1885, 1983.

[40] K. J. Mukamal, B. M. Psaty, P. M. Rautaharju et al., "Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study," *American Heart Journal*, vol. 153, no. 2, pp. 260–266, 2007.

[41] G. M. Marcus, L. M. Smith, D. Whiteman et al., "Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period," *Pacing and Clinical Electrophysiology*, vol. 31, no. 3, pp. 266–272, 2008.

[42] N. Wanahita, F. H. Messerli, S. Bangalore, A. S. Gami, V. K. Somers, and J. S. Steinberg, "Atrial fibrillation and obesity—results of a meta-analysis," *American Heart Journal*, vol. 155, no. 2, pp. 310–315, 2008.

[43] T. J. Wang, H. Parise, D. Levy et al., "Obesity and the risk of new-onset atrial fibrillation," *Journal of the American Medical Association*, vol. 292, no. 20, pp. 2471–2477, 2004.

[44] C. S. Ku, S. L. Lin, D. J. Wang, S. K. Chang, and W. J. Lee, "Left ventricular filling in young normotensive obese adults," *American Journal of Cardiology*, vol. 73, no. 8, pp. 613–615, 1994.

[45] L. Frost, L. J. Hune, and P. Vestergaard, "Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study," *American Journal of Medicine*, vol. 118, no. 5, pp. 489–495, 2005.

[46] S. Dublin, B. French, N. L. Glazer et al., "Risk of new-onset atrial fibrillation in relation to body mass index," *Archives of Internal Medicine*, vol. 166, no. 21, pp. 2322–2328, 2006.

[47] A. S. Gami, D. O. Hodge, R. M. Herges et al., "Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation," *Journal of the American College of Cardiology*, vol. 49, no. 5, pp. 565–571, 2007.

[48] L. Mont, D. Tamborero, R. Elosua et al., "Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individualsEuropace," vol. 10, no. 1, pp. 15–20, 2008.

[49] F. Furlanello, A. Bertoldi, M. Dallago et al., "Atrial fibrillation in elite athletes," *Journal of Cardiovascular Electrophysiology*, vol. 9, no. 8, supplement, pp. S63–S68, 1998.

[50] L. Molina, L. Mont, J. Marrugat et al., "Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study," *Europace*, vol. 10, no. 5, pp. 618–623, 2008.

[51] L. Mont, A. Sambola, J. Brugada et al., "Long-lasting sport practice and lone atrial fibrillation," *European Heart Journal*, vol. 23, no. 6, pp. 477–482, 2002.

[52] R. Elosua, A. Arquer, L. Mont et al., "Sport practice and the risk of lone atrial fibrillation: a case-control study," *International Journal of Cardiology*, vol. 108, no. 3, pp. 332–337, 2006.

[53] J. Karjalainen, U. M. Kujala, J. Kaprio, S. Sarna, and M. Viitasalo, "Lone atrial fibrillation in vigorously exercising middle aged men: case-control study," *British Medical Journal*, vol. 316, no. 7147, pp. 1784–1785, 1998.

[54] J. Abdulla and J. R. Nielsen, "Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis," *Europace*, vol. 11, no. 9, pp. 1156–1159, 2009.

[55] J. D. Edwards and R. G. Wilkins, "Atrial fibrillation precipitated by acute hypovolaemia," *British Medical Journal*, vol. 294, no. 6567, pp. 283–284, 1987.

[56] I. Olivotto, F. Cecchi, S. A. Casey, A. Dolara, J. H. Traverse, and B. J. Maron, "Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy," *Circulation*, vol. 104, no. 21, pp. 2517–2524, 2001.

[57] J. Bouchardy, J. Therrien, L. Pilote et al., "Atrial arrhythmias in adults with congenital heart disease," *Circulation*, vol. 120, no. 17, pp. 1679–1686, 2009.

[58] A. V. Mattioli, S. Bonatti, M. Zennaro, and G. Mattioli, "The relationship between personality, socio-economic factors, acute life stress and the development, spontaneous conversion and recurrences of acute lone atrial fibrillation," *Europace*, vol. 7, no. 3, pp. 211–220, 2005.

[59] E. D. Eaker, L. M. Sullivan, M. Kelly-Hayes, R. B. D'Agostino, and E. J. Benjamin, "Anger and hostility predict the development of atrial fibrillation in men in the framingham offspring study," *Circulation*, vol. 109, no. 10, pp. 1267–1271, 2004.

[60] A. V. Mattioli, S. Bonatti, M. Zennaro, R. Melotti, and G. Mattioli, "Effect of coffee consumption, lifestyle and acute life stress in the development of acute lone atrial fibrillation," *Journal of Cardiovascular Medicine*, vol. 9, no. 8, pp. 794–798, 2008.

[61] A. Rashid, M. Hines, B. J. Scherlag, W. S. Yamanashi, and W. Lovallo, "The effects of caffeine on the inducibility of atrial fibrillation," *Journal of Electrocardiology*, vol. 39, no. 4, pp. 421–425, 2006.

[62] L. Frost and P. Vestergaard, "Caffeine and risk of atrial fibrillation or flutter: the Danish diet, cancer, and health study," *American Journal of Clinical Nutrition*, vol. 81, no. 3, pp. 578–582, 2005.

[63] A. Goette, U. Lendeckel, A. Kuchenbecker et al., "Cigarette smoking induces atrial fibrosis in humans via nicotine," *Heart*, vol. 93, no. 9, pp. 1056–1063, 2007.

[64] K. M. Ryder and E. J. Benjamin, "Epidemiology and significance of atrial fibrillation," *American Journal of Cardiology*, vol. 84, no. 9, pp. R131–R138, 1999.

[65] R. B. Schnabel, L. M. Sullivan, D. Levy et al., "Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study," *The Lancet*, vol. 373, no. 9665, pp. 739–745, 2009.

[66] M. A. Rosenberg, J. S. Gottdiener, S. R. Heckbert et al., "Echocardiographic diastolic parameters and risk of atrial fibrillation: the Cardiovascular Health Study," *European Heart Journal*, vol. 33, no. 7, pp. 904–912, 2012.

[67] K. K. Patton, P. T. Ellinor, S. R. Heckbert et al., "N-Terminal pro-b-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the cardiovascular health study," *Circulation*, vol. 120, no. 18, pp. 1768–1774, 2009.

[68] T. Agner, T. Almdal, B. Thorsteinsson, and E. Agner, "A reevaluation of atrial fibrillation in thyrotoxicosis," *Danish medical bulletin*, vol. 31, no. 2, pp. 157–159, 1984.

[69] M. Haissaguerre, P. Jais, D. C. Shah et al., "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins1998," *The New England Journal of Medicine*, vol. 339, no. 10, pp. 659–666.

[70] P. Jaïs, M. Hocini, L. Macle et al., "Distinctive electrophysiological properties of pulmonary veins in patients with atrial fibrillation," *Circulation*, vol. 106, no. 19, pp. 2479–2485, 2002.

[71] A. Frustaci, C. Chimenti, F. Bellocci, E. Morgante, M. A. Russo, and A. Maseri, "Histological substrate of atrial biopsies in patients with lone atrial fibrillation," *Circulation*, vol. 96, no. 4, pp. 1180–1184, 1997.

[72] A. Frustaci, M. Caldarulo, A. Buffon, F. Bellocci, R. Fenici, and D. Melina, "Cardiac biopsy in patients with 'primary' atrial fibrillation; Histologic evidence of occult myocardial diseases," *Chest*, vol. 100, no. 2, pp. 303–306, 1991.

[73] M. K. Stiles, B. John, C. X. Wong et al., "Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the 'second factor'," *Journal of the American College of Cardiology*, vol. 53, no. 14, pp. 1182–1191, 2009.

[74] F. Holmqvist, M. S. Olesen, A. Tveit et al., "Abnormal atrial activation in young patients with lone atrial fibrillation," *Europace*, vol. 13, no. 2, pp. 188–192, 2011.

[75] P. Korantzopoulos, T. Kolettis, K. Siogas, and J. Goudevenos, "Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress," *Medical Science Monitor*, vol. 9, no. 9, pp. RA225–RA229, 2003.

[76] C. J. Garratt, M. Duytschaever, M. Killian, R. Dorland, F. Mast, and M. A. Allessie, "Repetitive electrical remodeling by paroxysms of atrial fibrillation in the goat: no cumulative effect on inducibility or stability of atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 10, no. 8, pp. 1101–1108, 1999.

[77] D. M. Todd, S. P. Fynn, A. P. Walden, W. J. Hobbs, S. Arya, and C. J. Garratt, "Repetitive 4-week periods of atrial electrical remodeling promote stability of atrial fibrillation: time course of a second factor involved in the self-perpetuation of atrial fibrillation," *Circulation*, vol. 109, no. 11, pp. 1434–1439, 2004.

[78] T. T. Issac, H. Dokainish, and N. M. Lakkis, "Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data," *Journal of the American College of Cardiology*, vol. 50, no. 21, pp. 2021–2028, 2007.

[79] D. S. G. Conway, P. Buggins, E. Hughes, and G. Y. H. Lip, "Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation," *American Heart Journal*, vol. 148, no. 3, pp. 462–466, 2004.

[80] C. J. Boos and G. Y. H. Lip, "C-reactive protein and lone atrial fibrillation: potential confounders," *American Journal of Cardiology*, vol. 98, no. 7, pp. 991–992, 2006.

[81] M. J. Mihm, F. Yu, C. A. Carnes et al., "Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation," *Circulation*, vol. 104, no. 2, pp. 174–180, 2001.

[82] P. T. Ellinor, A. Low, K. K. Patton, M. A. Shea, and C. A. MacRae, "C-reactive protein in lone atrial fibrillation," *American Journal of Cardiology*, vol. 97, no. 9, pp. 1346–1350, 2006.

[83] R. J. Aviles, D. O. Martin, C. pperson-Hansen et al., "Inflammation as a risk factor for atrial fibrillation," *Circulation*, vol. 108, no. 24, pp. 3006–3010, 2003.

[84] E. Hatzinikolaou-Kotsakou, D. Tziakas, A. Hotidis et al., "Relation of C-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation," *American Journal of Cardiology*, vol. 97, no. 5, pp. 659–661, 2006.

[85] E. I. Skalidis, M. I. Hamilos, I. K. Karalis, G. Chlouverakis, G. E. Kochiadakis, and P. E. Vardas, "Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation," *Journal of the American College of Cardiology*, vol. 51, no. 21, pp. 2053–2057, 2008.

[86] P. Jais, J. T. Peng, D. C. Shah et al., "Left ventricular diastolic dysfunction in patients with so-called lone atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 11, no. 6, pp. 623–625, 2000.

[87] K. C. Roberts-Thomson, P. M. Kistler, P. Sanders et al., "Fractionated atrial electrograms during sinus rhythm: relationship to age, voltage, and conduction velocity," *Heart Rhythm*, vol. 6, no. 5, pp. 587–591, 2009.

[88] N. Ono, H. Hayashi, A. Kawase et al., "Spontaneous atrial fibrillation initiated by triggered activity near the pulmonary veins in aged rats subjected to glycolytic inhibition," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 292, no. 1, pp. H639–H648, 2007.

[89] O. A. Centurión, S. Isomoto, A. Shimizu et al., "The effects of aging on atrial endocardial electrograms in patients with paroxysmal atrial fibrillation," *Clinical Cardiology*, vol. 26, no. 9, pp. 435–438, 2003.

[90] W. Wongcharoen, Y. C. Chen, Y. J. Chen et al., "Aging increases pulmonary veins arrhythmogenesis and susceptibility to calcium regulation agents," *Heart Rhythm*, vol. 4, no. 10, pp. 1338–1349, 2007.

[91] W. Wongcharoen, Y. C. Chen, Y. J. Chen, C. I. Lin, and S. A. Chen, "Effects of aging and ouabain on left atrial arrhythmogenicity," *Journal of Cardiovascular Electrophysiology*, vol. 18, no. 5, pp. 526–531, 2007.

[92] E. P. Anyukhovsky, E. A. Sosunov, A. Plotnikov et al., "Cellular electrophysiologic properties of old canine atria provide a

substrate for arrhythmogenesis," *Cardiovascular Research*, vol. 54, no. 2, pp. 462–469, 2002.

[93] E. P. Anyukhovsky, E. A. Sosunov, P. Chandra et al., "Age-associated changes in electrophysiologic remodeling: a potential contributor to initiation of atrial fibrillation," *Cardiovascular Research*, vol. 66, no. 2, pp. 353–363, 2005.

[94] K. Sakabe, N. Fukuda, T. Nada et al., "Age-related changes in the electrophysiologic properties of the atrium in patients with no history of atrial fibrillation," *Japanese Heart Journal*, vol. 44, no. 3, pp. 385–393, 2003.

[95] K. Sakabe, N. Fukuda, T. Soeki et al., "Relation of age and sex to atrial electrophysiological properties in patients with no history of atrial fibrillation," *Pacing and Clinical Electrophysiology*, vol. 26, no. 5, pp. 1238–1244, 2003.

[96] B. Brembilla-Perrot, G. Burger, D. Beurrier et al., "Influence of age on atrial fibrillation inducibility," *Pacing and Clinical Electrophysiology*, vol. 27, no. 3, pp. 287–292, 2004.

[97] L. Hove-Madsen, A. Llach, A. Bayes-Genís et al., "Atrial fibrillation is associated with increased spontaneous calcium release from the sarcoplasmic reticulum in human atrial myocytes," *Circulation*, vol. 110, no. 11, pp. 1358–1363, 2004.

[98] J. A. Vest, X. H. T. Wehrens, S. R. Reiken et al., "Defective cardiac ryanodine receptor regulation during atrial fibrillation," *Circulation*, vol. 111, no. 16, pp. 2025–2032, 2005.

[99] A. El-Armouche, P. Boknik, T. Eschenhagen et al., "Molecular determinants of altered Ca^{2+} handling in human chronic atrial fibrillation," *Circulation*, vol. 114, no. 7, pp. 670–680, 2006.

[100] P. M. Kistler, P. Sanders, S. P. Fynn et al., "Electrophysiologic and electroanatomic changes in the human atrium associated with age," *Journal of the American College of Cardiology*, vol. 44, no. 1, pp. 109–116, 2004.

[101] L. Brorson and S. B. Olsson, "Right atrial monophasic action potential in healthy males. Studies during spontaneous sinus rhythm and atrial pacing," *Acta Medica Scandinavica*, vol. 199, no. 6, pp. 433–446, 1976.

[102] N. Toda, "Age-related changes in the transmembrane potential of isolated rabbit sino-atrial nodes and atria," *Cardiovascular Research*, vol. 14, no. 1, pp. 58–63, 1980.

[103] N. Su, J. Duan, M. P. Moffat, and N. Narayanan, "Age related changes in electrophysiological responses to muscarinic receptor stimulation in rat myocardium," *Canadian Journal of Physiology and Pharmacology*, vol. 73, no. 10, pp. 1430–1436, 1995.

[104] W. Dun and P. A. Boyden, "Aged atria: electrical remodeling conducive to atrial fibrillation," *Journal of Interventional Cardiac Electrophysiology*, vol. 25, no. 1, pp. 9–18, 2009.

[105] A. Michelucci, L. Padeletti, and G. A. Fradella, "Ageing and atrial electrophysiologic properties in man," *International Journal of Cardiology*, vol. 5, no. 1, pp. 75–81, 1984.

[106] C. Huang, W. Ding, L. Li, and D. Zhao, "Differences in the aging-associated trends of the monophasic action potential duration and effective refractory period of the right and left atria of the rat," *Circulation Journal*, vol. 70, no. 3, pp. 352–357, 2006.

[107] P. Kojodjojo, P. Kanagaratnam, V. Markides, D. W. Davies, and N. Peters, "Age-related changes in human left and right atrial conduction," *Journal of Cardiovascular Electrophysiology*, vol. 17, no. 2, pp. 120–127, 2006.

[108] S. Baba, W. Dun, M. Hirose, and P. A. Boyden, "Sodium current function in adult and aged canine atrial cells," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 291, no. 2, pp. H756–H761, 2006.

[109] W. Dun, T. Yagi, M. R. Rosen, and P. A. Boyden, "Calcium and potassium currents in cells from adult and aged canine right atria," *Cardiovascular Research*, vol. 58, no. 3, pp. 526–534, 2003.

[110] C. C. Wu, M. J. Su, J. F. Chi, M. H. Wu, and Y. T. Lee, "Comparison of aging and hypercholesterolemic effects on the sodium inward currents in cardiac myocytes," *Life Sciences*, vol. 61, no. 16, pp. 1539–1551, 1997.

[111] H. Hayashi, C. Wang, Y. Miyauchi et al., "Aging-related increase to inducible atrial fibrillation in the rat model," *Journal of Cardiovascular Electrophysiology*, vol. 13, no. 8, pp. 801–808, 2002.

[112] S. Sossalla, B. Kallmeyer, S. Wagner et al., "Altered Na^+ currents in atrial fibrillation. effects of ranolazine on arrhythmias and contractility in human atrial myocardium," *Journal of the American College of Cardiology*, vol. 55, no. 21, pp. 2330–2342, 2010.

[113] R. Gaspo, R. F. Bosch, E. Bou-Abboud, and S. Nattel, "Tachycardia-induced changes in Na^+ current in a chronic dog model of atrial fibrillation," *Circulation Research*, vol. 81, no. 6, pp. 1045–1052, 1997.

[114] P. Kanagaratnam, A. Cherian, R. D. L. Stanbridge, B. Glenville, N. J. Severs, and N. S. Peters, "Relationship between connexins and atrial activation during human atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 15, no. 2, pp. 206–213, 2004.

[115] S. A. Jones, M. K. Lancaster, and M. R. Boyett, "Ageing-related changes of connexins and conduction within the sinoatrial node," *Journal of Physiology*, vol. 560, no. 2, pp. 429–437, 2004.

[116] T. Koura, M. Hara, S. Takeuchi et al., "Anisotropic conduction properties in canine atria analyzed by high-resolution optical mapping: preferential direction of conduction block changes from longitudinal to transverse with increasing age," *Circulation*, vol. 105, no. 17, pp. 2092–2098, 2002.

[117] M. S. Spach, J. F. Heidlage, P. C. Dolber, and R. C. Barr, "Mechanism of origin of conduction disturbances in aging human atrial bundles: experimental and model study," *Heart Rhythm*, vol. 4, no. 2, pp. 175–185, 2007.

[118] C. Chimenti, M. A. Russo, A. Carpi, and A. Frustaci, "Histological substrate of human atrial fibrillation," *Biomedicine and Pharmacotherapy*, vol. 64, no. 3, pp. 177–183, 2010.

[119] S. Verheule, E. Tuyls, A. Van Hunnik, M. Kuiper, U. Schotten, and M. Allessie, "Fibrillatory conduction in the atrial free walls of goats in persistent and permanent atrial fibrillation," *Circulation: Arrhythmia and Electrophysiology*, vol. 3, no. 6, pp. 590–599, 2010.

[120] M. S. Spach and P. C. Dolber, "Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle: evidence for electrical uncoupling of side-to-side fiber connections with increasing age," *Circulation Research*, vol. 58, no. 3, pp. 356–371, 1986.

[121] P. H. Lin, S. H. Lee, C. P. Su, and Y. H. Wei, "Oxidative damage to mitochondrial DNA in atrial muscle of patients with atrial fibrillation," *Free Radical Biology and Medicine*, vol. 35, no. 10, pp. 1310–1318, 2003.

[122] N. H. Pan, H. M. Tsao, N. Chang, Y. J. Chen, and S. A. Chen, "Aging dilates atrium and pulmonary veins: implications for the genesis of atrial fibrillation," *Chest*, vol. 133, no. 1, pp. 190–196, 2008.

[123] S. A. Nazir and M. J. Lab, "Mechanoelectric feedback and atrial arrhythmias," *Cardiovascular Research*, vol. 32, no. 1, pp. 52–61, 1996.

[124] A. Ruigómez, S. Johansson, M. A. Wallander, and L. A. García Rodríguez, "Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK," *BMC Cardiovascular Disorders*, vol. 5, article no. 20, 2005.

[125] C. R. Kerr, K. H. Humphries, M. Talajic et al., "Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation," *American Heart Journal*, vol. 149, no. 3, pp. 489–496, 2005.

[126] S. A. Lopez, F. Formiga, X. Bosch et al., "Prevalence of atrial fibrillation and related factors in hospitalized old patients: ESFINGE study," *Medicina Clínica*, vol. 138, no. 6, pp. 231–237, 2012.

[127] C. B. de Vos, R. Pisters, R. Nieuwlaat et al., "Progression from paroxysmal to persistent atrial fibrillation. clinical correlates and prognosis," *Journal of the American College of Cardiology*, vol. 55, no. 8, pp. 725–731, 2010.

[128] C. Kerr, J. Boone, S. Connolly et al., "Follow-up of atrial fibrillation: the initial experience of the Canadian Registry of Atrial Fibrillation," *European Heart Journal*, vol. 17, no. 7, supplement, pp. 48–51, 1996.

[129] N. D. Brunetti, L. De Gennaro, P. L. Pellegrino, G. Dellegrottaglie, G. Antonelli, and M. Di Biase, "Atrial fibrillation with symptoms other than palpitations: incremental diagnostic sensitivity with at-home tele-cardiology assessment for emergency medical service," *European Journal of Preventive Cardiology*, vol. 19, no. 3, pp. 306–313, 2011.

[130] U. Lotze, J. Liebetrau, I. Malsch et al., "Medical treatment of patients with atrial fibrillation aged over 80 years in daily clinical practice: influence of age and CHADS2 score," *Archives of Gerontology and Geriatrics*, vol. 50, no. 1, pp. 36–41, 2010.

[131] S. Kralev, K. Schneider, S. Lang et al., "Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography," *PLoS One*, vol. 6, no. 9, Article ID e24964, 2011.

[132] J. Liao, Z. Khalid, C. Scallan, C. Morillo, and M. O'Donnell, "Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review," *Stroke*, vol. 38, no. 11, pp. 2935–2940, 2007.

[133] K. Lakshminarayan, C. A. Solid, A. J. Collins, D. C. Anderson, and C. A. Herzog, "Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002)," *Stroke*, vol. 37, no. 8, pp. 1969–1974, 2006.

[134] P. A. Wolf, R. D. Abbott, and W. B. Kannel, "Atrial fibrillation as an independent risk factor for stroke: the Framingham Study," *Stroke*, vol. 22, no. 8, pp. 983–988, 1991.

[135] R. G. Hart, O. Benavente, R. McBride, and L. A. Pearce, "Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis," *Annals of Internal Medicine*, vol. 131, no. 7, pp. 492–501, 1999.

[136] D. N. Salem, P. D. Stein, A. Al-Ahmad et al., "Antithrombotic therapy in valvular heart disease—native and prosthetic: the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy," *Chest*, vol. 126, no. 3, supplement, pp. 457S–482S, 2004.

