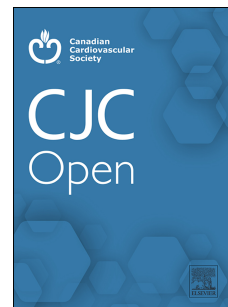


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Validation of the use of discharge diagnostic codes for the verification of secondary atrial fibrillation in administrative databases

Short title: Validation study of secondary atrial fibrillation

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1 **Abstract (246 words)**

2 *Background:* “Secondary atrial fibrillation” (AF) denotes AF precipitated by short-term triggers
3 and which may be reversible. There is interest in using administrative data to study secondary
4 AF but their ability to verify secondary AF has not been studied.

5 *Methods:* We conducted a cross-sectional analysis of 1000 randomly selected hospitalizations of
6 patients discharged alive between January 1st, 2016 and March 31st, 2020 with AF coded as the
7 most responsible diagnosis (Type 1), post-admit Comorbidity (Type 2), or secondary diagnosis
8 (Type 3). We compared diagnosis types to AF category (secondary or not) as determined by a
9 physician blinded to the discharge diagnosis type. We calculated the positive predictive value
10 (PPV) of the designation of secondary AF in comparison to physician determination.

11 *Results:* A total of 421 hospitalizations had AF documented as a Type 2 diagnosis; this had a
12 PPV of 94.8% for physician determination of secondary AF. After excluding hospitalizations
13 with pre-existing AF and those for whom AF type could not be determined by the physician, the
14 PPV of a Type 2 diagnosis (N=391) for secondary AF was 99.7%. Type 3 diagnoses of AF
15 (N=222) mostly captured hospitalizations with pre-existing AF (87.8% of Type 3 diagnoses).

16 *Conclusions:* A Type 2 diagnosis can be used to verify secondary AF in people who were first
17 diagnosed with AF while hospitalized for other causes. This facilitates cohort studies and clinical
18 trial recruitment of people with this AF subtype, although it should not be used to determine
19 prevalence/ incidence of secondary AF.

20

21

22 Introduction

23 Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1], which portends
24 substantially increased risks of death, heart failure, and stroke [2-4]. While AF is mostly a
25 chronic disease, it can also be precipitated in-hospital by short-term triggers such as surgery,
26 infection, electrolyte disturbances, pneumonia, and chronic obstructive pulmonary disorder
27 (COPD) exacerbations [5-8]. AF that is triggered by a short-term precipitant often appears to
28 resolve after its reversal. Such temporary cases of AF have been designated as “secondary AF”,
29 in contrast to “primary AF” that develops without acute provocation and that is expected to be
30 longer-lasting[9, 10]. Secondary AF comprises a large portion of new-onset AF that is diagnosed
31 in-hospital[5, 6]. Despite this, there are limited data on management patterns or the prognosis of
32 secondary AF. This has resulted in minimal guidance about secondary AF in clinical practice
33 guidelines [8, 11-14].

34 The knowledge gaps about the management patterns and outcomes of people with secondary
35 AF can be informed using population-based studies leveraging administrative datasets, as they
36 can be used to create highly inclusive cohorts with long-term follow-up. Administrative datasets
37 can also be used to verify diagnosis of secondary AF in people who may be candidates for
38 clinical trials investigating management approaches. In theory, this can be accomplished by
39 leveraging administrative datasets to verify first-ever AF diagnoses of secondary AF in people
40 who were hospitalized for a different diagnosis. Since these data are collected primarily for
41 administrative purposes, it is important to determine their validity before using them for clinical
42 research. Accordingly, the goal of this study was to study the performance of an algorithm for
43 verification of secondary AF in people who were first documented with AF during an acute
44 hospitalization where the AF was not the primary reason for hospitalization. Our hypothesis was

45 that AF that was first diagnosed in-hospital under such circumstances would have a high positive
46 predictive value (PPV) for secondary AF.

