



Postoperative Atrial Fibrillation: Year 2011 Review of Predictive and Preventative Factors of Atrial Fibrillation Post Cardiac Surgery

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Abstract

Background: Post cardiac surgery atrial fibrillation is common after cardiac surgery. Despite the advances in medical and surgical treatment, its incidence remains high and unchanged for decades. The aim of this review was to summarize studies published in 2011 on identifying factors, prevention strategies, treatment and effect of post operative atrial fibrillation (POAF) on the outcome after cardiac surgery.

Methods: A review was performed on Medline, Embase and Chocrane on all of the English-language, peer-reviewed published clinical studies on POAF; studies investigating the mechanism of developing POAF, prevention, treatment and outcome were all included and analyzed. Case reports, studies on persistent/preoperative atrial fibrillation (AF), POAF after cardiac transplant, congenital cases and nonclinical studies were all excluded. We have also valuated these studies based on the type of the study, their originality, impact factor of the journal and their limitations.

Results: Overall 62 studies were reviewed and analyzed; 26 on POAF predictive factors, 31 on preventative strategies and 6 on the outcome of POAF. Of these studies only two were original and the remaining were either performed in AF in general population (n=10) or had been studied and reported several times before in cardiac surgery (n=50). The average impact factor of the journals that POAF was published in was only 2.8 ranging between 0.5 and 14.5.

Conclusion: Post cardiac surgery atrial fibrillation is a multi-factorial and complex condition. Cardiac surgery may be a risk factor for developing POAF in patients already susceptible to this condition and may not be a complication of cardiac surgery. Future studies should mainly focus on histological changes in the conductive tissue of atrium and related treatment strategies rather than predictive factors of POAF and more funding should be made available to study this condition from new and entirely different perspectives.

Introduction

Post Operative Atrial fibrillation (POAF) is common after cardiac surgery. POAF predisposing factors are unclear and its incidence is reported to be

between 15-50%.^{1,2} POAF is considered a favorite research topic and hundreds of original articles and reviews investigate POAF every year. These studies focus on predictive and risk factors of developing POAF, strategies to prevent POAF,

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treatment options and effect of POAF in short and long-term, on the outcome and survival of the patients post cardiac surgery. Majority of these studies have adopted a similar trend that repeat previously published data describing certain predictive factors that increase POAF rate. These studies still find their way into the literature without any additional value to what we already know about POAF.

In this review, we have assessed all the published studies in 2011 investigating POAF; we aimed to create a summary of all the recent studies published in one year and also we have evaluated them and their contribution to the current literature. We also discussed possible future studies that may add benefit to this morbid condition post cardiac surgery.

Methods

A review was performed on Medline, Embase and Chocrane on all the English-language, peer-reviewed published clinical studies on POAF as primary or secondary endpoint. Animal models, studies on chronic/persistent AF, case reports and AF after congenital cardiac surgery, thoracic surgery and transplant cases were all excluded. Overall 61 studies that met our criteria were reviewed.

They were divided into three main categories (Figure 1); A) Predictive/identifying factors, B) Preventative measures and C) Outcome and Consequences.

We also developed a scoring system to assess these studies based on their originalities; The studies were scored.^{1, 2 or 3} based on their originality, 3) Original topic that has never been studied previously in cardiology or cardiac surgery, (2) Studies that have been reviewed in cardiac patients and in general but it is the first time that the hypothesis is being investigated in cardiac surgery, (1) Studies that have been assessed in cardiac surgery before and data has been published several times with similar or different conclusion (Table 1).

Results

Summary of the publications are listed in Table 1. There were only two original articles (scoring 3), 10 scored 2 (studies preformed on cardiac patients and general population but not on POAF), and the rest or 50 papers were studies

and reports that were not original and were performed several times before by different authors and in various institutions reporting similar results as the previous ones with only minor differences. The average impact factor of the journals that these articles were published was only 2.83 ranging between ^{0.5-14.5}. Of all the 62 studies, 26 were on POAF predictive factors (A), 30 on prevention (B), and 6 on the outcome (C). In all of these studies POAF rate has been reported to be between 3 to 50%.

A. Predictive factors

In 2011, over 40% of studies on POAF were analyzing predictive factors of developing POAF and are divided in three categories:

A1. Patient factors

The main patient related predictive factor studied in 2011 was the effect of race on POAF; studies were performed on over 30,000 North American patients who underwent cardiac surgery. They have emphasized the findings of many other studies published previously and showed a link between genetic specifications /race and atrial fibrillation in the normal population as well as POAF.³⁻⁵ All of these reports have concluded that despite higher incidences of preoperative co-morbidities in black people and African/Americans, the risk of developing POAF is 30-40% less compared to the European/Americans (p<0.05)⁶. Besides genetic association, another explanation was linked to the smaller size of left atri-

