ORIGINAL RESEARCH

# Intraoperative Inducibility of Atrial Fibrillation Does Not Predict Early Postoperative Atrial Fibrillation

Eva A. H. Lanters, MD; Christophe P. Teuwen, MD; Ameeta Yaksh, MD, PhD; Charles Kik, MD; Lisette J. M. E. van der Does, MD; Elisabeth M. J. P. Mouws, MD; Paul Knops, BSc; Nicole J. van Groningen, BSc; Thijmen Hokken, BSc; Ad J. J. C. Bogers, MD, PhD; Natasja M. S. de Groot, MD, PhD

***Background*—**Early postoperative atrial fibrillation (EPoAF) is associated with thromboembolic events, prolonged hospitalization, and development of late PoAF (LPoAF). It is, however, unknown if EPoAF can be predicted by intraoperative AF inducibility. The aims of this study are therefore to explore (1) the value of intraoperative inducibility of AF for development of both EPoAF and LPoAF and (2) the predictive value of de novo EPoAF for recurrence of LPoAF.

***Methods and Results*—**Patients (N=496, 75% male) undergoing cardiothoracic surgery for coronary and/or valvular heart disease were included. AF induction was attempted by atrial pacing, before extracorporeal circulation. All patients were on continuous rhythm monitoring until discharge to detect EPoAF. During a follow-up period of 2 years, LPoAF was detected by ECGs and Holter recordings. Sustained AF was inducible in 56% of patients. There was no difference in patients with or without AF before surgery ($P$=0.159), or between different types of surgery ($P$=0.687). In patients without a history of AF, incidence of EPoAF and LPoAF was 37% and 2%, respectively. EPoAF recurred in 58% patients with preoperative AF, 53% developed LPoAF. There were no correlations between intraoperative inducibility and EPoAF or LPoAF ($P$>0.05). EPoAF was not correlated with LPoAF in patients without a history of AF ($P$=0.116), in contrast to patients with AF before surgery ($P$<0.001).

***Conclusions*—**Intraoperative AF inducibility does not predict development of either EPoAF or LPoAF. In patients with AF before surgery, EPoAF is correlated with LPoAF recurrences. This correlation is absent in patients without AF before surgery. **(*J Am Heart Assoc*. 2018;7:e007879. DOI: 10.1161/JAHA.117.007879.)**

**Key Words:** atrial fibrillation • cardiac surgery • intraoperative induction • postoperative complication arrhythmia

Over the past decades, cardiac surgery has become an established treatment modality for various cardiovascular diseases. However, despite improved surgical techniques and health care over the years, atrial fibrillation (AF) is still frequently observed in the early postoperative period. Reported incidences of early postoperative AF (EPoAF) range from 10% to 65%.[1–4] EPoAF is associated with thromboembolic complications and prolonged hospitalization.[3,5,6] A previous study demonstrated, although in a small population (N=50) with coronary artery disease, that intraoperative inducibility of AF could be a predictor for development of EPoAF.[7] However, this was never validated in a larger population with a variety of cardiovascular diseases.

In addition, EPoAF is known to increase the risk of late postoperative AF (LPoAF),[6,8,9] yet the predictive value of intraoperative inducibility was never investigated. The latest European guidelines advise to consider long-term oral anticoagulants in cases of EPoAF as prevention for thromboembolic complications (Class IIa).[10] However, they also concluded that additional research is mandatory to investigate the predictive value of short-lasting (<24 hours) EPoAF episodes for development of LPoAF. Hence, there is a need to identify patients at risk for EPoAF and, subsequently, to determine whether these patients are also at risk for LPoAF.

The aims of this study are therefore to explore (1) the value of intraoperative inducibility of AF for development of both

*From the Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands (E.A.H.L., C.P.T., A.Y., L.J.M.E.v.d.D., E.M.J.P.M., P.K., N.J.v.G., T.H., N.M.S.d.G.); Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, the Netherlands (C.K., E.M.J.P.M., A.J.J.C.B.).*

**Correspondence to:** Natasja M. S. de Groot, MD, PhD, Department of Cardiology, Erasmus Medical Center, 's-Gravendijkwal 230, 3015CE Rotterdam, the Netherlands. E-mail: n.m.s.degroot@erasmusmc.nl

Received October 17, 2017; accepted February 1, 2018.

© 2018 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

## Clinical Perspective

### What Is New?

- Intraoperative atrial fibrillation inducibility does not predict development of early postoperative atrial fibrillation.
- In patients without a history of atrial fibrillation, early postoperative atrial fibrillation is not correlated with late recurrences of atrial fibrillation; hence, a more conservative approach with regard to initiation of oral anticoagulants may be justified in this subpopulation.

### What Are the Clinical Implications?

- In patients with a history of atrial fibrillation, early postoperative atrial fibrillation is correlated with late recurrences of atrial fibrillation; thus, these patients should be monitored closely for recurrences, before discontinuation of oral anticoagulants can even be considered.

