Supplementary Method

We used the terms “Cancer”, “neoplasms” and “paraneoplastic” to identify potentially relevant studies for sepsis; “chronic obstructive pulmonary disease”, “COPD” and “chronic bronchitis” for COPD; “sleep apnea”, “obstructive sleep apnea” and “sleep-disordered breathing” for OSA; and “chronic kidney disease” and “renal disease” for CKD.

Coronary heart disease, hypertension, heart failure and valvular heart disease were not included as they were classified as cardiovascular diseases. Other noncardiovascular diseases, namely hyperthyroidism and diabetes mellitus, although associated with AF, were similarly excluded as they were considered conventional risk factors,1 and thus their association with AF has already been explored in previous studies. Obesity, however, although consistently emerges as a risk factor for AF, was not included due to its intrinsic connection with OSA.

Bibliographic references of relevant articles consisted of journals and articles associated. The search was not limited to a unique publication, language or specific quality criteria.

Suplementary Results

Cancer

Pathophysiology

AF may act as an adverse drug reaction and complicate the course of cancer patients. AF may be induced by various cytostatics, such as Anthracyclines (Doxorubicin, Mitoxantrone), Ifosfamide, Cemcitabine, Melphalan, Cisplatin, Docetaxel, 5-Fluorouracil and Etoposide, high doses of Corticosteroids, Bisphosphonates, antiemetic agents like Ondansetron, and targeted therapies, by several mechanisms, including cytotoxicity2-5.

AF may also represent an inflammatory complication of cancer. Indeed, AF was more commonly observed in patients with elevated postoperative neutrophil counts (OR 3.2, 95% CI 1.3-7.8, p = 0.01), and after open versus laparoscopic colectomy (OR 3.3, 95% CI 1.3-8, p = 0.008), suggesting that open colectomy causes a more severe systemic inflammatory response.

Prophylaxis

Administration of 300 mg of amiodarone intravenously over 20 minutes immediately after surgery for lung cancer and an oral dose of 600mg twice daily during the first five postoperative days reduced the risk of AF by 23%6. Nojiri et al11 reported that patients with elevated BNP levels (> 30 pg/mL) who received low-dose human atrial natriuretic peptide had lower incidence of postoperative AF than patients who received placebo.

Treatment

Landiolol, an ultra-short-acting beta-blocker, when administered to a small group of patients who developed AF after lung resection, experienced a significant reduction in heart rate and early restoration of sinus rhythm as compared to verapamil and digoxin12.

Sepsis

Prophylaxis

A recent study investigated the effect of esmolol in patients with septic shock13. Although reduction in heart rate may lead to improvement of cardiovascular function, treatment of sinus tachycardia, and consequently potentially prevent AF, the use of esmolol in sepsis is still controversial. Further studies to establish the recommendations regarding prophylaxis are needed14.

COPD

Treatment

According to current recommendations, reversal of hypoxemia and acidosis should be the first therapeutic approaches in new-onset AF. However, in patients who become hemodynamically unstable, synchronized cardioversion should be considered, although the strategy for rhythm control may be ineffective until the respiratory decompensation is corrected.

For ventricular rate control, diltiazem or verapamil are the recommended drugs for COPD patients. The use of β-adrenergic agonists and theophylline is discouraged, since they may precipitate atrial fibrillation and make ventricular rate control difficult. Non-selective beta-blockers, sotalol, propafenone and adenosine are contraindicated in patients with bronchospasm15.

Obstructive Sleep Apnea

Prognosis

Few studies have investigated the effect of AF on OSA. OSA is associated with increased risk of stroke, but it is not clear whether AF increases the risk of stroke in OSA. The Sleep Heart Health study16, a prospective study which followed up 5,422 individuals with no history of stroke for a mean of 8.7 years, reported that OSA increases the risk of stroke, particularly in men in the highest severity quartile (obstructive apnea-hypopnea index > 19; adjusted HR 2.86, 95% CI 1.1-7.4). After secondary analyses that excluded individuals with AF, lower OR for stroke was observed in OSA patients, with no change in overall results, suggesting that AF does not fully explain the association between OSA and AF. However, the proportion of patients with AF in this study was small (2%), and the authors suggested that underdiagnosed paroxysmal AF was a mediating factor.