[137] B. F. Gage, A. D. Waterman, W. Shannon, M. Boechler, M. W. Rich, and M. J. Radford, "Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation," *Journal of the American Medical Association*, vol. 285, no. 22, pp. 2864–2870, 2001.

[138] M. Hughes and G. Y. H. Lip, "Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data," *Thrombosis and Haemostasis*, vol. 99, no. 2, pp. 295–304, 2008.

[139] Stroke in AF Working Group, "Independent predictors of stroke in patients with atrial fibrillation: a systematic review," *Neurology*, vol. 69, no. 6, pp. 546–554, 2007.

[140] G. Y. H. Lip, R. Nieuwlaat, R. Pisters, D. A. Lane, and H. J. G. M. Crijns, "Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation," *Chest*, vol. 137, no. 2, pp. 263–272, 2010.

[141] D. E. Singer, Y. Chang, M. C. Fang et al., "The net clinical benefit of warfarin anticoagulation in atrial fibrillation," *Annals of Internal Medicine*, vol. 151, no. 5, pp. 297–305, 2009.

[142] A. S. Go, E. M. Hylek, L. H. Borowsky, K. A. Phillips, J. V. Selby, and D. E. Singer, "Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study," *Annals of Internal Medicine*, vol. 131, no. 12, pp. 927–934, 1999.

[143] D. Pugh, J. Pugh, and G. E. Mead, "Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review," *Age Ageing*, vol. 40, no. 6, pp. 675–683, 2011.

[144] R. Marinigh, G. Y. H. Lip, N. Fiotti, C. Giansante, and D. A. Lane, "Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis," *Journal of the American College of Cardiology*, vol. 56, no. 11, pp. 827–837, 2010.

[145] M. C. Fang, A. S. Go, Y. Chang et al., "Death and disability from warfarin-associated intracranial and extracranial hemorrhages," *American Journal of Medicine*, vol. 120, no. 8, pp. 700–705, 2007.

[146] E. M. Hylek, C. Evans-Molina, C. Shea, L. E. Henault, and S. Regan, "Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation," *Circulation*, vol. 115, no. 21, pp. 2689–2696, 2007.

[147] M. Man-Son-Hing, G. Nichol, A. Lau, and A. Laupacis, "Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls," *Archives of Internal Medicine*, vol. 159, no. 7, pp. 677–685, 1999.

[148] R. Pisters, D. A. Lane, R. Nieuwlaat, C. B. De Vos, H. J. G. M. Crijns, and G. Y. H. Lip, "A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro heart survey," *Chest*, vol. 138, no. 5, pp. 1093–1100, 2010.

[149] D. J. Stott, R. I. Dewar, C. J. Garratt et al., "RCPE UK consensus conference on 'Approaching the comprehensive management of atrial fibrillation: evolution or revolution?'," *The Journal of the Royal College of Physicians of Edinburgh*, vol. 42, supplement 18, pp. 3–4.

[150] S. J. Connolly, M. D. Ezekowitz, S. Yusuf et al., "Dabigatran versus warfarin in patients with atrial fibrillation," *The New England Journal of Medicine*, vol. 361, no. 12, pp. 1139–1151, 2009.

[151] J. W. Eikelboom, L. Wallentin, S. J. Connolly et al., "Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) Trial," *Circulation*, vol. 123, no. 21, pp. 2363–2372, 2011.

[152] M. R. Patel, K. W. Mahaffey, J. Garg et al., "Rivaroxaban versus warfarin in nonvalvular atrial fibrillation," *The New England Journal of Medicine*, vol. 365, no. 10, pp. 883–891, 2011.

[153] C. B. Granger, J. H. Alexander, J. J. McMurray et al., "Apixaban versus warfarin in patients with atrial fibrillation," *The New England Journal of Medicine*, vol. 365, no. 11, pp. 981–992, 2011.

[154] D. G. Wyse, "Rate control vs rhythm control strategies in atrial fibrillation," *Progress in Cardiovascular Diseases*, vol. 48, no. 2, pp. 125–138, 2005.

[155] I. C. Van Gelder, H. F. Groenveld, H. J. G. M. Crijns et al., "Lenient versus strict rate control in patients with atrial fibrillation," *New England Journal of Medicine*, vol. 362, no. 15, pp. 1363–1373, 2010.

[156] I. C. Van Gelder, D. G. Wyse, M. L. Chandler et al., "Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies," *Europace*, vol. 8, no. 11, pp. 935–942, 2006.

[157] M. Brignole, G. L. Botto, L. Mont et al., "Predictors of clinical efficacy of 'Ablate and Pace' therapy in patients with permanent atrial fibrillation," *Heart*, vol. 98, no. 4, pp. 297–302, 2012.

[158] A. N. Ganesan, A. G. Brooks, K. C. Roberts-Thomson et al., "Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review," *Journal of the American College of Cardiology*, vol. 59, no. 8, pp. 719–726, 2012.

[159] A. E. Epstein, "Relationships between snus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study," *Circulation*, vol. 109, no. 12, pp. 1509–1513, 2004.

[160] A. J. Camm, P. Kirchhof, G. Y. Lip et al., "Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)," *European Heart Journal*, vol. 31, no. 19, pp. 2369–2429, 2010.

[161] C. Lafuente-Lafuente, S. Mouly, M. A. Longas-Tejero, and J. F. Bergmann, "Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD005049, 2007.

[162] J. Y. Le Heuzey, G. M. De Ferrari, D. Radzik, M. Santini, J. Zhu, and J. M. Davy, "A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the dionysos study," *Journal of Cardiovascular Electrophysiology*, vol. 21, no. 6, pp. 597–605, 2010.

[163] S. J. Connolly, H. J. G. M. Crijns, C. Torp-Pedersen et al., "Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter," *Circulation*, vol. 120, no. 13, pp. 1174–1180, 2009.

[164] M. R. Reynolds, J. Walczak, S. A. White, D. J. Cohen, and D. J. Wilber, "Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs," *Circulation: Cardiovascular Quality and Outcomes*, vol. 3, no. 6, pp. 615–623, 2010.

[165] J. P. Piccini, R. D. Lopes, M. H. Kong, V. Hasselblad, K. Jackson, and S. M. Al-Khatib, "Pulmonary vein isolation for the maintenance of sinus rhythm in patients with atrial fibrillation a meta-analysis of randomized, controlled trials," *Circulation: Arrhythmia and Electrophysiology*, vol. 2, no. 6, pp. 626–633, 2009.

[166] R. Cappato, H. Calkins, S. A. Chen et al., "Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation," *Circulation: Arrhythmia and Electrophysiology*, vol. 3, no. 1, pp. 32–38, 2010.

[167] A. Noheria, A. Kumar, J. V. Wylie, and M. E. Josephson, "Catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation: a systematic review," *Archives of Internal Medicine*, vol. 168, no. 6, pp. 581–586, 2008.

[168] P. Jaïs, B. Cauchemez, L. Macle et al., "Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study," *Circulation*, vol. 118, no. 24, pp. 2498–2505, 2008.

[169] H. Calkins, M. R. Reynolds, P. Spector et al., "Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses," *Circulation: Arrhythmia and Electrophysiology*, vol. 2, no. 4, pp. 349–361, 2009.

[170] L. M. Haegeli, F. Duru, E. E. Lockwood et al., "Ablation of atrial fibrillation after the retirement age: considerations on safety and outcome," *Journal of Interventional Cardiac Electrophysiology*, vol. 28, no. 3, pp. 193–197, 2010.

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Review Article

The Use of Cardiac Magnetic Resonance Imaging in the Diagnostic Workup and Treatment of Atrial Fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and imposes a huge clinical and economic burden. AF is correlated with an increased morbidity and mortality, mainly due to stroke and heart failure. Cardiovascular imaging modalities, including echocardiography, computed tomography (CT), and cardiovascular magnetic resonance (CMR), play a central role in the workup and treatment of AF. One of the major advantages of CMR is the high contrast to noise ratio combined with good spatial and temporal resolution, without any radiation burden. This allows a detailed assessment of the structure and function of the left atrium (LA). Of particular interest is the ability to visualize the extent of LA wall injury. We provide a focused review of the value of CMR in identifying the underlying pathophysiological mechanisms of AF, its role in stroke prevention and in the guidance of radiofrequency catheter ablation. CMR is a promising technique that could add valuable information for therapeutic decision making in specific subpopulations with AF.

1. Introduction

Atrial fibrillation is the most common cardiac arrhythmia. The prevalence of AF is estimated at 1% in the general population and increases with age up to 10% in octogenarians [1]. Every adult older than 45 years has a 25% lifetime risk of developing AF [2]. The prevalence of AF is increasing and will reach epidemiological proportions that could pose a huge socioeconomical challenge [3]. AF is a progressive disease, which evolves from limited paroxysms to a persistent and sometimes permanent presence [4]. Structural, electrical and contractile remodeling processes underlying this progressive nature have been identified. The treatment of AF remains challenging and the longer AF exists the more difficult treatment becomes. Pulmonary vein ablation has emerged as a promising novel nonpharmacological treatment for AF. However, this is associated with significant complications, with little evidence of clear survival benefits [5].

Cardiovascular magnetic resonance imaging (CMR) is a noninvasive imaging technique which is used to assess the structure and function of the cardiovascular system. CMR is based on the same basic principles as magnetic resonance imaging (MRI), but with optimized features specific for cardiac imaging such as ECG gating and rapid imaging sequences. Different CMR sequences can be used to enhance the signal of the diseased tissue of interest. It is a very useful diagnostic tool and the therapy guidance's of various heart diseases. The major advantages of CMR are the absence of radiation exposure, the high temporal and spatial resolution, and the ability to characterize the composition of the tissue. However several disadvantages are also evident, such as cost, limited availability, incompatibility of certain prosthetic materials and time consuming analysis. In this paper we

will focus on the possible use of CMR in AF. AF itself and the morphology of the atria impose additional obstacles for CMR. The complex geometry and the thin-walled anatomy make the structural analysis of the atria more challenging. Furthermore, as CMR depends heavily on ECG gating, the irregularity of the ventricular rhythm during AF can make its implementation problematic.

However, CMR could improve ablation outcome by more effective preablation structure analysis, predicting the change of recurrence and the detection of postablation complications. Furthermore, CMR could help to reveal some of the underlying remodeling processes and could add important information, allowing more effective decisions on which patients would benefit most from anticoagulation. We will review the available scientific data on these possible advantages and challenges of CMR in the diagnostic workup and treatment of patients with AF.

2. Cardiovascular Magnetic Resonance and the Assessment of Left Atrial Remodeling

The knowledge of the pathophysiological mechanisms of AF has expanded rapidly the last decades [6, 7]. Atrial dilation can be found in the setting of diverse cardiac and pulmonary diseases and plays an important role in the development of AF. AF itself can also induce atrial dilation and in this way leads to the perseveration of AF [8, 9]. Measurements of left atrial (LA) dimensions play an important role in the workup of AF, since atrial enlargement is an important marker of LA structural remodeling and predictor of AF (re)occurrence and mortality [10]. B-mode or two-dimensional echocardiography is most commonly used in clinical practice to assess atrial and ventricular volume. However, echocardiographic volume measurements require correct angulations and two-dimensional based calculations of volumes depend on geometric assumptions about the LA shape. Three-dimensional echocardiography allows a more accurate LA volume assessment [11]. However, feasibility and correct interpretation may be more difficult during AF, due to the irregular heart rhythm, which results in a substantial variation of the LA volume.

CMR has the advantage of providing an exact detailed image of the LA morphology, the pulmonary veins (PV), and the surrounding structures. Furthermore, CMR can assess the reservoir, conduit, and contractile function based on phasic changes in volumes [12]. A tight correlation between measured atrial volumes by CMR and true volumes measured in cadaveric casts has been observed [13]. Scanning during an irregular heart rhythm can result in a loss of image quality, which makes it sometimes necessary to repeat slices and to adjust the trigger window. However, the drawback of CMR to record every image slice during several heartbeats can be taken as an advantage since it would tend to compensate for the irregular heart rhythm during AF, allowing a more averaged LA volume. Therkelsen et al. demonstrated the feasibility of measuring atrial and ventricular volumes in AF patients with an irregular heart rhythm [14]. Several CMR studies demonstrated that in general patients with paroxysmal AF have larger LA volumes than control subjects [15, 16]. However, patients with paroxysmal AF without structural heart disease ("lone AF") had no significant difference in atrial volumes compared with healthy volunteers [17]. CMR also demonstrated that the LA enlargement further increases when AF evolves from paroxysmal to persistent AF [18]. Therkelsen et al. compared atrial and ventricular volumes and ejection fraction (EF) between healthy volunteers and patients with persistent and permanent AF. The mean atrial volumes were similar between patients with persistent and permanent AF, but significantly larger compared to healthy volunteers. This suggests that LA dilation stabilizes when patients evolve from persistent to permanent AF [14].

CMR was also used to document the restoration of the function and structure of the atria and ventricles after cardioversion. Therkelsen et al. showed an immediate reversal of atrial systolic volumes and contractile function the day after cardioversion of patients with persistent AF. There was a further recovery of atrial dimensions and function at 30 days and 180 days. However, only the right atrial volumes were completely normalized 180 days after cardioversion. The restoration of ventricular function and dimensions started only 30 days after cardioversion and was incomplete at 180 days. These results suggest that structural remodeling of the atria and ventricles during AF could be permanent [19].

The pulmonary veins (PVs) play a critical role in the pathophysiology and treatment of AF [20]. CMR allows an accurate measurement of the PV dimensions and the branching pattern. However, identification of the true ostia remains problematic due to the lack of a clear anatomic border between the PVs and the LA. The PV size also varies significantly during the cardiac cycle [21]. Measuring the PVs in the sagittal plane at which the PVs separate from each other and the LA appears to be highly reproducible and may be advantageous for serial examinations [22]. Tsao et al. demonstrated significant dilation of the superior PVs with simultaneous LA dilation in paroxysmal and permanent AF. However, PV size couldn't predict the origin of arrhythmogenic trigger foci [23]. Similarly, Kato et al. have shown that patients with AF have larger PVs [15].

One of the unique features of CMR is the ability to characterize the tissue composition of the LA wall. Oakes et al. reported the feasibility to detect and quantify late gadolinium enhancement in the left atrium, assessed by delayed enhancement MRI (DE-MRI). They showed an association between regions of enhancement and low-voltage regions on electroanatomic maps. This suggests that late gadolinium enhancement may be a feasible way to detect LA fibrosis. They also identified two distinct patterns of enhancement: a more continuous pattern and a scattered pattern. The extent of LA wall enhancement was a significant predictor for the type of AF, with significant more LA enhancement in patients with persistent AF compared to paroxysmal AF [24]. Kuppahally et al. showed that the extent of LA enhancement on DE-MRI was inversely related with echocardiographic measured regional myocardial function, assessed with LA strain and strain rate [25].

3. Cardiovascular Magnetic Resonance and Stroke Management in AF Patients

Stroke is one of the most devastating complications of AF. However, thrombus formation in the LA is incompletely understood. The pathophysiological mechanisms can be summarized in the classic Virchow's triad: blood stasis, abnormal changes in the LA wall, and abnormal changes in blood constituents [26]. The left atrial appendage (LAA) is the suspected culprit in the majority of thromboembolic phenomena related to AF [27]. Transoesophageal echocardiography (TEE) is the clinical standard to evaluate thrombus formation in the LAA. However, TEE is semi-invasive and possesses a small risk of serious complications. Preliminary studies have shown that combined two-dimensional and three-dimensional transthoracic echocardiography (TTE) had comparable accuracy to two-dimensional TEE in evaluating the LAA for thrombus. However, a significant number of patients have a suboptimal acoustic window which limits the use of TTE evaluation of the LAA [28, 29]. CMR is an alternative, noninvasive tool, which allows a detailed evaluation of the LAA. Ohyama et al. showed that unenhanced CMR (without administration of contrast media) is a sensitive alternative for thrombus detection in the LAA. It has been shown that CMR can correctly differentiate thrombus from slow blood flow, appearing as spontaneous contrast in echocardiography [30]. However, in another study contrast-enhanced CMR (after the administration of contrast media) lacked diagnostic accuracy compared with the clinical reference TEE. It is postulated that the limited data acquisition time window in contrast-enhanced CMR resulted in insufficient spatial resolution precluding the accurate detection of LAA thrombus [31]. Caution should be taken in the use of CMR in clinical practice until the promising diagnostic accuracy of unenhanced CMR is confirmed in a larger multicenter study.

Stroke risk prediction is a key factor in the management of AF. This is crucial in the selection of patients which will benefit most from chronic anticoagulation therapy. There are several risk stratification schemes, of which the $CHADS_2$ score is easy to apply and clinically well established [32]. However, the classic risk schemes have only a limited overall ability to predict thromboembolism, particularly in low-risk patients. Additional independent risk factors are needed to improve patient selection [33]. The more recent CHA_2DS_2VASc risk score takes additional clinically relevant nonmajor risk factors into account [34]. This approach leads to a better risk prediction in the patients with a $CHADS_2$ score of 0 to 1 [35]. However, novel risk factors based on individual LA pathophysiological properties could further improve this risk stratification. CMR could help to identify some of the factors of the classic Virchow's triad. Beinart et al. showed a relation between stroke risk and larger LAA volumes, LAA depths, and necks. LAA neck dimensions remained predictive of stroke risk after adjustment for traditional stroke risk factors, indicating a possible role for its use in additional risk stratification [36]. Fyrenius et al. looked at the global flow patterns of the LA in healthy volunteers. They observed vortical flow in all subjects during systole and diastolic diastasis. This vortex formation may have beneficial effects in avoiding left atrial stasis and clot formation during sinus rhythm [37]. Further study is necessary to confirm loss of vortex formation during AF and it is relation with stroke risk. As suggested by Virchow's triad, structural changes to the LA wall may also contribute to the prothrombotic state in AF [26]. The extent of LA late gadolinium enhancement may be used as a marker for the severity of LA wall injury in AF. Daccarett et al. studied the association between LA late enhancement and the $CHADS_2$ score. They found a clear association between patients with previous stroke and a higher percentage of LA late enhancement. This association was independent of all clinical stroke risk variables (CHAD score). However, it is unclear if this association was also independent from LA dilation [38]. As demonstrated by Fatema et al., there is a significant association between LA volume index, assessed by transthoracic echocardiography, and first-ever ischemic stroke [39]. Further research is necessary to evaluate which of these additional markers has the ability to substantially improve the predictive power of the current risk models.

4. CMR to Guide Atrial Fibrillation Ablation

Haissaguerre et al. were the first to report that the pulmonary veins play an important role in the initiation of AF. They demonstrated that local radiofrequency catheter ablation of these ectopic beats could stop AF in the majority of patients [20]. However, recurrence rate was high and was associated with recurrent ectopic beats, indicating the need for a better mapping and ablation technique. As a result of leading-edge technologic advances, AF ablation has evolved into a safer and commonly performed procedure [40]. However, the success rate of AF ablation remains moderate, with a single-procedure success rate of 57% and multiple-procedure success rate of 71%, with a complication rate of 4.9% in a recent meta-analysis [5]. CMR could play an important role in the optimization of AF ablation, by accurate selection of candidates, improving the success rate of the procedure and reducing the chance of complications.

4.1. The Role of Preablation CMR. Preprocedural CMR can be used as a non-invasive imaging tool to delineate the relevant anatomical structures and to assess the parameters which are predictive for recurrent AF.

Electrical isolation of the PV is the cornerstone in AF ablation. This requires a detailed regional anatomic visualisation before the ablation procedure. The integration of pre-procedural anatomic information and electroanatomic mapping is associated with superior procedural success and safety [41]. A comparison of CMR with CT showed similar details which allowed effective evaluation of the PV anatomy [42]. A study by Kato et al. demonstrated that 38% of the AF patients have a variant PV anatomy [15]. Similar results were observed by Anselmino et al. where only 40% of the patients had a typical PV branching pattern (2 left and 2 right PVs). The most frequent variant branching patterns are a common left trunk and an additional right middle PV [18].

Besides the identification of the PV branching pattern and LA morphology, CMR can also assess parameters predictive for recurrent AF after ablation. Several CMR studies have identified various potential predictive parameters, such as LA volume, extent and pattern of LA wall late gadolinium enhancement, and pericardial fat. LA volume was an independent predictor for recurrence after ablation in a mixed group of patients with paroxysmal and persistent AF [43]. However, LA volume couldn't predict the success of ablation in patients with exclusive paroxysmal AF [44]. Oakes et al. showed that the extent of LA wall enhancement was the most significant predictor for the success of AF ablation. Furthermore, the location of late enhancement appeared to predict the success. Success was higher when late enhancement was limited primarily to the posterior wall and septum. Also LA volume was predictive for recurrent AF, although the extent of LA wall enhancement had a greater adjusted odds ratio [24]. Another interesting finding by Wong et al. is the association between pericardial fat and presence of AF, severity of AF, LA volume, and poorer outcomes after AF ablation. However, the study design did not allow any conclusions to be drawn on causality [45].

4.2. The Role of Postablation CMR. A particular strength of CMR in the post-procedural period is the ability to visualize scar formation. CMR can also be used to study the effects of ablation on LA structure and function, and to detect PV stenosis.

Several investigators demonstrated the feasibility to assess postablation scar with DE-MRI [46–48]. McGann et al. detected hyperenhancing and nonenhancing lesions. The nonenhancing lesions demonstrated no-reflow characteristics and were a better predictor for scar formation at 3 months [46]. A correlation between procedure outcome and the extent of scar formation has also been described. Patients with minimal scar formation had a higher rate of AF recurrences [47]. Furthermore, visualization of postablation scar can detect incomplete isolation and thus can be useful in assessing the reason for failure. Moreover, detection of the location of the isolation gaps can be helpful in planning a redo procedure [47].

Radiofrequency ablation results in a significant decrease of the LA size. However, a similar decrease in LA size was noted in patients with a successful ablation as in patients with AF recurrence. These data suggest that the reduction in LA size may be induced by the ablation procedure itself, rather than reverse remodeling [49]. Nori et al. studied the effects of ablation on global and regional LA function. Global LA transport function and regional LA motion were decreased 3 months following ablation in patients with paroxysmal AF. However, in patients with persistent AF, global, and regional functions were improved. Here, the positive reverse remodeling due to restoration of sinus rhythm seemed to outweigh the negative effects of the ablation procedure [16]. It was also demonstrated by Wylie Jr. et al. that the extent of LA scar formation influences the atrial systolic function after ablation, with a more pronounced decrease in LA systolic function in extensive scar formation [48]. AF ablation also influence the PVs. Tsao et al. noted a reduction of the ostial area of the superior PVs after successful ablation, as well as a geometric adaptation towards a rounder shape of the ostia. In patients with AF recurrence there was further LA and PV enlargement [50].

AF ablation can induce unwanted and harmful effects on the PVs. Case reports of PV stenosis with severe pulmonary hypertension appeared shortly after the introduction of catheter ablation of AF [51]. CMR allows sequential PV analysis without repeated radiation exposure and is comparable to radiographic angiography for the detection of PV stenosis [52]. Dong et al. reported a ≥ 3 mm PV narrowing in 38% of PVs 8–10 weeks following ablation. However, moderate (50–70%) and severe (>70%) stenosis was only noted in 3.2 and 0.6%, respectively [53]. Distal ablations inside the PV, individual PV encircling lesions, and larger PV size are all associated with a higher risk of stenosis [53, 54].