Figure 1: Publications on POAF in 2011

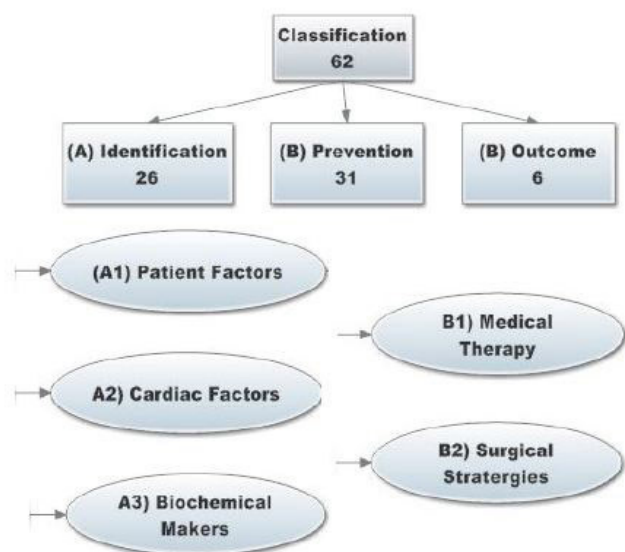


Table 1 Comparison of Apixaban with Dabigatran and Rivaroxaban

Author	Journal	Country	Impact factor	Originality	Group	Study type	Aim	Main study substance/technique/endpoint	Patient No	Group	AF incidence %	Results	End point P value	Limitations	Conclusions
Rader F [3]	Circ Arrhythm Electro-physiol	USA	3.4	1	A1	Retro-spective Observational Single centre	Identification	Race	23524	CABG and valve	35 vs 22	White → POAF increase	<0.0001	No mechanism is identified	Genetic predisposition to PAF in white patients Should be considered for risk stratification
Lahiri MK [4]	Am J Cardiol	USA	3.767	1	A1	Retro-spective Observational Single centre	Identification	Race	1001	CABG	29 vs 18	White race → POAF increase	0.02 0.001	Several characteristics have not been taken into account	Observed LA anatomy variation between races Different response to surgical stress Smaller LA size
Sun X [5]	Am J Cardiol	USA	3.767	1	A1	Retro-spective Observational Single centre	Identification	Race	8366	CABG	39 vs 22	European American → POAF increase compared to S-az African American	<0.01	Single centre Retrospective	African had more preop risk factors and still showed lower PAF, this difference remained significant despite risk adjustment

Shen J [7]	J Thorac Cardiovasc Surg	USA	3.61	1	A1	Retrospective Observational Single centre	Identification	Patient characteristics	10390	All cardiac operations	30	Age, MV surgery, race (caucasian), heart failure, high blood pressure → POAF increase	<0.0001	Single centre Not original	Limited progress in the topic of POAF
Topal AE [8]	Gen Thorac Cardiovasc Surg	Turkey	3.328	1	A1	Retrospective Observational Single centre	Identification	Preoperative characteristics	98	CABG	34	All known preop characteristics, postop urea, pneumonia and transfusion → POAF increase	<0.05	Retrospective Small numbers Not original Association between postop events and AF cannot be conclusive	Not original Wrong conclusion
Sabzi F [9]	Clin Med Insights Cardiol	Iran	-	1	A1	Retrospective Observational Single centre	Identification	Patient and operative characteristics	670	ON-CAB	15	Opium use Age, x clamp, CPB time, IABP, Inotropic support → POAF increase	0.02	Observational Retrospective Several risk factors identified before	Not original Several other studies have Shown similar risk factors Opium use is new?
Ambrosetti M [14]	J Cardiovasc Med (Hagers-town)	Italy	-	1	A1	Retrospective Observational Single centre	Identification	Preop, op factors	2256	All cardiac operations	10	Postop ventricular arrhythmia, valve → Late POAF	<0.05	Retrospective Very small numbers Hypoperfusion can be the result	6% of late PAF was recurrence Medication? Manuscript

Sun X [10]	Ann Thorac Surg	USA	3.039	1	A1	Retro-spective Observational	Identification	BMI	12367	CABG	21-32	High BMI → POAF increased	<0.001	Retrospective Clinical applicability is unclear Atrial size Not novel unlike their claims	Interesting predictive factor
Bramer S [11]	Eur J Cardiothorac Surg	Netherlands	2.370	1	A1	Retro-spective Observational Single centre	Identification	BMI	9348	All cardiac operations	27	High BMI → increase POAF	<0.001	Retrospective Previously high BMI showed high AF in general population but when adjusted for atrial size the effect disappeared	The real role of BMI on PAF is unclear but an interesting concept obesity is not a cause but may be a manifestation of underlying pathology resulting in high BMI rate
Giaccardi M [13]	Am J Phys Med Rehabil	Italy	1.762	2	A1	Prospective Observational Single centre	Identification	Physical activity	158	All cardiac operations	32 vs 8	Preop more physical activity → less POAF after discharge	0.029	Observational and subjective based on patients own reports High incidence of AF post discharge Preop AF was not excluded	Very week study and week results
Ambrosetti M [14]	J Cardiovasc Med (Hagerstown)	Italy	-	1	A1	Retro-spective Observational	Identification	Preop, op factors	2256	All cardiac operations	10	Postop ventricular arrhythmia, valve → Late POAF	<0.05	Retrospective Very small numbers Hypoperfusion can be the result	6% of late PAF was recurrence Medication? Manuscript

Kinoshita T [15]	Ann Thorac Surg	Japan	3,039	1	A2	Prospective Observational Single centre	Identification	390	OP-CAB	25	Longer preop SDNN AND RMSSD → PAF increase	<0.05	Only on OPCAB Beta-blocker effect and other preop medications not assessed Mechanism is not well understood	Can be applied in clinical practice and identification of patients at the risk of PAF
Rader F [16]	J Electrocardiol	USA	1,105	1	A2	Retrospective Cohort study Single centre	Identification	13356	All cardiac operations	35	P-wave amplitude in leads aVR and V(1) and a less negative P-wave amplitude in aVR → increase POAF	<0.0001	Not original	It can be used alongside other predicting factors for PAF prevention
Melduni R [17]	J Am Coll Cardiol	USA	13,090	2	A2	Prospective Observational Single centre	Identification	351	All cardiac operations	38	Diastolic dysfunction, reduced LV compliance elevated LV filling pressure → POAF increase	<0.001	Clinical applicability is not unclear	More prevention in this group of patients is required