EPoAF and LPoAF and (2) the predictive value of de novo EPoAF episodes of any duration >30 seconds for recurrence of LPoAF.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Study Population

The study population consisted of 496 adult patients, scheduled for elective cardiac surgery, including isolated coronary artery bypass grafting (CABG), isolated valvular heart surgery (VHS), a combination of VHS and CABG (VHS+CABG) or correction of a congenital heart defect (Figure 1). Patients with an atrial pacing device, previous ablation of atrial arrhythmias, or severe renal failure or patients requiring mechanical or inotropic support before the surgical procedure were not eligible for inclusion. Surgical pulmonary vein isolation was performed in a selection of patients with a history of AF. Classification of AF was performed according to the latest guidelines.[10]

Patients were included in either the QUASAR[11] (Quest for the Arrhythmogenic Substrate of Atrial Fibrillation) or HALT&REVERSE[12] (HSF1 activators lower cardiomyocyte damage; towards a novel approach to reverse AF) project, which were both approved by the institutional medical ethical committee (MEC2010-054 and MEC2014-393). All patients provided written informed consent before inclusion. Clinical characteristics were obtained from electronic patient files.

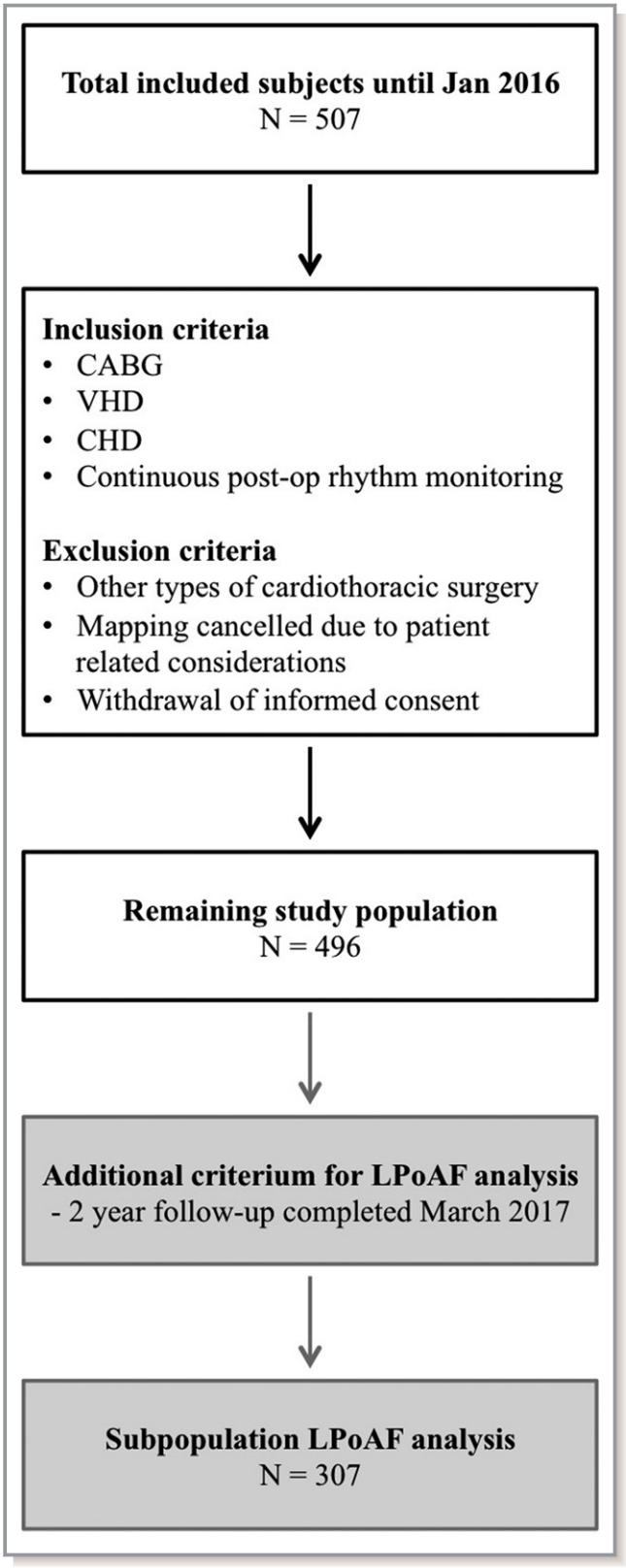


**Figure 1.** Flowchart patient inclusion. CABG indicates coronary artery bypass grafting; CHD, congenital heart disease; LPoAF, late postoperative atrial fibrillation; VHD, valvular heart disease.

## Intraoperative Induction of AF by Electrical Stimulation

QUASAR and HALT&REVERSE are high-resolution epicardial mapping studies, designed to investigate the arrhythmogenic substrate underlying AF. For this purpose, mapping is performed during either spontaneous or electrically induced AF. AF induction is attempted in every patient before commencement of extracorporeal circulation by fixed-rate pacing at the right atrial appendage, delivered by a temporary pacemaker wire (pulse width: 2 ms, output 10 mA). Pacing started at a rate of 200 bpm, and if AF was not induced after 2 attempts, the rate was gradually increased by steps of 50 bpm. If AF was not induced at a pacing rate of 400 bpm or loss of capture occurred, attempts were terminated and AF was considered noninducible.[13] Attempts for inducibility of AF were categorized as (1) noninducibility; (2) nonsustained AF (self-terminating during mapping procedure); (3) nonsustained atrial flutter; (4) sustained AF (not self-terminating during mapping procedure, ≈4 minutes); and (5) sustained atrial flutter.

## Early Postoperative AF

Postoperative cardiac rhythms were continuously recorded during the first 4 to 5 days. Telemetry recordings, ECGs, and patient records were all manually evaluated for the presence of AF episodes. EPoAF was defined as irregular RR intervals in the absence of distinct *P* waves, with a duration of at least 30 seconds occurring within 14 days after the surgery.