47 **Material and methods**

48 All medical diagnoses made in hospitalized patients in Canada are recorded in the Canadian
49 Institute for Health Information's Discharge Abstract Database (CIHI-DAD). The diagnoses are
50 classified into diagnosis types based on the impact the condition had on the patient's in-hospital
51 care[15]. Diagnosis type M (most responsible diagnosis) refers to a condition that is the most
52 responsible for a patient's stay in hospital. If a patient is hospitalized for more than one
53 condition, the one responsible for the greatest portion of the stay is selected as the most
54 responsible. Diagnosis type 1 (pre-admit comorbidity) refers to a condition that existed prior to
55 the patient's stay in hospital. Diagnosis type 2 (post-admit comorbidity) refers to a condition that
56 arises after the patient is admitted to the hospital. Both diagnoses type 1 and 2 are comorbid
57 diagnoses and require fulfillment of at least one of the following criteria of significance: requires
58 treatment beyond maintenance of the pre-existing condition, increases length of stay by at least
59 24 hours, and/or significantly affects the treatment received. Diagnosis type 3 refers to a
60 secondary diagnosis for which a patient may or may not receive treatment. A diagnosis type 3
61 cannot meet any of the criteria of significance listed above[15].

62 We conducted a cross-sectional analysis using electronic medical record data, which was
63 approved by the University Health Network research ethics board. The hospital's data services
64 department provided us with a randomly selected sample of 1000 hospitalizations of patients
65 who were discharged alive between January 1st, 2016 and March 31st, 2020 from Toronto
66 General Hospital (TGH), Toronto Western Hospital (TWH), or Princess Margaret Cancer Centre
67 (PMCC) with a Type M, Type 2, or Type 3 diagnosis of AF. These three hospitals together

68 comprise the University Health Network in Toronto. Patients who were coded to have a Type 1
69 diagnosis of AF were not included since our objective was to study AF that was first recognized
70 in-hospital (rather than a pre-admit comorbidity).

71 A second-year Internal Medicine resident (BS) reviewed the discharge summary
72 associated with each hospitalization. The reviewer was blinded to the diagnosis type that had
73 been recorded by the hospital's medical records department. The description of the clinical
74 course and any available ECGs were used to verify the diagnosis of AF. The physician reviewer
75 was asked to determine whether the AF was more aptly characterized as primary or secondary
76 AF based on whether the AF was felt to be the primary cause of hospitalization or a secondary
77 issue that arose during hospitalization. The reviewer also determined if the AF was newly
78 diagnosed or documented in the patient's past medical history. She also collected patient age,
79 sex, hospital (TGH, TWH, or PMH) and calendar year of discharge. The presence of sinus
80 rhythm at time of discharge was also recorded if that could be determined from the discharge
81 summary. No personal health information (e.g., date of birth) was collected. The AF category
82 and prior AF status were classified as undetermined for hospitalizations where the discharge
83 summary could not be accessed.

84 *Statistical analysis*

85 Baseline characteristics were summarized using the median, with 25th-75th percentiles
86 (Q1-Q3) for continuous variables, while counts with percentages were used for categorical
87 variables. The physician reviewer's determination of AF category (primary vs. secondary) was
88 treated as the reference standard for the purposes of this analysis. This was compared against the
89 categorization of AF as per the discharge diagnosis type assigned in the hospital discharge
90 record. If AF was coded as the most responsible diagnosis in the hospital discharge record (i.e.,

91 diagnosis type M), it was categorized as primary. Our main approach to the determination of
92 secondary AF was if it was documented as a Post-Admit Comorbidity (diagnosis type 2). We
93 also explored the performance of AF as a Secondary Diagnosis (diagnosis Type 3) for
94 determination of secondary AF.