Tadic M [18]	Med Sci Monit	Serbia	-	1	A2	Retro-spective Observational Single centre	Identification	LV segmental kinetic disturbances	322	CABG	22	All known factors, LV dyskinesia → POAF increase	<0.001	Retrospective	Not original studied more	Not original LV dysfunction to be studied more
Haffajee JA [19]	JACC Cardiovasc Imaging	USA	5.528	1	A2	Pro-spective Observational Single centre	Identification	LA total emptying fraction (TEF)	101	All cardiac operations	41	Lower TEF → POAF increase	0.04	Small sample size	Mechanism is not well understood	Clinical implication is unclear
Kolestis EN [22]	J Cardiothorac Surg	Greece	2.5	1	A1, A2	Retro-spective Cohort study Single centre	Identification	RCA lesion	348	ON-CAB	45	Proximal RCA lesion → POAF increase	0.02	Small sample size, RCA lesion was not the primary outcome	Similar preoperative factors were investigated	
Shingu Y [23]	Eur J Cardiothorac Surg	Japan	2.370	2	A2	Pro-spective Observational	Identification	LV electromechanical delay	16	All cardiac operations	37	Prolonged D1 LV electromechanical delay → Increase POAF	0.02	Small number of cases	Mixed cardiac cases	
Garcia L [24]	J Thorac Cardiovasc Surg	Chile	3.610	3	A2	Pro-spective Observational Experimental	Identification	RA appendage samples for accumulation of aurotophagic vesicles and lipofuscin	170	ON-CAB	22	Increased RA ultrastructural remodeling intraoperatively → increase POAF	<0.05	Ahead of print	No clinical applicability but can initiate further experimental studies into identifying the mechanism	

Kourliouros A [25]	Ann Thorac Surg	UK	3.039	3	A2	Propective Observational	Identification	LA sample	20	ON-CAB	50	Changes in 19 proteins, pro-inflammatory state, apoptosis → POAF increase	Further explains a pre-existing condition predisposing to PAF	Conflicting data with the authors best evidence report
Virani S [26]	Am J Cardiol	USA	3.767	1	A2	Retropective database cohort study	Identification	Single nucleotide Polymorphism (SNP) in chromosome 4q25	1166	CABG	36	Alleles rs2200733 and rs10033464 → PAF increase	One ethnicity No control cohort	Clinical applicability is unclear
Krzych Lj [27]	Kardiol Pol	Poland	-	1	A3	Retropective Observational	Identification	NT-proBNP	900	CABG	34	High NT-proBNP → PAF increase	Retrospective Several risk factors assessed Conflicting results	Not original
Leal J [28]	Interact Cardiovasc Thorac Surg.	Brazil	2.106	1	A3	Observational Retropective Single centre	Identification	Troponin I	95	ON-CAB	26	High pre and post op Troponin I → higher POAF	Small number of patients	Needs further studies
Iskesen I [29]	Thorac Cardiovasc Surg	Turkey	3.610	1	A3	Propective Observational	Identification	NT-proBNP	117	CABG	28	High NT-proBNP → PAF increase	Not original Conflicting with some other studies Atrial dimensions	Larger atrial dimensions Higher BNP and higher AF This can be the explanation

Kinoshita T [30]	Eur J Cardiothorac Surg	Japan	2.370	1	A3	Retro-spective Observational Single centre	Identification	CRP	552	OP-CAB	21	Higher CRP → POAF increase	0.001	Data not widely available
Skuladottir GV [31]	Eur J Clin Invest	Iceland	2.736	2	A3, B1	Pro-spective Observational	Identification Prevention	1. Long-chain → 3 fatty acids PUFA and n-6 LC-PUFA 2. docosahexaenoic acid (DHA) 3. arachidonic acid (AA)	170	CABG	49	Lower pre and post op AA → increase POAF Higher pre and post op DHA → increase POAF 3 PUFA pre and postop → no POAF rate difference	Small number of patients	
Kinoshita T [33]	Eur J Cardiothorac Surg	Japan	2.370	1	A3	Retro-spective Observational Single centre	Identification	HbA1C	912	OP-CAB	19	Lower HbA1C → POAF increase	0.01	Contradicting with the previous studies in the community and the fact that DM increases POAF
Sun Y [32]	Int Heart J	China	1.04	1	B1, A3	RCT Pro-spective Single centre	Prevention	Atorvastatin CRP	100	ON-CAB	18 vs 41	Preop statin for 1 week → POAF reduction Lower postop CRP → POAF reduction	0.017 <0.0001	Small number Small dose of atorvastatin 20 mg They discussed that RCA is dominant in Chinese population a???

Sorice M [36]	Monaldi Arch Chest Dis.	Italy	0	1	B1	RCT Prospective Single centre	Prevention	N-3 polyunsaturated fatty acids preoperative	201	ON-CAB	17 vs 22	Preop PUFAS → POAF reduction	<0.05	Conflicts with previous meta-analyses	No evidence
Farquharson AL [37]	Am J Cardiol	Australia	3,767	1	B1	RCT Prospective Single centre	Prevention	Fish oil (long-chain ω-3 fatty acids) PUFA	200	All cardiac operations	36 vs 47	Preop PU-FAS → no change in POAF rate	0.25	Small number In homogeneous study	Inconclusive results
Benedetto U [38]	J Cardiovasc Med (Hagerstown).	Italy	0.71	1	B1	Meta-analysis	Prevention	N-3 Polyunsaturated fatty acids (n-3 PUFAs)	431	All cardiac operations	24-54	Preop PU-FAS → no change in POAF rate but slightly decreased in patients with lower beta-blocker	0.63	Only three studies were analyzed	Evidence is inconclusive
Armaganian L [39]	Clinics (Sao Paulo)	Brazil	0.394	1	B1	Meta-analysis	Prevention	Omega 3 fatty acid	538	All cardiac operations	-	Preop PU-FAS → no change in POAF rate	0.195	Conflicting results Heterogeneity in trials	Inconclusive data
Imazio M [40]	Circulation	Italy	14,595	2	B1	RCT Prospective Multicentric	Prevention	Colchicine	336	All cardiac operations	12 vs 22	Postop Colchicine → POAF reduction	0.021	1. Small group 2. Drug started on D3 4. All cardiac operations	Pre and postop application and further studies