More recently, a case-control study involving 108 individuals reported a significant association between AF and stroke, even after adjusting for other risk factors (corrected OR 5.34, 95% CI 1.79-17.29)17. Further studies to confirm whether AF increases the risk of stroke in patients with OSA are necessary.
Chronic Kidney Disease

Pathophysiology

In addition to cardiovascular diseases, other comorbidities are commonly encountered in AF and CKD. Curiously, the combination of CKD and anemia increases substantially the risk of stroke (HR 5.43, 95% CI 2.04-14.41)\(^{18}\), which may be related to an increased risk for AF. In fact, anemia, a common complication of CKD, and CKD are independent risk factors of AF, and a recent study demonstrated a synergic association between CKD and anemia for AF onset\(^{19}\).

Treatment

Several international anticoagulation therapy guidelines in CKD are currently available. In 2011, the Kidney Disease Outcomes Quality Initiative recommended that anticoagulation therapy should only be prescribed for patients with CKD as a secondary prevention of stroke and careful monitoring of patients, and not as primary prevention, since these patients were not included in controlled, randomized studies\(^{20}\). However, the 2014 AHA/ACC/HRS guidelines support the prescription of warfarin (INR 2.0-3.0) for oral anticoagulation for patients with nonvalvular AF, CHA\(_2\)DS\(_2\)-VASc \(\geq 2\), and who have ESRD or are on hemodialysis, recognizing that anticoagulation increases the hemorrhagic risk in this population. With respect to AF in moderate to severe CKD with CHA2DS2-VASc \(\geq 2\), treatment with lower doses of direct thrombin or factor Xa inhibitors may be considered, although safety and efficacy have not been established\(^{15}\).

Supplementary table 1 – Atrial fibrillation and cancer

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Study design</th>
<th>Population (patients)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guzzetti et al(^{21}), 2002</td>
<td>Retrospective unicenter</td>
<td>1,463</td>
<td>Prevalence of AF: 5% in patients with CRC vs 2% in controls</td>
</tr>
<tr>
<td>Guzzetti et al(^{22}), 2008</td>
<td>Retrospective unicenter</td>
<td>2,339</td>
<td>Prevalence of AF: 3.6% in patients with CRC and breast cancer vs 1.6% in controls</td>
</tr>
<tr>
<td>Hu et al(^{23}), 2013</td>
<td>Retrospective population-based</td>
<td>24,125</td>
<td>Prevalence of AF at cancer diagnosis: 2.4%. New-onset AF: 1.8%</td>
</tr>
<tr>
<td>Erichsen et al(^{24}), 2012</td>
<td>Retrospective population-based</td>
<td>Cases: 28,333 Controls: 283,260</td>
<td>Diagnosis of CRC: 0.59% in patients with AF vs 0.05% without AF</td>
</tr>
<tr>
<td>Dyszkiewicz et al(^{25}), 1998</td>
<td>Retrospective unicenter</td>
<td>298</td>
<td>Prevalence of FA after pulmonary resection for lung cancer: 8.4%</td>
</tr>
<tr>
<td>Roselli et al(^{26}), 2005</td>
<td>Retrospective unicenter</td>
<td>604</td>
<td>Prevalence of FA after pulmonary resection for lung cancer: 19%</td>
</tr>
<tr>
<td>Salvatici et al(^{27}), 2010</td>
<td>Prospective unicenter</td>
<td>400</td>
<td>Prevalence of AF after pulmonary resection for lung cancer: 18%</td>
</tr>
<tr>
<td>Nojiri et al(^{28}), 2010</td>
<td>Prospective unicenter</td>
<td>126</td>
<td>Prevalence of AF after pulmonary resection for lung cancer: 23%</td>
</tr>
<tr>
<td>Imperatori et al(^{29}), 2012</td>
<td>Prospective unicenter</td>
<td>454</td>
<td>Prevalence of AF after pulmonary resection for lung cancer: 9.9%</td>
</tr>
<tr>
<td>Murthy et al(^{30}), 2003</td>
<td>Retrospective unicenter</td>
<td>921</td>
<td>Prevalence of AF after esophagectomy: 22%</td>
</tr>
<tr>
<td>Nojiri et al(^{31}), 2012</td>
<td>Prospective unicenter</td>
<td>40</td>
<td>Prevalence of AF after pulmonary resection for lung cancer: 60%</td>
</tr>
<tr>
<td>Onaitis et al(^{32}), 2010</td>
<td>Retrospective using The Society of Thoracic Surgeons database</td>
<td>13,906</td>
<td>Prevalence of AF after pulmonary resection for lung cancer: 12.6%</td>
</tr>
<tr>
<td>Siu et al(^{33}), 2005</td>
<td>Retrospective unicenter</td>
<td>563</td>
<td>Prevalence of AF after colectomy for CRC: 4.4%</td>
</tr>
</tbody>
</table>

