ORIGINAL ARTICLE

Prognostic significance of new onset atrial fibrillation in acute coronary syndrome patients treated conservatively

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Abstract

Background: *The purpose of this study was to assess the association between new onset of atrial fibrillation (AF) and in-hospital management and mortality in acute coronary syndrome patients admitted to hospitals without on-site invasive facilities.*

Methods: *We assessed data concerning in-hospital management and mortality of 24 patients with, and 977 patients without, new onset of AF from the Krakow Registry of Acute Coronary Syndromes database.*

Results: *Patients with new onset of AF were older and more likely to have diabetes, chronic obstructive pulmonary disease, cardiogenic shock and chest pain on admission, and a shorter time from the onset of symptoms to admission. These patients more frequently received glycoprotein IIb/IIIa inhibitors, thrombolytics, and were less likely to be treated with statins during their hospital stay. Risk of AF occurrence was lower in patients treated with statins (1.9% vs 5.2%; p = 0.021). Among patients treated conservatively, in-hospital mortality was higher in patients with new onset of AF (8.1% vs 33.3%; p = 0.001). Independent predictors of in-hospital death in this group of patients were: new onset of AF, age, cardiogenic shock, chronic obstructive pulmonary disease, history of renal insufficiency, and discharge diagnosis.*

Conclusions: *New onset of AF is associated with excessive in-hospital mortality in acute coronary syndrome patients staying on conservative treatment in community hospitals without on-site invasive facilities.* (Cardiol J 2010; 17, 1: 57–64)

Key words: atrial fibrillation, acute coronary syndrome, myocardial infarction, management, mortality

Introduction

Atrial fibrillation (AF) is a very common supraventricular arrhythmia which complicates the course of acute coronary syndrome (ACS). Previous studies have shown that new onset of AF is associated with increased short- and long-term mortality in patients presenting either with or without ST-segment elevation ACS [1–12]. Other studies however have not shown this [12–14]. On the other hand, in most previous studies there has been very little usage of guideline-recommended therapies, especially statins, which have been shown to be associated with a decreased risk of AF onset [15, 16].

The purpose of our study was to assess the association between new onset of AF and in-hospital outcomes in patients with ACS admitted to hospitals without on-site invasive facilities.

Methods

The Krakow Registry of Acute Coronary Syndromes was a prospective, multi-center, observational registry designed to examine current epidemiology, in-hospital management and outcome of patients with ACS in this region of Poland (Krakow, Malopolska Region). The design and main results of the Registry have been described previously [17, 18]. Cardiogenic shock was defined as reduced blood pressure (systolic blood pressure < 90 mm Hg or a drop of mean arterial pressure > 30 mm Hg) and/or low urine output (< 0.5 mL/kg/h), with a pulse rate > 60 beats per minute with or without evidence of organ congestion [19]. Patients were classified as non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) based on their final diagnosis. STEMI was diagnosed if ST-segment elevation ≥ 1 mm occurred in ≥ 1 lead or new left bundle branch block was found in electrocardiogram with biochemical evidence of myocardial necrosis (≥ 1 positive biochemical cardiac necrosis markers measurement). NSTEMI was diagnosed in patients with ≥ 1 positive biochemical cardiac necrosis markers measurement without new ST-segment elevation in electrocardiogram. The primary end point was in-hospital mortality. New onset of AF was defined as new AF that occurred during hospital stay in patients presenting with sinus rhythm on admission. It was diagnosed by local physicians.

The study was approved by the local bioethical committee.

Statistical analysis

Data was analyzed according to the established standards of descriptive statistics. Values were expressed as mean ± standard deviation. Categorical variables were presented as percentages. Statistical comparisons between groups were performed using χ^2 test and Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables, as appropriate. Logistic regression analysis was performed to find independent predictors of new onset of AF occurrence. In the first model, the following covariates were tested: gender, age, body mass index, presence of diabetes mellitus, arterial hypertension, hyperlipidaemia, prior angina, prior myocardial infarction, prior heart failure symptoms, left ventricular ejection fraction, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior stroke/ /transient ischemic attack, history of smoking, peripheral arterial disease, chronic renal insufficiency, chronic obstructive pulmonary disease, parameters on admission (chest pain presence, cardiogenic shock presence, heart rate, systolic blood pressure, diastolic blood pressure), time from chest pain onset to admission, and discharge diagnosis.