Horbach SJ [41]	Am J Med	Brazil	5.115	2	B1	RCT Prospective Multicentric	Prevention	Naproxen	161	ON-CAB	15 vs 7	Preopnaproxen → No difference in POAF but decreases POAF duration	0.19	No difference Small group of patients Type 2 error	No justification for further studies
Mirhosseini SJ [42]	Acta Med Iran	Iran	-	1	B1	RCT Prospective Multicentric	Prevention	Methylprednisolone	120	OP-CAB poor LV	19 vs 21	Methylprednisolone intraop → no POAF change	0.47	Small number Not original	
Kilger E [43]	Minerva Anesthesiol	Germany	1.61	1	B1	RCT Prospective Multicentric	Prevention	Hydrocortisone	305	OP-CAB		Hydrocortisone → no difference in POAF rate	NS	Small number	In off pump maybe the use of hydrocortisone is not beneficial as there is less possibility of RS But outcome was generally improved
Ensor CR [44]	Ann Pharmacother	USA	2.45	1	B1	Retropective cohort study	Prevention	Hydrocortisone	147	All cardiac operations		Hydrocortisone postop → POAF reduction	<0.001	Small number Retrospective study	
Folkeringa RJ [45]	Neth Heart J	Netherlands	1.4	1	B1	Retropective Observational	Prevention	Statin	272	All cardiac operations	49 vs 50	Statin preop 1 week → no change in POAF	0.86	Retrospective	Previous AF was included before adjusting and was the main predictor of PAF

Baran C [46]	Stem Cell Rev	Turkey	5.08	1	B1	RCT Prospective Single centre	Prevention	Atorvastatin	60	CABG	3 vs 23	Statin preop 2 weeks → POAF reduction	0.02	Not study's main endpoint	Very low incidence of PAF in suspicious patients with CAD were not already on statins preoperatively
Rader F [47]	Am J Cardiol	USA	3.767	1	B1	Retrospective Observational	Prevention	Statin	200	All cardiac operations	7 vs 22	Statin post op in 48 h → POAF reduction	0.041	No reason for not having statins in early postop, is that because they were unwell?	
Dong L [48]	Ann Med	China	0.512	1	B1	Meta-analysis 8 RCTs	Prevention	Statin	841	All cardiac operations	19 vs 33	Preop statin → POAF reduction	<0.001	Not homogeneous treatments	
Sakamoto H [49]	Ann Thorac Cardiovas Surg	Japan	0.731	1	B1	Retrospective Cohort Single centre	Prevention	Statin	203	CABG	16 vs 33	Preop statin → POAF reduction	0.005	Small number retrospective	

El-Haddad MA [50]	Am J Cardiovasc Drugs	Egypt	2.026	1	B1	RCT Prospective Single centre	Prevention	Irbesartan	100	CABG	6 vs 22	Preop Irbesartan for 5 days → POAF reduction	0.021	Small number Conflict- ing data on OPCAB patients in a previous study	No MS
Radaelli G [51]	Res Bras Cir Cardiovasc	Brazil	0.963	1	B1	Retro- speculative Cohort	Pre- ven- tion	ACEI	3139	CABG	20 vs 22	After adjusting for age, ACEI preop → POAF increase	0.032	Preop AF was also assessed	More preop AF in ACEI group although not significant but can increase POAF risk affecting the results
Disertori M [52]	Car- diovasc drugs Ther	Italy	3.098	1	B1	Review of 10 papers	Pre- ven- tion	ACEI and ARB	355 4040	All car- diac opera- tions	-	ACEI → POAF decrease ARB → no change in POAF	<0.05 0.24	No manu- script	
Harling L [53]	Heart	UK	4.706	1	B1	Meta- analy- sis of 5 RCTs	Pre- ven- tion	Anti- oxidant vitamins (E, C)	567	All car- diac opera- tions	-	Preop vitamins → POAF reduction	0.02	Only 5 RCT identified Mixture of Vit C and E were used Effect of Preop medi- cations was not assessed	Cost effectiveness to be assessed To apply as a pro- phylactic measures in several centers
Papoulidis P [54]	Interact Car- diovasc Thorac Surg.	Greece	2.106	1	B1	RCT Prospective Single centre	Pre- ven- tion	Antioxi- dant (C)	215	OP- CAB	44 vs 61	Preop vitamins → PAF reduction	0.041	Not original	
Marazzi G [56]	Am J Cardiol	Italy	3.767	2	B1	RCT Prospective Single centre	Pre- ven- tion	Beta blockers (Biso- prolol vs Carve- dilol)	320	CABG EF <40%	14 vs 23	Bisoprolol → POAF reduction compared to Carve- dilol	0.032	No con- trol no beta-blocker group	Great results encour- ages the use of beta bocker

