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

Marco Proietti^{1,2}, Alessandro Nobili³, Valeria Raparelli^{2,4}, Laura Napoleone^{2,4},

Pier Mannuccio Mannucci⁵, Gregory Y H Lip^{1,6} on behalf of REPOSI Investigators⁷

¹University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; ²Department of Internal Medicine and Medical Specialties, Sapienza-University of Rome, Rome, Italy; ³IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Department of Neuroscience, Milan, Italy; ⁴Department of Experimental Medicine, Sapienza-University of Rome, Rome, Italy; ⁵IRCCS Fondazione Cà Granda, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Milan Italy; ⁶Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; ⁷Listed in the Appendix.

Co-Corresponding Authors:

GYH Lip (g.y.h.lip@bham.ac.uk)

Marco Proietti (marco.proietti@uniroma1.it)

University of Birmingham, Institute of Cardiovascular Sciences, City Hospital

Dudley Road, B18 7QH, Birmingham, United Kingdom

Tel: +44 121 5075080

Fax: +44 121 5544083

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

1 deaths. Efforts to improve guideline adherence would lead to better outcomes for elderly AF
2 patients.
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5 **Keywords:** atrial fibrillation; antithrombotic therapy; elderly; guidelines; outcomes.
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INTRODUCTION

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2 The incidence and prevalence of atrial fibrillation (AF) have progressively increased over the last
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5 20 years, especially in the elderly [1, 2]. In patients aged ≥ 65 years, the prevalence of AF has more
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7 than doubled from 1993 to 2007[1]. Because many patients are asymptomatic, guidelines now
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9 recommend screening for AF in all subjects age 65 and over[3].
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12 AF is associated with an increased risk for both thromboembolic events and mortality, whether all-
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14 cause or from cardiovascular (CV) causes[1, 4]. Oral anticoagulant (OAC) therapy significantly
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16 reduces the risk of thromboembolism and mortality amongst AF patients[4]. Both OAC persistence
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18 and good quality anticoagulation control reduce major adverse events among AF patients[5–8].
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23 Nonetheless, physician attitudes towards prescribing OAC and their adherence to guidelines
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25 vary[9]. Recent data from the EURObservational Research Programme AF (EORP-AF) Pilot Registry
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27 reported that up to 40% of patients managed by European cardiologists are non-adherent to the
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29 European Society of Cardiology (ESC) guidelines, and that both under- and overtreatment were
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31 associated with worst outcomes[10]. Elderly patients seem to be less likely to be treated with
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33 OAC, due to their perceived frailty and higher risk of bleeding[11]. When properly prescribed, OAC
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35 thromboprophylaxis using a vitamin K antagonist (VKA, *e.g.* warfarin) with good anticoagulation
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37 control is associated with better outcomes, even amongst the elderly[11, 12].
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45 The aims of this study were as follows: i) to assess physician adherence to guidelines in a cohort of
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47 Italian AF elderly patients admitted acutely to Italian internal medicine and geriatric wards; ii) to
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49 describe the main factors associated with guideline non-adherence; and iii) to evaluate the risk of
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51 all-cause and CV deaths according to adherence or non-adherence to guidelines.
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METHODS

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2 We studied an elderly AF population from the REPOSI (REgistro POLiterapie SIMI) study[13]. The
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4 latter is a multicentre collaborative observational registry jointly held by the Italian Society of
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6 Internal Medicine (SIMI), the Ca' Granda Maggiore Policlinico Hospital Foundation and the Mario
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8 Negri Institute of Pharmacological Research and based on a network of both internal medicine and
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10 geriatric wards in Italy and Spain. Full details on the study design and specific aims have been
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12 reported[13].
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19 Briefly, REPOSI was held for four non-consecutive years: 2008, 2010, 2012 and 2014. In each of
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21 those years over a period of 4 weeks, quarterly (*i.e.* February, June, September and December),
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23 consecutive patients admitted to the participating wards aged more than 65 years were enrolled.
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25 For the present study, only patients enrolled in the 2012 and 2014 study cohorts were considered,
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27 as data recorded were more comprehensive than those initially collected in 2008 and 2010. The
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29 study protocol was first approved by the Ethics Committee of the Ca' Granda Maggiore Policlinico
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31 Hospital Foundation, then ratified for every enrolling site by local Ethics Committee. The study was
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33 conducted according to Good Clinical Practice recommendations and the Declaration of Helsinki.
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35 Patients were selected according to the International Classification of Diseases – 9th Edition (ICD-9)
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37 system. For the purposes of this analysis, all patients discharged with the 427.31 ICD-9 code,
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39 corresponding to AF diagnosis, were considered.
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51 Thromboembolic risk was defined according to the CHA₂DS₂-VASc score[4], that defines 'Low risk'
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53 patients males with a CHA₂DS₂-VASc 0 or females with a CHA₂DS₂-VASc equal to 1; 'moderate risk',
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55 male patients with a CHA₂DS₂-VASc score 1; and 'high risk', all patients with CHA₂DS₂-VASc score
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≥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.