Prophylaxis and treatment

| Riber et al\(^{34}\), 2012 | Prospective unicenter, double-blind, randomized, controlled study | 254 | Postoperative amiodarone as prophylaxis: reduced the risk of AF from 32% to 9% |
| Nojiri et al\(^{35}\), 2012 | Prospective unicenter, double-blind, randomized, controlled study | 40 | Prophylaxis with atrial natriuretic peptide: reduced the postoperative AF (10% vs 60%) |
| Nojiri et al\(^{36}\), 2011 | Prospective unicenter | 30 | Landiolol vs verapamil+digoxin: time to cardioversion was shorter in the landiolol group (8.1 vs 23 horas) |

AF: Atrial fibrillation; CRC: Colorectal cancer.
### Supplementary table 2 – Atrial fibrillation and sepsis

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Study design</th>
<th>Population (patients)</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Kuipers et al[14], 2014 | Systematic review and meta-analysis | 460,096               | - Incidence of AF: 8% (0-14%) in sepsis, 10% (4-23%) in severe sepsis and 23% (6-46%) in septic shock  
- Increased mortality in acute phase with estimated adjusted OR between 1.07 e 3.28 |
| Christian et al[22] 2008 | Retrospective unicenter            | 274                   | - Incidence of AF: 3% in severe sepsis and 11% in septic shock  
- ICU mortality: 69% in patients with AF vs 40% without AF  
- Increased hospital stay length in patients with AF |
| Salman et al[33], 2008 | Retrospective unicenter            | 81                    | - Incidence of AF: 14% in sepsis, 23% in severe sepsis and 37% in septic shock  
- Increased mortality in the first 28 days: 72% in patients with AF vs 38% without AF |
| Meierhenrich et al[34], 2010 | Prospective unicenter            | 629                   | - No statistically significant increase in ICU mortality was observed  
(44% with AF vs 33% without AF)  
- Incidence of AF: 5.9% in severe sepsis vs 0.65% without severe sepsis  
- Risk of in-hospital stroke: 2.6% in severe sepsis and new-onset AF vs 0.6% in severe sepsis without AF |
| Lee-Iannotti et al[35], 2012 | Retrospective, population-based     | 3,144,787             | New-onset AF during sepsis was associated with increased 5-year of risk of hospitalization for heart failure (11.2% vs 8.2%), ischemic stroke (5.3% vs 4.7%) and death (74.8% vs 72.1%) |
| Walkey et al[36], 2014 | Retrospective using The Medicare 5% database | 138,722 | New-onset AF during sepsis was associated with increased 5-year of risk of hospitalization for heart failure (11.2% vs 8.2%), ischemic stroke (5.3% vs 4.7%) and death (74.8% vs 72.1%) |

#### Profilaxia

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Study design</th>
<th>Population (patients)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morelli et al[13], 2013</td>
<td>Open-label, randomized phase 2, unicenter</td>
<td>154</td>
<td>Esmolol: reduction of heart rate in the first 96 hours (-28/min vs -6/min)</td>
</tr>
</tbody>
</table>

AF: Atrial fibrillation; ICU: Intensive care unit.