In the second model, usages of each pharmacological agent during hospital stay were tested as covariates. The third model was a combination of the previous two models. Results were presented as odds ratios with 95% confidence intervals. Occurrence of primary end point was assessed in pre-specified groups (cardiogenic shock vs. no cardiogenic shock presence, final diagnosis of STEMI vs NSTEMI vs unstable angina) and the Breslow-Day test for homogeneity was used to prove possible interactions. In addition, multivariate Cox regression analysis was performed to find significant predictors of in-hospital death. The same covariates as used in logistic regression analysis model number 1 were tested and forward selection in Cox regression with the probability value for covariates to enter the model set at 0.05 level. Risk of in-hospital death was expressed as hazard ratio with 95% confidence interval. All tests were two-tailed, and a p value of < 0.05 was considered statistically significant.

Results

The Krakow Registry of Acute Coronary Syndromes database included 1,414 patients with sus-
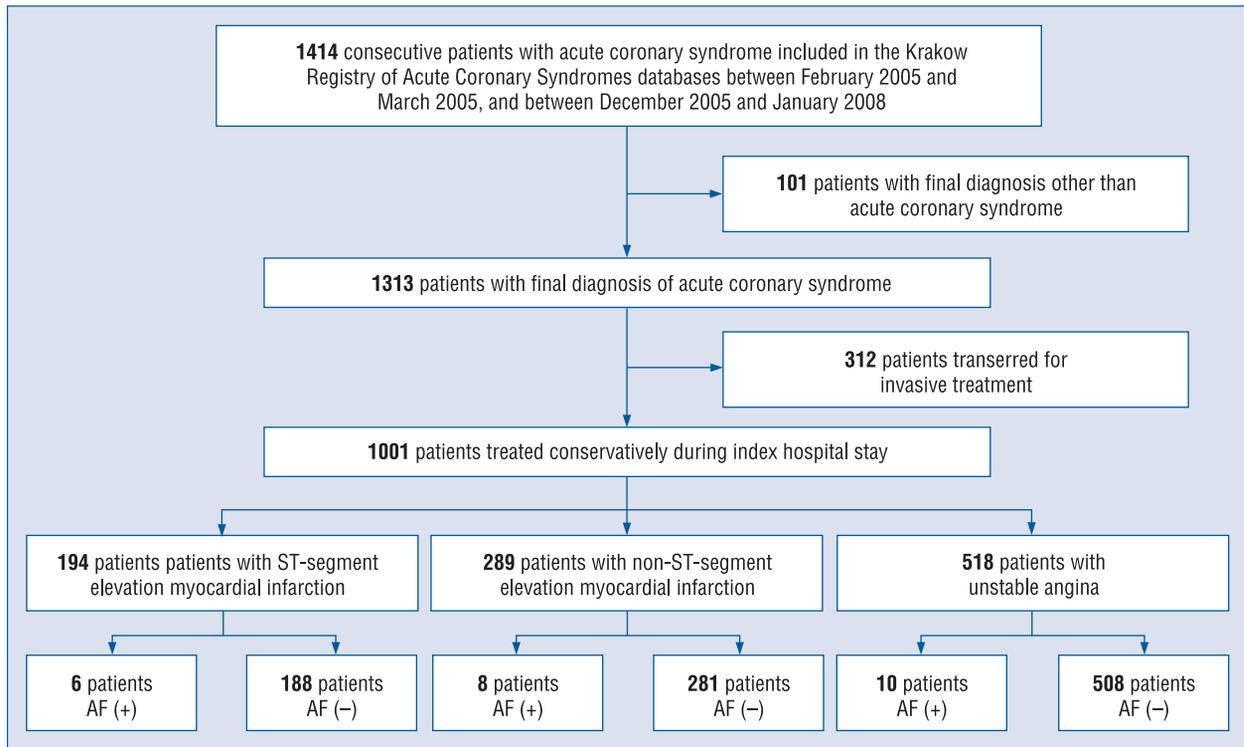
Figure 1. Scheme of groups distribution in the registry; AF — atrial fibrillation.

