Adherence to Antithrombotic Therapy Guidelines Improves Mortality among Elderly Patients with Atrial Fibrillation: Insights from the REPOSI Study

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ABSTRACT

Background: Atrial fibrillation (AF) is associated with a substantial risk of thromboembolism and mortality, significantly reduced by oral anticoagulation. Adherence to guidelines may lower the risks for both all cause and cardiovascular (CV) deaths.

Methods: Our objective was to evaluate if antithrombotic prophylaxis according to the 2012 European Society of Cardiology (ESC) guidelines are associated to a lower rate of adverse outcomes. Data were obtained from REPOSI, a prospective observational study enrolling inpatients aged ≥65 years. Patients enrolled in 2012 and 2014 discharged with an AF diagnosis were analysed.

Results: Among 2,535 patients, 558 (22.0%) were discharged with a diagnosis of AF. Based on ESC guidelines, 40.9% of patients were on guideline-adherent thromboprophylaxis, 6.8% were overtreated and 52.3% undertreated. Logistic analysis showed that increasing age (p=0.01), heart failure (p=0.04), coronary artery disease (p=0.013), peripheral arterial disease (p=0.03) and concomitant cancer (p=0.003) were associated with *non-adherence* to guidelines. Specifically, undertreatment was significantly associated with increasing age (p=0.001) and cancer (p<0.001), and inversely associated with HF (p=0.023).

AF patients who were guideline adherent had a lower rate of both all-cause death (p=0.007) and CV death (p=0.024) compared to those non-adherent. Kaplan-Meier analysis shows that guideline-adherent patients had a lower cumulative risk for both all-cause (p=0.002) and CV deaths (p=0.011). On Cox regression analysis, *guideline adherence* was independently associated with a lower risk of all-cause and CV deaths (p=0.019 and p=0.006).

Conclusions: Non-adherence to guidelines is highly prevalent among elderly AF patients, despite guideline-adherent treatment being independently associated with lower risk of all-cause *and* CV

deaths. Efforts to improve guideline adherence would lead to better outcomes for elderly AF patients.

Keywords: atrial fibrillation; antithrombotic therapy; elderly; guidelines; outcomes.

INTRODUCTION

The incidence and prevalence of atrial fibrillation (AF) have progressively increased over the last 20 years, especially in the elderly [1, 2]. In patients aged ≥65 years, the prevalence of AF has more than doubled from 1993 to 2007[1]. Because many patients are asymptomatic, guidelines now recommend screening for AF in all subjects age 65 and over[3].

AF is associated with an increased risk for both thromboembolic events and mortality, whether all-cause or from cardiovascular (CV) causes[1, 4]. Oral anticoagulant (OAC) therapy significantly reduces the risk of thromboembolism and mortality amongst AF patients[4]. Both OAC persistence and good quality anticoagulation control reduce major adverse events among AF patients[5–8].

Nonetheless, physician attitudes towards prescribing OAC and their adherence to guidelines vary[9]. Recent data from the EURObservational Research Programme AF (EORP-AF) Pilot Registry reported that up to 40% of patients managed by European cardiologists are non-adherent to the European Society of Cardiology (ESC) guidelines, and that both under- and overtreatment were associated with worst outcomes[10]. Elderly patients seem to be less likely to be treated with OAC, due to their perceived frailty and higher risk of bleeding[11]. When properly prescribed, OAC thromboprophylaxis using a vitamin K antagonist (VKA, *e.g.* warfarin) with good anticoagulation control is associated with better outcomes, even amongst the elderly[11, 12].

The aims of this study were as follows: i) to assess physician adherence to guidelines in a cohort of Italian AF elderly patients admitted acutely to Italian internal medicine and geriatric wards; ii) to describe the main factors associated with guideline non-adherence; and iii) to evaluate the risk of all-cause and CV deaths according to adherence or non-adherence to guidelines.

METHODS

We studied an elderly AF population from the REPOSI (REgistro POliterapie SIMI) study[13]. The latter is a multicentre collaborative observational registry jointly held by the Italian Society of Internal Medicine (SIMI), the Ca' Granda Maggiore Policlinico Hospital Foundation and the Mario Negri Institute of Pharmacological Research and based on a network of both internal medicine and geriatric wards in Italy and Spain. Full details on the study design and specific aims have been reported[13].