Sezai A [57]	J Thorac Cardiovasc Surg	Japan	3,610	2	B1	RCT Prospective Single centre	Prevention	Landilol hydrochloride	140	CABG	10 vs 34	Intraop to 48 h Landilol → POAF reduction compared to saline	0.0006	Nil	When was it given? Need the manuscript
Miles RH [58]	Am J Cardiol	USA	3,767	1	B1	Retropective Cohort Observational	Prevention	Ranolazine vs Amiodarone	393	CABG	17 vs 26	Preop Ranolazine 2 weeks → POAF reduction compared to Amiodarone	0.035	Retrospective No placebo group	Shorter half life Promising results Other positive effects
Kar SK [59]	Ann Card Anaesth	India	0,743	1	B1	RCT Prospective Single centre	Prevention	Amiodarone vs saline	56	Valve surgery	7 vs 28	Preop amiodarone infusion → POAF	0.035	Small number Other arrhythmias were included Small dose of amiodarone preop was given No maintenance dose was added Arrhythmia recurrence post op was not investigated	Not original small dose preop and no proper loading
Fan Y [60]	Eur J Cardiothorac Surg	China	2,106	1	B1	Meta-analytic	Prevention	Glucose-Insulin-Potassium (GIK)	2113	All cardiac operations	ND	GIK pre, intra and post op → no change in POAF rate GIK in diabetic patients → POAF reduction	0.49 0.02	AF rate was not documented Not homogeneous the population timing and dosage	Contradiction with previous results which have showed reduction in PAF with GIK

Rosenfeldt F [61]	BMC Complement Altern Med	Australia	-	1	B1	RCT Prospective Single centre	Prevention	Holistic therapy	117	All cardiac operations	36 vs 33	Preop holistic therapy two weeks → no change in POAF	0.71	Short period of time Small number of patients Time to operation varies All the parameters were not matched	No evidence to justify further trials
Kaygin MA [62]	Tohoku J Exp Med	Turkey	1.35	1	B2	RCT Prospective Single centre	Prevention	Posterior pericardiotomy	425	ON-CAB	14 vs 3	Intraop pericardiotomy → POAF reduction	<0.0001	Not original	An accepted method but should have a small incision to prevent cardiac herniation prevention
El-Essawi A [63]	Perfusion	Germany	0.745	2	B2	RCT Prospective Multicentric	Prevention	Minimized perfusion circuits	503	ON-CAB AVR	16 vs 24	Minimized perfusion circuits → POAF reduction	0.03	Not study's main endpoint	Decrease in circulatory inflammatory markers may have played a role in decrease in PAF
Nasso G [64]	Interac Cardiovasc Thorac Surg	Italy	2.106	2	B2	RCT Prospective Single centre	Prevention	Extracorporeal vacuum-assisted device optimized	169	All cardiac operations	14 vs 42	EVADO → POAF reduction	<0.001	AF was not the primary endpoint of the study Study shows the benefits of EVADO to add to mini CTPB	EVADO itself does not reduce AF but can add a safe guard and versatility to minibypass which in turn decreases PAF

Caputo M [65]	Eur J Cardiothorac Surg	UK	2.106	1	B2	RCT	Pro-spective Single centre	Pre-vention	Warm car-dioplegia with low/high Mg	691	ON-CAB	32 vs 32	High MG in warm car-dioplegia → no change in POAF	0.82	Cross over patients producing some errors	High Mg may improve myocardial function but not PAF
An drejaitiene J [68]	Perfu-sion	Lithu-ania	0.754	1	C	Retro-spec-ive	Ob-serva-tional	Out-come	Postop delirium	90	All car-diac opera-tions	81 vs 47	Post op delirium → POAF increase	0.01	Retrospec-tive	Is related with other risk factors such as icu stay, x clamp time, can be only an association and not direct effect or cause
Lotfi [69]	Clin Cardiol	USA	1.807	1	C	Retro-spec-ive	Data-base Multi centric	Out-come	Postop stroke	3068	CABG	38	POAF → LOS, read-mission, mortality increase No change in stroke rate and number of grafts	<0.009	Retrospec-tive	Stroke will increase after a long standing AF and AF is not expected to increase the risk
Hedberg M [70]	Eur J Cardiothorac Surg	Swe-den	2.370	1	C	Retro-spec-ive	Data-base Multi centric	Out-come	Postop stroke	7839	All car-diac opera-tions	2.5	POAF increased →stroke	<0.001	Retrospec-tive	Not the primary factor, one of the risk factors of developing stroke,
Saxena A [71]	Clinics (Sao Paulo)	Aus-tralia	1.422	1	C	Retro-spec-ive	Ob-serva-tional	Out-come	Postop stroke	19497	CABG	28	POAF → Stroke, re-nal failure, infection, gastrointes-tinal com-lications, return to the theater, shorter long-term survival	<0.001	Retrospec-tive	Conflicting results on the Stroke rate association with PAF

Kaw R [72]	J Clin lipidol	USA	1.46	1	C	C	Meta-analysis	Outcome	Postop stroke	40112	ON-CAB and Valve plus CABG	POAF → stroke, complications, mortality	<0.0001	Non-homogenous group
Attaran S [73]	Interact Cardiovasc Thorac Surg.	UK	2.106	1	C	C	Retrospective Observational	Outcome	Survival	17379	All cardiac operations	POAF → stroke, other postop complications, survival	<0.001	Retrospective Not original
														Conflicting results on the Stroke rate association with PAF

um in black people compared to the white patients which resulted in lower risk of developing POAF.⁴