pected ACS admitted between February 2005 and March 2005, and between December 2005 and January 2006. A total of 101 patients with a final diagnosis other than ACS (stable angina or extracardiac cause of chest pain) were excluded from the analysis. Of the remaining 1,313 patients, 312 (23.8%) were transferred for invasive treatment. The other 1,001 (76.2%) patients were treated conservatively during hospital stay: this was the studied group, as set out in Figure 1. A total of 44 (4.4%) patients were in cardiogenic shock on admission. At discharge, 194 (19.4%) patients had a final diagnosis of STEMI, 289 (28.9%) a diagnosis of NSTEMI, and 517 (51.7%) a diagnosis of unstable angina. New onset of AF was diagnosed in 24 (2.4%) patients. The observed frequency was similar among patients with discharge diagnosis of STEMI, NSTEMI, and unstable angina (3.1% *vs*. 2.8% *vs*. 1.9% respectively; p = 0.53). It was observed more frequently in shock than in non-shock patients (16.7% *vs*. 4.1%; p = 0.018).

Baseline demographic and clinical characteristics of patients with and without new onset of AF are summarized in Table 1. Patients with new onset of AF were older and were more likely to have diabetes mellitus, chronic obstructive pulmonary disease, chest pain on admission, and a shorter time from the onset of symptoms to admission. Patients with new onset of AF were more likely to be in cardiogenic shock, with higher heart rate and lower systolic blood pressure on admission. Importantly, there was no difference in discharge diagnosis between study groups. Diabetes mellitus and presence of chest pain on admission, as well as heart rate and systolic blood pressure on admission, were independent predictors of new onset of AF (Table 2, model 1).

As shown in Table 3, patients with new onset of AF were more likely to receive glycoprotein IIb/ /IIIa inhibitors, thrombolytics, and less likely to be treated with statins during hospital stay. Trends toward less frequent use of aspirin and more frequent use of low-molecular-weight heparin in patients with new onset of AF were also observed. Patients treated with statins were at lower risk of AF than untreated patients (1.9% *vs*. 5.2%; p = 0.021). Use of glycoprotein IIb/IIIa inhibitors, thrombolytics, low-molecular-weight heparin, and statins were independently associated with new onset of AF (Table 2, model 2), but this association was no longer significant after adjustment for clinical covariates (Table 2, model 3).

Among patients treated conservatively during hospital stay, the highest in-hospital mortality was

Table 1. Baseline demographic and clinical characteristics.

Characteristics	New onset of AF		OR (95% CI)	P
	No (n = 977)	Yes (n = 24)		
Male	54.0	50.0	0.85 (0.38–1.91)	0.84
Age (years)	69.0 ± 11.7	74.8 ± 8.6	–	0.014
Age >75 years	31.8	50.0	2.14 (0.95–4.82)	0.08
Body mass index [kg/m²]	27.3 ± 6.0	27.0 ± 2.9	–	0.71
Diabetes mellitus	22.8	45.8	2.86 (1.26–6.48)	0.014
Arterial hypertension	78.9	79.2	1.02 (0.38–2.75)	0.99
Hyperlipidemia	57.8	45.8	0.62 (0.27–1.39)	0.30
Prior angina	71.3	75.0	1.21 (0.47–3.07)	0.82
Prior myocardial infarction	33.2	29.2	0.83 (0.34–2.02)	0.83
Prior heart failure symptoms	23.7	29.2	1.32 (0.54–3.23)	0.63
Prior PCI	7.8	0.0	–	0.25
Prior CABG	4.3	0.0	–	0.62
Prior stroke/TIA	6.0	4.2	0.68 (0.09–5.10)	0.99
Current smoker	26.7	33.3	1.37 (0.58–3.24)	0.49
Family history of CAD	13.2	12.5	0.94 (0.28–3.19)	0.99
COPD	10.6	29.2	3.46 (1.40–8.53)	0.012
Peripheral arterial disease	11.9	4.2	0.32 (0.04–2.41)	0.35
History of renal insufficiency	6.1	0.0	–	0.39
Chest pain on admission	59.4	91.7	7.53 (1.76–32.20)	0.001
Time from chest pain onset to admission [h]	17.6 ± 21.4	12.0 ± 18.2	–	0.048
Time from chest pain onset to admission ≤ 12 h	37.9	29.2	0.67 (0.28–1.64)	0.41
Heart rate on admission [beat/min]	83.7 ± 23.0	104.7 ± 36.7	–	0.002
SBP on admission [mmHg]	145.0 ± 31.9	125.5 ± 40.9	–	0.004
DBP on admission [mm Hg]	86.8 ± 15.1	81.7 ± 16.0	–	0.27
Cardiogenic shock on admission	4.1	16.7	4.69 (1.53–14.35)	0.018
LVEF (%)	53.4 ± 13.2	51.0 ± 10.4	–	0.20
Discharge diagnosis:				
STEMI	19.2	25.0		
NSTEMI	28.8	33.3	–	0.53
Unstable angina	52.0	41.7		