5. Summary

Atrial fibrillation is a very frequent disorder, with an underlying continuously evolving atrial substrate. Detailed imaging of the LA, PVs, and surrounding structures during AF progression is crucial for good patient management. CMR has multiple advantages over other imaging modalities. This allows a detailed assessment of the LA morphology and function and is currently the only technique which allows an appraisal of the extent of LA wall injury. However, cost and time will limit routine use of CMR in clinical practice. Many of these techniques are new and need to be confirmed in larger multicenter studies. Nevertheless, it is clear that CMR can play an important role in specific AF patient subpopulations, such as patients undergoing pulmonary vein ablation.

References

[1] A. S. Go, E. M. Hylek, K. A. Phillips et al., "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study," *Journal of the American Medical Association*, vol. 285, no. 18, pp. 2370–2375, 2001.

[2] D. M. Lloyd-Jones, T. J. Wang, E. P. Leip et al., "Lifetime risk for development of atrial fibrillation: the framingham heart study," *Circulation*, vol. 110, no. 9, pp. 1042–1046, 2004.

[3] Y. Miyasaka, M. E. Barnes, B. J. Gersh et al., "Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence," *Circulation*, vol. 114, no. 11, p. e498, 2006.

[4] C. R. Kerr, K. H. Humphries, M. Talajic et al., "Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation," *American Heart Journal*, vol. 149, no. 3, pp. 489–496, 2005.

[5] H. Calkins, M. R. Reynolds, P. Spector et al., "Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses," *Circulation*, vol. 2, no. 4, pp. 349–361, 2009.

[6] Y. K. Iwasaki, K. Nishida, T. Kato, and S. Nattel, "Atrial fibrillation pathophysiology: implications for management," *Circulation*, vol. 124, no. 20, pp. 2264–2274, 2011.

[7] U. Schotten, S. Verheule, P. Kirchhof, and A. Goette, "Pathophysiological mechanisms of atrial fibrillation: a translational appraisal," *Physiological Reviews*, vol. 91, no. 1, pp. 265–325, 2011.

[8] H. C. Dittrich, L. A. Pearce, R. W. Asinger et al., "Left atrial diameter in nonvalvular atrial fibrillation: an echocardiographic study," *American Heart Journal*, vol. 137, no. 3, pp. 494–499, 1999.

[9] A. J. Sanfilippo, V. M. Abascal, M. Sheehan et al., "Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study," *Circulation*, vol. 82, no. 3, pp. 792–797, 1990.

[10] W. P. Abhayaratna, J. B. Seward, C. P. Appleton et al., "Left atrial size: physiologic determinants and clinical applications," *Journal of the American College of Cardiology*, vol. 47, no. 12, pp. 2357–2363, 2006.

[11] C. Jenkins, K. Bricknell, and T. H. Marwick, "Use of real-time three-dimensional echocardiography to measure left atrial volume: comparison with other echocardiographic techniques," *Journal of the American Society of Echocardiography*, vol. 18, no. 9, pp. 991–997, 2005.

[12] W. Y. I. Tseng, T. Y. Liao, and J. L. Wang, "Normal systolic and diastolic functions of the left ventricle and left atrium by cine magnetic resonance imaging," *Journal of Cardiovascular Magnetic Resonance*, vol. 4, no. 4, pp. 443–457, 2002.

[13] V. M. Jarvinen, M. M. Kupari, P. E. Hekali, and V. P. Poutanen, "Right atrial MR imaging studies of cadaveric atrial casts and comparison with right and left atrial volumes and function in healthy subjects," *Radiology*, vol. 191, no. 1, pp. 137–142, 1994.

[14] S. K. Therkelsen, B. A. Groenning, J. H. Svendsen, and G. B. Jensen, "Atrial and ventricular volume and function in persistent and permanent atrial fibrillation, a magnetic resonance imaging study," *Journal of Cardiovascular Magnetic Resonance*, vol. 7, no. 2, pp. 465–473, 2005.

[15] R. Kato, L. Lickfett, G. Meininger et al., "Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging," *Circulation*, vol. 107, no. 15, pp. 2004–2010, 2003.

[16] D. Nori, G. Raff, V. Gupta, R. Gentry, J. Boura, and D. E. Haines, "Cardiac magnetic resonance imaging assessment of regional and global left atrial function before and after catheter ablation for atrial fibrillation," *Journal of Interventional Cardiac Electrophysiology*, vol. 26, no. 2, pp. 109–117, 2009.

[17] N. Ishimoto, M. Ito, and M. Kinoshita, "Signal-averaged P-wave abnormalities and atrial size in patients with and without idiopathic paroxysmal atrial fibrillation," *American Heart Journal*, vol. 139, no. 4, pp. 684–689, 2000.

[18] M. Anselmino, A. Blandino, S. Beninati et al., "Morphologic analysis of left atrial anatomy by magnetic resonance angiography in patients with atrial fibrillation: a large single center experience," *Journal of Cardiovascular Electrophysiology*, vol. 22, no. 1, pp. 1–7, 2011.

[19] S. K. Therkelsen, B. A. Groenning, J. H. Svendsen, and G. B. Jensen, "Atrial and ventricular volume and function evaluated by magnetic resonance imaging in patients with persistent atrial fibrillation before and after cardioversion," *American Journal of Cardiology*, vol. 97, no. 8, pp. 1213–1219, 2006.

[20] M. Haissaguerre, P. Jaïs, D. C. Shah et al., "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins," *The New England Journal of Medicine*, vol. 339, pp. 659–666, 1998.

[21] T. H. Hauser, S. B. Yeon, K. V. Kissinger, M. E. Josephson, and W. J. Manning, "Variation in pulmonary vein size during the cardiac cycle: implications for non-electrocardiogram-gated imaging," *American Heart Journal*, vol. 152, no. 5, pp. 974.e1–974.e6, 2006.

[22] T. H. Hauser, S. B. Yeon, S. McClennen et al., "A method for the determination of proximal pulmonary vein size using contrast-enhanced magnetic resonance angiography," *Journal of Cardiovascular Magnetic Resonance*, vol. 6, no. 4, pp. 927–936, 2004.

[23] H. M. Tsao, W.-C. Yu, H.-C. Cheng et al., "Pulmonary vein dilation in patients with atrial fibrillation: detection by magnetic resonance imaging," *Journal of Cardiovascular Electrophysiology*, vol. 12, pp. 809–813, 2001.

[24] R. S. Oakes, T. J. Badger, E. G. Kholmovski et al., "Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation," *Circulation*, vol. 119, no. 13, pp. 1758–1767, 2009.

[25] S. S. Kuppahally, N. Akoum, N. S. Burgon et al., "Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI," *Circulation*, vol. 3, no. 3, pp. 231–239, 2010.

[26] T. Watson, E. Shantsila, and G. Y. Lip, "Mechanisms of thrombogenesis in atrial fibrillation: virchow's triad revisited," *The Lancet*, vol. 373, no. 9658, pp. 155–166, 2009.

[27] T. Narumiya, T. Sakamaki, Y. Sato, and K. Kanmatsuse, "Relationship between left atrial appendage function and left atrial thrombus in patients with nonvalvular chronic atrial fibrillation and atrial flutter," *Circulation Journal*, vol. 67, no. 1, pp. 68–72, 2003.

[28] G. Karakus, V. Kodali, V. Inamdar, N. C. Nanda, T. Suwanjutah, and K. R. Pothineni, "Comparative assessment of left atrial appendage by transesophageal and combined two- and three-dimensional transthoracic echocardiography," *Echocardiography*, vol. 25, no. 8, pp. 918–924, 2008.

[29] I. Agoston, T. Xie, F. L. Tiller, A. M. Rahman, and M. Ahmad, "Assessment of left atrial appendage by Live Three-Dimensional Echocardiography: early experience and comparison with transesophageal echocardiography," *Echocardiography*, vol. 23, no. 2, pp. 127–132, 2006.

[30] H. Ohyama, N. Hosomi, T. Takahashi et al., "Comparison of magnetic resonance imaging and transesophageal echocardiography in detection of thrombus in the left atrial appendage," *Stroke*, vol. 34, no. 10, pp. 2436–2439, 2003.

[31] O. K. Mohrs, B. Nowak, S. E. Petersen et al., "Thrombus detection in the left atrial appendage using contract-enhanced MRI: a pilot study," *American Journal of Roentgenology*, vol. 186, no. 1, pp. 198–205, 2006.

[32] B. F. Gage, A. D. Waterman, W. Shannon, M. Boechler, M. W. Rich, and M. J. Radford, "Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation," *Journal of the American Medical Association*, vol. 285, no. 22, pp. 2864–2870, 2001.

[33] M. C. Fang, A. S. Go, Y. Chang, L. Borowsky, N. K. Pomernacki, and D. E. Singer, "Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation," *Journal of the American College of Cardiology*, vol. 51, no. 8, pp. 810–815, 2008.

[34] G. Y. H. Lip, R. Nieuwlaat, R. Pisters, D. A. Lane, and H. J. G. M. Crijns, "Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation

using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation," *Chest*, vol. 137, no. 2, pp. 263–272, 2010.

[35] J. B. Olesen, C. Torp-Pedersen, M. L. Hansen, G. Y. Lip et al., "The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study," *Journal of Thrombosis and Haemostasis*, vol. 107, no. 6, pp. 1172–1179, 2012.

[36] R. Beinart, E. K. Heist, J. B. Newell, G. Holmvang, J. N. Ruskin, and M. Mansour, "Left atrial appendage dimensions predict the risk of Stroke/TIA in patients with atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 22, no. 1, pp. 10–15, 2011.

[37] A. Fyrenius, L. Wigström, T. Ebbers, M. Karlsson, J. Engvall, and A. F. Bolger, "Three dimensional flow in the human left atrium," *Heart*, vol. 86, no. 4, pp. 448–455, 2001.

[38] M. Daccarett, T. J. Badger, N. Akoum et al., "Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation," *Journal of the American College of Cardiology*, vol. 57, no. 7, pp. 831–838, 2011.

[39] K. Fatema, K. R. Bailey, G. W. Petty et al., "Increased left atrial volume index: potent biomarker for first-ever ischemic stroke," *Mayo Clinic Proceedings*, vol. 83, no. 10, pp. 1107–1114, 2008.

[40] H. Calkins, K. H. Kuck, R. Cappato et al., "HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design," *Europace*, vol. 14, no. 4, pp. 528–606, 2012.

[41] M. Martinek, H. J. Nesser, J. Aichinger, G. Boehm, and H. Purerfellner, "Impact of integration of multislice computed tomography imaging into three-dimensional electroanatomic mapping on clinical outcomes, safety, and efficacy using radiofrequency ablation for atrial fibrillation," *Pacing and Clinical Electrophysiology*, vol. 30, no. 10, pp. 1215–1223, 2007.

[42] A. Hamdan, K. Charalampos, R. Roettgen et al., "Magnetic resonance imaging versus computed tomography for characterization of pulmonary vein morphology before radiofrequency catheter ablation of atrial fibrillation," *American Journal of Cardiology*, vol. 104, no. 11, pp. 1540–1546, 2009.

[43] A. Montefusco, L. Biasco, A. Blandino et al., "Left atrial volume at MRI is the main determinant of outcome after pulmonary vein isolation plus linear lesion ablation for paroxysmal-persistent atrial fibrillation," *Journal of Cardiovascular Medicine*, vol. 11, no. 8, pp. 593–598, 2010.

[44] C. von Bary, C. Dornia, C. Eissnert et al., "Predictive value of left atrial volume measured by non-invasive cardiac imaging in the treatment of paroxysmal atrial fibrillation," *Journal of Interventional Cardiac Electrophysiology*, vol. 34, no. 2, pp. 181–188, 2012.

[45] C. X. Wong, H. S. Abed, P. Molaee et al., "Pericardial fat is associated with atrial fibrillation severity and ablation outcome," *Journal of the American College of Cardiology*, vol. 57, pp. 1745–1751, 2011.

[46] C. McGann, E. Kholmovski, J. Blauer et al., "Dark regions of no-reflow on late gadolinium enhancement magnetic resonance imaging result in scar formation after atrial fibrillation ablation," *Journal of the American College of Cardiology*, vol. 58, no. 2, pp. 177–185, 2011.

[47] C. J. McGann, E. G. Kholmovski, R. S. Oakes et al., "New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation," *Journal of the American College of Cardiology*, vol. 52, no. 15, pp. 1263–1271, 2008.

[48] J. V. Wylie Jr., D. C. Peters, V. Essebag, W. J. Manning, M. E. Josephson, and T. H. Hauser, "Left atrial function and scar after catheter ablation of atrial fibrillation," *Heart Rhythm*, vol. 5, no. 5, pp. 656–662, 2008.

[49] I. E. Hof, B. K. Velthuis, S. M. Chaldoupi et al., "Pulmonary vein antrum isolation leads to a significant decrease of left atrial size," *Europace*, vol. 13, no. 3, pp. 371–375, 2011.

[50] H. M. Tsao, M. H. Wu, B. H. Huang et al., "Morphologic remodeling of pulmonary veins and left atrium after catheter ablation of atrial fibrillation: insight from long-term follow-up of three-dimensional magnetic resonance imaging," *Journal of Cardiovascular Electrophysiology*, vol. 16, no. 1, pp. 7–12, 2005.

[51] I. M. Robbins, E. V. Colvin, T. P. Doyle et al., "Pulmonary vein stenosis after catheter ablation of atrial fibrillation," *Circulation*, vol. 98, no. 17, pp. 1769–1775, 1998.

[52] T. Dill, T. Neumann, O. Ekinci et al., "Pulmonary vein diameter reduction after radiofrequency catheter ablation for paroxysmal atrial fibrillation evaluated by contrast-enhanced three-dimensional magnetic resonance imaging," *Circulation*, vol. 107, no. 6, pp. 845–850, 2003.

[53] J. Dong, C. R. Vasamreddy, V. Jayam et al., "Incidence and predictors of pulmonary vein stenosis following catheter ablation of atrial fibrillation using the anatomic pulmonary vein ablation approach: results from paired magnetic resonance imaging," *Journal of Cardiovascular Electrophysiology*, vol. 16, no. 8, pp. 845–852, 2005.

[54] T. Arentz, N. Jander, J. Von Rosenthal et al., "Incidence of pulmonary vein stenosis 2 years after radiofrequency catheter ablation of refractory atrial fibrillation," *European Heart Journal*, vol. 24, no. 10, pp. 963–969, 2003.

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Review Article

Left Atrial Appendage Exclusion for Stroke Prevention in Atrial Fibrillation

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The public health burden of atrial fibrillation (AF) and associated thromboembolic stroke continues to grow at alarming rates. AF leads to a fivefold increase in the risk of stroke. Therefore, stroke prevention remains the most critical aspect of AF management. Current standard of care focuses on oral systemic anticoagulation, most commonly with warfarin and now with newer agents such as dabigatran, rivaroxaban, and apixaban. However, the challenges and limitations of oral anticoagulation have been well documented. Given the critical role of the left atrial appendage (LAA) in the genesis of AF-related thromboembolism, recent efforts have targeted removal or occlusion of the LAA as an alternative strategy for stroke prevention, particularly in patients deemed unsuitable for oral anticoagulation. This paper highlights recent advances in mechanical exclusion of the LAA. The problem of AF and stroke is briefly summarized, followed by an explanation for the rationale behind LAA exclusion for stroke prevention. After briefly reviewing the history of LAA exclusion, we highlight the most promising LAA exclusion devices currently available. Finally, we discuss future challenges and opportunities in this growing field.

1. Introduction: Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is the most common arrhythmia in modern clinical practice, currently affecting up to 5 million people in the United States [1, 2]. The prevalence rises sharply with age, from approximately 1% among people aged 55–59 years to over 10% among those aged greater than 80 years [3]. Importantly, the burden of AF is expected to rise threefold by 2050 to an estimated 12–16 million Americans [4].

The most feared clinical consequence of AF is stroke due to thromboembolism. Stroke is the third leading cause of death and the number one cause of major disability in the United States [5]. AF is a powerful risk factor for stroke; a diagnosis of AF increases stroke risk fivefold and conveys an overall stroke rate of 5% per year [5]. Of the estimated 800,000 annual strokes in the USA, the percentage attributable to AF ranges from 1.5% (50–59 years old) to 23.5% (80–89 years old) [5]. As AF is commonly silent and undiagnosed, the influence of AF on stroke is almost certainly underestimated.

2. The Role of the Left Atrial Appendage

AF promotes thromboembolism through a variety of mechanisms, most significantly mechanical dysfunction in the atria leading to impaired blood flow and stasis. Additional factors including endothelial dysfunction, inflammation, platelet activation, and a hypercoagulable state have also been implicated [6–8]. The left atrial appendage (LAA) is particularly vulnerable to thrombus formation due to its complex anatomy and low blood flow during AF. A review of 23 studies found that thrombi were present in 17% of patients with nonrheumatic AF, of which 91% were located in the LAA [9]. A consistent theme has emerged that the vast majority of strokes due to AF represent thromboembolism originating from the left atrial appendage.

Johnson et al. described the LAA as "our most lethal human attachment" [10]. The LAA is derived from the left atrium and forms a blind pouch approximately 2–4 cm long. Most commonly, it lies on the anterior surface of the heart although variation is present. The neck of the LAA is relatively narrow and the endocardial surface is irregular due to

pectinate muscles. The number of lobes can vary; one autopsy survey of 500 patients showed that 77% of LAA had two or three lobes while 20% had one lobe [11]. This trabeculated and crypt-rich structure provides an ideal substrate for stasis and clotting. Magnetic resonance imaging and transesophageal echocardiography (TEE) have shed light on the influence of LAA anatomy on the risk of thrombus formation. There are signals that larger LAA ostia (perhaps due to a lower emptying velocity), larger neck diameter, and greater length all portend a higher risk of stroke [12].

3. Stroke Prevention: Oral Anticoagulation and Its Limitations

Stroke prophylaxis is one of the pillars of AF management. The current standard of care for stroke prevention in AF is oral systemic anticoagulation [13]. Importantly, stroke risk is not homogenous across the entire population of AF patients. Therefore, the decision to anticoagulate is based on a patient-by-patient assessment of stroke risk in the presence of known clinical risk factors. The most widely used risk assessment tool for nonvalvular AF is the $CHADS_2$ scoring system, which incorporates the risk factors of congestive heart failure, hypertension, age over 75 years, diabetes, and prior stroke or transient ischemic attack [14]. Aspirin therapy is recommended for a $CHADS_2$ score of 0, systemic anticoagulation is recommended for a $CHADS_2$ score of 2 or higher, and either option is reasonable for a $CHADS_2$ score of 1. This strategy attempts to balance the bleeding risk from systemic anticoagulation with the thromboembolic stroke risk from untreated AF across the spectrum of $CHADS_2$ scores. The newer $CHADS_2$-VASc score, which adds the risk factors of vascular disease and female gender, has become useful to further refine stroke risk in patients with an otherwise low $CHADS_2$ score [15]. Oral anticoagulation has been undeniably effective as a stroke reduction strategy. Warfarin, the predominant anticoagulant in clinical use, was shown to reduce AF-related stroke by 64% in a large meta-analysis [16].

However, the widespread use of systemic anticoagulation in AF has brought to light important limitations and disadvantages of this management strategy. Most notably, systemic anticoagulation has the unavoidable consequence of elevated bleeding risk. This has led to relative or absolute contraindications to anticoagulation in up to 40% of AF patients, usually due to a history of significant bleeding or a perceived elevated risk of falls and trauma [17, 18]. Aside from bleeding risk, anticoagulation use is further limited by the inconvenience of frequent blood testing and widespread interactions with food and other medications. In fact, anticoagulation is not utilized in up to 50% of eligible AF patients, often due to the limitations highlighted [19]. Furthermore, patients who are actually treated with warfarin spend up to half of the treatment time outside the therapeutic range [20]. This means that the full potential of warfarin to reduce stroke risk has never been fully realized.

Largely in response to the challenges of using warfarin, the newer oral anticoagulants dabigatran (a direct thrombin inhibitor) and rivaroxaban (a factor Xa inhibitor) have been recently developed and are now commercially available. A third agent, apixaban, has also been evaluated in a large clinical trial but has yet to gain the approval of the Food and Drug Administration (FDA) [21]. These newer agents minimize food and drug interactions and eliminate the need for INR monitoring, thus increasing the ease of administration and compliance. Unfortunately, they still suffer from comparable bleeding risk and a not insignificant level of drug intolerance; the two-year discontinuation rates for dabigatran and rivaroxaban are 21% and 24%, respectively [22, 23]. In addition, unlike warfarin, the newer agents are not easily reversible with blood product transfusion, raising serious concerns in the event of a bleeding incident. Finally, the novel agents come at a significantly higher cost than warfarin. Whether these agents are truly cost-effective in comparison to warfarin is an open question.

4. Stroke Prevention: Targeting the Left Atrial Appendage

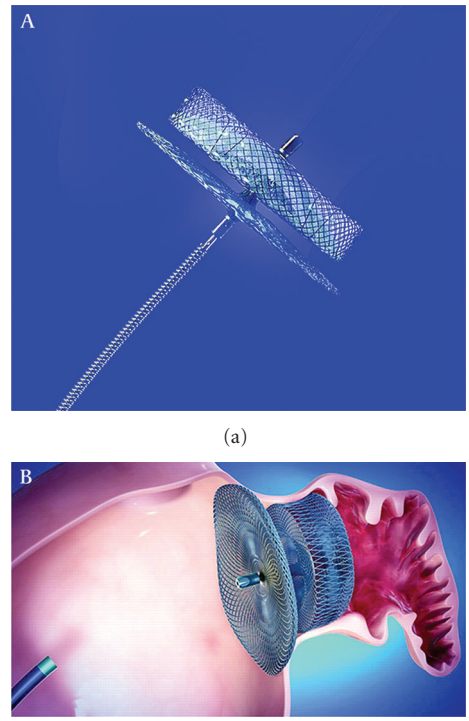
While oral anticoagulation options have certainly improved, there remains another glaring question: is systemic anticoagulation the best strategy for treating a pathological process that is largely focal, namely, thromboembolism originating from the LAA? Theoretically, a strategy focused on excluding the LAA should offer similar stroke prophylaxis while also eliminating the disadvantages of systemic anticoagulation, not the least of which is the lifelong commitment to daily medication. LAA exclusion would be an especially appealing option for patients with intolerance or contraindications to anticoagulation. Therefore, in recent years interest has emerged in mechanical exclusion of the LAA as an alternative strategy for AF stroke prevention.