95 We calculated the positive predictive value (PPV) of the designation of secondary or
96 primary AF in the hospital discharge record, in comparison to the reference standard (physician
97 determination). The primary analysis included all hospitalizations, including those where the AF
98 category could not be determined after chart review, and hospitalizations of patients with pre-
99 existing AF. We conducted sensitivity analyses after excluding people documented in the
100 discharge summary as having pre-existing AF, and charts in which the AF diagnosis type could
101 not be determined by the reviewer (i.e., a complete case analysis). As a secondary analysis,
102 Kappa statistics were calculated to determine the agreement between the physician determination
103 of AF diagnosis type versus discharge summaries [16]. We also conducted a *post hoc* analysis to
104 determine the distribution of AF diagnosis types and the PPV at each of the 3 hospitals in the
105 University Health Network. All statistical analyses were conducted using SPSS[17].

106 **Results**

107 *Patient Characteristics*

108 Of the 1000 hospital discharges provided, 14 charts could not be accessed, while 3 were
109 duplicates of patients that were already included. The characteristics of the 983 included patients
110 are summarized in Table 1. Most patients were male (60.9%), and the median age at hospital
111 admission was 70 years (Q1-Q3 62-78 years).

112 Of the 1000 hospitalizations with AF diagnoses, most (78.2%) were discharges from
113 Toronto General Hospital (TGH). With regards to AF diagnosis type, 357 (35.7%) were

114 classified in the hospital discharge record as having diagnosis type M, 421 (42.1%) as diagnosis
115 type 2, and 222 (22.2%) as diagnosis type 3. Based on physician chart review, 442 (44.2%) of
116 hospitalizations involved patients documented as having a diagnosis of AF prior to their hospital
117 admission.

118 *Validation of Diagnostic Codes*

119 We included all 1000 hospitalizations with a type M, 2, or 3 AF diagnosis in the primary
120 analysis. A breakdown of the 1000 hospitalizations according to the hospital discharge record
121 and whether they were determined to be primary or secondary AF according to physician review
122 is presented in Table 2. The PPV of a Type 2 diagnosis of AF in the hospital discharge record for
123 classifying AF as secondary was 94.8%, while the PPV of a Type 3 diagnosis was 87.4%. The
124 PPV of a Type M diagnosis for classifying AF as primary was 86.0%. The overall kappa score
125 was 0.55. The analysis stratified by each specific hospital revealed significant differences in the
126 distribution of AF diagnosis, as summarized in Table 3 ($p < 0.001$). Nonetheless, the PPV of a
127 Type 2 diagnosis for predicting secondary AF was above 90% in all three hospital sites (97.1%
128 at TGH, 90.4% at TWH, 100% at PMH).

129 Among 357 hospitalizations with a type M diagnosis, 237 (66.4%) were documented in
130 the medical record to have AF prior to hospital admission. Similarly, of 222 hospitalizations with
131 a type 3 diagnosis of AF, 195 (87.8%) were documented found to have AF pre-admission. In
132 contrast, only 10 (2.4%) of the 421 hospitalizations with a type 2 diagnosis had AF pre-
133 admission. The results of the analyses after excluding the 442 hospitalizations with pre-existing
134 AF and 18 hospitalizations whose prior AF status was unknown are presented in Table 4. For
135 hospitalizations where the AF was newly recognized, the PPV of a Type 2 diagnosis for
136 classifying AF as provoked was 96.8%, while the PPV of a type M diagnosis for classifying AF

137 as primary was 84.2%. Conversely, the PPV for classifying AF as provoked was only 52.2% for
138 a Type 3 AF diagnosis in hospitalizations with newly recognized AF in-hospital. However, for
139 10 of these hospitalizations with a Type 3 diagnosis (43.5%), the reviewing physician could not
140 classify the AF as primary versus provoked. The overall kappa score for this subset of the study
141 sample was 0.79.