Briefly, REPOSI was held for four non-consecutive years: 2008, 2010, 2012 and 2014. In each of those years over a period of 4 weeks, quarterly (*i.e.* February, June, September and December), consecutive patients admitted to the participating wards aged more than 65 years were enrolled. For the present study, only patients enrolled in the 2012 and 2014 study cohorts were considered, as data recorded were more comprehensive than those initially collected in 2008 and 2010. The study protocol was first approved by the Ethics Committee of the Ca' Granda Maggiore Policlinico Hospital Foundation, then ratified for every enrolling site by local Ethics Committee. The study was conducted according to Good Clinical Practice recommendations and the Declaration of Helsinki. Patients were selected according to the International Classification of Diseases – 9th Edition (ICD-9) system. For the purposes of this analysis, all patients discharged with the 427.31 ICD-9 code, corresponding to AF diagnosis, were considered.

Thromboembolic risk was defined according to the CHA_2DS_2-VASc score[4], that defines 'Low risk' patients males with a CHA_2DS_2-VASc 0 or females with a CHA_2DS_2-VASc equal to 1; 'moderate risk', male patients with a CHA_2DS_2-VASc score 1; and 'high risk', all patients with CHA_2DS_2-VASc score

≥2[4]. Given the inclusion criteria (*i.e.* age ≥65), no patients with low risk were included in this analysis.

Guideline adherence was defined according to ESC 2012 Guidelines[3]. AF patients at moderate or high risk treated with OAC alone were considered as guideline adherent. *Undertreatment* was defined for patients at moderate or high risk not treated with any OAC or treated with antiplatelet drugs (AP); conversely, *overtreatment* was considered for all patients, both with moderate or high risk, treated with OAC plus AP[3]. Medication use was assessed according to the Anatomic Therapeutic Chemical (ATC) Classification System. As reported in the Supplementary Materials, treatment with AP was defined according to for ATC codes B01AC* and N02BA01, while treatment with OAC was defined according to ATC codes B01AA* and B01AE*.

Concomitant diagnoses were evaluated according to the ICD-9 codes as reported in the Supplementary Materials. Interactions of comorbidities were evaluated by the Cumulative Illness Rating Scale (CIRS) severity index and comorbidity Index[14, 15]. Polypharmacy was defined for the contemporary use of 5 or more drugs[13]. Cognitive status was evaluated with the short blessed test[16]; elderly depression was investigated with the geriatric depression scale[17]. Functional status was assessed with the Barthel index[18].

Follow-up data were collected at 3 and 12 months after discharge through telephone interview or, if patients were not alive, data were collected from the next of kin. According to death causes reported into the electronic case report form, based on investigator judgement. A CV death was defined when it was related to any cardiac or vascular reason. Both all-cause and CV deaths were considered as study outcomes.

Statistical Analysis

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as means and standard deviations (SD), and tested for differences with the Student t test. Non-normal variables were expressed as medians and interquartile ranges (IQR) and differences tested with the Mann-Whitney U test. Categorical variables, expressed as counts and percentages, were analysed by a chi-square test.

A regression analysis was performed to establish clinical factors significantly associated with guideline non-adherence, undertreatment or overtreatment. All variables with a $p<0.10$ in the comparison between the two groups at the baseline were included in a univariate analysis and those univariate predictors with a statistical significance of less than 10% were included into a forward multivariate logistic model.

A logistic regression analysis was also performed (adjusted for CIRS severity index, CIRS comorbidity Index and thromboembolic risk) in order to establish the association between undertreatment and study outcomes. This analysis was not performed for the overtreatment group, given the very small number of events recorded in this group.

A survival analysis was performed both according to parametric and semi-parametric methods, comparing guideline adherence or non-adherence. A log-rank test was performed to establish whether or not there was a difference in survival between the two groups. A Cox regression analysis, adjusted for CIRS severity index, CIRS comorbidity index and thromboembolic risk was

also performed and survival curves plotted. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, NY, USA).

RESULTS

Of the 2,535 patients enrolled in the 2012 and 2014 cohorts, 558 (22.0%) were discharged with a diagnosis of AF (median [IQR] age: 82 [76-90] years, 297 [53.2%] females). Amongst AF patients, hypertension was the most common risk factor (n=471, 84.4%) [Table 1]. Median [IQR] CHA_2DS_2-VASc score was 4 [3-5], with 554 patients (99.3%) being at high thromboembolic risk.

Antithrombotic prophylaxis amongst patients at high thromboembolic risk is shown in Figure 1. Among the patients at high thromboembolic risk, only 41.0% were treated with OAC, while 6.7% were treated with OAC plus AP. Of those treated with OAC, 223 out of 227 (97.8%) patients were treated with a VKA and only 5 (2.2%) with a non-vitamin K antagonist oral anticoagulant (NOAC); all patients treated with OAC plus AP used a VKA.