## Late Postoperative AF

For this subanalysis, we included only those patients who completed a 2-year follow-up period by March 2017 or developed AF within this period. LPoAF was detected on either ECGs or 24-hour Holter recordings. If applicable, additional rhythm registrations obtained during the follow-up period were requested from the referring hospital.

## Statistical Analysis

All data were tested for normality. Continuous, normally distributed data are expressed as mean±SD and skewed data as median (P25–P75). Student *t* tests were used to compare normally distributed continuous clinical parameters. Non–normally distributed clinical parameters were compared by nonparametric tests including Mann-Whitney *U*-test. Fisher exact or $\chi^2$ tests were applied for categorical variables. The correlation among EPoAF, LPoAF, AF induction, and clinical characteristics was examined using Pearson or Spearman tests where applicable. A *P* value of <0.05 was considered statistically relevant. Statistical analyses were performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY).

# Results

## Study Population

The study population consisted of 496 patients (age 67±11 years, 373 [75%] male). Baseline characteristics are summarized in Table 1. The majority of patients (N=273, 55%) underwent CABG surgery, whereas VHS, or VHS+CABG was performed in 122 (25%) and 82 (16%) patients, respectively. The remaining 19 (4%) patients underwent first-time surgical correction of a congenital heart defect including mainly patients with either atrial or ventricular septal defects.

A history of AF was present in 125 (25%) patients and was either paroxysmal (N=54, 43.2%), persistent (N=47, 37.6%), long-standing persistent (N=22, 17.6%), or permanent (N=2, 1.6%). Eighty (64%) of these patients underwent concomitant surgical pulmonary vein isolation.

## Intraoperative Inducibility of AF

At the start of the mapping procedure, spontaneous AF was present in 77 (15.5%) patients with a history of AF. In addition, 7 (1.4%) patients without a history of AF converted spontaneously to AF during surgery, before mapping. Pacing was not performed due to patient-related or technical issues in another 11 (2.2%) patients.

AF induction was attempted in all 401 remaining patients. As depicted in Figure 2A, sustained AF was successfully induced in 56% of these patients, whereas in 10% AF was nonsustained. Either sustained atrial flutter or nonsustained atrial flutter was induced in 6% and 7%, respectively. In 21% of patients, arrhythmias were not inducible despite adequate pacing attempts.

Figure 2B shows AF inducibility for patients without (N=357) and with preoperative (N=44) AF separately. Induction of sustained AF was equally successful in patients with preoperative AF (73%) and patients without (54%, *P*=0.159). Intraoperative inducibility per type of surgery is indicated in Figure 2C. There was no difference in AF inducibility between the various groups, *P*=0.687.

## Early Postoperative Atrial Fibrillation

Overall, EPoAF developed in 211 (43%) patients, including 138 (37%) patients without and 73 (58%) patients with preoperative AF (*P*<0.001). Clinical characteristics of patients with and without EPoAF are depicted in Table 2. Most initial EPoAF episodes occurred at Day 3 (N=76, 36%) and Day 4 (N=53, 25%), as opposed to Day 1 (N=17, 8%), Day 2 (N=23, 11%), Day 5

**Table 1.** Baseline Characteristics

| | Total study population | No AF | AF | *P* value* |
|---|---|---|---|---|
| Population, N (%) | 496 (100) | 371 (75) | 125 (25) | |
| Group, N (%) | | | | <0.001 |
| CABG | 273 (55) | 246 (66) | 27 (22) | |
| VHS | 122 (25) | 58 (16) | 64 (51) | |
| VHS/CABG | 82 (16) | 56 (15) | 26 (21) | |
| CHD | 19 (4) | 11 (3) | 8 (6) | |
| Age (years), mean±SD | 67±11 | 65±11 | 71±9 | <0.001 |
| Male sex, N (%) | 373 (75) | 289 (78) | 84 (67) | 0.017 |
| Hypertension, N (%) | 276 (56) | 206 (56) | 70 (56) | 0.926 |
| Diabetes mellitus, N (%) | 129 (26) | 102 (27) | 27 (22) | 0.194 |
| Hyperlipidemia, N (%) | 162 (33) | 136 (37) | 26 (21) | 0.001 |
| BMI (kg/m$^2$), mean±SD | 27.7±4.3 | 27.8±4.2 | 27.7±4.5 | 0.935 |
| Antiarrhythmic drugs,† N (%) | 367 (75) | 271 (73) | 96 (77) | 0.408 |
| Class I | 2 (0.4) | 2 (1) | 0 (0) | 0.399 |
| Class II | 367 (66) | 254 (68) | 75 (60) | <0.001 |
| Class III | 27 (5) | 5 (1) | 22 (18) | <0.001 |
| Class IV | 17 (3) | 13 (4) | 4 (3) | 0.801 |
| Left ventricular function, N (%) | | | | 0.059 |
| Normal | 364 (73) | 282 (76) | 82 (66) | 0.023 |
| Mild impairment | 96 (19) | 68 (18) | 28 (22) | 0.319 |
| Moderate impairment | 34 (7) | 20 (51) | 14 (11) | 0.026 |
| Severe impairment | 2 (1) | 1 (1) | 1 (1) | 0.418 |
| Left atrial dilatation,‡ N (%) | 132 (27) | 66 (18) | 66 (53) | <0.001 |
| AF type before CS, N (%) | | | | |
| Paroxysmal AF | | | 54 (43.2) | |
| Persistent AF | | | 47 (37.6) | |
| Long-standing persistent AF | | | 22 (17.6) | |
| Permanent AF | | | 2 (1.6) | |
| Surgical ablation | | | 80 (64) | |

AF indicates atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CHD, congenital heart disease; CS, cardiac surgery; and VHS, heart valve surgery.