Other preoperative patient factors such as history of high blood pressure, heart failure, and age, as well as, operative and postoperative features such as mitral valve surgery, prolonged cross-clamp and cardio-pulmonary bypass time, use of cardioplegia, inotropic use and intra-aortic balloon pump have all have been reported again and shown to be associated with higher incidence of POAF.⁷⁻⁹ Most of these studies were retrospective, single institutional reports and on a small number of patients undergoing cardiac surgery. They have also shown that the use of opium preoperatively and postoperative complications such as pneumonia, renal impairment and transfusion rate can all increase POAF.^{8, 9}

Another important patient related factor is body mass index (BMI) and reports in over 20,000 patients showed higher incidence of POAF with high BMI.^{10, 11} The mechanism of this association have been reported to be increased plasma volume and left ventricular mass, ventricular diastolic dysfunction, increased basal sympathetic tone, and a hypercoagulable state in obese patients that promotes systemic inflammation that are known to be responsible for POAF in obese patients.¹²

Despite these frequently published studies on POAF, one paper has focused on POAF post discharge; the authors have concluded a significant decrease in the AF rate on a small number of patients with higher physical activity during the year before cardiac surgery. Although an interesting concept, the validity of the study is questionable as preoperative arrhythmias and medications on discharge have not been taken into consideration when analysing the results.¹³ Incidence of post discharge AF was also shown to be associated with the presence of postoperative arrhythmias as well as early onset POAF.¹⁴

A2. Cardiac factors

Studies in this category investigated cardiac related predisposing factors. The association between POAF with preoperative ECG specifications, echocardiographic and angiographic features, as well as some histological changes were investigated: Kinoshita et al investigated standard deviation

of all normal-to-normal QRS complexes (SDNN) and square root of mean of sum of squares of differences between adjacent normal-to-normal QRS complexes (RMSSD) of the patients admitted days before their cardiac operations and concluded that reduced heart rate variability decreases the rate of POAF significantly.¹⁵ In over 13,000 patients undergoing cardiac surgery P-wave amplitude in leads aVR and V(1) and a less negative P-wave amplitude in aVR were strong predictors of POAF.¹⁶ The differences in the ECG patterns seen in these patients can be a demonstration of the morphological changes in the diameter of the cardiac chambers and some studies have focused on identifying the predictors of POAF based on the echocardiographic features; left ventricular diastolic dysfunction, decreased ventricular compliance, left ventricular segmental kinetic disturbances, decreased left atrial emptying capacity all have been identified to be associated with increased risk of POAF.¹⁷⁻¹⁹ These changes in the morphology and compliance of cardiac muscles can result in stretch of the pulmonary veins and increase in their arrhythmogenic activity.^{20, 21} It has also been shown that proximal lesion in the right coronary artery, increases the risk of developing POAF.²²

Another study has compared left ventricular electro-mechanical delay (LVEMD) by echocardiogram and Doppler imaging postoperatively and concluded that despite comparable LVEMD preoperatively, LVEMD is prolonged postoperatively in patients who develop POAF.²³ Conclusions from these findings can be rather confusing as some studies suggest preoperative differences in cardiac morphology that can result in POAF and the other group showed change in postoperative characteristics that can predict developing POAF. Latter was done on only 16 patients.²³ and will require further studies prior to a concrete conclusion and preoperative characteristics have been found to be more important than postoperative parameters in developing POAF.

Based on these findings, some investigators have analyzed atrial samples for any identifiable differences between the patients who develop POAF and who remain in sinus rhythm. Samples were tested for the accumulation of autophagic vesicles and lipofucin, and have shown that impaired cardiac autophagy and ultrastructural remodeling were predictive factors for developing POAF.²⁴ Similarly, left

atrial samples have shown changes in 19 special proteins, proinflammatory state and apoptosis to be different between patients who develop POAF and patients with no AF.²⁵ These studies further stress the theory of the presence of an organic factor preoperatively which can result in POAF. Even genetic studies have indicated variants in 4q25 to be associated with higher incidence of POAF.²⁶

A3. Biochemical markers

Presence of higher level of certain circulatory biochemical markers preoperatively in patients with POAF compared to those in SR also has attracted investigators' interest for years. In 2011 alone, several studies were published on this topic and results showed, not for the first time, that high circulatory Brain Natriuretic Peptide (BNP), troponin I, C-reactive protein (pre and postoperatively) and Docosahexaenoic acid (DHA) was associated with increased POAF rare.²⁷⁻³² Conversely, circulatory Arachidonic acid levels are shown to be lower pre and postoperatively in patients with POAF.³¹ This was a novel finding. However prostaglandin series derived from AA have been shown to have arrhythmic effects, which is contrary to the effect of free AA in the circulation described in this study.

In addition, lower Hemoglobin A1C (HbA1C) preoperatively was shown to increase POAF.³³ This was in accordance with another study from 2008 on a large number of patients undergoing cardiac surgery; Halkos et al revealed that high levels of HbA1C results in more postoperative morbidities, but less POAF.³⁴ These findings, surprisingly contradicts with studies showing higher incidence of POAF in diabetic patients and studies on the general population that supports a positive and independent relationship between HbA1C levels and incidence of AF.³⁵

B. Prevention

Despite no clear etiological factor for POAF, in 2011, more studies (n=29) were conducted investigating prevention from POAF. They mainly focused on medical therapy (B1) and some on surgical techniques (B2) to reduce POAF.