Based on the 2012 ESC guidelines, only 40.9% (n=228) of the patients were guideline-adherent, while 52.3% (n=292) were undertreated and 38 (6.8%) were overtreated. Baseline characteristics according to guidelines adherence or non-adherence status are in Table 1. Guidelines-adherent patients were younger (p=0.005) and had a lower CIRS severity index (p=0.046). Guideline-adherent patients also had more HF (p=0.014) but less CAD (p=0.005), PAD (p=0.009) and cancer (p=0.002). Functional status indexes were similar in both groups.

Associations with guideline adherence and non-adherence

Multivariable logistic analysis showed that age (odds ratio [OR]: 1.03 per year, 95% confidence interval: 1.01-1.06, p=0.01), concomitant diagnoses of CAD (OR: 1.71, 95% CI: 1.12-2.61, p=0.04), PAD (OR: 5.25, 95% CI: 1.18-23.41, p=0.03) and cancer (OR: 2.31, 95% CI: 0.47-0.98, p=0.03) were significantly associated with guideline non-adherence. Concomitant diagnosis of HF (OR: 0.68, 95% CI: 0.47-0.98, p=0.04) was inversely associated with guideline non-adherence.

Undertreatment was significantly associated with increasing age (p=0.001) and concomitant diagnosis of cancer (p<0.001) and inversely associated with HF (p=0.023) (Table 2). Increasing age (p=0.036), female sex (p=0.023) and COPD diagnosis (p=0.007) were inversely associated with overtreatment (Table 2). A clinical history of CAD (p<0.001), PAD (p=0.015) and stroke/TIA (p=0.004) were positively associated with overtreatment (Table 2).

Survival Analysis

In the overall cohort, follow-up data for at least one follow-up time point were available in 74.6% patients (n=416). No major differences were found when compared with lost at follow-up patients, except for CIRS severity index and alcohol consumption that were lower in patients lost to follow-up (see Table S1 in Supplementary Materials).

Median [IQR] follow-up time was 115 [98-371] days. A total of 73 (13.1%) all-cause deaths and 27 (4.8%) CV deaths were recorded. Guideline non-adherent patients had higher rates for all-cause (8.9% vs. 3.4%, p=0.007 vs. guideline adherent) and CV death (21.9% vs. 11.7%, p=0.024 vs. guideline adherent). No significant difference was detected in rates of non CV death (13.1% vs. 8.4% for guideline non-adherent vs. adherent patients; p=0.130). Undertreatment was significantly associated with all-cause deaths (OR: 2.30, 95% CI: 1.32-4.02, p=0.003) and CV deaths (OR: 2.88, 95% CI: 1.13-7.39, p=0.027). This association remained statistically significant even after

adjustment for CIRS severity index, CIRS comorbidity Index and thromboembolic risk (OR: 2.78, 95% CI: 1.07-7.23, p=0.036 and OR: 2.12, 95% CI:1.21-3.72, p=0.009, respectively).

Kaplan-Meier curves show that guideline-adherent patients had a lower cumulative risk for both all-cause deaths (Log-Rank: 9.631, p=0.002) and CV deaths (Log-Rank: 6.497, p=0.011) compared to guideline non-adherent patients [Figure 2]. Cox regression analysis shows that guideline adherent patients had a lower risk for all-cause death (HR: 0.47, 95% CI: 0.29-0.81, p=0.006) and CV death (hazard ratio [HR]: 0.33, 95% CI: 0.13-0.83, p=0.019) even after adjustment for CIRS severity index, CIRS comorbidity index and thromboembolic risk.

DISCUSSION

The principal findings of this study are that firstly, almost 60% of Italian *elderly* patients with AF were managed with a guideline non-adherent approach for OAC, with most being undertreated (52.3%). Second, the main clinical factors associated with guideline non-adherence were older age and a clinical history of HF, CAD and PAD, as well as the concomitant diagnosis of cancer. In particular, increasing age was associated with undertreatment, along and the diagnosis of cancer, while HF was inversely associated with undertreatment. Conversely, a younger age, female sex and a previous history of CAD, PAD and stroke/TIA were associated with overtreatment with concomitant OAC and AP. Third, undertreatment was associated with a significant risk for both all-cause and CV deaths, whilst guideline-adherent AF patients had a lower risk for both endpoints.