*Comparing No AF and AF.

†Patients could use more than one type of AAD; therefore, the sum of all classes is not 100%.

‡Dimension >45 mm.

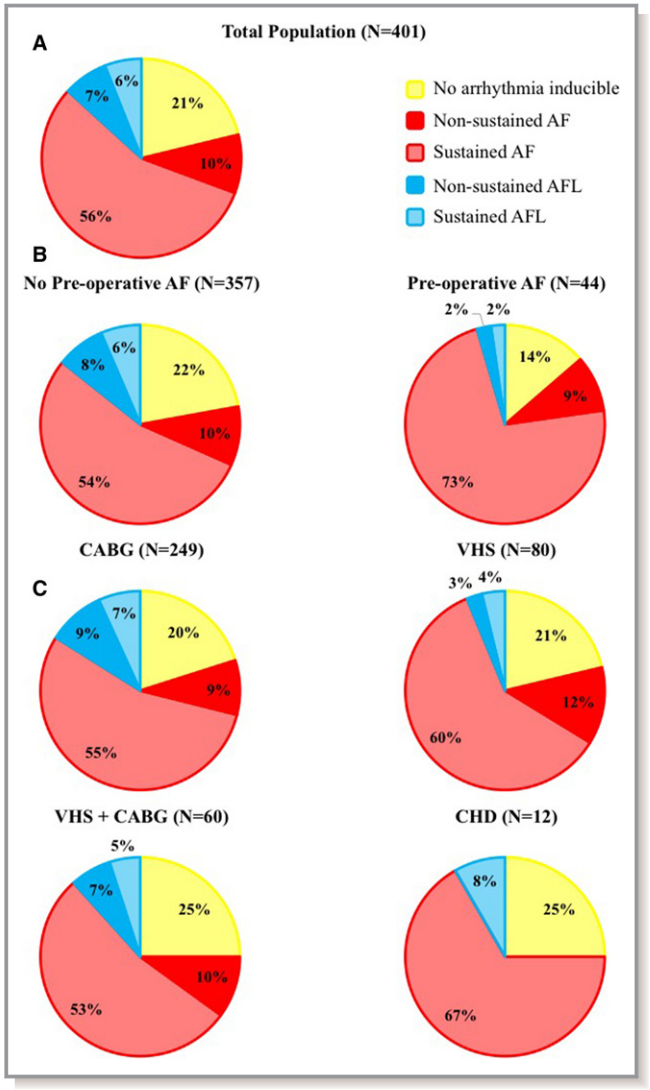


**Figure 2.** Intraoperative inducibility. Results of intraoperative inducibility of various atrial tachyarrhythmias for the total study population (A), for patients without or with AF before surgery (B) and per type of cardiac surgery (C). AF indicates atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass grafting; CHD, congenital heart disease; VHS, heart valve surgery.

(N=25, 12%), Day 6 (N=9, 4%), Day 7 (N=5, 2%), Day 8 (N=2, 1%), and Day 11 (N=1, 1%). Figure 3 shows the cumulative onset of EPoAF per postoperative day, for patients with (red bars) and without (green bars) preoperative AF separately. EPoAF developed earlier ($P$<0.001). in patients with AF before surgery (Day 3±2) before surgery, than in patients without (Day 4±1).

In the subpopulation of 80 patients in whom surgical pulmonary vein isolation was performed, EPoAF developed in 44% (N=35), compared with the recurrence of EPoAF in 84% (N=38) of the patients in whom ablation was not performed ($P$<0.001).

EPoAF terminated spontaneously in only 6 patients. Patients received Class II (N=113), Class III (N=68), and/or digoxin (N=45) as treatment for EPoAF. In 33 patients, EPoAF