B1. Medical therapy

Several reports focused on long-chain, omega 3

fatty acids; previously there were some initial promising results with preoperative use of Omega-3 in reducing POAF, however further analyzes and studies on larger population showed no statistically proven benefit of this group of fatty acids in reducing POAF. In 2011, one report on a small group showed positive results³⁶, however another study³⁷ and two meta-analysis published in 2011 showed no real place for Omega-3 in decreasing the risk of POAF.^{38, 39}

Other groups investigated the effect of medications that reduces inflammation; Postoperative Colchicine has been tried which showed POAF reduction but adverse effects are seen with its use that prevented further studies.⁴⁰ Naproxen, despite being an anti-inflammatory medication, has shown to have no effect in the reduction of POAF but its preoperative use has decreased POAF duration.⁴¹

The inflammation theory has encouraged the investigators to use corticosteroids but no reduction in POAF in patients who underwent OPCAB (Off Pump Coronary Artery Bypass).^{42, 43} was observed, however its use postoperatively showed reduction in POAF after a study in all cardiac procedures.⁴⁴ The authors believed that in OPCAB due to a less inflammatory response, no major effect of these anti-inflammatory steroids can be observed.

Another group of medications with anti-inflammatory properties that have been used for several years is Statins. In 2011, of five studies and one meta-analysis on the role of pre and postoperative Statins in POAF, except in one retrospective study⁴⁵ all have concluded that Statin reduces POAF.^{32, 46-49} In the study that showed no benefit with the use of Statin, patients with preoperative AF were also included which may have influenced the results. Overall, Statins have been shown to have a great role in prevention from POAF, however treatment with Statins failed to eradicate POAF completely.

Angiotensin-converting enzyme inhibitors (ACEI) and alpha-receptor blockers (ARB) are another group of medications that have been assessed for the prevention of POAF. Their anti-inflammatory properties alongside several other characteristics such as lowering blood pressure and reducing volume overload were expected to reduce POAF, however results from several studies were conflicting; a RCT with Irbesartan showed significant

decrease in POAF.⁵⁰ On the other hand, a retrospective study on over 3000 CABG patients showed in fact, ACEI was a risk factor for developing POAF. However, in their study patients with preoperative AF were not excluded and higher number of AF patients were on ACEI, which could have affected the results.⁵¹ These two studies published in 2011 were contradictory to the previous reviews that showed a statistically significant decrease in POAF recurrence but no benefits with the use of ARBs.⁵² Benefits of antioxidants such as vitamins C and E have been studied extensively; a meta-analysis on five randomized controlled trials (RCT) and a RCT have shown reduction in POAF.^{53, 54} These findings were in accordance with previously published data, however data on cost effectiveness and the duration required for the use of these vitamins are yet to be determined.

Amongst all the medications that have been tried in prevention of POAF, the value of anti-arrhythmic medications in the prevention and treatment of POAF remains invincible and the evidence has been considered (I) and (IIa) for beta-blockers and Amiodarone respectively.⁵⁵ Studies continue to explore new and old anti-arrhythmic agents and different regimes; Bisoprolol in a recent RCT has been shown superior to Carvedilol in POAF reduction in patients with impaired ventricular function.⁵⁶ This is possible that its greater beta selectivity increases its anti-arrhythmogenic effects. Landilol, an ultra short acting beta-blocker, with very high beta-1 selectivity has been infused intra-operatively and which showed a significant POAF reduction compared to saline.⁵⁷ but did not compare Landilol with other beta-blockers. Landilol was introduced in 2002 however data regarding its clinical usage is yet to be investigated. Another treatment against POAF that has been tried recently is Ranolazine, an antianginal agent that inhibits abnormal late sodium channel current in atrial and ventricular tissue. In comparison with preoperative administration of Amiodarone, Ranolazine was shown to be more effective in decreasing POAF.⁵⁸ However, in that study patients in the Amiodarone group had lower ejection fraction compared to the patients on Ranolazine, which could have affected the results. It is well known that Amiodarone is one of the best antiar-

rhythmic agents for POAF and still some centers continue to publish their data on Amiodarone.⁵⁹

Besides the studies on medical agents, a meta-analysis on the infusion of glucose/insulin/potassium (GIK) pre- intra- and postoperatively, has shown that POAF decreased in patients with diabetes but the incidence of POAF in the rest of the patients was unchanged.⁶⁰ With the results of this report and the study on hemoglobin A1C described earlier,³³ no conclusion can be drawn from these contradictory results, one showing worse diabetic control preoperatively decreases POAF,³³ and the other one confirms better diabetic control peri-operatively to decrease POAF.⁶⁰ Finally, in this category a small study investigated the role of holistic therapy preoperatively on a small group of patients and found no effect on POAF.⁶¹

B2. Surgical strategies

Despite the importance of different surgical strategies, only a few papers were published last year on this topic; posterior pericardiotomy is one of the well-known techniques to decrease POAF, and another RCT in 2011 has shown POAF to be as low as 3%.⁶² Despite, its usefulness the technique is not widely adopted by the cardiac surgeons and care must be taken to make a small incision to prevent cardiac herniation. Significant POAF reduction has also been reported with minimized perfusion circuits,⁶³ and extracorporeal vacuum assisted devices,⁶⁴ on small group of patients. The authors have concluded less hemodilution, transfusion requirement and less inflammatory marker release with short circuit and better organ perfusion with vacuum device that result in better outcome and less POAF. Changes on cardioplegia have been tried and despite the myocardio-protective effects of magnesium a study by Caputo has shown no reduction in POAF with high dose magnesium in warm blood cardioplegia.⁶⁵ Interestingly, same authors found a two-fold decrease in POAF with high Magnesium in warm blood cardioplegia in a study published in 2002.⁶⁶