Values are presented as percentages or mean ± standard deviation; AF — atrial fibrillation; CABG — coronary artery bypass grafting; CAD — coronary artery disease; CI — confidence interval; COPD — chronic obstructive pulmonary disease; DBP — diastolic blood pressure; LVEF — left ventricular ejection fraction; NSTEMI — non-ST-segment elevation myocardial infarction; OR — odds ratio; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; STEMI — ST-segment elevation myocardial infarction; TIA — transient ischemic attack

observed among patients with discharge diagnosis of STEMI (STEMI *vs* NSTEMI *vs* unstable angina, 22.7% *vs* 12.1% *vs* 1.5% respectively; p < 0.0001). Also mortality was higher in shock than in non-shock patients (shock *vs* non-shock, 63.6% *vs* 6.2%; p < 0.0001). In-hospital mortality was higher in patients with new onset of AF [AF (–) *vs* AF (+), 8.1% *vs* 33.3%; p = 0.001]. In-hospital mortality rates for patients with and without new onset of AF, stratified by cardiogenic shock presence on admission and discharge diagnosis, are shown in Figure 2. Tests for interaction and multivariate Cox regression analysis (Table 4) have confirmed that new onset of AF was independently associated with

excess of in-hospital mortality in patients with ACS treated conservatively during hospital stay. Influence of new onset of AF on in-hospital mortality was especially expressed in lower risk individuals (non-shock, unstable angina). In patients with new onset of AF, a trend toward higher risk of ischemic stroke [AF (–) *vs* AF (+), 0.6% *vs* 4.2%; p = 0.16], but not hemorrhagic stroke (0.1% *vs* 0.0%; p = 0.99) occurrence during hospital stay was observed. There was no difference in blood transfusion rate between groups (1.5% *vs* 0.0%; p = 0.99). Among survivors, mean hospital stay was significantly shorter in patients without AF (9.1 ± 5.0 *vs* 12.4 ± ± 6.1 days; p = 0.008).

Table 2. Logistic regression analysis for new onset of atrial fibrillation occurrence.

Variable	OR	95% CI	P
Model 1			
Diabetes mellitus	4.07	1.53–10.88	0.005
Chest pain on admission	7.11	1.59–31.91	0.010
Heart rate on admission (per 1 beat/min)	1.02	1.00–1.04	0.012
Systolic blood pressure on admission (per 1 mm Hg)	0.98	0.96–1.00	0.020
Model 2			
Glycoprotein IIb/IIIa inhibitor	4.00	1.00–16.08	0.050
Thrombolysis	5.53	1.37–22.27	0.016
Low-molecular-weight heparin	5.76	1.28–25.92	0.023
Statins	0.28	0.11–0.68	0.005
Model 3			
Diabetes mellitus	2.53	1.04–6.11	0.040
Chest pain on admission	7.62	1.71–33.85	0.008
Chronic obstructive pulmonary disease	3.22	1.22–8.51	0.019
Heart rate on admission (per 1 beat/min)	1.02	1.01–1.04	0.002
Systolic blood pressure on admission (per 1 mm Hg)	0.98	0.97–1.00	0.041
Thrombolysis	3.65	0.93–14.32	0.063

CI — confidence interval; OR — odds ratio

Table 3. Pharmacological treatment during hospital stay.