**Table 2.** Clinical Charateristics of Patients With and Without EPoAF

| | No AF | | | AF | | |
|---|---|---|---|---|---|---|
| | No EPoAF (N=233) | EPoAF (N=138) | *P* Value | No EPoAF (N=52) | EPoAF (N=73) | *P* value |
| Group, N (%) | | | 0.006 | | | 0.951 |
| CABG | 160 (69) | 86 (62) | | 10 (19) | 17 (23) | |
| VHS | 38 (16) | 20 (15) | | 27 (52) | 37 (51) | |
| VHS/CABG | 25 (11) | 31 (22) | | 12 (23) | 14 (19) | |
| CHD | 10 (4) | 1 (<1) | | 3 (6) | 5 (7) | |
| Age (years), mean±SD | 63±12 | 69±8 | <0.001 | 68±10 | 72±7 | 0.014 |
| Sex (male, %) | 182 (78) | 107 (78) | 0.897 | 33 (63) | 47 (64) | 0.427 |
| Hypertension, N (%) | 128 (55) | 78 (57) | 0.766 | 28 (54) | 42 (58) | 0.682 |
| Diabetes mellitus, N (%) | 65 (28) | 37 (27) | 0.821 | 7 (13) | 20 (28) | 0.062 |
| Hyperlipidemia, N (%) | 87 (37) | 49 (36) | 0.723 | 11 (21) | 15 (21) | 0.934 |
| BMI ($kg/m^2$), mean±SD | 28±4 | 27±4 | 0.554 | 27±4 | 28±5 | 0.107 |
| Antiarrhythmic drugs, N (%) | | | 0.081 | | | 0.978 |
| Class I | 1 (<1) | 1 (<1) | | 0 | 0 | |
| Class II | 153 (66) | 101 (73) | | 30 (58) | 45 (62) | |
| Class III | 4 (2) | 1 (<1) | | 11 (21) | 11 (15) | |
| Class IV | 8 (3) | 5 (4) | | 2 (4) | 2 (3) | |
| Left ventricular function, N (%) | | | 0.180 | | | 0.148 |
| Normal | 185 (79) | 97 (70) | | 38 (73) | 44 (60) | |
| Mild impairment | 36 (15) | 32 (23) | | 7 (13) | 21 (29) | |
| Moderate impairment | 11 (5) | 9 (7) | | 6 (12) | 8 (11) | |
| Severe impairment | 1 (<1) | 0 | | 1 (2) | 0 | |
| Left atrial dilatation, N (%) | 40 (17) | 26 (19) | 0.684 | 21 (40) | 45 (62) | 0.019 |
| AF type before CS, N (%) | | | | | | 0.116 |
| Paroxysmal AF | | | | 26 (50) | 28 (38) | |
| Persistent AF | | | | 15 (29) | 32 (44) | |
| Long-standing Persistent AF | | | | 11 (21) | 10 (14) | |
| Permanent AF | | | | 0 | 3 (4) | |
| Surgical ablation, N (%) | | | | 45 (87) | 35 (48) | <0.001 |

AF indicates atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CHD, congenital heart disease; CS, cardiac surgery; EPoAF, early postoperative atrial fibrillation; and VHS, valvular heart surgery.

was treated by a combination of electrical cardioversion and antiarrhythmic drugs.

At discharge to the center of referral after 5 (5–7) days, AF was present in 55 (11%) patients, including 14 (4%) patients without preoperative AF and 41 (34%) patients with preoperative AF, despite failed attempts to restore sinus rhythm in 75% (N=42).

## Relation With Intraoperative Inducibility

The upper panel of Figure 4 indicates the proportion of patients (N=357) that developed de novo EPoAF, for each type of induced arrhythmia separately. There was no correlation between the type of intraoperatively induced arrhythmia and development of EPoAF ($P>0.05$). Similar results were obtained for patients with preoperative AF (N=44) who developed EPoAF recurrences, as indicated in the lower panel of Figure 4 ($P>0.05$).

## Late Postoperative AF

A total of 307 (62%) patients completed the 2-year follow-up period, and/or reached the study end point (LPoAF). Forty-four patients (14%) developed LPoAF during follow-up, including only 4 (2%) patients without preoperative AF. AF

recurred in 40 (53%) patients with preoperative AF ($P$<0.001). As expected, the incidence of LPoAF recurrences was lower in patients who underwent ablation than in patients in whom ablation was not performed: 25% versus 44%, $P$=0.021. Table 3 shows additional clinical characteristics of patients with and without LPoAF.

Overall time to LPoAF diagnosis was 6 (3–6) months and was similar in patients with (N=40, 6 [3–6]) and patients without (N=4, 8 [3–21]) preoperative AF ($P$=0.708).

## Relation Between Late Postoperative AF and Intraoperative Inducibility

In 3 (75%) patients with de novo LPoAF, intraoperative induction resulted in sustained AF, the fourth patient had sustained atrial flutter. In patients with AF before surgery, 2 patients with LPoAF were noninducible during surgery, 2 patients had nonsustained AF, 8 patients had sustained AF, and 1 had sustained atrial flutter. However, in the majority of patients (N=27, 35%), AF was spontaneously present at the start of the procedure. As a consequence, there was no correlation between type of arrhythmia induced and development of LPoAF for either patients without ($P$=0.163) or with ($P$=0.211) AF before surgery.

## Relation Between Early Postoperative and Late Postoperative AF

Four patients without AF before surgery developed LPoAF, including 1 patient without and 3 patients with EPoAF. Consequently, there was no correlation between EPoAF and LPoAF in this subgroup ($P$=0.116). LPoAF recurrences in the subgroup with AF before surgery was observed in 6 patients without and 34 patients with EPoAF episodes, resulting in a significant correlation between EPoAF and LPoAF: ρ=0.370 and $P$<0.001. Day of EPoAF onset did not correlate with LPoAF development ($P$=0.390).

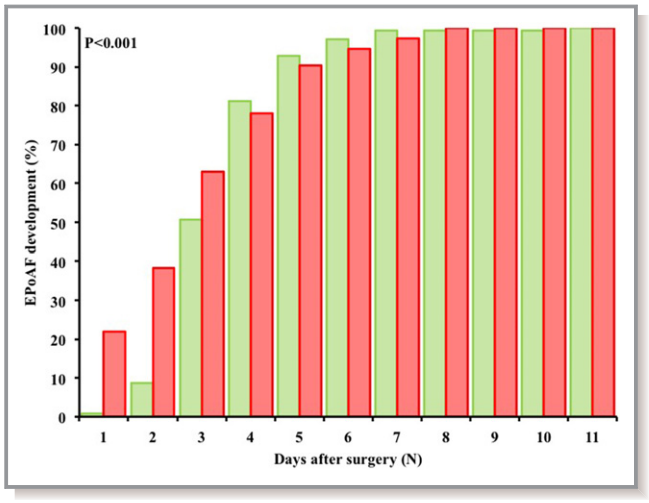


**Figure 3.** Early postoperative AF. Cumulative proportion of EPoAF onset per postoperative day for patients without (green bars) or with (red bars) AF before surgery. AF indicates atrial fibrillation; EPoAF, early postoperative atrial fibrillation.