In this study, the percentage of AF patients treated with a guideline-adherent approach was lower than in previous reports[10, 19]. More recently, the EURObservational Research Programme AF (EORP-AF) Pilot Phase reported that, based on the 2012 ESC guidelines, AF patients were

guideline-adherent in 60.6%. The EORP-AF reflected patient management by European cardiologists from both in- and outpatient settings, whilst in the REPOSI study all the in-patients enrolled were elderly and from internal medicine or geriatric wards.

In the EORP-AF ancillary analysis on guidelines adherence, the South European region (which included Italy) was associated with undertreatment, confirming several previous reports of a significantly low rate of patients treated with OAC among Italian AF patients[20–24]. This seems to occur despite several reports on effectiveness and safety, showing that elderly patients treated with a VKA had a significant benefit in reducing both thromboembolic events and mortality, irrespective of age[12]. A recent position paper from the ESC Working Group on Thrombosis also stated that whilst elderly patients were underrepresented in various clinical trials investigating antithrombotic drugs, OAC treatment with VKA or NOACs was effective and safe in elderly patients[25]. The BALKAN-AF survey also reported that age was inversely associated with OAC prescription, but was positively associated with undertreatment with AP[26].

Age and the concomitant diagnosis of cancer were clinical factors associated with guideline non-adherence in this study while clinical history of HF was inversely associated with guideline non-adherence, at variance with previous reports such as the EORP-AF registry[10]. Specifically, both age and malignancy were significantly associated with undertreatment in REPOSI, while only malignancy was associated with undertreatment in the EORP-AF cohort[10]. This perhaps suggests that frailty in elderly patient influences physician decision for non-treatment with OAC. Similar observations were made in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), where frailty was reported in a large proportion of patients as the main contraindication for OAC prescription[27]. Further, similar findings were reported in a recent

observational Canadian study in the setting of octogenarian AF patients[28]. In the REPOSI cohort, we found no significant difference in functional status indexes *(i.e.* Barthel Index) between patients treated with a guideline-adherent approach and those who were non-guideline adherent.

When investigating factors significantly associated with overtreatment, most AF patients with CAD, PAD and Stroke/TIA were overtreated with OAC and AP. Similar findings were also reported in the EORP-AF[10] and the BALKAN-AF surveys[26]. This approach seems to be maintained widely by physicians despite explicit guideline recommendations to only prescribe OAC for stroke prevention in AF patients with stable vascular disease[3, 29].

Our results emphasise the importance of OAC for AF patients in reducing all-cause mortality and CV, even in the elderly. Physician adherence to guidelines in terms of OAC use represents an important clinical step. In the Euro Heart Survey, undertreatment was significantly associated with thrombosis-related events, with a 2-fold higher risk compared to a guideline-adherent approach[19]. Conversely, undertreatment was associated with an increase in the composite outcome of any thromboembolic event, major bleeding and CV death[19]. The analysis from 1-year follow-up of the EORP-AF study also confirms that both undertreatment and overtreatment are associated with higher risk for the composite endpoint of all-cause death plus any thromboembolic event, with a more than 60% higher risk for both undertreatment and overtreatment[10]. Indeed, undertreatment per se was associated with a higher risk for any thromboembolic event (OR: 1.72)[10]. Of note, our results provide a “real world” validation for the degree of implementation of the ESC guidelines in a large unselected population of elderly AF patients. Given that many elderly (or very elderly) patients are excluded or under-represented in

randomized clinical trials specifically evaluating OAC therapy (as discussed above), our data strengthen and underscore the necessity for large prospective studies in the elderly AF population.

Limitations

The main limitation of the study is its observational nature, with relatively limited power to detect differences in survival. Lack of follow-up data for some of our patients represents another important limitation and no precise details about the cause(s) of death were obtained. We could not evaluate how effective anticoagulation could impact on outcomes occurrence given the absence in the registry dataset of any index of anticoagulation control (*e.g.* time in therapeutic range, TTR). Furthermore, evaluation of OAC therapy adequacy based solely on the thromboembolic risk assessment may not be comprehensive enough. Possible contraindications to OAC therapy, as well as possible comorbidities interacting with OAC (i.e. chronic kidney disease), must be taken into account during the prescription process. Finally, given the low number of the subgroups considered, our results should be interpreted cautiously.

In conclusion, guideline non-adherence was evident for a large proportion of elderly patients with AF. Guideline-adherent treatment was independently associated with a significantly lower risk of all-cause and CV death. Efforts to improve guideline adherence would lead to better outcomes for elderly AF patients.