Characteristics	New onset of AF		OR (95% CI)	P
	No (n = 977)	Yes (n = 24)		
Aspirin	95.3	87.5	0.35 (0.10–1.20)	0.11
Clopidogrel	9.3	4.2	0.42 (0.06–3.17)	0.72
Ticlopidine	18.6	20.8	1.15 (0.42–3.12)	0.79
Glycoprotein IIb/IIIa inhibitor	3.0	12.5	4.67 (1.32–16.54)	0.038
Thrombolysis	2.6	12.5	5.44 (1.52–19.43)	0.027
Low-molecular-weight heparin	73.3	91.7	4.01 (0.94–17.17)	0.06
Beta-blocker	81.0	70.8	0.57 (0.23–1.40)	0.20
ACEI/angiotensin II antagonist	75.9	58.3	0.44 (0.19–1.01)	0.06
Calcium antagonist	11.2	0.0	–	0.10
Nitrates	69.7	66.7	0.87 (0.37–2.05)	0.82
Statins	85.1	66.7	0.35 (0.15–0.84)	0.02

Values are presented as percentages; ACEI — angiotensin-converting enzyme inhibitor; AF — atrial fibrillation; CI — confidence interval; OR — odds ratio

Discussion

Our study is the first to show the prognostic influence of new onset AF on outcomes of a specific subgroup of ACS patients: patients treated conservatively during hospital stay. Regardless of the risk profile (age, discharge diagnosis, and presence of cardiogenic shock, chronic obstructive pulmonary disease, history of renal insufficiency) new onset AF has been shown to be an independent predictor of in-hospital death.

Observed frequency of AF was the one of the lowest ever reported in an ACS setting [1–15]. Several explanations can be suggested. In many previous studies, the impact of AF was assessed combining patients with pre-existing or new AF [1, 4, 14], not just new onset AF patients [2, 3, 5–9, 13]. Most studies were limited to acute myocardial
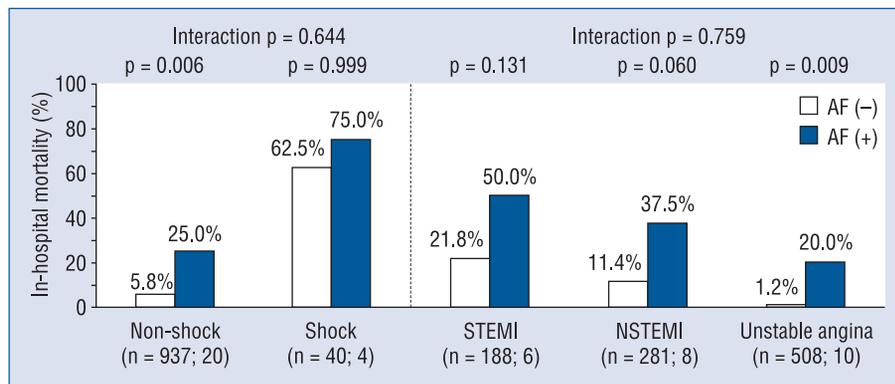
Figure 2. In-hospital mortality in patients without (empty bars) and with (solid bars) new onset of atrial fibrillation stratified by cardiogenic shock presence on admission and discharge diagnosis; AF — new onset of atrial fibrillation; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction.

Table 4. Multivariate Cox regression analysis for in-hospital death.

Variable	Hazard ratio	95% CI	P
STEMI (*vs* unstable angina)	6.98	3.19–15.25	< 0.001
NSTEMI (*vs* unstable angina)	3.91	1.78–8.56	0.001
Cardiogenic shock	5.34	3.25–8.77	< 0.001
New onset of atrial fibrillation	2.66	1.26–5.62	0.010
Chronic obstructive pulmonary disease	1.97	1.20–3.25	0.008
History of renal insufficiency	1.77	1.00–3.13	0.050
Age (per 1 year)	1.02	1.00–1.04	0.040

CI — confidence interval; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

infarction patients, especially STEMI patients [2–7, 13, 14]. In our study, associations between AF and outcomes were assessed in a broad spectrum of unselected ACS patients, including unstable angina patients with a potentially lower risk of new onset AF occurrence. Also, a significant decline in the incidence of AF complicating acute myocardial infarction has been recently reported [13, 14]. It may be associated with higher adherence to guideline-recommended therapies, especially a higher use of statins. Statins were used in almost of 85% of patients and in line with previous reports their use was associated with a decreased risk of AF occurrence [15, 16].