# Discussion

## Key Findings

Intraoperative AF is inducible in the vast majority of patients. However, it is not correlated with development of EPoAF or LPoAF. In patients without AF before surgery, the incidence of LPoAF is very low and not related to the presence of EPoAF. Clinical patient characteristics did not influence intraoperative AF inducibility or development of either EPoAF or LPoAF.

## Relation Between Inducibility and Early Postoperative Atrial Fibrillation

The predictive value of AF inducibility for development of EPoAF after cardiothoracic surgery has so far solely been

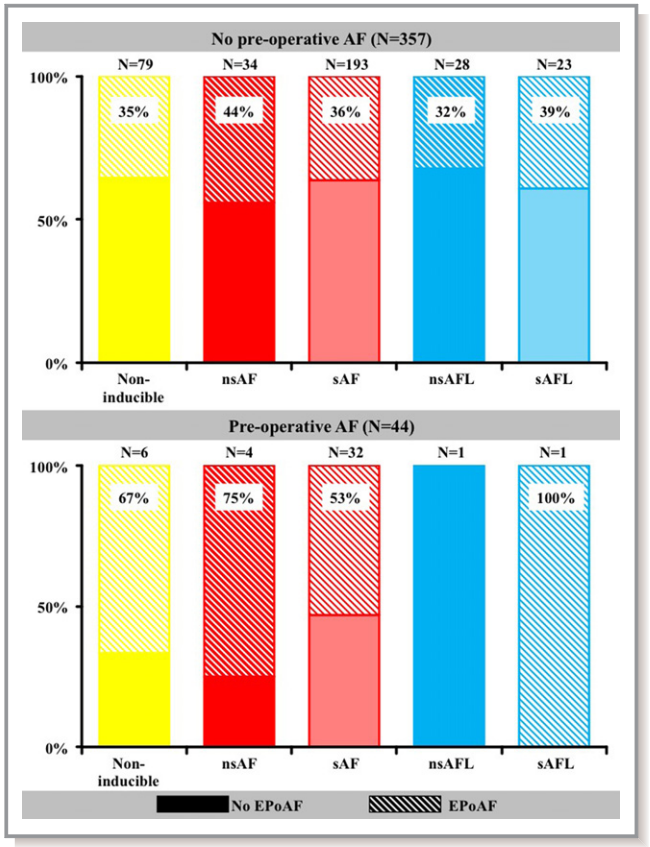


**Figure 4.** Relation between intraoperative inducibility and early postoperative AF. Proportion of patients who develop EPoAF (dashed) per type of arrhythmia induced, for patients without (upper panel) and with (lower panel) AF before surgery. AF indicates atrial fibrillation; EPoAF, early postoperative atrial fibrillation; nsAF, non-sustained atrial fibrillation; nsAFL, non-sustained atrial flutter; sAFL, sustained atrial flutter.

**Table 3.** Clinical Charateristics of Patients With and Without LPoAF

| | No AF | | | AF | | |
|---|---|---|---|---|---|---|
| | No LPoAF (N=367) | LPoAF (N=4) | *P* Value | No LPoAF (N=85) | LPoAF (N=40) | *P* value |
| Group, N (%) | | | 0.010 | | | 0.498 |
| CABG | 245 (67) | 1 (25) | | 19 (22) | 8 (20) | |
| VHS | 58 (16) | 0 | | 42 (49) | 22 (55) | |
| VHS/CABG | 53 (14) | 3 (75) | | 20 (24) | 6 (15) | |
| CHD | 11 (3) | 0 | | 4 (5) | 4 (10) | |
| Age (years), mean±SD | 65±11 | 69±9 | 0.486 | 70±9 | 71±8 | 0.613 |
| Sex (male, %) | 285 (78) | 4 (100) | 0.284 | 54 (64) | 30 (75) | 0.203 |
| Hypertension, N (%) | 205 (56) | 1 (25) | 0.217 | 51 (60) | 19 (48) | 0.189 |
| Diabetes mellitus, N (%) | 101 (28) | 1 (25) | 0.911 | 18 (21) | 9 (23) | 0.867 |
| Hyperlipidemia, N (%) | 153 (42) | 1 (25) | 0.627 | 19 (22) | 7 (18) | 0.533 |
| BMI (kg/m$^2$), mean±SD | 28±4 | 27±3 | 0.798 | 27±4 | 29±5 | 0.163 |
| Antiarrhythmic drugs, N (%) | | | 0.929 | | | 0.032 |
| Class I | 2 (1) | 0 | | 0 | 0 | |
| Class II | 251 (68) | 3 (75) | | 54 (64) | 21 (53) | |
| Class III | 5 (1) | 0 | | 17 (55) | 5 (13) | |
| Class IV | 13 (4) | 0 | | 4 (5) | 0 | |
| Left ventricular function, N (%) | | | 0.303 | | | 0.604 |
| Normal | 279 (76) | 3 (75) | | 58 (68) | 24 (60) | |
| Mild impairment | 68 (19) | 0 | | 18 (21) | 10 (25) | |
| Moderate impairment | 19 (5) | 1 (25) | | 8 (9) | 6 (15) | |
| Severe impairment | 1 (<1) | 0 | | 1 (1) | 0 | |
| Left atrial dilatation, N (%) | 64 (17) | 2 (50) | 0.090 | 37 (44) | 28 (70) | 0.002 |
| AF type before CS, N (%) | | | | | | 0.260 |
| Paroxysmal AF | | | | 34 (40) | 20 (50) | |
| Persistent AF | | | | 33 (39) | 13 (33) | |
| Long-standing Persistent AF | | | | 17 (20) | 4 (10) | |
| Permanent AF | | | | 1 (1) | 2 (5) | |
| Surgical ablation, N (%) | | | | 60 (71) | 20 (50) | 0.025 |