5. LAA Exclusion: Surgical Techniques

Left atrial appendage exclusion is not a new idea. The first report of LAA exclusion in the surgical literature was in 1949, when Madden published his account of LAA removal in two patients as a prophylactic measure against recurrent arterial emboli [24]. The high complication rate of the procedure prevented its widespread adoption until the 1990s, when interest in the procedure was rekindled by the development of the Cox-Maze III procedure, which included removal of the LAA [25]. Surgical techniques have evolved around the two basic strategies of LAA exclusion (using various suture techniques) and LAA excision (via surgical stapler or removal with oversewing).

The data for surgical LAA exclusion consist primarily of retrospective case series and case reports. An important problem in the interpretation of these data is that surgical techniques are nonuniform across the literature. Outcomes measurements, especially pertaining to visual confirmation of surgical success, are also variable. The use of transesophageal echocardiography, considered the gold standard for LAA visualization, is absent in many reports. A large review found that surgical success is highly technique and operator dependent, with complete closure rates ranging from 17% to

Figure 1: The PLAATO device shown mounted on its delivery catheter. (*Image courtesy of Nature Publishing Group.*)



(a)

(b)

Figure 2: The AMPLATZER Cardiac Plug shown (a) mounted on its delivery catheter and (b) properly deployed at the ostium of the left atrial appendage. (*Image courtesy of BMJ Publishing Group Ltd and British Cardiovascular Society.*)

93% [26]. Excision and oversewing appears to demonstrate the best results. Of note, no data exist to support the notion that surgical LAA exclusion prevents future strokes; that question is the subject of an ongoing clinical trial (LAAOSII; http://clinicaltrials.gov/ NCT00908700).

The high morbidity of surgical LAA exclusion has prevented its adoption as a stand-alone procedure. Thus, current guidelines limit surgical LAA exclusion as an adjunctive procedure during mitral valve or Maze surgery [27].

6. LAA Exclusion: Percutaneous Techniques

A minimally invasive percutaneous approach to LAA exclusion should theoretically reduce the procedural risks inherent in open surgical techniques. Over the last decade, several percutaneous LAA exclusion devices have been developed and tested in humans. The procedures involve transseptal access, pericardial access, or a combination of both.

6.1. PLAATO Device (ev3 Endovascular, Plymouth, MN, USA). In 2001, the percutaneous LAA transcatheter occlusion (PLAATO) system became the first percutaneous LAA exclusion device employed in humans. It consists of a self-expanding nitinol cage covered with a blood-impermeable polytetrafluoroethylene membrane (Figure 1). Anchors along the maximum circumference of the device hold it securely to the LAA wall. The device is deployed in the LAA via transseptal catheterization under fluoroscopic and TEE guidance.

Clinical experience has been reported in three studies. Sievert et al. implanted the device in fifteen patients with chronic AF and contraindications to anticoagulation, achieving 100% procedural success with one incident of hemopericardium during LAA access [28]. An international multicenter registry of 111 patients with contraindications to anticoagulation demonstrated a 97% implant success rate and a 6% adverse event rate, including one death [29]. The ten-month stroke rate of 2.2% compared favorably to the $CHADS_2$ predicted rate of 6.3%. Finally, the five-year North American registry reported 100% procedural success in sixty-four AF patients at high risk for stroke [30]. In this cohort the five-year stroke rate was 3.8%, again superior to the expected 6.6% (relative risk reduction of 42%). Despite these promising early experiences, the manufacturer did not pursue further refinement of the device and instead withdrew it from the market in 2006 due to financial reasons.

6.2. AMPLATZER Cardiac Plug (St. Jude Medical, Plymouth, MN, USA). Following the success of the AMPLATZER Septal Occluder for patent foramen ovale and atrial septal defect closure, the AMPLATZER Cardiac Plug (ACP) was developed specifically for the LAA (Figure 2). The device consists of a self-expanding nitinol mesh constructed as a distal lobe (designed to prevent migration) and a proximal disk (designed to occlude the LAA ostium). The lobe and disk are connected by an articulating waist to accommodate anatomic variation among patients. The device is also delivered to the LAA via transseptal catheterization.

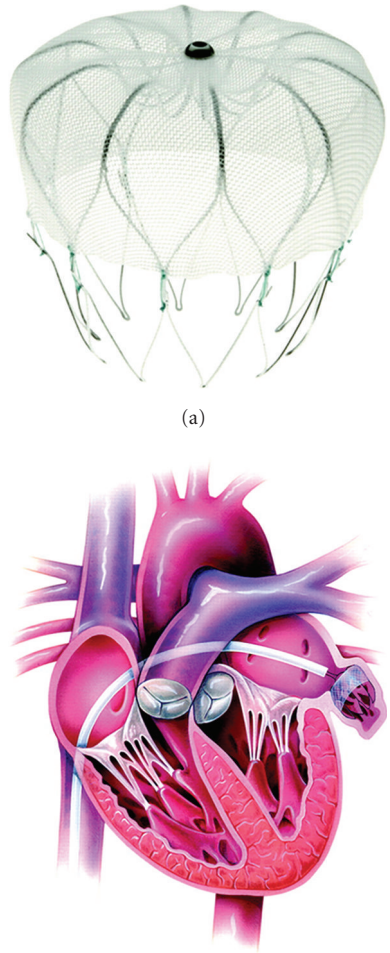
The initial human trials, conducted in Europe, demonstrated a 96% procedural success rate in 137 patients [31]. Serious complications occurred in ten patients (ischemic stroke in three; device embolization in two, both percutaneously recaptured; transient ischemia in two; pericardial effusions in five). The initial Asian-Pacific experience in

twenty patients was also recently published, highlighting a 95% procedural success rate and complications in three patients (catheter-related thrombus, coronary artery air embolism, and TEE-induced esophageal injury); one year followup showed no incidence of stroke or death [32]. Importantly, ACP implantation protocols have not involved periprocedural anticoagulation, instead employing dual antiplatelet therapy for one month followed by aspirin monotherapy for six months. The ACP has received CE mark approval and is currently in Phase I clinical trials in the United States (http://clinicaltrials.gov/ NCT01118299).

6.3. WATCHMAN LAA Closure Device (Atritech, Plymouth, MN, USA). The WATCHMAN device, first implanted in 2002, shares similarities with the ACP and PLAATO systems. It consists of a self-expanding, open-ended nitinol frame with fixation anchors and a polyethylene membrane (Figures 3 and 4). It also has a catheter-based transseptal delivery system. With this device, the membrane is permeable and covers only the part of the device exposed to the left atrium. The WATCHMAN device protocols have required warfarin for at least 6 weeks to prevent thrombus formation prior to endothelialization of the device. Warfarin has been discontinued once a follow-up TEE demonstrates complete occlusion of the LAA. Recently, a strategy of substituting dual antiplatelet therapy for warfarin postimplantation was evaluated in 150 patients in the ASAP registry. Results suggest that this strategy may be safe and effective in patients with contraindications even to short-term warfarin (Heart Rhythm Society Scientific Sessions 2012).

After the initial feasibility studies, which included a major product redesign, a landmark randomized clinical trial compared the WATCHMAN device with warfarin therapy [33–35]. In PROTECT-AF, 707 patients from fifty-nine centers in the USA and Europe were randomized 2 : 1 to device versus standard warfarin therapy. These patients did not have contraindications to warfarin and their stroke risk was somewhat lower than the PLAATO population (68% had a $CHADS_2$ score of 1 or 2). The trial was designed to assess noninferiority of WATCHMAN to standard warfarin therapy. After 1065 patient-years of followup, the primary efficacy endpoint (stroke, systemic embolism, or cardiovascular or unexplained death) was superior in the WATCHMAN group over the warfarin group (3.0% versus 4.9% per 100 patient-years) and achieved the criteria for noninferiority. However, the primary safety endpoint (excessive bleeding or procedure-related complications) was significantly worse in the WATCHMAN group (7.4% versus 4.4% per 100 patient-years). Periprocedural complications included 22 pericardial effusions (4.8%), four air emboli (0.9%), and three device embolizations (0.6%). On the other hand, the warfarin group had a higher incidence of major bleeding (4.1% versus 3.5%) and hemorrhagic stroke (2.5% versus 0.2%). Overall implantation success was 91% and at six months, 92% of patients in the WATCHMAN group were able to discontinue warfarin after a TEE confirmed complete LAA closure.

Of note, procedure-related and device-related adverse events were greater in the first half of PROTECT AF than



(a)

(b)

Figure 3: The WATCHMAN LAA Closure Device (a) highlighting the permeable membrane covering its left atrial face and (b) properly deployed within the ostium of the left atrial appendage. (*Image courtesy of BMJ Publishing Group Ltd and British Cardiovascular Society.*)

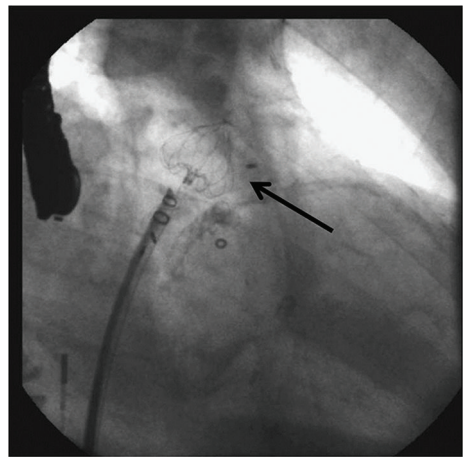


Figure 4: Fluoroscopic image of the WATCHMAN device (arrow) deployed in the left atrial appendage.

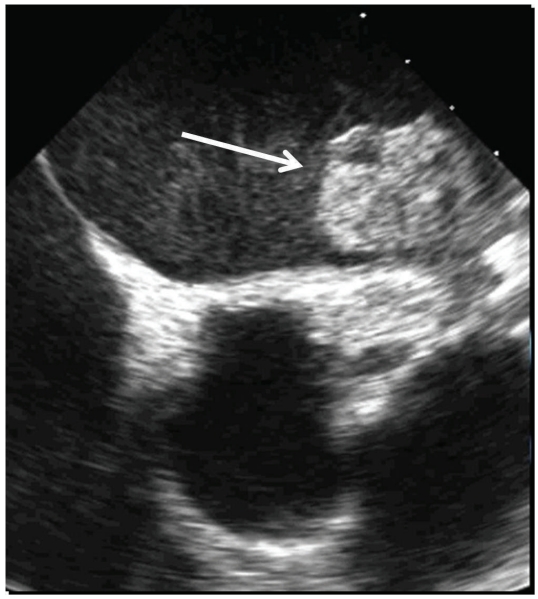


Figure 5: Transesophageal echocardiographic image of a large thrombus (arrow) on a WATCHMAN device several months after anticoagulation was discontinued.

in the second half, highlighting the learning curve involved with device implantation [36]. The adverse events rate continued to remain low in the Continued Access Protocol (CAP) Registry of 460 patients. A second randomized trial, PREVAIL, is currently underway in hopes of obtaining FDA approval for the WATCHMAN device. This trial is similar in design to PROTECT AF but with stricter inclusion criteria.

Thus far, the WATCHMAN device is the only transseptal LAA exclusion device that has demonstrated non-inferiority to warfarin for stroke prevention. However, concerns remain regarding peri-procedural complications and thrombus formation on the device prior to endothelialization (Figure 5).

6.4. LARIAT Suture Delivery System (SentreHeart, Palo Alto, CA, USA). The newest LAA exclusion device with promising human data is the LARIAT suture delivery system, which received FDA approval in 2009 for soft-tissue occlusion. This hybrid system involves the epicardial and transseptal placement of magnet-tipped guidewires, forming a single rail for the delivery of an endocardial balloon and an epicardial snare with a pretied suture loop (Figure 6). The inflated endocardial balloon acts as a marker for the placement of the epicardial snare around the base of the LAA. Under fluoroscopic and TEE guidance, the suture is then released and cinched to ligate the LAA at its base (Figure 7). Importantly, LAA closure can be evaluated in real time with TEE and left atrial angiography prior to irreversible suture delivery. If closure is not satisfactory, the snare can be opened and repositioned (Figure 8).

There are several advantages to this approach, including complete control of the pericardial space in the event of cardiac perforation, lack of any endovascular hardware left behind, and possible elimination of the need for post-procedure anticoagulation. The major disadvantage of the LARIAT system is the need for simultaneous transseptal and pericardial access. In addition, anatomic variables can limit candidacy for the device, such as LAA diameter greater than 40 mm, posteriorly rotated LAA, or pericardial adhesions from prior cardiac surgery or pericarditis.

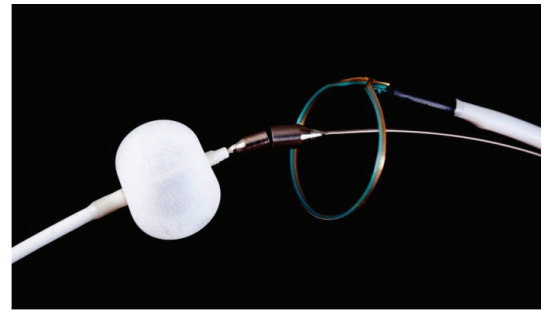


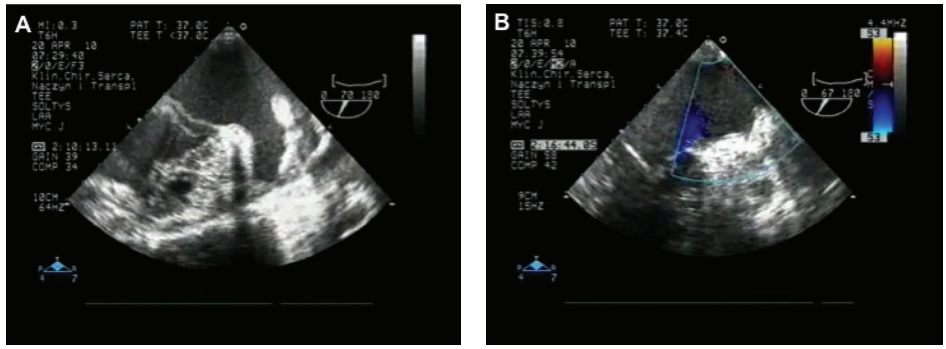
Figure 6: Major components of the LARIAT Suture Delivery System, including magnet-tipped guidewires, endovascular balloon catheter, and epicardial snare mounted with a pretied suture loop. (*Image courtesy of SentreHeart, Inc.*)

Initial experience in a canine model has confirmed the safety and feasibility of the LARIAT system [37]. In the first human experience, ten patients successfully underwent LAA exclusion with the LARIAT suture, one of whom required thorascopic removal of the snare owing to pectus excavatum [38]. Complete exclusion was confirmed in all ten patients using left atrial angiography and TEE. In a single center, nonrandomized study (PLACE II), LAA exclusion with the LARIAT system was attempted in 89 patients and was successful in 85 (96%). There were three adverse events (3.3%) involving bleeding—two pericardial related, one transseptal related. There were no device-related complications or embolic strokes. Persistent LAA closure (defined as less than 1 mm residual flow) was achieved in 95% of patients at day ninety and 98% of patients at one year (Heart Rhythm Society Scientific Sessions 2012).

7. Conclusions

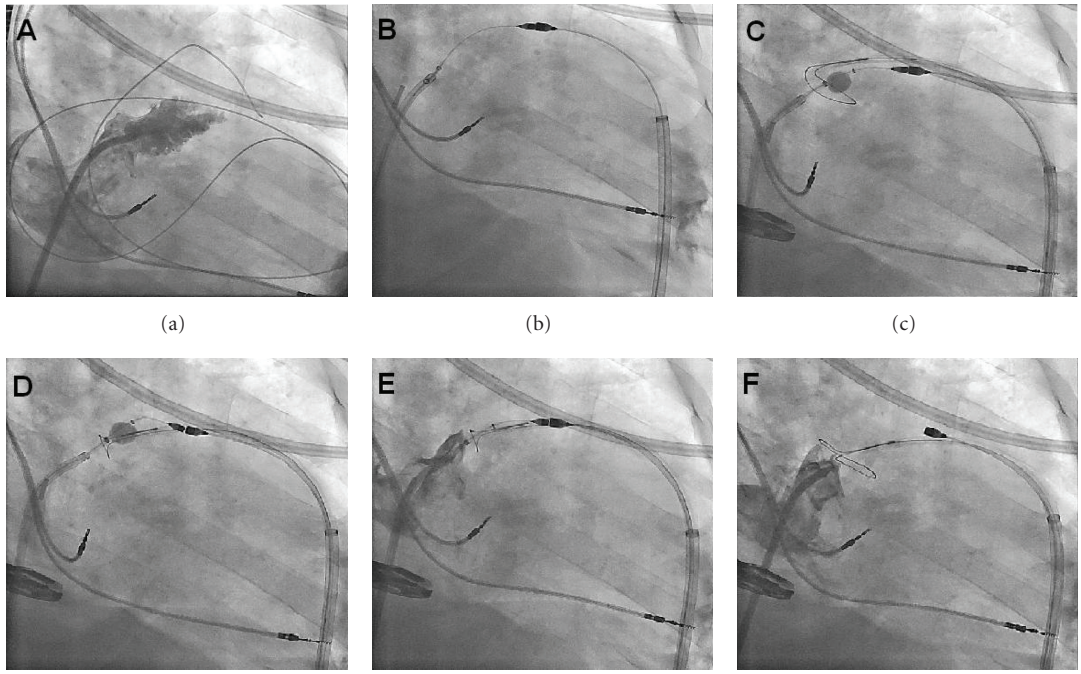
Stroke prevention in AF presents significant challenges as well as opportunities. Current treatment strategies with systemic anticoagulation, while effective, are fraught with limitations involving poor compliance, intolerance, and inconvenience. While newer oral anticoagulants overcome many of these limitations, all anticoagulants suffer from an unavoidable lifelong commitment to medication and elevated bleeding risk.

Given that the LAA is the source of thromboembolism in the vast majority of patients with AF and stroke, a newer paradigm of targeting the LAA has naturally evolved. Several strategies are available, although surgical LAA removal will likely not have a large role as a stand-alone procedure due to its significant morbidity. The minimally invasive strategies involve foreign body occlusion of the LAA ostium and pericardial suture ligation of the LAA base.



(a) (b)

Figure 7: Transesophageal echocardiographic images of the left atrial appendage (a) prior to and (b) immediately after LARIAT suture deployment, highlighting acute LAA exclusion. (*Image courtesy of SentreHeart, Inc.*)



(a) (b) (c)

(d) (e) (f)

Figure 8: Fluoroscopic sequence of the LARIAT procedure. (a) After transseptal and pericardial access, baseline left atrial angiography identifies the left atrial appendage. (b) Magnet-tipped endocardial and epicardial guidewires make contact across the wall of the left atrial appendage. (c) The balloon catheter is inflated just within the ostium of the left atrial appendage, guiding the placement of the epicardial snare. (d) The snare is tightened at the base of the left atrial appendage. (e) The balloon catheter is pulled back and left atrial angiography confirms occlusion of the left atrial appendage. (f) The suture is cinched down permanently, the snare is retracted, and a final left atrial angiogram reconfirms complete occlusion of the left atrial appendage.

Several questions remain regarding LAA exclusion. Aside from the PLAATO device, which is no longer available, the information regarding long-term durability of percutaneous LAA exclusion is not yet available. Even after acute procedural success, there is commonly a small diverticulum or "beak" left behind at the LAA ostium. In light of the surgical data that incomplete closure is worse than no closure at all [26], there are concerns about the thrombogenicity of this unnatural diverticulum.

The data also highlight that success rates are operator and experience dependent. As every new procedure necessarily involves a learning curve, the hope is that the second- and third- generation data with LAA exclusion will show improving procedural success rates with decreasing complication rates. The WATCHMAN experience has already demonstrated this.

The ultimate dominance of one percutaneous technique over the rest is unlikely. A more likely outcome is that

device selection will be tailored to patient characteristics. For instance, prior cardiac surgery or pericardial adhesions would make endocardial occlusion devices more feasible than the LARIAT system. On the other hand, an absolute contraindication to antiplatelet drugs or oral anticoagulation makes the LARIAT system more attractive as it appears to have no requirement for postprocedure anticoagulation. Similarly, a patient deemed at high risk for infection may benefit from the LARIAT system given its lack of endovascular hardware.

An even larger issue is the selection of appropriate candidates for these devices. Current focus has been on patients with intolerance or contraindications to warfarin. Whether these devices will be offered as an equal (or preferred) alternative to anticoagulation remains to be seen. PROTECT AF confirmed the non-inferiority of LAA exclusion to warfarin, but superiority data is still lacking. In addition, all LAA exclusion trials excluded patients with valvular AF or with prosthetic valves; the role of LAA exclusion in these patients is unknown. Finally, to date the comparison arm for these devices has only been warfarin. As some of the newer anticoagulants have reduced bleeding risk compared with warfarin, it is possible that the benefit of mechanical LAA exclusion would diminish in head-to-head trials against the newer agents.

The ultimate goal of LAA exclusion is to replace the lifelong need for anticoagulation with a single procedure associated with a small upfront risk and tremendous long-term benefit. This paradigm rests on the assumption that thromboembolism in AF is due solely to the anatomic presence of the LAA. However, data suggests that AF is associated with a systemic hypercoagulable state which may contribute to stroke risk in an independent and meaningful way [39]. This argues against discontinuation of anticoagulation, regardless of the patency of the LAA. Larger and longer-term studies will help shed light on this important question.

Despite the remaining challenges, LAA exclusion represents a promising alternative to systemic anticoagulation for the prevention of stroke in patients with AF. Already, studies have established that LAA exclusion is a viable option in patients with intolerance or contraindications to anticoagulation. Whether LAA exclusion is a superior strategy to anticoagulation in all AF patients remains to be seen. In addition, whether mechanical LAA exclusion reduces risk of stroke over the long term will require further clinical trials.

References

[1] A. S. Go, E. M. Hylek, K. A. Phillips et al., "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study," *The Journal of the American Medical Association*, vol. 285, no. 18, pp. 2370–2375, 2001.

[2] O. Wazni, B. Wilkoff, and W. Saliba, "Catheter ablation for atrial fibrillation," *The New England Journal of Medicine*, vol. 365, pp. 2296–2304, 2011.

[3] W. M. Feinberg, J. L. Blackshear, A. Laupacis, R. Kronmal, and R. G. Hart, "Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications," *Archives of Internal Medicine*, vol. 155, no. 5, pp. 469–473, 1995.

[4] Y. Miyasaka, M. E. Barnes, B. J. Gersh et al., "Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence," *Circulation*, vol. 114, no. 11, pp. 119–125, 2006.

[5] V. L. Roger, A. S. Go, D. M. Lloyd-Jones et al., "Heart disease and stroke statistics—2012 update: a report from the American heart association," *Circulation*, vol. 125, 1, Article ID e2-e220, 2012.

[6] G. Y. H. Lip and A. D. Blann, "Atrial fibrillation and abnormalities of hemostatic factors," *American Journal of Cardiology*, vol. 87, no. 9, pp. 1136–1137, 2001.