C. Outcomes and consequences

Despite POAF being a short-lived and self-limiting complication, it has been shown to affect the outcome after cardiac surgery in short- and long-term

and result in devastating complications. Postoperative delirium has been shown to be associated with several factors one of them POAF. Delirium was previously related to preoperative AF,⁶⁷ however a direct link between POAF and developing delirium postoperatively that was reported in this study is questionable as POAF commonly occurred on the third postoperative day whereas signs of delirium in the study by Andrejaitiene et al was observed prior to that and during their stay at intensive care unit.⁶⁸ Other studies, showed statistically significant association between POAF and stroke.⁶⁹⁻⁷² A study on over 17000 all cardiac patients by the author of this manuscript showed significantly lower survival rate in patients who develop POAF at five and ten years. However, after propensity matching for the preoperative characteristics only in the CABG patients POAF increased the postoperative complications, stroke rate and survival.⁷³ This has been reported before and it was speculated that unlike in CABG cases, patients undergoing valve or other cardiac operations are subjected to better and more frequent follow ups and in cases of mechanical valves regular anticoagulation reduces stroke in this group of patients who may develop AF even after discharge.⁷⁴

Discussion

Postoperative Atrial Fibrillation is a common arrhythmia with no clear etiology. Studies over the decades have tried to analyze the role of intrinsic and extrinsic cardiac nervous system in developing AF; it is believed that stimulation of the vagosympathetic trunks and autonomic innervation from the ganglionated plexus of the heart to heterogeneously shorten refractoriness across the atria, results in a premature or series of atrial premature beats to induce and sustain atrial fibrillation.⁷⁵⁻⁷⁶, especially the presence of this intrinsic cardiac autonomic nervous system, in conjunction with the extrinsic projections of the vagosympathetic system from the brain and spinal cord to the heart are thought to be involved in the development of the AF.⁷⁷⁻⁸⁰

However, the main reason for activation of these intrinsic and extrinsic nervous systems after cardiac surgery is not fully understood. It has been shown that cardiac surgery may lead to decreased baroreflex sensitivity and result in heart rate variability.⁸¹ However, this concept has not been thoroughly investigated. In addition, it is not clear that

why some patients and not all develop POAF.

In this review, we have summarized all the studies that have been published on postoperative atrial fibrillation in a full year. This gives the reader an overview of what has been new on POAF and will encourage the investigators to focus on new ideas of identifying the causes, and prevention from and treatment of POAF, rather than repeating and publishing the same results every year. Based on our analysis, only two articles out of 62 were original with another ten being previous reports of AF in general population, which now examines the same theory on POAF for the first time. The low impact factor of the journals that these articles were published in also signifies that this important morbidity that occurs or manifest after cardiac surgery is not studied widely from new perspective and not many laboratories and research funds are dedicated to investigate POAF in the recent years.

Based on this review and several other publications from previous years, we know that POAF is a common complication that despite all the advances in cardiac surgery no etiology or treatment for it has yet been identified. The main reason is that POAF is a multi-factorial condition and unanswered questions are dominating our knowledge regarding all types of atrial fibrillation including POAF. Up to date and without any conflicting results, age is considered an independent predictor of all types of AF; at the age of 40 life-time risk of developing AF is one in four.⁸² Other factors such as valvular heart disease, ischemic heart disease, heart failure, high blood pressure, and several other co-morbidities increase the risk even more.⁷⁻⁹ Some investigators believe the mechanism of the POAF is completely different from that of AF in the community.⁸³ Many other authors and investigators believe that POAF is a complication of cardiac surgery. However, by reviewing the published studies, we believe that atrial fibrillation is a complex disease that can manifest itself after certain conditions, one of them being cardiac surgery.

Several studies each year investigate POAF from different angles, some hope to offer new strategies to prevent POAF and some still report predictive factors of POAF. Of the studies investigating the

topic this year, only the ones assessing the histological changes within atrial samples were original.^{24,25} This is an unexplored area, which can influence what we already know or hope to achieve regarding POAF. It is clear that atrial fibrillation is the manifestation of changes in automaticity levels of the conductive atrial cells. Age increases the degree of atrial fibrosis affecting the configuration of conductive cells. Similarly, factors such as size of the atrium in valvular heart disease or race related atrial appendage sizes described in this review,³⁻⁵ decreased cardiac compliance stretching atria and pulmonary vasculature all affect cellular morphology.¹⁷⁻¹⁹ Presence of circulatory markers, on the other hand, has shown varying degree of association with POAF, therefore the effect of cardiac surgery, inflammation, inflammatory markers and the use of cardiopulmonary bypass can all be considered predisposing factors of POAF. Based on these findings, cell membrane stabilisers and medications decreasing sympathetic activities such as beta-blockers are considered best prevention for POAF.⁵⁵⁻⁵⁷

Furthermore, low survival rate in CABG patients who develop POAF was significantly affected by POAF.⁷³ It is hard to accept that a condition that may have lasted only a few hours to a few days can increase the mortality rate even after 10 years. It is clear that POAF is the result of preoperative changes in the atrial tissue and maybe these patients without cardiac surgery would have developed AF at some point in the future but this is a theory that cannot easily be investigated.

In conclusion, we believe that studies should move away from just reporting AF rate and common predicting factors, as they do not offer a lot of benefit, and concentrate on changes at the histological level or the role of intrinsic and extrinsic autoimmune nervous system in developing postoperative AF, and hopefully treatment options that aim to improve, revert or slow down these changes. With POAF still being a common post cardiac surgery morbidity that can increase the cost of treatment postoperatively with devastating effects on the outcome in short and long-term, more funds and research laboratories should be dedicated to investigate POAF.

Disclosures

No disclosures relevant to this article were made by the authors.

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