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DECLARATIONS OF INTEREST

GYHL: Steering committees for various Phase II and III studies, Health Economics & Outcomes Research. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids. Consultant for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. All the other authors have no interest to disclose.

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Table 1: Baseline characteristics at hospital discharge according to guideline adherence

	Whole Cohort	**Guideline Adherent**	**Guideline Non-Adherent**	**p**
	n= 558	**n= 228**	**n= 330**	
Age, (*years)* median [IQR]	82 [76-86]	81 [75-85]	83 [77-87]	0.005
Female, n (%)	297 (53.2)	122 (53.5)	175 (53.0)	0.911
Education, *(years)* median [IQR] *491*	5 [5-8]	5 [5-8]	5 [5-8]	0.416
Working Class, n (%) *511*				0.289
Low Income	411 (80.4)	179 (83.6)	232 (78.1)	
Middle Income	64 (12.5)	23 (10.7)	41 (13.8)	
High Income	36 (7.0)	12 (5.6)	24 (8.1)	
Short Blessed Test, median [IQR] *504*	8 [4-14]	8 [4-14]	8 [2-15]	0.918
Geriatric Depression Scale, median [IQR] *460*	1 [0-2]	1 [0-2]	1 [0-2]	0.406
Barthel Index, median [IQR] *434*	86 [52-100]	88 [57-100]	83 [52-100]	0.179
Cumulative Index Rating Scale, median [IQR] *548*				
Severity Index	1.77 [1.54-2.00]	1.69 [1.46-2.00]	1.77 [1.54-2.08]	0.046
Comorbidity Index	4 [3-5]	3 [2-5]	4 [2-5]	0.167
Smoking Habit, n (%) *543*				0.289
Never Smoker	304 (59.5)	142 (63.4)	181 (56.7)	
Former Smoker	236 (36.3)	74 (33.0)	123 (38.6)	
Current Smoker	23 (4.2)	8 (3.6)	15 (4.7)	

Alcohol Consumption, n (%) *540*	236 (43.7)	97 (43.1)	139 (44.1)	0.814
Polypharmacy, n (%) *546*	513 (94.0)	215 (94.3)	298 (93.7)	0.776
Hypertension, n (%)	471 (84.4)	192 (84.2)	279 (84.5)	0.915
Hypercholesterolemia, n (%)	45 (8.1)	22 (9.6)	23 (7.0)	0.253
Heart Failure, n (%)	185 (33.2)	89 (39.0)	96 (29.1)	0.014
Coronary Artery Disease, n (%)	137 (24.6)	42 (18.4)	95 (28.8)	0.005
Myocardial Infarction, n (%)	13 (2.3)	5 (2.2)	8 (2.4)	0.859
Peripheral Artery Disease, n (%)	18 (3.2)	2 (0.9)	16 (4.8)	0.009
Stroke/TIA, n (%)	87 (15.6)	28 (12.3)	59 (17.9)	0.073
Diabetes, n (%)	184 (33.0)	82 (36.0)	102 (30.9)	0.212
Chronic Kidney Disease, n (%)	160 (28.7)	66 (28.9)	94 (28.5)	0.905
COPD, n (%)	144 (25.8)	58 (25.4)	86 (26.1)	0.869
Cancer, n (%)	76 (13.6)	19 (8.3)	57 (17.3)	0.002
CHA_2DS_2-VASc, median [IQR]	4 [2-5]	4 [3-5]	4 [3-5]	0.732
Thromboembolic Risk, n (%)				0.517
Moderate Risk	4 (0.7)	1 (0.4)	3 (0.9)	
High Risk	554 (99.3)	227 (99.6)	327 (99.1)	

Legend: COPD= chronic obstructive pulmonary disease; IQR= interquartile range; TIA= transient ischemic attack.

Table 2: Multivariable logistic regression analysis for undertreatment and overtreatment

	OR	95% CI	p
Undertreatment			
Age *(per year)*	1.05	1.02-1.07	0.001
Heart Failure	0.64	0.44-0.94	0.023
Cancer	2.67	1.53-4.68	0.001
Overtreatment			
Age *(per year)*	0.92	0.85-0.99	0.036
Female	0.32	0.12-0.85	0.023
Coronary Artery Disease	12.15	4.61-32.03	<0.001
Peripheral Arterial Disease	28.83	1.91-435.72	0.015
Stroke/TIA	4.46	1.61-12.32	0.004
COPD	0.17	0.05-0.62	0.007

Legend: CI= confidence interval; COPD= chronic obstructive pulmonary disease; OR= odds ratio; TIA= transient ischemic attack.