[7] M. K. Chung, D. O. Martin, D. Sprecher et al., "C-reactive protein elevation in patients with atrial arrhythmias: Inflammatory mechanisms and persistence of atrial fibrillation," *Circulation*, vol. 104, no. 24, pp. 2886–2891, 2001.

[8] M. Guazzi and R. Arena, "Endothelial dysfunction and pathophysiological correlates in atrial fibrillation," *Heart*, vol. 95, no. 2, pp. 102–106, 2009.

[9] J. L. Blackshear and J. A. Odell, "Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation," *Annals of Thoracic Surgery*, vol. 61, no. 2, pp. 755–759, 1996.

[10] W. D. Johnson, A. K. Ganjoo, C. D. Stone et al., "The left atrial appendage: our most lethal human attachment! surgical implications," *European Journal Cardio-Thoracic Surgery*, vol. 17, no. 6, pp. 718–722, 2000.

[11] J. P. Veinot, P. J. Harrity, F. Gentile et al., "Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination," *Circulation*, vol. 96, no. 9, pp. 3112–3115, 1997.

[12] R. Beinart, E. K. Heist, J. B. Newell, G. Holmvang, J. N. Ruskin, and M. Mansour, "Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation," *Journal of Cardiovascular Electrophysiology*, vol. 22, no. 1, pp. 10–15, 2011.

[13] V. Fuster, L. E. Rydén, D. S. Cannom et al., "2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American college of cardiology foundation/American heart association task force on practice guidelines," *Circulation*, vol. 123, no. 10, pp. e269–e367, 2011.

[14] B. F. Gage, A. D. Waterman, W. Shannon, M. Boechler, M. W. Rich, and M. J. Radford, "Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation," *The Journal of the American Medical Association*, vol. 285, no. 22, pp. 2864–2870, 2001.

[15] G. Y. H. Lip, R. Nieuwlaat, R. Pisters, D. A. Lane, and H. J. G. M. Crijns, "Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation," *Chest*, vol. 137, no. 2, pp. 263–272, 2010.

[16] R. G. Hart, L. A. Pearce, and M. I. Aguilar, "Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation," *Annals of Internal Medicine*, vol. 146, no. 12, pp. 857–867, 2007.

[17] M. Sudlow, R. Thomson, B. Thwaites, H. Rodgers, and R. A. Kenny, "Prevalence of atrial fibrillation and eligibility for anticoagulants in the community," *The Lancet*, vol. 352, no. 9135, pp. 1167–1171, 1998.

[18] L. M. Brass, H. M. Krumholz, J. M. Scinto, and M. Radford, "Warfarin use among patients with atrial fibrillation," *Stroke*, vol. 28, no. 12, pp. 2382–2389, 1997.

[19] A. S. Go, E. M. Hylek, L. H. Borowsky, K. A. Phillips, J. V. Selby, and D. E. Singer, "Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study," *Annals of Internal Medicine*, vol. 131, no. 12, pp. 927–934, 1999.

[20] A. M. Walker and D. Bennett, "Epidemiology and outcomes in patients with atrial fibrillation in the United States," *Heart Rhythm*, vol. 5, no. 10, pp. 1365–1372, 2008.

[21] C. B. Granger, J. H. Alexander, J. J. McMurray et al., "Apixaban versus warfarin in patients with atrial fibrillation," *The New England Journal of Medicine*, vol. 365, pp. 981–992, 2011.

[22] S. J. Connolly, M. D. Ezekowitz, S. Yusuf et al., "Dabigatran versus warfarin in patients with atrial fibrillation," *The New England Journal of Medicine*, vol. 361, pp. 1139–1151, 2009.

[23] M. R. Patel, K. W. Mahaffey, J. Garg et al., "Rivaroxaban versus warfarin in nonvalvular atrial fibrillation," *The New England Journal of Medicine*, vol. 365, pp. 883–891, 2011.

[24] J. L. Madden, "Resection of the left auricular appendix; a prophylaxis for recurrent," *The Journal of the American Medical Association*, vol. 140, no. 9, pp. 769–772, 1949.

[25] T. Weimar, S. Schena, M. S. Bailey et al., "The cox-maze procedure for lone atrial fibrillation: a single-center experience over 2 decades," *Circulation: Arrhythmia and Electrophysiology*, vol. 5, pp. 8–14, 2012.

[26] A. G. Dawson, S. Asopa, and J. Dunning, "Should patients undergoing cardiac surgery with atrial fibrillation have left atrial appendage exclusion?" *Interactive Cardiovascular and Thoracic Surgery*, vol. 10, no. 2, pp. 306–311, 2010.

[27] R. O. Bonow, B. A. Carabello, K. Chatterjee et al., "2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease): endorsed by the society of cardiovascular," *Circulation*, vol. 118, no. 15, pp. e523–e661, 2008.

[28] H. Sievert, M. D. Lesh, T. Trepels et al., "Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience," *Circulation*, vol. 105, no. 16, pp. 1887–1889, 2002.

[29] S. H. Ostermayer, M. Reisman, P. H. Kramer et al., "Percutaneous left atrial appendage transcatheter occlusion (PLAATO System) to prevent stroke in high-risk patients with nonrheumatic atrial fibrillation: results from the international multi-center feasibility trials," *Journal of the American College of Cardiology*, vol. 46, no. 1, pp. 9–14, 2005.

[30] P. C. Block, S. Burstein, P. N. Casale et al., "Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for Warfarin therapy. 5-year results of the PLAATO (percutaneous left atrial appendage transcatheter occlusion) study," *Journal of the American College of Cardiology: Cardiovascular Interventions*, vol. 2, no. 7, pp. 594–600, 2009.

[31] J. W. Park, A. Bethencourt, H. Sievert et al., "Left atrial appendage closure with Amplatzer Cardiac Plug in atrial fibrillation: initial European experience," *Catheterization and Cardiovascular Interventions*, vol. 77, no. 5, pp. 700–706, 2011.

[32] Y. Y. Lam, G. W. Yip, C. M. Yu et al., "Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience," *Catheterization and Cardiovascular Interventions*, vol. 79, no. 5, pp. 794–800, 2012.

[33] D. R. Holmes, V. Y. Reddy, Z. G. Turi et al., "Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial," *The Lancet*, vol. 374, no. 9689, pp. 534–542, 2009.

[34] P. B. Sick, G. Schuler, K. E. Hauptmann et al., "Initial worldwide experience with the watchman left atrial appendage system for stroke prevention in atrial fibrillation," *Journal of the American College of Cardiology*, vol. 49, no. 13, pp. 1490–1495, 2007.

[35] Y. L. Bayard, S. H. Ostermayer, and H. Sievert, "Transcatheter occlusion of the left atrial appendage for stroke prevention," *Expert Review of Cardiovascular Therapy*, vol. 3, no. 6, pp. 1003–1008, 2005.

[36] V. Y. Reddy, D. Holmes, S. K. Doshi, P. Neuzil, and S. Kar, "Safety of percutaneous left atrial appendage closure: results from the watchman left atrial appendage system for embolic protection in patients with AF (PROTECT AF) clinical trial and the continued access registry," *Circulation*, vol. 123, no. 4, pp. 417–424, 2011.

[37] R. J. Lee, K. Bartus, and S. J. Yakubov, "Catheter-based left atrial appendage (LAA) ligation for the prevention of embolic events arising from the LAA initial experience in a canine model," *Circulation: Cardiovascular Interventions*, vol. 3, no. 3, pp. 224–229, 2010.

[38] K. Bartus, J. Bednarek, J. Myc et al., "Feasibility of closed-chest ligation of the left atrial appendage in humans," *Heart Rhythm*, vol. 8, no. 2, pp. 188–193, 2011.

[39] T. Watson, E. Shantsila, and G. Y. Lip, "Mechanisms of thrombogenesis in atrial fibrillation: virchow's triad revisited," *The Lancet*, vol. 373, no. 9658, pp. 155–166, 2009.

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Research Article

Long-Term Costs of Ischemic Stroke and Major Bleeding Events among Medicare Patients with Nonvalvular Atrial Fibrillation

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Purpose. Acute healthcare utilization of stroke and bleeding has been previously examined among patients with nonvalvular atrial fibrillation (NVAF). The long-term cost of such outcomes over several years is not well understood. *Methods*. Using 1999–2009 Medicare medical and enrollment data, we identified incident NVAF patients without history of stroke or bleeding. Patients were followed from the first occurrence of ischemic stroke, major bleeding, or intracranial hemorrhage (ICH) resulting in hospitalization. Those with events were matched with 1–5 NVAF patients without events. Total incremental costs of events were calculated as the difference between costs for patients with events and matched controls for up to 3 years. *Results*. Among the 25,465 patients who experienced events, 94.5% were successfully matched. In the first year after event, average incremental costs were $32,900 for ischemic stroke, $23,414 for major bleeding, and $47,640 for ICH. At 3 years after these events, costs remained elevated by $3,156–$5,400 per annum. *Conclusion*. While the costs of stroke and bleeding among patients with NVAF are most dramatic in the first year, utilization remained elevated at 3 years. Cost consequences extend beyond the initial year after these events and should be accounted for when assessing the cost-effectiveness of treatment regimens for stroke prevention.

1. Introduction

Atrial fibrillation (AF) affects more than 3 million Americans and is characterized by an irregularly irregular heart rhythm, often with a rapid heart rate that may result in blood clots, shortness of breath, and overall weakness [1]. Primarily a disease of the elderly, the prevalence of AF doubles with each decade of life after the age of 60 years and occurs in about 10% of the population by 80 years [2, 3]. AF is associated with a five-fold increase in the risk of ischemic stroke and accounts for 15%–20% of all strokes [3]. Anticoagulation therapy with warfarin is recommended for patients with AF who are at moderate to high risk of stroke based on clinical guidelines [4], but it has been well documented that proper dosing and close monitoring are imperative to attain the correct level of anticoagulation to balance the risk of stroke without introducing a disproportionate risk of bleeding [5–7].

Costs to manage AF in the USA are estimated at $6.65 billion, including $4.88 billion in hospitalization expenses and $1.53 billion in outpatient management costs (in 2005 US$) [8]. Accounting for some fraction of these costs are expenses related to occurrence of stroke and hemorrhagic events. While numerous studies have estimated direct and indirect costs of stroke and bleeding outcomes among AF patients in the first year following the event [9–11], long-term US cost estimates have generally relied on modeling techniques extrapolating available data covering a shorter

period of time. Lifetime and other long-term cost modeling estimates would be expected to be more accurate if based on data covering a period of time extended beyond 1 year [12]. Furthermore, direct estimates of stroke and bleeding costs over several years could show whether costs for patients with these events remain elevated or eventually return to baseline levels, that is, the expected cost to treat AF without stroke or major bleeding.

The objective of the current study was to quantify the direct long-term costs, up to 3 years, of both stroke and bleeding events among patients with non-valvular AF (NVAF), which comprises approximately 90% of the overall AF population [13]. To separate the costs attributable to these events from the general costs of healthcare associated with NVAF, we conducted a retrospective cohort study of Medicare beneficiaries newly diagnosed with NVAF who later developed stroke or hemorrhagic events and were matched with NVAF patients who did not experience these outcomes based on demographic and NVAF disease characteristics.

2. Methods

2.1. Data Source. The study was conducted using 1999–2009 data from the Centers for Medicare & Medicaid Services (CMS) 5% sample standard analytical files (SAF)—limited data set (LDS). In contrast to commercial claims data sources, Medicare has a large number of patients over the age of 65 years, when incidence and prevalence of AF begin to increase dramatically. The analysis used fee-for-service (FFS), nondisabled Medicare patients who were not eligible for Medicaid. The files contain final action claims with all adjustments resolved for a 5% sample of all Medicare beneficiaries in each calendar year, including inpatient, outpatient, emergency room (ER), skilled nursing facility (SNF), hospice, home health agency, durable medical equipment (DME), and carrier (formerly Part B physician/supplier) claims. As this study was a retrospective analysis of existing, deidentified claims data, an institutional review board evaluation was not applicable and therefore, not conducted.

2.2. Patient Identification. Patients with AF were identified by at least 1 inpatient claim or 2 outpatient claims in the same calendar quarter with International Statistical Classification of Diseases and Related Health Problems, 9th Edition (ICD-9) code 427.31. Included patients were required to have a baseline period of 1 year (4 quarters) of continuous enrollment prior to the quarter of AF diagnosis. Patients with evidence of valvular conditions during the baseline period or quarter of AF diagnosis (codes in Table 1) were excluded.

Because the stage of NVAF disease progression has an impact on medical utilization (e.g., newly diagnosed patients tend to have higher costs than prevalent patients), the study was limited to patients with incident NVAF, defined as no AF claims during the baseline period, to allow patients to be matched on duration of NVAF. Similarly, strokes and/or bleeding events prior to AF diagnosis could lead to elevated baseline costs and would bias the estimate of long-term event costs after diagnosis. Thus, patients with prevalent AF (any claim with ICD-9 diagnosis code 427.31 during the baseline period) and patients with a principal inpatient claim with a code for stroke [14, 15] or bleeding [16, 17] events (Table 1) in the baseline period (1 year prior to AF diagnosis) or quarter of AF diagnosis were excluded.

2.3. Matching. All incident NVAF patients without a history of ischemic stroke or major bleeding event were then followed for first ischemic stroke or major bleeding event using validated ICD-9 codes (Table 1) [14–17]. Patients with events were matched with NVAF patients without events on age group at NVAF diagnosis, gender, race, geographic region, year of NVAF diagnosis, duration of enrollment, and warfarin use. The data did not include prescription claims; therefore, warfarin therapy was inferred for patients with at least 3 prothrombin tests (ICD-9 codes V58.61, CPT codes 85610, 85611, 99363, and 99364) during a 1-year period after NVAF diagnosis. This methodology has been validated previously in the Medicare data with 89% sensitivity and 92% specificity [6].

Each patient with an event was matched to up to 5 control patients via the greedy matching algorithm [18, 19]. Allowing more than 1 control to be matched to each patient with an event has been shown to improve statistical efficiency [20, 21]. While efficiency gains are limited beyond 3 or 4 matches, the low cost of obtaining additional matches in claims data permitted us to extend the maximal number of matches to 5. The number of matches were allowed to differ for each patient with an event, since varying numbers of controls have been shown to reduce bias [18]. Any patients not matched (either unmatchable patients with events or remaining controls) were excluded from the analysis.

2.4. Followup. Although the primary objective was to estimate costs up to 3 years following events, we did not limit the study population to those with 3 years of followup because doing so would have biased the population toward healthier patients. As such, no minimum duration of enrollment following the initial event was required. The quarter of the stroke or bleeding event was considered the start of followup for the patient with the event and for all controls matched to that patient.

The risk of stroke and bleeding events is somewhat intertwined (e.g., prior stroke is a stated risk factor for major bleeding), and it is possible that patients with an initial stroke (or bleed) may later experience a major bleed (or stroke). To keep the costs of these events distinct, if a patient experienced a bleeding event after stroke or a stroke after a major bleed, we ended followup for this patient in the quarter prior to the alternate event. A new followup period began with the quarter of the alternate event, and utilization measures were calculated separately for patients with both events. Thus, patients (and their matched controls) were categorized by the type(s) of events they experienced during followup as (1) patients with stroke events only or whose first event was a stroke, (2) patients with bleeding events only or whose first event was a major bleed, or (3) patients with both stroke and major bleeding events. To illustrate, a patient who first

Table 1: Study codes.

Condition	ICD-9 codes	CPT codes
Patient identification		
Atrial fibrillation	427.31	
Valvular conditions	Procedure codes: 35.0, 35.00–35.04, 35.1, 35.10–35.14, 35.2, 35.20–35.28, 35.96	33400, 33401, 33403, 33405, 33406, 33410–33415, 33417, 33420, 33422, 33425–33427, 33430, 33460, 33463–33465, 33468, 33470, 33472, 33474–33476, 33478, 33496, 33600, 33602
Outcomes		
Ischemic stroke	433.x1, 434.x1, 436, 437.1, 437.9	
Major bleeding		
Intracranial hemorrhage	430, 431, 432	
Other major bleeds	423.0, 455.2, 455.5, 455.8, 456.0, 456.2, 459.0, 530.7, 530.8, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 562.0, 562.1, 569.3, 569.85, 578, 599.7, 626.2, 626.6, 719.1, 784.7, 786.3, 852, 853	
CHA_2DS_2-VASc components		
Cardiac failure	398.91, 402.x1, 404.x3, 425, 428	
Hypertension[1]	362.11, 401, 402, 403, 404, 405	
Diabetes mellitus[1]	250, 357.2, 362.0, 366.41	
Prior TIA[2]	362.34, 435	
Vascular disease	410, 411, 412, 413, 414, 440, 441, 442, 443, 444, 445 Procedure codes: 00.66, 36.0, 36.1, 39.25	33510–33545, 34051, 34151, 34201, 34203, 34800–34834, 34900, 35081–35103, 35131, 35132, 35141, 35142, 35151, 35152, 35331, 35341, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35450, 35452, 35454, 35456, 35459, 35470, 35471, 35472, 35473, 35474, 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495, 35521, 35531, 35533, 35541, 35546, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 92980, 92981, 92982, 92984
HAS-BLED components		
Hypertension[1]	362.11, 401, 402, 403, 404, 405	
Abnormal renal function	582, 583, 585, 586	
Abnormal liver function	570, 571, 572, 573, 790.4	
Prior TIA[2]	362.34, 435	
Excessive alcohol use	291.0, 291.1, 291.2, 303, 305.0, 535.3, V11.3	

Note: With the exception of valvular conditions, ICD-9 codes reported as 3 digits will include all 4-digit and 5-digit codes beginning with the same 3 digits. For 4-digit codes, any 5-digit code beginning with the same 4 digits will also be included. ICD-9 codes reported are diagnosis codes unless otherwise indicated.
[1]Patient must have at least 2 diagnoses documented in the same calendar quarter to be considered as having the condition.
[2]Risk score definition includes prior stroke, but with the exclusion of patients with prior stroke, only prior TIA is applicable in this study.

experienced a stroke and then later had a major bleeding event was categorized both in the ischemic stroke group (to allow followup before the latter event to contribute to the estimation of stroke utilization) as well as in the group for patients with both events for the remainder of follow-up beginning with the subsequent bleeding event. Under this definition, some patients were double-counted across groups, although each quarter of followup was assigned to only one event group (stroke, major bleeding, or both). Patients who had an initial stroke and a major bleeding event in the same quarter (and their matched controls) contributed only to the group of patients with both events. Because patients with strokes or bleeds in the baseline period were excluded, recent history of these events had no impact on cost estimates. Recurrent strokes (a new stroke event following the initial stroke) or bleeds (a new bleeding event following the initial bleed) are an important contributor to long-term event costs and were included during followup.

Thus, followup began with the initial event of interest and ended with the first occurrence of (1) Medicare disenrollment (including patients changing from FFS to capitation, dropping Part B coverage, becoming eligible for state Medicaid services, becoming disabled, or dying), (2) for patients with stroke events, a subsequent bleeding event or for patients with bleeding events, a subsequent stroke event, or (3) 3 years after initial stroke or bleeding event. For patients with both stroke and bleeding events, the second followup will begin in the quarter of the latter event and end with either disenrollment or 3 years after the start of the second follow-up period, whichever occurs first.

2.5. Patient Characteristics. Basic demographic information including age, gender, race, and geographic region were assessed at the time of AF diagnosis. We also reported risk factors for both stroke and bleeding events. Risk factors were assessed during the baseline period and in the quarter of AF diagnosis. Stroke risk was quantified using the CHA_2DS_2-VASc score [22]. Bleeding risk was assessed using the HAS-BLED score, which had the best predictive value of several hemorrhage risk scores [23–27] in a recent assessment [28]; however, time in the therapeutic international normalized ratio (INR) range and drug use were unavailable in the data source and thus, were excluded from the HAS-BLED definition for this study. Definitions of stroke and bleeding risk factors used to calculate these scores are provided in Table 1.

2.6. Identification of Events. Stroke and major bleeding events were identified using principal ICD-9 codes on inpatient hospitalization claims only. Previously validated ICD-9 codes for identifying stroke [14, 15] and bleeding [16, 17] outcomes are provided in Table 1. Major bleeding events were divided into intracranial hemorrhage (ICH) and other major bleeding event, and results were produced separately for these hemorrhagic events. Because the Medicare 5% sample data only have calendar quarter reported on claims, events were recorded starting in the quarter following NVAF diagnosis.

2.7. Definition of Outcomes. The primary outcome was the incremental costs of stroke and bleeding events up to 3 years after the event. Costs were from a Medicare perspective (limited to Parts A and B paid amounts) and did not include oral medications or copayments from any supplemental insurance. Control patients with NVAF but no study events (stroke or major bleeding) were used to estimate the baseline cost of treating NVAF. Costs for patients with stroke or major bleeding events beyond the baseline treatment cost of NVAF were attributed to the event. Thus, the incremental costs of stroke and major bleeding were estimated as the difference in costs between patients with events and their matched controls, with cost accrual beginning in the quarter of the event and up to 3 years afterward. For example, if a patient had a stroke in the third quarter following the NVAF diagnosis, then we began summing costs for this patient and any controls matched to this patient in the third quarter after the NVAF diagnosis. Incremental costs were also broken down by costs occurring in inpatient, outpatient, ER, SNF, hospice, and home healthcare settings, as well as DME costs to determine aspects of care driving the potential cost consequences associated with management and treatment of NVAF. Other utilization measures included number of inpatient admissions and associated length of stay and number of outpatient or office visits.

Patients with recurrent stroke, ICH, or other major bleeding events were also identified, as well as the time from the initial event until recurrence. Recurrent events were only identified in the quarter following the initial event since the dating system in the data source made it impossible to discern between separate events occurring in the same quarter.

2.8. Analysis. All variables will be reported descriptively as means with standard deviations and medians with ranges for continuous variables and counts with percentages for categorical measures for patients with and without study events. Cost measures were adjusted to 2011 US dollars (USD) using the medical care component of the Consumer Price Index (CPI) annual inflation measures. Total and incremental utilization variables after a stroke/bleeding event were reported for 3 months (quarter of the event), 6 months, 9 months, 12 months, 18 months, 24 months, and 36 months. Because not all patients had the full 3 years of followup, the patient denominator declined over time. Comparison of total costs for patients with events and matched controls were conducted using standard 2-sided t-tests assuming unequal variances and a significance level of $\alpha = 0.05$.