AF indicates atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CHD, congenital heart disease; CS, cardiac surgery; LPoAF, late postoperative atrial fibrillation; and VHS, valvular heart surgery.

investigated by Lowe et al.[7] AF was induced in 72% of 50 patients without a history of AF undergoing CABG, slightly more than in our population. They reported a sensitivity and specificity of AF inducibility for predicting EPoAF of 94% and 41%, respectively.

In the present study, AF was inducible in the majority of patients, and the incidence of de novo EPoAF was 37% (*overall* EPoAF: 43%), which is comparable to incidences reported by other investigators.[2,6,8] However, a correlation between inducibility of AF and development of EPoAF was absent. Not only did we include a larger study population, but we also tested our hypothesis in patients with various underlying heart diseases. Within all these subgroups, these correlations were lacking. In the study by Lowe et al, all antiarrhythmic drugs were discontinued peri- and postoperatively, whereas in our study all preoperatively prescribed drugs were continued. As a result, AF inducibility is less likely to occur in our cohort.

Although the exact mechanisms of EPoAF are not fully understood, it is generally accepted that it is highly multifactorial in nature.[14] Factors promoting development of EPoAF following cardiothoracic surgery include, for example, inflammatory response, sympathetic activation, and oxidative stress. In addition, EPoAF is not solely initiated by the presence of these triggers, but also depends on the presence and extensiveness of an arrhythmogenic substrate.[13,15] Atrial alterations on structural, electrical, and contractile levels

cause a higher vulnerability for development of AF.[16] Previous studies showed that, in patients in sinus rhythm, the extent of this arrhythmogenic substrate is highly variable in patients with similar clinical profiles.[17–19] Hence, all these factors might contribute to the lacking correlation between AF inducibility alone and development of EPoAF.

## Late Postoperative AF

The incidence of LPoAF in patients without AF before surgery in our study was only 2%. Subsequently, correlations between either AF inducibility or EPoAF and development of LPoAF were absent. This is in contrast to other reports, in which incidence of LPoAF was both higher and correlated to EPoAF.[9] In a matched cohort of 488 patients without AF undergoing off-pump CABG, development of LPoAF was evaluated during a 41±23 month follow-up period. LPoAF developed in 1.4% of patients without EPoAF, compared with 10.2% of patients with EPoAF ($P<0.001$). The difference in LPoAF prevalence is most likely due to the longer follow-up period (up to 87 months) in the latter study group.

In another cohort, consisting of 571 CABG patients, EPoAF developed in 29%. Patients with EPoAF had an 8-fold increase in the risk of LPoAF development during a 3-year follow-up period.[6] Ambrosetti[8] followed 710 patients after CABG and/or VHS. The overall LPoAF prevalence was 11% and was associated with development of EPoAF. However, it is unknown whether patients had AF or other arrhythmias before surgery. In the present study, the overall LPoAF incidence was 14% and is thus comparable to the results provided by Ambrosetti.

Given the variances in prevalence of LPoAF and the low prevalence in our cohort, the causative relation between cardiothoracic surgery and LPoAF might be questionable. Although one can advocate for the presence of such a relation if LPoAF develops shortly after surgery, this becomes uncertain when LPoAF develops more than several months after surgery. By that time, surgery-associated triggers including, for example, sterile inflammatory responses and oxidative stress are no longer present. However, general risk factors for AF such as decompensated heart failure and infections are more likely to be responsible for triggering of LPoAF episodes.

Development of LPoAF recurrences after surgical ablation in the present study was 25%. This is somewhat similar to previous studies, reporting 66% to 69% success rates 1 year after concomitant surgical ablation.[20,21]

## Clinical Implications

EPoAF episodes in the current population are usually transient and not predictive for LPoAF. Based on our findings, one could argue whether long-term oral anticoagulants are indeed mandatory, although included as a Class IIa indication in the AF guidelines.[10] A more conservative approach in this subpopulation may be justified with the present data set.

In patients with AF before surgery in whom surgical ablation for AF was performed, recurrence rates remain relatively high. As a consequence, these patients should be monitored closely for LPoAF recurrences, before discontinuation of oral anticoagulants can even be considered.

## Study Limitations

During long-term follow-up, LPoAF had to be documented on ECGs or Holter recordings. Consequently, asymptomatic short-lasting AF episodes could have been missed. For the subanalysis regarding late postoperative AF we chose to include only patients who completed the 2-year follow-up or developed LPoAF within this period. Since a selection of patients had not yet reached the 2-year end point, they were not included for the subanalysis.