FIGURE LEGENDS

Figure 1: Distribution of antithrombotic treatments in patients with high thromboembolic risk.

Legend: AP= antiplatelet; OAC= oral anticoagulant; TE= thromboembolic.

Figure 2: Kaplan-Meier curves for major adverse outcomes.

Legend: Solid line= guideline adherent; Dashed line= guideline non-adherent.

APPENDIX

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Figure 1

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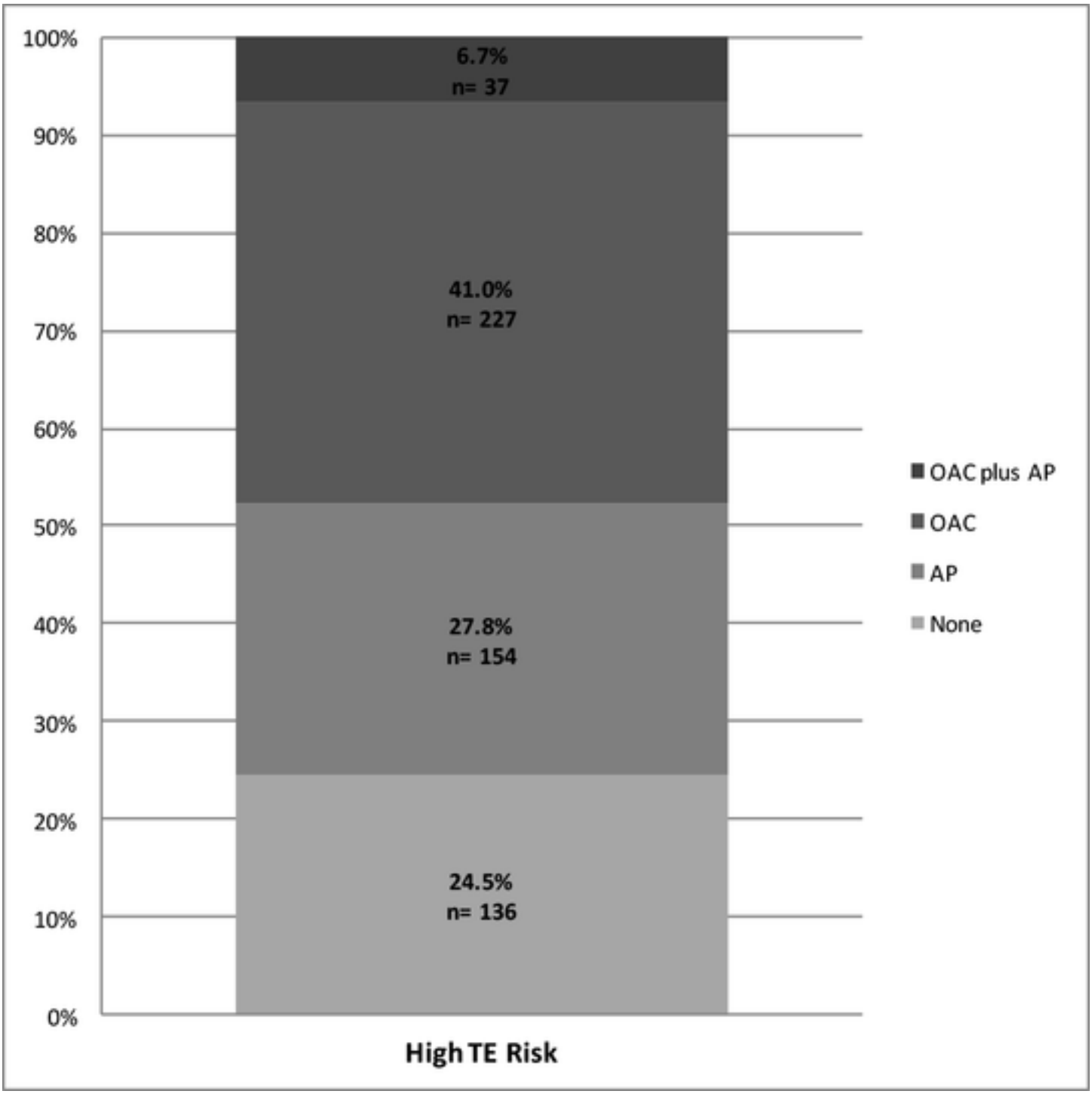

Figure 2

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