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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] CHA₂DS₂-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

1 Multivariable logistic analysis showed that age (odds ratio [OR]: 1.03 per year, 95% confidence
2 interval: 1.01-1.06, $p=0.01$), concomitant diagnoses of CAD (OR: 1.71, 95% CI: 1.12-2.61, $p=0.04$),
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4 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
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6 significantly associated with guideline non-adherence. Concomitant diagnosis of HF (OR: 0.68, 95%
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8 CI: 0.47-0.98, $p=0.04$) was inversely associated with guideline non-adherence.
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15 Undertreatment was significantly associated with increasing age ($p=0.001$) and concomitant
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17 diagnosis of cancer ($p<0.001$) and inversely associated with HF ($p=0.023$) (Table 2). Increasing age
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19 ($p=0.036$), female sex ($p=0.023$) and COPD diagnosis ($p=0.007$) were inversely associated with
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21 overtreatment (Table 2). A clinical history of CAD ($p<0.001$), PAD ($p=0.015$) and stroke/TIA
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23 ($p=0.004$) were positively associated with overtreatment (Table 2).
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31 *Survival Analysis*

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33 In the overall cohort, follow-up data for at least one follow-up time point were available in 74.6%
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35 patients ($n=416$). No major differences were found when compared with lost at follow-up
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37 patients, except for CIRS severity index and alcohol consumption that were lower in patients lost
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39 to follow-up (see Table S1 in Supplementary Materials).
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43 Median [IQR] follow-up time was 115 [98-371] days. A total of 73 (13.1%) all-cause deaths and 27
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45 (4.8%) CV deaths were recorded. Guideline non-adherent patients had higher rates for all-cause
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47 (8.9% vs. 3.4%, $p=0.007$ vs. guideline adherent) and CV death (21.9% vs. 11.7%, $p=0.024$ vs.
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49 guideline adherent). No significant difference was detected in rates of non CV death (13.1% vs.
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51 8.4% for guideline non-adherent vs. adherent patients; $p=0.130$). Undertreatment was
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53 significantly associated with all-cause deaths (OR: 2.30, 95% CI: 1.32-4.02, $p=0.003$) and CV deaths
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55 (OR: 2.88, 95% CI: 1.13-7.39, $p=0.027$). This association remained statistically significant even after
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1 adjustment for CIRS severity index, CIRS comorbidity Index and thromboembolic risk (OR: 2.78,
2 95% CI: 1.07-7.23, p=0.036 and OR: 2.12, 95% CI:1.21-3.72, p=0.009, respectively).
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7 Kaplan-Meier curves show that guideline-adherent patients had a lower cumulative risk for both
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9 all-cause deaths (Log-Rank: 9.631, p=0.002) and CV deaths (Log-Rank: 6.497, p=0.011) compared
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11 to guideline non-adherent patients [Figure 2]. Cox regression analysis shows that guideline
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13 adherent patients had a lower risk for all-cause death (HR: 0.47, 95% CI: 0.29-0.81, p=0.006) and
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15 CV death (hazard ratio [HR]: 0.33, 95% CI: 0.13-0.83, p=0.019) even after adjustment for CIRS
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17 severity index, CIRS comorbidity index and thromboembolic risk.
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25 **DISCUSSION**