Although matching should eliminate the need to adjust for all variables that were matched in the analysis of cost differentials, in order to adjust for any potential residual confounding, total incremental costs of strokes and bleeding events were adjusted for both matching variables and individual measures within the CHA_2DS_2-VASc and HAS-BLED scores, respectively. Multivariate adjusted costs were estimated using generalized estimating equation (GEE) models with a gamma distribution and log link function [29]. Bootstrapping techniques were employed to estimate standard errors of adjusted costs once the parameter estimate was retransformed from the log form. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

3. Results

A total of 445,796 patients with at least 1 inpatient or 2 outpatient claims with diagnosis codes for AF were identified in the data. After excluding patients without continuous enrollment in the baseline period (24.3%), disabled and Medicaid-eligible patients (4.6%), patients with valvular conditions (1.9%), patients with prevalent AF (9.5%), and patients with a history of stroke or hemorrhagic conditions (4.8%), 245,052 patients with NVAF was available for the study. Of these patients, 8,243 (3.4%) experienced an ischemic stroke during followup, 1,406 (0.5%) had an ICH,

and 15,816 (6.5%) had other types of major bleeding events. A total of 1,291 (0.5%) patients had both an ischemic stroke and major bleeding event (either ICH or other bleeding outcome). Matching was successful for 94.5% of all patients with stroke and major bleeds, with an average of 4 matched controls for each patient with an event. Among patients with events who were matched, the average time from NVAF diagnosis to event was 30 months for all events.

Descriptive statistics of matching characteristics show that patients with events and controls were balanced on all measures (Table 2). Average age was similar for patients with ischemic stroke, ICH, and other major bleeding events at approximately 80 years. Duration of followup was at least 2 years for 44% of patients, with 29% having data for all 3 years examined. Although patients were not matched on stroke or bleeding risk, patients with events and controls had similar CHA_2DS_2-VASc and HAS-BLED scores (Table 3).

Patients with both events had an average age of 81.1 years (81.3 years for matched controls), with 61.8% of patients female (62.7% controls). Warfarin use was prevalent for 37.5% of patients with both stroke and major bleeding events. CHA_2DS_2-VASc score averaged 4.02 points (3.80 for controls), and mean HAS-BLED was 1.37 (1.31 for controls). Approximately one-third (32.8%) of patients with both events had data for at least 2 years after the secondary event, and 19.4% had data at 3 years.

3.1. Ischemic Stroke Cohort. The ischemic stroke cohort consisted of 7,799 patients with stroke and 33,084 matched controls without study events. At 1 year poststroke, 62.9% of patients were still contributing data. By 2 years, 41.2% remained in the cohort, and at the end of followup 3 years after the event, 27.1% of patients were available. Among patients with stroke, 6.7% died, with 52.4% of deaths occurring in the quarter of the event. A total of 7.0% of stroke patients later went on to experience major bleeding events (either ICH or other major bleeds). Average quarterly total Medicare-reimbursed costs for patients with ischemic stroke and their matched controls without events are presented in Figure 1. The mean acute incremental cost of stroke in the quarter of the event was $20,604, and the average total 1-year cost was $32,900 more for patients with stroke than among controls. Total cumulative cost of stroke at 2 years was $36,515 and at 3 years was $38,712 for patients contributing data at these time points. In the second year after the event, total costs were $5,621 higher for stroke patients than for matched patients without events. Costs remained elevated in the third year after stroke, with an average incremental cost of $3,775. After adjusting for stroke risk factors and matching characteristics, the acute and annual incremental costs of stroke were slightly higher than in unadjusted analyses (Table 4). The largest contributors to second-year and third-year incremental costs associated with stroke were inpatient costs, SNF costs, and home healthcare costs (Table 5). In the third year after the event, patients with stroke averaged 5.2 more office visits than those without events. Recurrent ischemic stroke occurred in 6.7% of stroke patients, with an average time to recurrence of 12.0 months. The total incremental costs for patients with recurrent stroke were approximately $3,000–$4,000 higher as compared to those without recurrence in each of the first 3 years following the initial event (Table 5).

3.2. Major Bleeding Cohorts. A total of 1,276 patients with ICH and 5,097 matched controls were included in the study. Follow-up data was available for 57.5% of patients at 1 year after event, 37.3% at 2 years, and 24.0% after 3 years. The overall mortality rate for this cohort was 11.4%; 78.1% of deaths occurred in the quarter of the event. Among ICH patients, 4.7% subsequently had an ischemic stroke. The acute incremental cost of ICH in the quarter of the event was $29,877 (Figure 2). Total costs in the first year following ICH (including the quarter of the event) were $47,640 more for patients with events than among controls. The total cumulative cost of ICH after 2 years was $53,074 and at 3 years was $54,158. Second-year post-ICH costs were $7,910, and by the third year after the event, costs continued to be $3,156 higher than controls. Adjustment for bleeding risk factors and matching characteristics resulted in marginally higher ICH cost estimates in the first 2 years after the event and a similar value in year 3 as compared to the unadjusted results (Table 4). Inpatient, outpatient, SNF, and hospice utilization were the principal cost drivers in year 2 (Table 5). In the third year after ICH, hospice and outpatient costs were most elevated as compared to control costs. A total of 3.1% of patients with this event had a recurrent ICH. Average time to recurrence was 8.1 months. Total incremental costs for patients with recurrent ICH were approximately $7,000 more than for those without recurrence in the first year after the event, but were not elevated in the second and third years thereafter (Table 5).

The cohort of patients with major bleeding events other than ICH had 14,996 patients with events and 60,058 controls. At 1, 2, and 3 years after the event, 69.4%, 46.6%, and 31.0% of these patients contributed data, respectively. The rate of mortality for patients with major bleeds was 4.3%, with 36.3% of those deaths taking place in the quarter of the event. Ischemic stroke followed the bleeding event in 3.1% of these patients. Patients with major bleeding events had an average acute incremental cost of $15,699 (Figure 3), with total first-year cost of $23,414 more than for matched controls. Total cumulative cost 2 years after major bleeding events averaged $28,064 and after 3 years was $31,393. The second-year and third-year incremental costs after major bleeds were $6,936 and $5,400. Similar to the ischemic stroke and ICH results, after controlling for bleeding risk factors and matching variables, estimates of the incremental costs of other major bleeds were comparable to, if slightly higher than, unadjusted figures (Table 5). Inpatient and outpatient costs were particularly elevated in the second and third years after the event (Table 4). In year 2, patients with major bleeding events had 0.5 more inpatient admissions and 11.0 additional outpatient visits as compared with control patients. Number of inpatient and outpatient visits remained increased by 0.3 admissions and 8.8 visits in the third year after the event. Recurrent major

Table 2: Matching characteristics of medicare patients with NVAF with and without stroke and bleeding events.

Matching characteristics	Ischemic stroke		Major bleeding events			
			ICH		Other major bleeds	
	Event N = 7,799	Control N = 33,084	Event N = 1,276	Control N = 5,097	Event N = 14,996	Control N = 60,058
Age at AF diagnosis, years						
Mean (SD)	81.1 (7.6)	81.1 (7.9)	79.9 (7.3)	79.9 (7.6)	80.0 (7.7)	79.8 (7.8)
Age, categorized, *n* (%)						
65–69 years	626 (8.0%)	2,676 (8.1%)	119 (9.3%)	482 (9.5%)	1,498 (10.0%)	6,282 (10.5%)
70–74 years	1,058 (13.6%)	4,569 (13.8%)	197 (15.4%)	815 (16.0%)	2,408 (16.1%)	9,916 (16.5%)
75–79 years	1,582 (20.3%)	6,647 (20.1%)	285 (22.3%)	1,156 (22.7%)	3,328 (22.2%)	13,537 (22.5%)
80–84 years	1,791 (23.0%)	7,318 (22.1%)	319 (25.0%)	1,235 (24.2%)	3,295 (22.0%)	12,696 (21.1%)
≥85 years	2,742 (35.2%)	11,874 (35.9%)	356 (27.9%)	1,409 (27.6%)	4,467 (29.8%)	17,621 (29.3%)
Gender, *n* (%)						
Male	2,913 (37.4%)	12,287 (37.1%)	634 (49.7%)	2,506 (49.2%)	6,507 (43.4%)	25,669 (42.7%)
Female	4,886 (62.7%)	20,797 (62.9%)	642 (50.3%)	2,591 (50.8%)	8,489 (56.6%)	34,389 (57.3%)
Race, *n* (%)						
White	7,194 (92.2%)	31,539 (95.3%)	1,191 (93.3%)	4,901 (96.2%)	14,018 (93.5%)	57,668 (96.0%)
Black	445 (5.7%)	1,012 (3.1%)	50 (3.9%)	120 (2.4%)	678 (4.5%)	1,628 (2.7%)
Hispanic	66 (0.9%)	202 (0.6%)	17 (1.3%)	29 (0.6%)	126 (0.8%)	306 (0.5%)
Other	85 (1.1%)	288 (0.9%)	16 (1.3%)	44 (0.9%)	156 (1.0%)	408 (0.7%)
Unknown	9 (0.1%)	43 (0.1%)	2 (0.2%)	3 (0.1%)	18 (0.1%)	48 (0.1%)
US geographic location, *n* (%)						
Northeast	1,547 (19.8%)	6,408 (19.4%)	251 (19.7%)	975 (19.1%)	3,251 (21.7%)	12,450 (20.7%)
South	1,970 (25.3%)	8,599 (26.0%)	317 (24.8%)	1,270 (24.9%)	4,151 (27.7%)	16,768 (27.9%)
Midwest	3,227 (41.4%)	14,034 (42.4%)	525 (41.1%)	2,160 (42.4%)	5,818 (38.8%)	24,257 (40.4%)
West	1,051 (13.5%)	4,043 (12.2%)	183 (14.3%)	692 (13.6%)	1,767 (11.8%)	6,570 (10.9%)
Other/unknown	4 (0.1%)	3 (0.0%)	0 (0.0%)	0 (0.0%)	9 (0.1%)	12 (0.0%)
Year of AF diagnosis, *n* (%)						
2000–2003	4,919 (63.1%)	20,082 (60.7%)	715 (56.0%)	2,651 (52.0%)	8,935 (59.6%)	33,254 (55.4%)
2004–2006	2,132 (27.3%)	9,449 (28.6%)	403 (31.6%)	1,700 (33.4%)	4,359 (29.1%)	18,786 (31.3%)
2007–2009	748 (9.6%)	3,553 (10.7%)	158 (12.4%)	746 (14.6%)	1,704 (11.4%)	8,018 (13.4%)
Duration of study enrollment, *n* (%)						
3–<6 months	1,571 (20.1%)	6,604 (20.0%)	342 (26.8%)	1,324 (26.0%)	2,123 (14.2%)	8,582 (14.3%)
6–<12 months	1,341 (17.2%)	5,671 (17.1%)	202 (15.8%)	839 (16.5%)	2,455 (16.4%)	9,838 (16.4%)
12–<18 months	933 (12.0%)	4,030 (12.2%)	138 (10.8%)	570 (11.2%)	1,812 (12.1%)	7,345 (12.2%)
18–<24 months	740 (9.5%)	3,160 (9.6%)	114 (8.9%)	468 (9.2%)	1,576 (10.5%)	6,354 (10.6%)
24–36 months	3,214 (41.2%)	13,621 (41.2%)	480 (37.6%)	1,896 (37.2%)	7,030 (46.9%)	27,939 (46.5%)
Warfarin use, *n* (%)						
Yes	2,568 (32.9%)	10,087 (30.5%)	532 (41.7%)	1,968 (38.6%)	5,594 (37.3%)	20,576 (34.3%)
No	5,231 (67.1%)	22,997 (69.5%)	744 (58.3%)	3,129 (61.4%)	9,402 (62.7%)	39,482 (65.7%)

ICH: intracranial hemorrhage; SD: standard deviation.

Table 3: Risk scores for Medicare patients with NVAF with and without stroke and bleeding events.

Matching characteristics	Ischemic stroke		Major bleeding events			
			ICH		Other major bleeds	
	Event N = 7,799	Control N = 33,084	Event N = 1,276	Control N = 5,097	Events N = 14,996	Control N = 60,058
CHA_2DS_2-VASc score						
Mean (SD)	3.89 (1.49)	3.81 (1.46)	3.72 (1.46)	3.68 (1.50)	3.91 (1.51)	3.69 (1.46)
Median (range)	4 (0–9)	4 (0–9)	4 (1–9)	4 (0–9)	4 (0–9)	4 (0–9)
CHA_2DS_2-VASc, categorized, n (%)						
0 points	7 (0.1%)	17 (0.1%)	0 (0.0%)	3 (0.1%)	13 (0.1%)	30 (0.1%)
1-2 points	1,353 (17.4%)	6,107 (18.5%)	272 (21.3%)	1,149 (22.5%)	2,647 (17.7%)	12,949 (21.6%)
3–5 points	5,337 (68.4%)	22,861 (69.1%)	858 (67.2%)	3,358 (65.9%)	10,086 (67.3%)	40,401 (67.3%)
6–9 points	1,102 (14.1%)	4,096 (12.4%)	146 (11.4%)	587 (11.5%)	2,249 (15.0%)	6,678 (11.1%)
HAS-BLED score						
Mean (SD)	1.33 (0.75)	1.30 (0.75)	1.32 (0.76)	1.27 (0.77)	1.33 (0.78)	1.25 (0.76)
Median (range)	1 (0–4)	1 (0–4)	1 (0–3)	1 (0–3)	1 (0–4)	1 (0–4)
HAS-BLED, categorized, n (%)						
0 points	1,036 (13.3%)	4,552 (13.8%)	181 (14.2%)	790 (15.5%)	2,099 (14.0%)	9,777 (16.3%)
1-2 points	6,481 (83.1%)	27,370 (82.7%)	1,042 (81.7%)	4,105 (80.5%)	12,139 (81.0%)	48,293 (80.4%)
3–5 points	282 (3.6%)	1,165 (3.5%)	53 (4.2%)	202 (4.0%)	757 (5.1%)	1,994 (3.3%)

ICH: intracranial hemorrhage; SD: standard deviation.

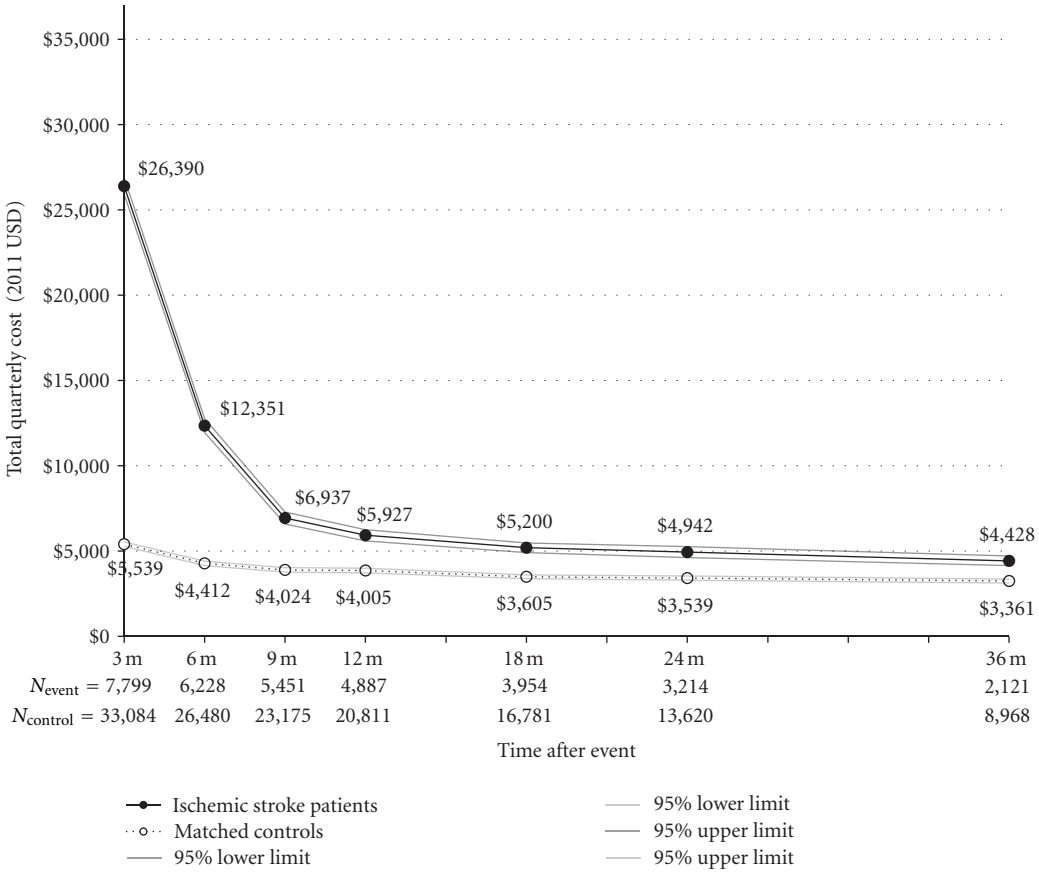

Figure 1: Total quarterly cost for Medicare patients with NVAF with and without ischemic stroke. Note: $P < 0.0001$ for difference in costs between patients with events and matched controls at all-time points using t-test assuming unequal variances and $\alpha = 0.05$ level.

Table 4: Adjusted total incremental cost of ischemic stroke, intracranial hemorrhage, and other major bleeding events (2011 USD).

Matching characteristics	Ischemic stroke[1] Adjusted cost (95% CI)	Major bleeding events	
		ICH[2] Adjusted cost (95% CI)	Other major bleeds[2] Adjusted cost (95% CI)
Acute and annual costs			
Acute (quarter of event)	\$22,204 (\$21,699–\$22,808)	\$33,887 (\$31,692–\$36,868)	\$16,437 (\$16,056–\$16,853)
Year 1	\$34,772 (\$33,691–\$35,870)	\$49,216 (\$45,490–\$53,431)	\$25,442 (\$24,700–\$26,190)
Year 2	\$6,186 (\$4,964–\$7,450)	\$8,572 (\$5,207–\$12,206)	\$7,193 (\$6,342–\$8,038)
Year 3	\$4,504 (\$3,383–\$5,617)	\$3,150 (\$475–\$5,764)	\$5,852 (\$5,010–\$6,671)

ICH: intracranial hemorrhage; CI: confidence interval.
Note: multivariate adjusted costs were estimated using generalized estimating equation (GEE) models with a gamma distribution and log link function. Year 1 costs include acute costs incurred during the quarter of the event.
[1]Adjusted for age group, gender, race, geographic region, year of NVAF diagnosis, warfarin use, cardiac failure, hypertension, diabetes, prior TIA, and vascular disease.
[2]Adjusted for age group, gender, race, geographic region, year of NVAF diagnosis, warfarin use, hypertension, abnormal renal function, abnormal liver function, and excessive alcohol use.

bleeding events (excluding ICH) were more common than repeat ischemic stroke or ICH events, occurring in 10.7% of stroke patients, with an average time to recurrence of 11.7 months. Patients with recurrent major bleeding events had substantially higher incremental costs in the first 3 years following the initial event as compared to those without recurrence, ranging from about \$4,000–\$7,000 in each year (Table 5).

3.3. Patients Experiencing Both Ischemic Stroke and Major Bleeding Events. Of the 1,291 patients (matched with 5,608 controls) who experienced both events, the first event was

Table 5: Incremental utilization for the first, second, and third years following ischemic stroke, intracranial hemorrhage, and other major bleeding events (2011 USD).

Incremental utilization	Ischemic stroke			ICH			Other major bleeds		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Patients with events, *n*	4,887	3,214	2,121	732	480	310	10,417	7,030	4,682
Controls, *n*	20,811	13,620	8,968	2,934	1,896	1,218	41,634	27,936	18,563
Visits, mean (SD)									
Inpatient admissions	1.8 (1.9)	0.2 (2.1)	0.1 (1.5)	1.9 (2.0)	0.2 (2.1)	0.1 (1.3)	1.7 (2.0)	0.5 (2.0)	0.3 (1.8)
Inpatient length of stay	13.0 (18.8)	1.7 (17.3)	0.8 (12.1)	17.5 (21.1)	1.8 (17.0)	0.4 (9.4)	9.3 (16.7)	2.8 (14.9)	1.9 (12.6)
Outpatient visits	29.3 (50.9)	7.6 (54.5)	5.2 (45.6)	37.5 (55.6)	3.9 (52.1)	2.5 (44.6)	29.7 (53.3)	11.0 (57.6)	8.8 (48.5)
Costs, mean (SD)									
Total cost for patients with recurrence	$36,446 ($46,915)	$5,651 ($24,653)	$6,425 ($36,941)	$54,132 ($48,830)	$3,960 ($20,287)	$355 ($27,807)	$29,168 ($44,457)	$6,866 ($23,571)	$11,368 ($38,379)
Total cost for patients without recurrence	$32,434 ($43,046)	$2,391 ($21,493)	$3,349 ($31,199)	$47,091 ($54,879)	$3,957 ($23,026)	$3,434 ($28,414)	$22,608 ($43,323)	$2,908 ($22,163)	$4,253 ($33,263)
Inpatient	$16,669 ($25,592)	$1,793 ($27,022)	$665 ($16,337)	$26,904 ($38,184)	$2,314 ($27,144)	$294 ($12,219)	$12,723 ($27,637)	$2,791 ($27,077)	$2,248 ($18,982)
Outpatient	$3,869 ($11,865)	$689 ($12,584)	$426 ($10,366)	$6,952 ($13,924)	$1,520 ($14,808)	$765 ($13,663)	$4,703 ($13,612)	$2,081 ($14,468)	$1,635 ($12,115)
ER	$1,556 ($2,556)	$288 ($2,706)	$133 ($1,976)	$2,029 ($3,329)	$318 ($2,809)	$239 ($1,819)	$1,709 ($2,885)	$443 ($2,984)	$372 ($2,294)
SNF	$7,160 ($14,392)	$1,381 ($12,890)	$1,130 ($9,303)	$7,832 ($14,374)	$1,560 ($12,664)	$444 ($8,112)	$2,688 ($10,366)	$751 ($11,270)	$587 ($7,886)
Home healthcare	$3,043 ($11,375)	$918 ($9,640)	$666 ($8,275)	$2,676 ($8,553)	$697 ($9,373)	$408 ($5,518)	$1,226 ($9,188)	$531 ($10,779)	$244 ($6,961)
Hospice	$341 ($6,376)	$406 ($8,440)	$629 ($8,093)	$874 ($6,856)	$1,364 ($10,438)	$806 ($7,627)	$54 ($5,504)	$84 ($6,897)	$46 ($5,446)
DME	$262 ($2,406)	$147 ($2,491)	$126 ($1,976)	$374 ($2,661)	$138 ($2,746)	$199 ($2,588)	$309 ($3,225)	$256 ($3,412)	$268 ($3,983)

ICH: intracranial hemorrhage; SD: standard deviation; ER: emergency room; SNF: skilled nursing facility; DME: durable medical equipment.
Note: incremental utilization is calculated as the difference between the utilization measure for each patient with an event and matched controls during the given time interval. All patients with data at each time point are included in the estimates.