## Conclusion

Intraoperative AF inducibility does not predict development of either EPoAF or LPoAF. In patients with AF before surgery, EPoAF is correlated with LPoAF recurrences. This correlation is absent in patients without AF before surgery, in whom the incidence of LPoAF is very low.

## Acknowledgments

We would like to thank R. van Valen and J. van der Ven from the Erasmus Medical Center for their participation in the project and their help with the visits at the outpatient clinic.

## Sources of Funding

Dr Groot is supported by LSH-Impulse grant (no. 40-43100-98-008), Cardiovasculair Onderzoek Nederland (CVON) research grant AFFIP (grant no. 914728), the Netherlands Organization for Scientific Research Vidi grant (grant no. 91717339), grants from the Erasmus Medical Center fellowship, Dutch Heart Foundation (2012T0046), CoolSingel Foundation (no. 212), Bayer, and Boehringer Ingelheim. Dr Teuwen is supported by a grant from the Dutch Heart Foundation (2016T071).

## Disclosures

None.

## References

1. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol*. 2008;51:793–801.

2. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. *Ann Thorac Surg*. 1993;56:539–549.
3. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT; Investigators of the Ischemia R, Education F, Multicenter Study of Perioperative Ischemia Research G. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA*. 2004;291:1720–1729.
4. Ahlsson A, Bodin L, Fengsrud E, Englund A. Patients with postoperative atrial fibrillation have a doubled cardiovascular mortality. *Scand Cardiovasc J*. 2009;43:330–336.
5. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, Leon AR, Puskas JD. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. *J Am Coll Cardiol*. 2010;55:1370–1376.
6. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardiothorac Surg*. 2010;37:1353–1359.
7. Lowe JE, Hendry PJ, Hendrickson SC, Wells R. Intraoperative identification of cardiac patients at risk to develop postoperative atrial-fibrillation. *Ann Surg*. 1991;213:388–392.
8. Ambrosetti M, Tramarin R, Griffo R, De Feo S, Fattirolli F, Vestri A, Riccio C, Temporelli PL, Ital III. Late postoperative atrial fibrillation after cardiac surgery: a national survey within the cardiac rehabilitation setting. *J Cardiovasc Med (Hagerstown)*. 2011;12:390–395.
9. Lee SH, Kang DR, Uhm JS, Shim J, Sung JH, Kim JY, Pak HN, Lee MH, Joung B. New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft. *Am Heart J*. 2014;167:593–600.e591.
10. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
11. van der Does LJ, Yaksh A, Kik C, Knops P, Lanters EA, Teuwen CP, Oei FB, van de Woestijne PC, Bekkers JA, Bogers AJ, Allessie MA, de Groot NM. QUest for the Arrhythmogenic Substrate of Atrial fibRillation in patients undergoing cardiac surgery (QUASAR Study): rationale and design. *J Cardiovasc Transl Res*. 2016;9:194–201.
12. Lanters EA, van Marion DM, Kik C, Steen H, Bogers AJ, Allessie MA, Brundel BJ, de Groot NM. HALT & REVERSE: Hsf1 activators lower cardiomyocyt damage; towards a novel approach to REVERSE atrial fibrillation. *J Transl Med*. 2015;13:347.
13. Yaksh A, van der Does LJ, Kik C, Knops P, Oei FB, van de Woestijne PC, Bekkers JA, Bogers AJ, Allessie MA, de Groot NM. A novel intra-operative, high-resolution atrial mapping approach. *J Interv Card Electrophysiol*. 2015;44:221–225.
14. Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. *Europace*. 2012;14:159–174.
15. Zaman JA, Harling L, Ashrafian H, Darzi A, Gooderham N, Athanasiou T, Peters NS. Post-operative atrial fibrillation is associated with a pre-existing structural and electrical substrate in human right atrial myocardium. *Int J Cardiol*. 2016;220:580–588.
16. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation*. 1995;92:1954–1968.
17. Mouws E, Lanters EAH, Teuwen CP, van der Does L, Kik C, Knops P, Bekkers JA, Bogers A, de Groot NMS. Epicardial breakthrough waves during sinus rhythm: depiction of the arrhythmogenic substrate? *Circ Arrhythm Electrophysiol*. 2017;10:e005145.
18. Lanters EAH, Yaksh A, Teuwen CP, van der Does L, Kik C, Knops P, van Marion DMS, Brundel B, Bogers A, Allessie MA, de Groot NMS. Spatial distribution of conduction disorders during sinus rhythm. *Int J Cardiol*. 2017;249:220–225.
19. Teuwen CP, Yaksh A, Lanters EA, Kik C, van der Does LJ, Knops P, Taverne YJ, van de Woestijne PC, Oei FB, Bekkers JA, Bogers AJ, Allessie MA, de Groot NM. Relevance of conduction disorders in Bachmann's bundle during sinus rhythm in humans. *Circ Arrhythm Electrophysiol*. 2016;9:e003972.
20. Beukema WP, Sie HT, Misier AR, Delnoy PP, Wellens HJ, Elvan A. Intermediate to long-term results of radiofrequency modified Maze procedure as an adjunct to open-heart surgery. *Ann Thorac Surg*. 2008;86:1409–1414.
21. Damiano RJ Jr, Badhwar V, Acker MA, Veeragandham RS, Kress DC, Robertson JO, Sundt TM. The CURE-AF trial: a prospective, multicenter trial of irrigated radiofrequency ablation for the treatment of persistent atrial fibrillation during concomitant cardiac surgery. *Heart Rhythm*. 2014;11:39–45.