142 After excluding hospitalizations with prior AF and those with undetermined AF category,
143 we were left with 517 hospitalizations with newly recognized AF and whose AF diagnosis type
144 could be characterized. A breakdown of diagnosis types is presented in Table 5. The PPV of a
145 Type 2 diagnosis for determining provoked AF was 99.7%, while the PPV of a Type 3 diagnosis
146 for determining provoked AF was 92.3%. The PPV of a Type M diagnosis for classifying AF as
147 primary AF was 85.0%. The overall kappa score for this subset of the cohort was 0.83.

148 **Discussion**

149 In this cross-sectional validation study, we demonstrated that appropriate utilization of
150 discharge diagnosis types in the CIHI-DAD can be used to categorize patients as likely having
151 primary or secondary AF. The PPV was high when compared to physician determination of AF
152 type after chart review. In particular, a discharge diagnosis of AF as a Type 2 diagnosis had a
153 PPV of >90% for detecting AF that was not the primary reason for hospitalization and that was
154 not recognized before hospital admission. When we further excluded people who had been
155 documented to have pre-existing AF, the PPV of a Type 2 diagnosis for determining secondary
156 AF rose to >95%. We would like to highlight to readers that the PPV in the sensitivity analyses
157 excluding people with undetermined AF status and pre-existing AF are likely overestimated. A
158 Type M diagnosis also performed well for verifying primary AF, with a PPV of 86%. Type 3
159 diagnoses of AF mostly captured people with pre-existing AF, which constituted 87.8% of such

160 diagnoses, indicating that they should not be used for the study of people with secondary AF in
161 administrative data.

162 Overall, our analysis suggests that a Type 2 discharge diagnosis of AF can be used to
163 leverage administrative datasets for the study of people whose AF was first recognized in-
164 hospital during an admission for another cause. The PPVs of the discharge diagnostic type 2 in
165 verifying patients with secondary AF were higher than 90% in all our analyses. This suggests
166 that Type 2 diagnoses can be used to verify patients with a high likelihood of having secondary
167 AF. The reliability of this approach can be increased further if the lookback period in
168 administrative datasets is used to exclude any diagnoses of AF that were made before hospital
169 admission.

170 There is a paucity of data regarding the management of patients with secondary AF,
171 especially in those admitted for non-cardiac and non-surgical reasons. This is particularly
172 relevant for stroke prophylaxis with anticoagulants which balances the risk of stroke with that of
173 bleeding [18]. The risk of stroke in patients with secondary AF is less established than people
174 with primary AF, and patients with secondary AF are also more likely to have multiple
175 comorbidities than similarly aged patients with primary AF [5, 19]. Lubitz *et al.* performed a
176 longitudinal observational study following participants from the Framingham Heart Study with
177 AF first detected between 1949 and 2012. The results of the study demonstrated that risk of
178 recurrent AF was high whether the AF was primary or secondary, and that long-term risks of
179 stroke and mortality were similar between participants with primary and secondary AF. The
180 authors called for future studies that could help determine whether increased AF surveillance and
181 adherence to primary AF management principles is warranted in patients with secondary AF [6].
182 Another study led by Siontis *et al* utilized administrative data from Minnesota to demonstrate

183 that patients with secondary AF after noncardiac surgery was associated with a lower risk of
184 recurrence but similar stroke risk as patients with primary AF that was unrelated to surgery[20].
185 However, it is unclear if patients with secondary AF would benefit from receiving
186 anticoagulation at the same thresholds as people with primary AF. Quon *et al.* conducted a
187 retrospective cohort study using Quebec administrative data to assess the risk of ischemic stroke
188 and hemorrhage in patients with secondary AF. The authors found that there was no association
189 between anticoagulation and lower risk of ischemic stroke in patients with secondary AF, thus
190 concluding that there is limited benefit in using anticoagulants in some patients with secondary
191 AF.