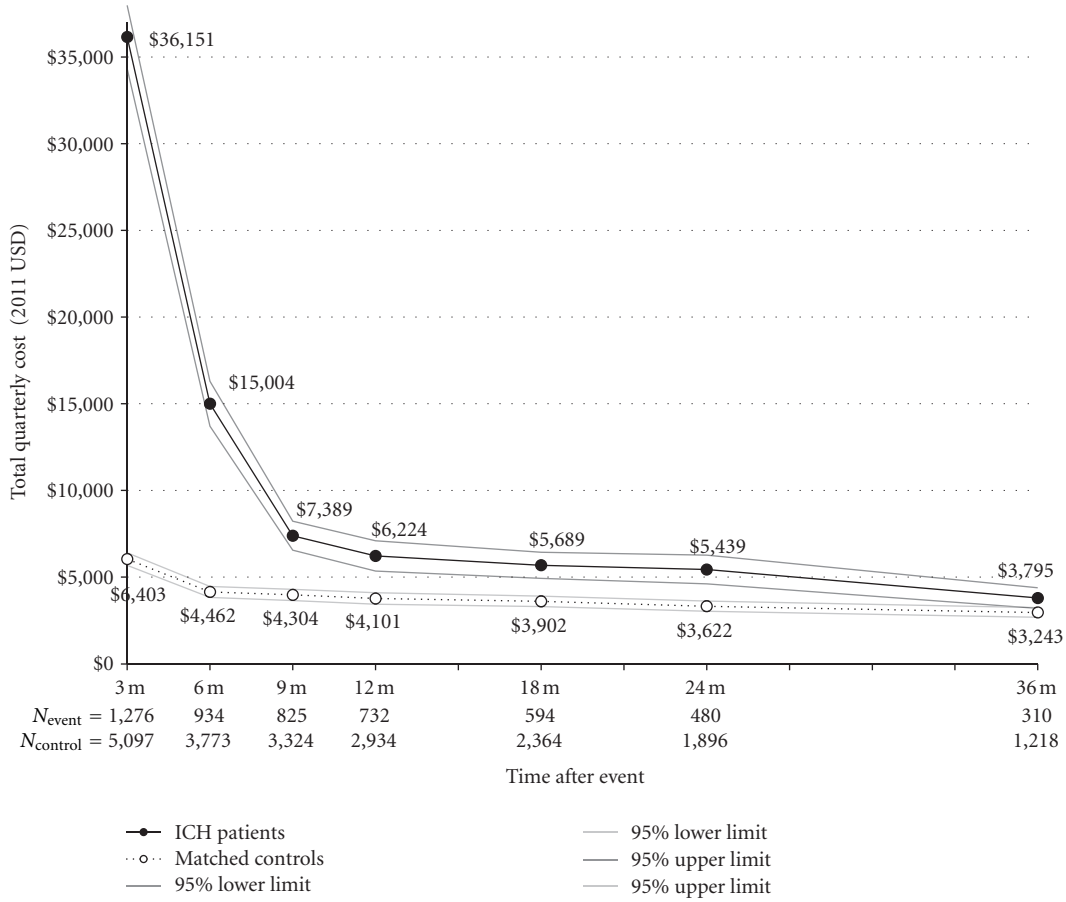

Figure 2: Total quarterly cost for Medicare patients with NVAF with and without ICH. Note: $P < 0.01$ for difference in costs between patients with events and matched controls at all-time points using t-test assuming unequal variances and $\alpha = 0.05$ level.

ischemic stroke for 544 (42.1%) patients, ICH for 60 (4.6%) patients, and other major bleeding for 461 (35.7%) patients. Initial stroke and major bleeding events occurred in the same quarter for the remaining 236 (18.3%) of patients. Average time from stroke to major bleeding event was 12.0 months for patients with an initial stroke. For patients with ICH as the first event, mean time to ischemic stroke was 9.8 months, and for patients with other types of major bleeds, the average time to stroke was 11.7 months. The mortality rate for patients with both types of events was 8.1%, and 43.3% of deaths occurred in the quarter of the secondary event. Total costs in the first year following the secondary event were \$37,691 more for patients with events than for controls. The total cumulative cost of patients with both events after 2 years was \$46.857 and at 3 years was \$60,511. Second-year incremental costs were \$10,519, and by the third year after the event, costs increased up to \$13,512 higher than controls. After adjusting for both stroke and bleeding risk factors, as well as matching characteristics, estimates of year 1, 2, and 3 costs for patients with both ischemic stroke and major bleeding events were \$42,271 (95% CI: \$39,542–\$45,907), \$10,146 (95% CI: \$6,696–\$14,192), and \$12,722 (95% CI: \$9,287–\$16,710), respectively. Recurrent events (either stroke or major bleeds) occurred in 14.2% of patients after the secondary event, with average time to recurrence of 10.5 months. Patients with recurrent events had costs \$19,042 higher in the first year and just over \$3,000 higher in the second and third years after the latter event as compared to those without recurrence.

4. Discussion

In this large population of Medicare beneficiaries with NVAF, the total direct medical costs of patients with incident ischemic stroke, ICH, and other major bleeding events were higher than for matched control patients in the first year following the event. Costs stabilized beyond the initial year after these events, but never returned to the same level as for patients with NVAF who never experienced a stroke or bleeding outcome. Even in the third year after these events, costs remained elevated by \$3,000–\$6,000 after adjusting for event risk factors and matching characteristics. Patients who experienced both ischemic stroke and major bleeding events suffered the highest rates of recurrence and had incremental costs of more than \$10,000 in the second and third years after the secondary event as compared to controls. These results imply that the cost consequences of ischemic stroke

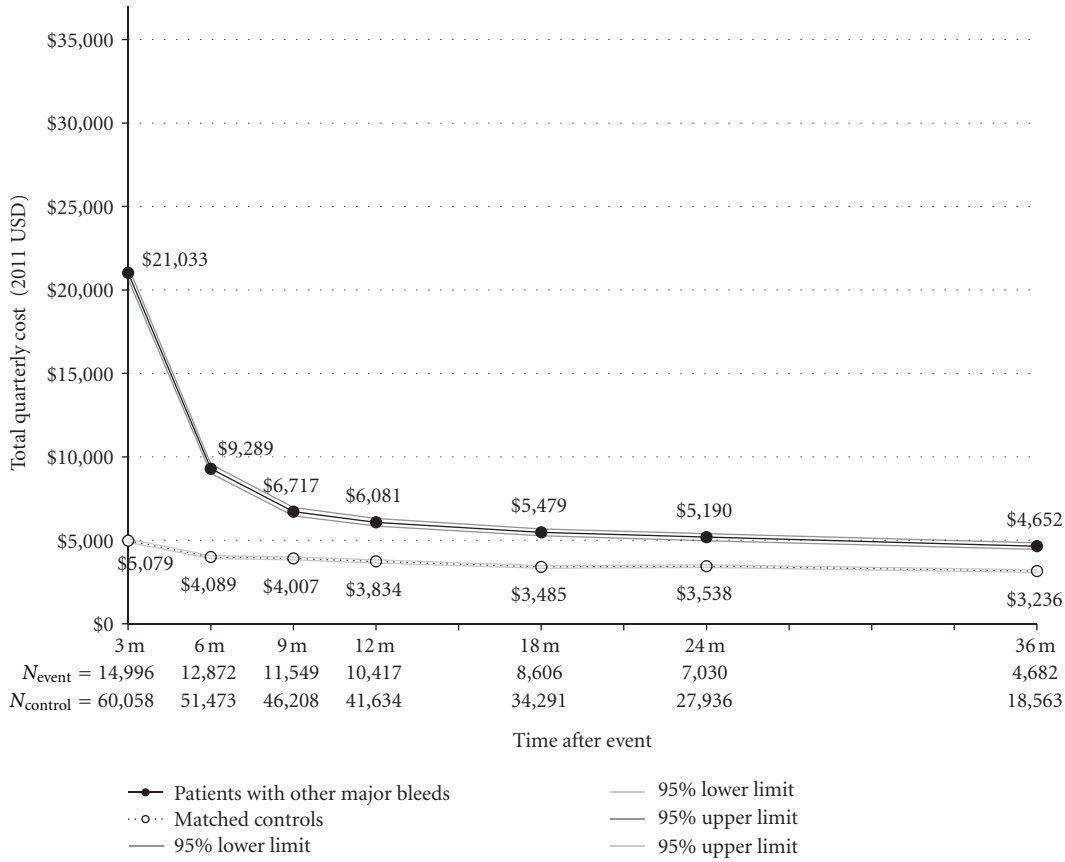

Figure 3: Total Quarterly Cost for Medicare Patients with NVAF with and without Other Major Bleeds. Note: $P < 0.0001$ for difference in costs between patients with events and matched controls at all time points using t-test assuming unequal variances and $\alpha = 0.05$ level.

occurring due to untreated NVAF and bleeding associated with anticoagulation treatment are observable beyond the first year after the event. This study builds on previous work estimating event costs in NVAF patients [30] by delineating between the costs attributable to new stroke and bleeding event versus expenses due to management of the underlying NVAF condition.

NVAF baseline costs were similar for all control groups. Because followup for some patients began shortly after NVAF diagnosis due to an early stroke or bleeding event, average costs for the control groups were higher in the initial quarters of the study due to the greater expense of establishing a treatment regimen for new NVAF patients versus managing patients with prevalent disease. Total costs for managing established NVAF ranged from approximately $3,000–$4,000 per quarter, confirming previous estimates of $10,100–$14,200 per year ($2,525–$3,550 quarterly) in the USA [11].

In the first year of followup, ICH was the most expensive of the events examined, followed by ischemic stroke and then other major bleeding events. Shorter-term costs for stroke and hemorrhagic events found in this study are largely consistent with prior work. We found first-year costs for ischemic stroke to be $34,772, which is within the range of estimates reported in a systematic review by Miller et al. ($24,991–$142,251) [12, 31–33]. Acute cost of major bleeding complications for patients receiving anticoagulation therapy was estimated to be $15,988 by Fanikos et al. in 2005, which is closely approximated by our total cost estimate of $16,437 in the quarter of the major bleed. To our knowledge, no previous study has reported direct cost estimates for stroke and bleeding events among NVAF patients beyond the first year after the event. By the third year after the event, patients with major bleeding events other than ICH had mean adjusted costs $5,852 higher than matched controls, as compared to $4,504 for ischemic stroke and $3,150 for ICH. This difference in long-term costs may be related to the rate of recurrence, as nearly as 11% of patients with major bleeds had a recurrent event versus 7% of ischemic stroke patients and only 3% of ICH patients. Patients with recurrent events tended to be more costly than those without recurrence, particularly those with repeat non-ICH major bleeding events. The reported differences in incremental costs among patients with and without recurrence confirms that repeat events are important cost drivers, although they do not fully explain the elevation in costs found over 3 years for patients with stroke and major bleeding as compared to those who never experienced these events, as the costs for patients with only one event were still more than $2,000–$4,000 greater than for patients without events.

Although analyses conducted using a claims database have several advantages, including large sample sizes and

the ability to examine real-world treatment patterns, some limitations were present. For one, we were restricted to the data that were available in the source (i.e., missing data, limited variables, etc.). Some uncertainty exists regarding the exact timing of events because only the quarter in which the claim occurred (rather than the exact date) was available in the data. For instance, if a stroke event occurred at the end of a quarter, costs may appear to be lower than had it happened in the beginning of the quarter. Because the primary objective of this study was to examine long-term costs, the impact of such temporal issues is expected to be small. In addition, data on use of medications such as nonsteroidal anti-inflammatory drugs or antiplatelet therapies were of interest, however, this information was not available in the data source. We were able to approximate the use of anticoagulants using previously validated algorithms examining INR tests, but the laboratory value of these tests was unknown, and therefore, we had no way to assess how adequately these patients are being treated via measures such as time in the target therapeutic INR range. Similarly, INR tests administered in anticoagulation clinics or using point-of-care systems during office visits were not available, allowing for potential misclassification of warfarin exposure. It is also possible that some patients may have become disabled or eligible for Medicaid as the result of a stroke or major bleeding event. Since we were unable to fully capture costs for patients for whom Medicare was not the primary payer, followup was ended for such patients once they qualified for these services. These patients may have been sicker than patients who did not become disabled or Medicaid eligible, so cost estimates from this study may have underestimated the true cost of stroke and major bleeding events in patients with NVAF.

The study methods aimed to compare patients with and without events at a similar stage in NVAF disease progression by matching on age and time of initial diagnosis, but it is possible that some patients were initially diagnosed at a more advanced stage of disease or that some patients' disease progressed more quickly than that of others. We found that patients with events and matched controls had similar stroke and bleeding risk as estimated by CHA_2DS_2-VASc and HAS-BLED scores, respectively, despite not having been matched on these measures. This provides some evidence that the health status of the comparator groups was similar at the time of NVAF diagnosis. Given the long timeframe of the study and advanced age of NVAF patients, as well as their poor health status and the severity of the health outcomes being examined, we expected a substantial amount of loss-to-followup prior to the end of the 3-year timeframe of interest. Having at least 2 years of postevent followup for 44% and complete data for 29% of the study population is therefore, a strength of the study. However, the patients remaining after 3 years of followup may not be representative of the general NVAF cohort. We attempted to account for this by not requiring a minimum duration of followup after events and also including all patients with data available at each time point, not just patients with the complete data for all 3 years. Furthermore, because nondisabled patients eligible for Medicare are almost exclusively over the age of 65 years, data on younger NVAF patients were unavailable in this study.

In spite of stated limitations, the results of this study offer a unique insight into costs of stroke and hemorrhagic outcomes among NVAF for up to several years following the events. While the acute costs of events associated with NVAF and anticoagulation treatment were most dramatic in the first year, the total healthcare costs for patients with events that were alive and contributing data for up to 3 years remained elevated as compared to patients with NVAF who did not have these events. Thus, a proper cost-effectiveness assessment that takes into account the true long-term costs of stroke and major bleeding events is required when weighing the risks (bleeding) and benefits (stroke prevention) of anticoagulation in patients with NVAF.

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Disclosure

C. J. Mercaldi, Y. Wu, N. Wu, and Q. Li are employees of United BioSource Corporation, which was contracted by BIPI to work in collaboration on this study. Authors K. Siu, D. R. Walker, and S. Sander are employees of BIPI. All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE); they were fully responsible for all content and editorial decisions and were involved at all stages of paper development.

References

[1] G. V. Naccarelli, H. Varker, J. Lin, and K. L. Schulman, "Increasing prevalence of atrial fibrillation and flutter in the United States," *American Journal of Cardiology*, vol. 104, no. 11, pp. 1534–1539, 2009.

[2] W. B. Kannel and E. J. Benjamin, "Status of the epidemiology of atrial fibrillation," *Medical Clinics of North America*, vol. 92, no. 1, pp. 17–40, 2008.

[3] P. A. Wolf, R. D. Abbott, and W. B. Kannel, "Atrial fibrillation as an independent risk factor for stroke: the Framingham Study," *Stroke*, vol. 22, no. 8, pp. 983–988, 1991.

[4] D. E. Singer, G. W. Albers, J. E. Dalen et al., "Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition)," *Chest*, vol. 133, no. 6, pp. 546–592, 2008.

[5] T. Darkow, A. M. Vanderplas, K. H. Lew, J. Kim, and O. Hauch, "Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system," *Current Medical Research and Opinion*, vol. 21, no. 10, pp. 1583–1594, 2005.

[6] K. Lakshminarayan, C. A. Solid, A. J. Collins, D. C. Anderson, and C. A. Herzog, "Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002)," *Stroke*, vol. 37, no. 8, pp. 1969–1974, 2006.

[7] L. Boulanger, J. Kim, M. Friedman, O. Hauch, T. Foster, and J. Menzin, "Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular

atrial fibrillation in clinical practice," *International Journal of Clinical Practice*, vol. 60, no. 3, pp. 258–264, 2006.

[8] K. S. Coyne, C. Paramore, S. Grandy, M. Mercader, M. Reynolds, and P. Zimetbaum, "Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States," *Value in Health*, vol. 9, no. 5, pp. 348–356, 2006.

[9] S. J. Boccuzzi, J. Martin, J. Stephenson et al., "Retrospective study of total healthcare costs associated with chronic nonvalvular atrial fibrillation and the occurrence of a first transient ischemic attack, stroke or major bleed," *Current Medical Research and Opinion*, vol. 25, no. 12, pp. 2853–2864, 2009.

[10] N. M. Engel-Nitz, S. D. Sander, C. Harley, G. G. Rey, and H. Shah, "Costs and outcomes of noncardioembolic ischemic stroke in a managed care population," *Vascular health and risk management*, vol. 6, pp. 905–913, 2010.

[11] S. E. Wolowacz, M. Samuel, V. K. Brennan, J. G. Jasso-Mosqueda, and I. C. Van Gelder, "The cost of illness of atrial fibrillation: a systematic review of the recent literature," *Europace*, vol. 13, pp. 1375–1385, 2011.

[12] P. S. J. Miller, F. L. Andersson, and L. Kalra, "Are cost benefits of anticoagulation for stroke prevention in atrial fibrillation underestimated?" *Stroke*, vol. 36, no. 2, pp. 360–366, 2005.

[13] T. J. Wang, J. M. Massaro, D. Levy et al., "A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham heart study," *Journal of the American Medical Association*, vol. 290, no. 8, pp. 1049–1056, 2003.

[14] E. Birman-Deych, A. D. Waterman, Y. Yan, D. S. Nilasena, M. J. Radford, and B. F. Gage, "Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors," *Medical Care*, vol. 43, no. 5, pp. 480–485, 2005.

[15] P. M. Wahl, K. Rodgers, S. Schneeweiss et al., "Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population," *Pharmacoepidemiology and Drug Safety*, vol. 19, no. 6, pp. 596–603, 2010.

[16] B. F. Gage, E. Birman-Deych, R. Kerzner, M. J. Radford, D. S. Nilasena, and M. W. Rich, "Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall," *American Journal of Medicine*, vol. 118, no. 6, pp. 612–617, 2005.

[17] R. H. White, R. J. Beyth, H. Zhou, and P. S. Romano, "Major bleeding after hospitalization for deep-venous thrombosis," *American Journal of Medicine*, vol. 107, no. 5, pp. 414–424, 1999.

[18] K. Ming and P. R. Rosenbaum, "Substantial gains in bias reduction from matching with a variable number of controls," *Biometrics*, vol. 56, no. 1, pp. 118–124, 2000.

[19] P. R. Rosenbaum, "Optimal matching for observational studies," *Journal of the American Statistical Association*, vol. 84, pp. 1024–1032, 1989.

[20] O. S. Miettinen, "Individual matching with multiple controls in the case of all-or-none responses," *Biometrics*, vol. 25, no. 2, pp. 339–355, 1969.

[21] H. K. Ury, "Efficiency of case control studies with multiple controls per case: continuous or dichotomous data," *Biometrics*, vol. 31, no. 3, pp. 643–649, 1975.

[22] A. J. Camm, P. Kirchhof, G. Y. H. Lip et al., "Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the european society of cardiology (esc)," *European Heart Journal*, vol. 31, pp. 2369–2429, 2010.

[23] R. J. Beyth, L. M. Quinn, and C. S. Landefeld, "Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin," *American Journal of Medicine*, vol. 105, no. 2, pp. 91–99, 1998.

[24] B. F. Gage, Y. Yan, P. E. Milligan et al., "Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF)," *American Heart Journal*, vol. 151, no. 3, pp. 713–719, 2006.

[25] P. M. M. Kuijer, B. A. Hutten, M. H. Prins, and H. R. Büller, "Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism," *Archives of Internal Medicine*, vol. 159, no. 5, pp. 457–460, 1999.

[26] R. Pisters, D. A. Lane, R. Nieuwlaat, C. B. De Vos, H. J. G. M. Crijns, and G. Y. H. Lip, "A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro heart survey," *Chest*, vol. 138, no. 5, pp. 1093–1100, 2010.

[27] T. I. Shireman, J. D. Mahnken, P. A. Howard, T. F. Kresowik, Q. Hou, and E. F. Ellerbeck, "Development of a contemporary bleeding risk model for elderly warfarin recipients," *Chest*, vol. 130, no. 5, pp. 1390–1396, 2006.

[28] G. Y. H. Lip, L. Frison, J. L. Halperin, and D. A. Lane, "Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score," *Journal of the American College of Cardiology*, vol. 57, no. 2, pp. 173–180, 2011.

[29] P. Diehr, D. Yanez, A. Ash, M. Hornbrook, and D. Y. Lin, "Methods for analyzing health care utilization and costs," *Annual Review of Public Health*, vol. 20, pp. 125–144, 1999.

[30] C. J. Mercaldi, M. Ciarametaro, B. Hahn et al., "Cost efficiency of anticoagulation with warfarin to prevent stroke in medicare beneficiaries with nonvalvular atrial fibrillation," *Stroke*, vol. 42, no. 1, pp. 112–118, 2011.

[31] J. J. Caro and K. F. Huybrechts, "Stroke treatment economic model (STEM): predicting long-term costs from functional status," *Stroke*, vol. 30, no. 12, pp. 2574–2579, 1999.

[32] H. M. Dewey, A. G. Thrift, C. Mihalopoulos et al., "Lifetime cost of stroke subtypes in Australia: findings from the North East Melbourne Stroke Incidence Study (NEMESIS)," *Stroke*, vol. 34, no. 10, pp. 2502–2507, 2003.

[33] P. Youman, K. Wilson, F. Harraf, and L. Kalra, "The economic burden of stroke in the United Kingdom," *PharmacoEconomics*, vol. 21, no. 1, pp. 43–50, 2003.

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Research Article

Effect of Preoperative Atrial Fibrillation on Postoperative Outcome following Cardiac Surgery

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Atrial fibrillation remains the commonest arrhythmia encountered in cardiac surgery. Data on the effect of preoperative atrial fibrillation on postoperative outcome remain limited. We sought to assess the effects preoperative atrial fibrillation on patients' outcome following cardiac surgery. This is a retrospective review of prospectively collected departmental data of all patients who underwent cardiac surgery over 8-year period. Our cohort consisted of 3777 consecutive patients divided into atrial fibrillation (n = 413, 11%) and sinus rhythm (n = 3364, 89%). Postoperative complications and in-hospital mortality were analysed. Univariate analysis showed significantly increased mortality and major complications in atrial fibrillation compared to sinus rhythm patients. Using multiple logistic regression analysis and after accounting for Euro SCORE as a confounding variable, we found that preoperative atrial fibrillation significantly increases the risk of mortality (OR 1.7), low cardiac output state (OR 1.3), prolonged ventilation (OR 1.4), infective complication (OR 1.5), gastrointestinal complications (OR 2.0), and intensive care unit readmission (OR 1.6). Preoperative atrial fibrillation in cardiac surgery patients increases their risk of mortality and major complications following cardiac surgery. Surgical strategies such as Cox-Maze procedure may be beneficial in these patients.