### Supplementary table 3 – Atrial fibrillation and chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Autor, referência</th>
<th>Desenho do estudo</th>
<th>Population (patients)</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Sidney et al[37], 2005 | Retrospective multicentric | 91,932               | - Prevalence of AF: 4.7% in patients with COPD vs 1.1% without COPD  
- A 1.98 fold-greater risk of hospitalization in COPD and AF vs COPD without AF |
| Buch et al[38], 2003  | Prospective multicentric  | 13,460                | Reduction in pulmonary function is an independent predictor of AF                                                                                   |
| Li et al[39], 2014    | Prospective population-based | 15,004              | - The incidence of AF inversely correlates with FEV1  
- Moderate/severe airflow obstruction associates with AF incidence                                                                 |
| Steer et al[40], 2012 | Prospective multicentric  | 920                   | AF is an independent predictor of mortality in COPD exacerbations                                                                               |
| Fusco et al[41], 1995 | Retrospective unicentric   | 590                   | AF is an independent predictor of mortality in COPD exacerbations                                                                               |

FEV1: Forced expiratory volume in 1 second; AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease.
### Supplementary table 4 – Atrial fibrillation and obstructive sleep apnea

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Study design</th>
<th>Population (patients)</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Mehra et al\(^a\), 2006 | Retrospective multicentric | 3,295 | – Prevalence of AF: 4.8% in patients with sleep disorders vs 0.9% without sleep disorders  
  – Patients with sleep disorders have 4-fold greater risk of AF |
| Gami et al\(^a\), 2007 | Retrospective unicentric | 3,542 | The magnitude of nocturnal oxygen desaturation is an independent risk factor for AF in patients aged less than 65 years. |
| Gami et al\(^a\), 2004 | Prospective unicentric | 524 | Prevalence of OSA: 49% in patients with AF vs 32% without AF  
  – Increased risk for stroke in patients with OSA, particularly in men with moderate/severe OSA  
  – AF does not explain the association between stroke and OSA  
  – Patients with OSA and stroke have a higher incidence of AF |
| Redline et al\(^a\), 2010 | Prospective multicentric | 5,422 | – Prevalence of AF: 4.8% in patients with sleep disorders vs 0.9% without sleep disorders  
  – Patients with sleep disorders have 4-fold greater risk of AF |
| Mansukhani et al\(^a\), 2014 | Retrospective multicentric | 108 | – Prevalence of AF: 4.8% in patients with sleep disorders vs 0.9% without sleep disorders  
  – Patients with sleep disorders have 4-fold greater risk of AF |
| Yaranov et al\(^a\), 2015 | Retrospective multicentric | 5,138 | – Stroke in patients with AF: 25.4% in patients with OSA vs 8.2% without OSA  
  – OSA is an independent factor for stroke in patients with AF |

AF: Atrial fibrillation; OSA: Obstructive sleep apnea.

### Tabela Suplementar 5 – Atrial fibrillation and chronic kidney disease

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Study design</th>
<th>Population (patients)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ananthapanyasut et al(^a), 2010</td>
<td>Retrospective multicentric</td>
<td>1,010</td>
<td>Prevalence of AF in nondialysis patients with CKD: 21.2%</td>
</tr>
</tbody>
</table>
| Soliman et al\(^a\), 2010 | Prospective multicentric | 3,267 | Prevalence of AF in CKD (but not ESRD) patients: 18%  
  – Presence of AF in CKD (stage 3-5): 7.7% |
| Bansal et al\(^a\), 2014 | Prospective multicentric | 81,088 | – AF is independently associated with an increased risk of death in adults with CKD |
| Alonso et al\(^a\), 2011 | Prospective population-based | 10,328 | Reduction in renal function and albuminuria have a strong association with the incidence of AF |
| Nelson et al\(^a\), 2012 | Retrospective using the Medicare 5% database | 1,092,649 | Prevalence of AF patients who developed ESRD in patients with advanced CKD than in patients without CKD  
  – AF was independently associated with an increased risk of ESRD in patients with CKD |
| Watanabe et al\(^a\), 2009 | Prospective multicentric | 235,818 | – AF increases the risk of CKD development |
| Bansal et al\(^a\), 2013 | Prospective multicentric | 206,229 | – AF was independently associated with an increased risk of ESRD in patients with CKD  
  – The presence of CKD in patients with AF increases the thromboembolic risk, particularly in patients with ESRD  
  – Warfarin reduced the incidence of thromboembolic events in patients with non-end-stage CKD |
| Providência et al\(^a\), 2014 | Systematic review and meta-analysis | 379,506 | – AF is associated with an increased risk of ESRD |

AF: Atrial fibrillation; CKD: Chronic kidney disease; ESRD: End-stage renal disease.
Supplementary Material

Supplementary figure 1 – Common mechanisms in some diseases associated with development of atrial fibrillation. COPD: Chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea.

References