192 A specific point of debate is the need for anticoagulation of secondary AF in the setting
193 of cardiac surgery. Oraili *et al* reported that new-onset post-operative AF following coronary
194 artery bypass graft (CABG) surgery was associated with increased risk of overall mortality and
195 stroke midway through their 49-month follow-up time but did not portend longer-term mortality
196 risk if people who had early stroke were censored [21]. In a systematic review of 9 observational
197 studies, Wang *et al* reported that anticoagulation of people with secondary AF following cardiac
198 surgery was associated with minimally lower risk of arterial thromboembolism (2 less events per
199 1000 person-years), but increased risk of bleeding (42 more events per 1000 person-years) [22].

200 Most prior studies on secondary AF have focused on stroke risk and the need for
201 anticoagulation. It is less appreciated that people discharged from hospital with AF have a high
202 risk of death,[19] and that stroke only contributes to a negligible proportion of the mortality risk
203 associated with AF [23, 24]. This highlights the importance for people with secondary AF to
204 receive close follow-up after their discharge geared at addressing their overall health status.
205 Indeed, the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart

206 Rhythm Society (HRS) guidelines recommend “careful follow-up” for patients with newly
207 diagnosed secondary AF. For cardiovascular diseases other than AF, there are ample data
208 demonstrating that early follow-up is associated with improved outcomes for patients after
209 discharge from hospital or the emergency department (ED), particularly if patient care is shared
210 between cardiologists and generalists [25-28].

211 When it comes to AF, there are less data on physician follow-up and its association with
212 patient outcomes. Most available data are specific to patients with primary AF discharged from
213 the ED. In a study of 14,907 patients discharged from Ontario ED’s with a new primary
214 diagnosis of AF between 2007 and 2012, only half the patients had follow-up within a week, and
215 18.0% had still not obtained follow-up care at 30 days [29]. Another study of 2902 propensity
216 score-matched pairs of individuals with newly diagnosed primary AF in the ED demonstrated
217 that cardiologist care within a year of diagnosis was associated with lower mortality (5.3% vs
218 7.7%) [30]. Data from Ontario indicated that less than half the patients who are diagnosed with
219 primary AF in the ED are started on anticoagulation after discharge despite being eligible for it
220 based on their age [31]. We suspect similar or larger gaps in care for hospitalized patients with
221 newly diagnosed secondary AF. These are important questions about secondary AF that can be
222 addressed using administrative data by applying the approach tested in this study.”

223 The Ontario administrative datasets potentially offer a valuable resource for investigating
224 patients with secondary AF, their management, and their prognosis following discharge. Tu *et al.*
225 demonstrated that Ontario administrative database diagnostic codes used to identify patients with
226 AF had a specificity of over 95% [32]. Validating the accuracy of diagnostic codes for
227 determining primary versus secondary AF, however, is crucial before conducting further studies
228 using administrative data. The Minnesota study led by Siontis *et al* identified patients with

229 secondary AF using ICD-9 diagnostic codes, and each diagnosis had to be validated by trained
230 nurse abstractors [20]. In contrast, the study by Quon *et al* utilized ICD-10 diagnostic codes to
231 identify and diagnose patients with secondary AF without reviewing the accuracy of these codes
232 and that was highlighted as a limitation of the study [7]. Collectively, these studies highlight that
233 administrative data can be useful to study secondary AF but require validation of the
234 appropriateness of using diagnostic codes in verifying secondary AF.

235 Our study has several limitations. First, all patients in our cohort received care from three
236 hospitals (TGH, TWH, PMH), but they all fall within one healthcare system (University Health
237 Network) in one urban centre (Toronto). Therefore, the results of this study might not be
238 generalizable to a wider population outside of this health system. Another limitation is that we
239 did not verify all diagnoses of AF with electrocardiograms. Thus, for most patients, we relied on
240 the description of the clinical course within the discharge summary. Additionally, we relied on
241 discharge summaries for identification of pre-existing AF, and this may have not been sensitive
242 enough to identify all previously recognized AF. We also did not collect data on whether the AF
243 was diagnosed before or after admission to hospital. Our approach was limited to reviewing AF
244 diagnoses made within the specific hospitalization, and we did not determine if AF was
245 provoked by an event preceding the admission to hospital (including previous hospitalizations).
246 Another limitation of our study was the use of only one physician chart reviewer. There were
247 several cases where the physician was not able to determine whether AF was primary or
248 secondary, and this may have been improved with the use of a second chart reviewer. Finally,
249 our sample was defined by people having been documented with AF as one of the discharge
250 diagnoses. This means that we did not include patients who would have had AF that was not
251 documented in the discharge diagnoses. Accordingly, we could only verify true and false