New onset of AF has been associated with advanced age [1–13, 15], diabetes mellitus [2, 4, 6, 7, 10, 15], chronic obstructive pulmonary disease [4], higher heart rate [1, 2, 5, 8–10] and lower systolic blood pressure on admission [5, 7, 8] and presence of cardiogenic shock on admission [1, 7]. Previous studies have also reported a higher prevalence of new onset AF in patients with congestive heart fail-

ure [4, 6–8], poor left ventricular function [10, 20], presence of mitral insufficiency [20], prior myocardial infarction [1, 7] and without previous coronary artery bypass grafting [1, 5, 8, 9]. Higher rates of new onset AF in patients treated with thrombolytics and glycoprotein IIb/IIIa inhibitors may be driven rather by differences in the discharge diagnosis and risk profile (these drugs were used in STEMI patients only) than by any direct association between the drugs and AF occurrence.

New onset of AF was associated with a more than doubling in in-hospital mortality in patients with ACS treated conservatively. There are many potential mechanisms responsible for poor short- and long-term prognosis in patients with ACS and new onset of AF. It is still debatable whether AF itself poses a risk for patients with ACS, or is merely a benign marker of disease severity [11, 12]. New onset of AF is frequently associated with congestive heart failure, advanced age and higher prevalence of age-related diseases (e.g. renal insufficiency, diabetes mellitus, chronic obstructive pulmo-

nary disease, stroke), which were themselves shown to be associated with adverse outcomes in ACS patients [21–25]. On the other hand, AF may cause rapid hemodynamic instability through loss of the atrial component of the cardiac output, increased ventricular response rate with decreased diastolic filling time, and irregular ventricular filling [26, 27]. Also, a recent study by Berton et al. [10] confirmed that patients with AF occurrence in an acute myocardial infarction setting were at higher risk of sudden death and chronic heart failure related death during seven-year follow-up.

Similarly to the GRACE Registry data, STEMI diagnosis was associated independently with worse in-hospital prognosis than NSTEMI and unstable angina [28]. The second independent predictor of in-hospital death in the analyzed patient population was cardiogenic shock (more than fivefold increased risk of in-hospital death). Interestingly, increase in in-hospital mortality associated with new onset of AF was expressed rather in lower risk individuals, non-shock and unstable angina patients. In line with previous papers, chronic obstructive pulmonary disease [23], renal insufficiency [21, 22], and age [29, 30] were independent predictors of an unfavorable outcome in ACS patients.

New AF may be associated not only with higher mortality, but also with other complications during short- and long-term follow-up [1, 2, 4, 5, 7, 8, 10, 12, 13]. In our study, a trend toward higher risk of ischemic stroke during hospital stay was observed in patients with new onset of AF. This has also been reported in previous studies [1, 5, 7, 8, 13]. Importantly, this increased risk of stroke may persist during long-term follow-up [1, 11–13]. Patients with AF are also at higher risk of ventricular fibrillation/ventricular tachycardia [2–4, 7, 8], conduction disturbances [3, 7], reinfarction [1, 2, 5, 7, 8], congestive heart failure [2, 4, 5, 7], and bleeding events [1, 8]. These complications may lead to prolongation of hospital stay [5, 8].

Limitations of the study

Several important limitations of the present study deserve discussion. First, the study has all the limitations of a registry. Secondly, a relatively small group size is also a limitation. The study focused only on in-hospital clinical outcomes of patients treated conservatively in centers without on-site invasive facilities. Data concerning mortality in the group of patients transferred for invasive treatment, as well as long-term clinical follow-up data for all patients, was not available. Additionally, new onset of AF was diagnosed based on local physician

assessment. Data concerning treatment used for AF, as well as timing, duration, and final outcome of AF was not assessed. However, observed associations between new onset of AF and in-hospital mortality are in line with previous reports and are clinically important.

Conclusions

New onset atrial fibrillation is associated with excessive in-hospital mortality in ACS patients remaining in community hospitals without on-site invasive facilities for conservative treatment.

Acknowledgements

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