1. Introduction

Atrial fibrillation (A Fib) is the most common arrhythmia seen in cardiac surgery. In addition, it has also been identified in nonsurgical patients as a marker of severe cardiac disease and a risk factor for decreased long-term survival [1]. Advancing age has been shown to have a significant association with the incidence of A Fib, a relationship that is particularly important as the number of elderly patients referred for surgical revascularization is increasing [2]. Data from the society of thoracic surgery national adults cardiac database collected during 2002 and 2003 revealed that the prevalence of A Fib was 5.3% among patients undergoing isolated coronary artery bypass graft (CABG) but it increased to 6.1% in 2005 [3]. Although previous studies have examined the effects of preoperative A Fib on mortality following cardiac surgery, the full spectrum of postoperative complications that might be encountered in such patients has not been reported. In addition, previous studies have concentrated on one type of cardiac surgery than the full spectrum of surgeries which might have impacted on the outcomes observed (e.g., CABG only, or aortic valve replacements alone or mitral surgeries only). We sought to assess the effect of preoperative A Fib on postoperative outcome in patients undergoing cardiac surgery in order to understand the potential deleterious effects of atrial fibrillation.

2. Patients and Methods

2.1. Patients. This is a retrospective review of a prospective database (Patient Analysis and Tracking System, Dendrite Clinical, UK). All patients who underwent isolated CABG, valve surgery, or combination of both at St James's hospital between January 2000 and July 2008 were reviewed. Three thousands and seven hundreds and seventy seven (n = 3777) consecutive patients were included in the study. Patients were

Table 1: Preoperative variables among sinus rhythm and atrial fibrillation patients ($n = 3777$).

Variable	Atrial fibrillation ($n = 413$)	Normal rhythm ($n = 3364$)	P-value
Age (years)			
Mean ± SD	67.9 ± 9.4	63.4 ± 10.1	<0.001
Gender			
Female	126 (31%)	808 (24%)	0.004
Euro SCORE (additive)			
Mean ± SD	6.3 ± 3.2	3.8 ± 2.8	<0.001
Angina class (CCS)			
CCS 3-4	179 (43%)	1777 (53%)	<0.001
NYHA score			
Moderate-severe	277 (67%)	1344 (40%)	<0.001
Congestive cardiac failure	203 (49%)	469 (14%)	<0.001
Number of previous MI			
None	294 (71%)	2032 (60%)	<0.001
One	92 (22%)	1103 (33%)	
Two or more	27 (7%)	229 (7%)	
Interval of MI to surgery			
None	294 (71%)	2032 (60%)	<0.001
<90 days	62 (15%)	591 (18%)	
>90 days	57 (14%)	741 (22%)	
Diabetes mellitus	76 (18%)	601 (18%)	0.789
Hypercholeterolemia	210 (51%)	2359 (70%)	<0.001
Hypertension	228 (55%)	1816 (54%)	0.638
Smoking status			
Current smoker	42 (10%)	532 (16%)	0.007
Former smoker	226 (55%)	1787 (53%)	
None smoker	145 (35%)	1045 (31%)	
Renal failure	51 (12%)	172 (5%)	<0.001
Chronic obstructive pulmonary disease	65 (16%)	295 (9%)	<0.001
Cerebrovascular accident	36 (9%)	175 (5%)	0.003
Peripheral vascular disease	63 (15%)	541 (16%)	0.665
Extracardiac arteriopathy	24 (6%)	189 (6%)	0.873
Extent coronary artery disease			
Single/double vessel	101 (24%)	770 (23%)	<0.001
Triple vessel	159 (39%)	2140 (64%)	
None	153 (37%)	454 (13%)	
Left main stem disease	67 (16%)	823 (24%)	<0.001
Ejection fraction			
<50%	209 (51%)	1198 (36%)	<0.001
>50%	204 (49%)	2166 (64%)	
Intra-aortic balloon pump	7 (2%)	34 (1%)	0.206
Operative priority			
Elective/urgent	394 (95%)	3252 (97%)	0.183
Emergency/salvage	19 (5%)	112 (3%)	

Table 1: Continued.

Variable	Atrial fibrillation ($n = 413$)	Normal rhythm ($n = 3364$)	P-value
Cardiac procedure			
CABG	140 (34%)	2624 (78%)	
CABG + valve	102 (25%)	263 (8%)	<0.001
Valve	171 (41%)	477 (14%)	
BMI (kg/m^2)			
Mean ± SD	26.9 ± 4.6	27.7 ± 4.8	0.003
Cardiopulmonary bypass time (min)			
Mean ± SD	121.0 ± 45.7	98.5 ± 40.8	<0.001
Cross-clamp time (min)			
Mean ± SD	79.0 ± 32.7	58.6 ± 24.9	<0.001

BMI: body mass index.
CABG: coronary artery bypass graft.
CCS: canadian cardiovascular society.
MI: myocardial infarction.
NYHA: New York heart association.

divided into two groups based on their preoperative rhythm status: A Fib ($n = 413$, 11%) and normal sinus rhythm ($n = 3364$, 89%). Patients with other types of arrhythmias or those with automated implantable cardioverter defibrillator (AICD) were excluded from the study. All data were collected prospectively in a departmental database through the input of a dedicated database manager. The database was strictly controlled with twice yearly departmental reports generated and an annual report of departmental performance generated for audit purposes. All missing information was collected by reviewing patients' charts. Outcome measures studied were all types of postoperative complications, in-hospital mortality and length of both hospital and intensive care unit (ICU) stay. This study and the database were both approved by our institutional review board. Individual patient consent was obtained for entry into the database. However, our institutional review board waived the need for individual patient consent for this study.

2.2. Definitions. All CABGs were performed through a median sternotomy. Operative priority was determined by cardiothoracic surgeons according to standard criteria. Emergency/salvage surgery refers to medical factors relating to patient's cardiac disease dictating that surgery should be performed within hours to prevent morbidity or death. Urgent operation means that medical factors require the patient to have an operation during the same admission (i.e., before discharge). Elective operation means that medical factors indicate the need for an operation through a readmission at a later date. Renal complications refer to postoperative renal failure that required dialysis or managed conservatively in patients with no prior history of same or patients with preexisting renal impairment that worsened after the surgery requiring dialysis. Neurologic complications refer to the incidence of transient ischemic attacks or permanent strokes. Gastrointestinal complications refer to gastrointestinal bleed, pancreatitis, as well as bowel ischemia and obstruction. Infective complications refer to sternal/leg wound infections (requiring antibiotics or surgical intervention) and sepsis. Pulmonary complications refer to postoperative chest infection, tracheostomy insertion, pleural effusion requiring drainage, acute respiratory distress syndrome, respiratory arrest, and reintubation. Blood transfusion requirement refers to the need of transfusion of packed red blood cells and excluding the need of isolated platelet or fresh frozen plasma transfusion.

2.3. Data Analysis. Data analysis began by exploring the differences between the two groups for clinical, admission, and outcome variables. Categorical variables were compared using the Z test for proportion or Fisher's exact test as appropriate. Continuous variables were compared using independent t-test or the nonparametric Mann-Whiteney test based on the satisfaction of the normality assumption (Tables 1 and 2). The effect of atrial fibrillation on mortality and other patient outcome variables was further analyzed using logistic regression methods. Effect size of Atrial fibrillation on each individual outcome was quantified by crude odds ratios (OR), followed by adjusted OR after accounting for Euro SCORE (Table 3). Subgroup analysis of the type of operation and the outcome variables in relation to presence of atrial fibrillation is depicted in Table 4. OR, 95% confidence intervals (CI) as well as exact P-values are reported. Statistical analysis was performed using SPSS version 17 (SPSS, Chicago, IL, USA). The P values were considered statistically significant when <0.05.

3. Results

Our cohort ($n = 3777$) consisted of 934 (25%) females and 2843 (75%) males. Age ranged from 19 to 89 years old with a mean (±1 S.D.) of 63.9 (±10.1) years old. In-hospital

Table 2: Postoperative outcome in atrial fibrillation patients undergoing cardiac surgery compared to sinus rhythm patients (n = 3777).

Outcome	Atrial fibrillation (n = 413)	Normal rhythm (n = 3364)	P-value
Low cardiac output requiring Inotropes ± IABP	241 (58%)	1308 (39%)	<0.001
Reoperation	34 (8%)	182 (5%)	0.020
Ventilation time			
<24 hours	348 (84%)	3161 (94%)	<0.001
>24 hours	65 (16%)	203 (6%)	
Pulmonary complication	97 (23%)	640 (19%)	0.031
Neurological complications	37 (9%)	228 (7%)	0.101
Renal failure			
Dialysis/nondialysis	53 (13%)	208 (6%)	<0.001
No	360 (87%)	3156 (94%)	
Infective complications	60 (15%)	253 (8%)	<0.001
Gastrointestinal complications	13 (3%)	39 (1%)	<0.001
ICU stay (days)			
Mean ± SD	3.4 ± 7.4	1.9 ± 4.3	<0.001
ICU readmission	29 (7%)	99 (3%)	<0.001
Length of hospital stay (days)			
Mean ± SD	12.7 ± 17.4	8.7 ± 11.4	<0.001
Blood transfusion	231 (56%)	1486 (44%)	<0.001
Status			
Alive	375 (91%)	3278 (97%)	<0.001
Dead	38 (9%)	86 (3%)	

ICU: intensive care unit.
IABP: intraaortic balloon pump.

Table 3: Logistic regression analysis for atrial fibrillation and outcome (unadjusted and Euro SCORE adjusted) (n = 3777).

	Unadjusted			Euro SCORE Adjusted		
	OR	95% C.I	P-value	OR	95% C.I	P-value
Death	3.9	(2.6–5.7)	<0.001	1.7	(1.1–2.7)	0.013
Low Cardiac	2.2	(1.8–2.7)	<0.001	1.3	(1.03–1.6)	0.026
Reoperation	1.6	(1.1–2.3)	0.020	1.1	(0.8–1.7)	0.501
Ventilation	3.0	(2.2–3.9)	<0.001	1.4	(1.0–1.96)	0.048
Pulmonary	1.3	(1.0–1.7)	0.030	0.96	(0.7–1.2)	0.734
Neurological	1.4	(0.9–2.0)	0.100	0.9	(0.6–1.3)	0.507
Renal	2.2	(1.6–3.1)	<0.001	1.3	(0.9–1.8)	0.197
Infective	2.1	(1.5–2.8)	<0.001	1.5	(1.1–2.1)	0.010
GI*	2.8	(1.5–2.2)	0.002	2.0	(1.0–3.9)	0.044
ICU	2.5	(1.6–3.8)	<0.001	1.6	(1.0–2.5)	0.047
Blood transfusion	1.6	(1.3–1.8)	<0.001	0.8	(0.6–0.99)	0.043

* GI: gastrointestinal complications.
ICU: intensive care unit readmission.

mortality overall was 3.3% (124 patients). The incidence of preoperative A Fib in our cohort was 11% (413 patients) while 89% of patients were in normal sinus rhythm preoperatively (n = 3364). Preoperative factors and patient characteristics among the two groups are summarized in Table 1. As shown in this table, patients with preoperative A Fib were on average 4.5 years older, more females, higher Euro SCORE, with higher New York heart association (NYHA) grades, but lower Canadian cardiovascular society (CCS) grades. The incidence of congestive heart failure, renal failure, chronic obstructive pulmonary disease, and cerebrovascular accidents were also higher in the A Fib group. A Fib patients had higher incidence of valve surgery or combination of CABG and valve surgery than sinus rhythm patients. There was no significant difference between the two groups in relation to diabetes, hypertension, peripheral vascular disease, extracardiac arteriopathy, preoperative intraaortic balloon pump (IABP) requirement, and operative priority.

The full spectrum of postoperative complications and in-hospital mortality among the two groups is summarized in Table 2. As shown, mortality was significantly higher in A Fib group (9% versus 3%, $P < 0.001$). In addition, the lengths of both hospital and ICU stay were significantly higher in the A Fib group. All types of postoperative complications including low cardiac output state, pulmonary complications, renal failure, infective complications, gastrointestinal complications, and reexploration were significantly higher in A Fib patients. Neurological complications were the only exception where no significant increase was noted.

By using logistic regression analysis (Table 3), crude and adjusted odds ratios (OR) were calculated. By adjusting for potential confounding variable such as Euro SCORE, we found that preoperative atrial fibrillation is significantly associated with in-hospital mortality (OR 1.7), low cardiac output (OR1.3), prolonged ventilation (OR 1.4), infective complications (OR 1.5), gastrointestinal complications (OR 2.0), and ICU readmission (OR 1.6) compared to normal sinus rhythm patients. Subgroup analysis of the type of surgical procedure and magnitude of the adverse influence of atrial fibrillation on each outcome variable is shown in Table 4.

4. Discussion

A Fib remains the most common arrhythmia seen in cardiac surgery both preoperatively and postoperatively. Various studies have examined the effect of postoperative A Fib on patients' outcome following cardiac surgery. However, only limited studies have examined the effect of preoperative A Fib on patients' outcome following cardiac surgery [4–8]. As summarized in Table 5, all these studies have inherent limitations such as type of surgery performed, the number of patients enrolled, and the type of morbidity examined. To date, our study remains the only study which comprehensively examined all types of postoperative complications in A Fib patients undergoing cardiac surgery. This is important as factors such as advancing age is a risk factor for A Fib, and cardiac surgery patients are increasingly referred at older age where this problem is most common. An understanding

Table 4: Subgroup analysis of the type of surgery and magnitude of adverse influence of atrial fibrillation on each outcome variable (n = 3777).

	CABG			CABG + valve			Isolated valve		
	OR	95% C.I	P-value	OR	95% C.I	P-value	OR	95% C.I	P-value
Death	2.0	0.98–4.2	0.056	2.5	1.0–5.9	0.045	1.5	0.7–3.5	0.319
Low cardiac	0.8	0.5–1.1	0.206	1.9	1.1–3.2	0.021	1.99	1.4–2.9	<0.001
Reoperation	1.3	0.6–2.7	0.503	1.1	0.5–2.2	0.834	0.7	0.3–1.4	0.299
Ventilation	0.97	0.5–1.9	0.926	1.6	0.9–2.9	0.135	1.4	0.8–2.4	0.284
Pulmonary	1.2	0.8–1.8	0.425	1.2	0.7–2.0	0.433	0.7	0.4–1.2	0.190
Neurological	0.7	0.3–1.4	0.337	0.9	0.4–1.9	0.815	0.97	0.5–1.8	0.927
Renal	0.9	0.5–1.8	0.806	2.3	1.2–4.2	0.011	0.99	0.5–1.8	0.973
Infective	1.1	0.6–1.9	0.769	2.7	1.5–4.8	0.001	1.7	0.9–3.4	0.132
GI*	2.1	0.7–6.4	0.177	2.7	0.9–7.8	0.075	0.9	0.1–5.3	0.889
ICU**	1.4	0.6–3.0	0.428	2.1	0.9–4.9	0.099	1.6	0.7–3.7	0.286
Blood	0.8	0.5–1.1	0.157	0.8	0.5–1.3	0.344	0.8	0.6–1.2	0.402

CABG: coronary artery bypass graft.
*GI: gastrointestinal complications.
**ICU: intensive care unit readmission.

of the pattern of such complications and the effect of A Fib on outcome following surgery can lead to potentially preventative strategies to decrease the burden of these complications such as the use of concomitant Cox-MAZE procedure.

As shown in Tables 3 and 4, there was an increase in the rate of in-hospital mortality among A Fib patients compared to those in sinus rhythm. This effect persisted after adjusting for confounding variable such as Euro SCORE. In addition, low output state, gastrointestinal complications, and ICU readmission were also significantly increased in A Fib patients. Various reasons can potentially explain these observed effects. Preoperative atrial fibrillation can lead to low cardiac output postoperatively, hence the requirement of both rate control and inotropic support which in itself is arrhythmogenic. Our finding of low output state in preoperative A Fib patients is supported by previous observations [7, Table 5]. The effect of preoperative A Fib on gastrointestinal complications is a direct result of both low output state and embolic nature of such cases. These can lead to bowel ischemic or unstable gastrointestinal haemorrhages from low perfusion state [9]. Data on short-term mortality in A Fib patients are rather conflicting (Table 5). Some have showed increase in hospital mortality [7] while others did not. The main reason for the conflicting results stem from the number of patients analysed in these studies. Larger series showed significant association with hospital mortality while smaller series did not. This rise in mortality could be related to the complications observed in A Fib patients such as low output state and gastrointestinal complications and prolonged hospitalization or could be related to other factors perpetuated by A Fib itself.

The use of Cox-Maze procedure as a surgical strategy in dealing with preoperative A Fib patients is increasingly used. Data supporting the use of such procedure showed success rate of over 90% with low postoperative risk [10]. In addition, it also showed significantly reduced cost compared to medical therapy alone [10]. Our data show the increased risks of mortality and major morbidities may lend support to the routine inclusion of such procedure in A Fib patients undergoing cardiac surgery. Although, this has to be studied in dedicated studies.

5. Limitation of Study

There are few inherent limitations in our study. Firstly, our study is a retrospective study and as such we can only report an association rather than causality which could only be established by a randomized controlled trial. Secondly, no long-term followup is available for our patients that were included in this series. Thirdly, our data base does not record type of atrial fibrillation preoperatively (i.e., whether paroxysmal or chronic) which may or may not have different impact on outcomes observed. However, within these limitations, we believe our work does raise important observation that will stimulate more research into some preventative strategies when dealing with patients with preoperative atrial fibrillation.

6. Conclusion

As shown by our work and supported by other observations from literature, preoperative atrial fibrillation does increase the risk of mortality and major complications following cardiac surgery. Surgical strategies such as Cox-Maze procedure may be beneficial in these patients.

Conflict of Interests

The authors declare they have no conflict of interests.

Table 5: Summary of previously published studies examining the effect of preoperative atrial fibrillation (A Fib) on outcome following cardiac surgery.

First author/year	Type of study/number	Main findings	limitations/comment
Ngaage et al. [4], 2006	Retrospective $n = 381$	(1) A Fib patients had significantly lower survival at 1, 5, and 7 years than sinus rhythm patients. (2) A Fib patients had higher incidences of stroke, congestive heart failure and rhythm-related intervention on followup. (3) A Fib was an independent predictor of late adverse cardiac and cerebrovascular events but not late death. (4) A trend towards increase in-hospital mortality among A Fib patients.	(1) Patients were matched for age, gender, and ejection fraction. (2) Only included aortic valve replacements.
Rogers et al. [5], 2006	Retrospective $n = 5092$	(1) A Fib occurred in 3.4% of patients undergoing isolated elective CABG. (2) No difference in hospital mortality between sinus rhythm and A Fib patients. (3) A Fib patients had longer hospital stay and higher requirement of intraaortic balloon pump. (4) A Fib patients had 49% higher risk of death after 5 years of surgery than sinus rhythm patients.	(1) Only elective CABG (on-pump and off-pump). (2) Limited morbidities were examined.
Ngaage et al. [6], 2007	Retrospective $n = 526$ (matched analysis)	(1) A Fib occurred in 8.3% of patients undergoing isolated CABG. (2) Operative mortality was similar between sinus rhythm and A Fib patients. (3) A Fib patients had longer hospitalization. (4) A Fib patients had more late hospital admission (median followup 6.7 years). (5) A Fib patients had 40% higher late mortality risk from all causes compared to sinus rhythm patients with more MACE in A Fib patients. (6) A Fib patients had 2.1 relative risk of pacemaker insertion than sinus rhythm patients.	(1) Only on-pump CABG included. (2) Small sample size overall. (3) Only examined MACE, stroke, mortality and hospital stay.
Banach et al. [7], 2008	Retrospective $n = 3000$	(1) A Fib patients had lower survival at 6, 12, and 36 months post CABG. (2) A Fib was an independent risk factor for in-hospital death. (3) A Fib patients had 20% lower survival difference than sinus rhythm patients. (4) A Fib was associated with prolonged ventilation, low output state and prolonged hospital stay and ICU stay	Only CABG patients were included. The risks of other major complications were not evaluated.
Fukahara et al. [8], 2010	Retrospective $n = 513$	(1) Preoperative A Fib occurred in 5.1% of patients. (2) No difference in operative mortality between A Fib and sinus rhythm patients. (3) A Fib patients had significantly lower survival at 5 years than sinus rhythm patients (70% versus 87%). (4) Freedom from cerebral complications was significantly decreased in A Fib patients. (5) No difference in cardiac mortality or MACE at 5 years. (6) A Fib was a significant adverse predictor of survival and independent predictor of late cerebral infarction.	(1) Only off-pump CABG included. (2) Transient ischemic attacks and cerebral haemorrhages were not counted as cerebrovascular events. (3) Sample size was small to detect early association between A Fib and postoperative mortality or morbidity. (4) Postoperative morbidities were not examined.

ICU: intensive care unit.
MACE: major adverse cardiac events.

References

[1] K. M. Ryder and E. J. Benjamin, "Epidemiology and significance of atrial fibrillation," *American Journal of Cardiology*, vol. 84, no. 9, pp. 131–138, 1999.

[2] T. Athanasiou, O. Aziz, O. Mangoush et al., "Do off-pump techniques reduce the incidence of postoperative atrial fibrillation in elderly patients undergoing coronary artery bypass grafting?" *Annals of Thoracic Surgery*, vol. 77, no. 5, pp. R1567–R1574, 2004.

[3] J. S. Gammie, M. Haddad, S. Milford-Beland et al., "Atrial fibrillation correction surgery: lessons from the society of thoracic surgeons national cardiac database," *Annals of Thoracic Surgery*, vol. 85, no. 3, pp. 909–914, 2008.

[4] D. L. Ngaage, H. V. Schaff, S. A. Barnes et al., "Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant Arrhythmia Surgery?" *Annals of Thoracic Surgery*, vol. 82, no. 4, pp. 1392–1399, 2006.

[5] C. A. Rogers, G. D. Angelini, L. A. Culliford, R. Capoun, and R. Ascione, "Coronary surgery in patients with preexisting chronic atrial fibrillation: early and midterm clinical outcome," *Annals of Thoracic Surgery*, vol. 81, no. 5, pp. 1676–1682, 2006.

[6] D. L. Ngaage, H. V. Schaff, C. J. Mullany et al., "Does preoperative atrial fibrillation influence early and late outcomes of coronary artery bypass grafting?" *Journal of Thoracic and Cardiovascular Surgery*, vol. 133, no. 1, pp. 182–189, 2007.

[7] M. Banach, A. Goch, M. Misztal et al., "Relation between postoperative mortality and atrial fibrillation before surgical revascularization—3-Year follow-up," *Thoracic and Cardiovascular Surgeon*, vol. 56, no. 1, pp. 20–23, 2008.

[8] K. Fukahara, K. Kotoh, T. Doi, T. Misaki, and S. Sumi, "Impact of preoperative atrial fibrillation on the late outcome of off-pump coronary artery bypass surgery," *European Journal of Cardio-thoracic Surgery*, vol. 38, no. 3, pp. 366–372, 2010.

[9] N. Chaudhuri, J. James, A. Sheikh, A. D. Grayson, and B. M. Fabri, "Intestinal ischaemia following cardiac surgery: a multivariate risk model," *European Journal of Cardio-thoracic Surgery*, vol. 29, no. 6, pp. 971–977, 2006.

[10] J. A. Poynter, D. J. Beckman, A. M. Abarbanell et al., "Surgical treatment of atrial fibrillation: the time is now," *Annals of Thoracic Surgery*, vol. 90, no. 6, pp. 2079–2086, 2010.