252 positives, i.e., we could not determine sensitivity and negative predictive value as we could not
253 distinguish true from false negatives. This means Type 2 diagnoses of AF should not be used to
254 interrogate administrative datasets to report on the population-wide incidence and/ or prevalence
255 of secondary AF. Rather, their use should be limited to determining the characteristics and
256 outcomes of a subset of people who have a high likelihood of secondary AF.

257 **Conclusions**

258 A Type 2 diagnosis can be used to verify secondary AF in people hospitalized for other
259 causes, particularly if pre-existing diagnoses of AF are excluded. This strategy can leverage
260 administrative datasets to study the management and outcomes of hospitalized patients with
261 secondary AF while allowing for comprehensive long-term follow-up. The high PPV can also be
262 useful to verify people with secondary AF for recruitment into pragmatic clinical trials
263 leveraging administrative datasets. However, this approach should not be used to determine
264 prevalence or incidence of secondary AF given its undetermined sensitivity.

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Table 1. Characteristics of patients included in the validation study (N=983)

Median Age (Q1-Q3)	70 (62-78)
Sex	
Male, N (%)	609 (60.9)
Female, N (%)	374 (37.4)
Hospital	
Toronto General Hospital, N (%)	781 (79.4)
Toronto Western Hospital, N (%)	183 (18.6)
Princess Margaret Hospital, N (%)	17 (1.7)
Not documented, N (%)	2 (0.2%)
Year of Discharge	
2016, N (%)	182 (18.5)
2017, N (%)	240 (24.4)
2018, N (%)	257 (26.1)
2019, N (%)	247 (25.1)
2020, N (%)	57 (5.8)
AF Prior to Hospital Admission	
Yes, N (%)	441 (44.9)
No, N (%)	540 (54.9)
Unknown, N (%)	2 (0.2)
Sinus Rhythm at Discharge	
Yes, N (%)	313 (31.8)
No, N (%)	29 (3.0)
Unknown, N (%)	641 (65.2)

Table 2. A comparison of the AF discharge diagnosis type against AF category as determined by physician review for all hospitalizations (N=1000)

	Primary	Secondary	Undetermined	Total
Type M	307	42	8	357
Type 2	1	399	21	421
Type 3	11	194	17	222
Total	319	635	46	1000

Table 3. A comparison of the AF discharge diagnosis type against hospital location (N=1000)

	TGH	TWH	PMH	Unknown	Total
Type M, N (% of hospital)	294 (37.6)	56 (30.6)	0 (0.0)	7 (38.9)	357
Type 2, N (% of hospital)	347 (44.4)	52 (28.4)	15 (88.2)	7 (38.9)	421
Type 3, N (% of hospital)	141 (18.0)	75 (41.0)	2 (11.8)	4 (22.2)	222
Total	782	183	17	18	1000

Table 4. A comparison of the AF discharge diagnosis type against AF category as determined by physician review after excluding hospitalizations with prior AF (N=540)

	Primary	Secondary	Undetermined	Total
Type M	96	17	1	114
Type 2	1	390	12	403
Type 3	1	12	10	23
Total	98	419	23	540

Table 5. A comparison of the AF discharge diagnosis type against AF category as determined by physician review after excluding patients with prior AF and/or unknown AF type according to physician review (N=517)

	Primary	Secondary	Total
Type M	96	17	113
Type 2	1	390	391
Type 3	1	12	13
Total	98	419	517

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