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27 The principal findings of this study are that firstly, almost 60% of Italian *elderly* patients with AF
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29 were managed with a guideline non-adherent approach for OAC, with most being undertreated
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31 (52.3%). Second, the main clinical factors associated with guideline non-adherence were older age
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33 and a clinical history of HF, CAD and PAD, as well as the concomitant diagnosis of cancer. In
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35 particular, increasing age was associated with undertreatment, along and the diagnosis of cancer,
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37 while HF was inversely associated with undertreatment. Conversely, a younger age, female sex
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39 and a previous history of CAD, PAD and stroke/TIA were associated with overtreatment with
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41 concomitant OAC and AP. Third, undertreatment was associated with a significant risk for both
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43 all-cause and CV deaths, whilst guideline-adherent AF patients had a lower risk for both endpoints.
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53 In this study, the percentage of AF patients treated with a guideline-adherent approach was lower
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55 than in previous reports[10, 19]. More recently, the EURObservational Research Programme AF
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57 (EORP-AF) Pilot Phase reported that, based on the 2012 ESC guidelines, AF patients were
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1 guideline-adherent in 60.6%. The EORP-AF reflected patient management by European
2 cardiologists from both in- and outpatient settings, whilst in the REPOSI study all the in-patients
3 enrolled were elderly and from internal medicine or geriatric wards.
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10 In the EORP-AF ancillary analysis on guidelines adherence, the South European region (which
11 included Italy) was associated with undertreatment, confirming several previous reports of a
12 significantly low rate of patients treated with OAC among Italian AF patients[20–24]. This seems to
13 occur despite several reports on effectiveness and safety, showing that elderly patients treated
14 with a VKA had a significant benefit in reducing both thromboembolic events and mortality,
15 irrespective of age[12]. A recent position paper from the ESC Working Group on Thrombosis also
16 stated that whilst elderly patients were underrepresented in various clinical trials investigating
17 antithrombotic drugs, OAC treatment with VKA or NOACs was effective and safe in elderly
18 patients[25]. The BALKAN-AF survey also reported that age was inversely associated with OAC
19 prescription, but was positively associated with undertreatment with AP[26].
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38 Age and the concomitant diagnosis of cancer were clinical factors associated with guideline non-
39 adherence in this study while clinical history of HF was inversely associated with guideline non-
40 adherence, at variance with previous reports such as the EORP-AF registry[10]. Specifically, both
41 age and malignancy were significantly associated with undertreatment in REPOSI, while only
42 malignancy was associated with undertreatment in the EORP-AF cohort[10]. This perhaps
43 suggests that frailty in elderly patient influences physician decision for non-treatment with OAC.
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54 Similar observations were made in the Outcomes Registry for Better Informed Treatment of Atrial
55 Fibrillation (ORBIT-AF), where frailty was reported in a large proportion of patients as the main
56 contraindication for OAC prescription[27]. Further, similar findings were reported in a recent
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1 observational Canadian study in the setting of octogenarian AF patients[28]. In the REPOSI cohort,
2 we found no significant difference in functional status indexes (*i.e.* Barthel Index) between
3 patients treated with a guideline-adherent approach and those who were non-guideline adherent.
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10 When investigating factors significantly associated with overtreatment, most AF patients with
11 CAD, PAD and Stroke/TIA were overtreated with OAC and AP. Similar findings were also reported
12 in the EORP-AF[10] and the BALKAN-AF surveys[26]. This approach seems to be maintained widely
13 by physicians despite explicit guideline recommendations to only prescribe OAC for stroke
14 prevention in AF patients with stable vascular disease[3, 29].
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25 Our results emphasise the importance of OAC for AF patients in reducing all-cause mortality and
26 CV, even in the elderly. Physician adherence to guidelines in terms of OAC use represents an
27 important clinical step. In the Euro Heart Survey, undertreatment was significantly associated
28 with thrombosis-related events, with a 2-fold higher risk compared to a guideline-adherent
29 approach[19]. Conversely, undertreatment was associated with an increase in the composite
30 outcome of any thromboembolic event, major bleeding and CV death[19]. The analysis from 1-
31 year follow-up of the EORP-AF study also confirms that both undertreatment and overtreatment
32 are associated with higher risk for the composite endpoint of all-cause death plus any
33 thromboembolic event, with a more than 60% higher risk for both undertreatment and
34 overtreatment[10]. Indeed, undertreatment per se was associated with a higher risk for any
35 thromboembolic event (OR: 1.72)[10]. Of note, our results provide a “real world” validation for the
36 degree of implementation of the ESC guidelines in a large unselected population of elderly AF
37 patients. Given that many elderly (or very elderly) patients are excluded or under-represented in
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1 randomized clinical trials specifically evaluating OAC therapy (as discussed above), our data
2 strengthen and underscore the necessity for large prospective studies in the elderly AF population.
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7 *Limitations*
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10 The main limitation of the study is its observational nature, with relatively limited power to detect
11 differences in survival. Lack of follow-up data for some of our patients represents another
12 important limitation and no precise details about the cause(s) of death were obtained. We could
13 not evaluate how effective anticoagulation could impact on outcomes occurrence given the
14 absence in the registry dataset of any index of anticoagulation control (*e.g.* time in therapeutic
15 range, TTR). Furthermore, evaluation of OAC therapy adequacy based solely on the
16 thromboembolic risk assessment may not be comprehensive enough. Possible contraindications
17 to OAC therapy, as well as possible comorbidities interacting with OAC (*i.e.* chronic kidney
18 disease), must be taken into account during the prescription process. Finally, given the low
19 number of the subgroups considered, our results should be interpreted cautiously.
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38 **In conclusion**, guideline non-adherence was evident for a large proportion of elderly patients with
39 AF. Guideline-adherent treatment was independently associated with a significantly lower risk of
40 all-cause and CV death. Efforts to improve guideline adherence would lead to better outcomes for
41 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
<i>Low Income</i>	411 (80.4)	179 (83.6)	232 (78.1)	
<i>Middle Income</i>	64 (12.5)	23 (10.7)	41 (13.8)	
<i>High Income</i>	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				
<i>Severity Index</i>	1.77 [1.54-2.00]	1.69 [1.46-2.00]	1.77 [1.54-2.08]	0.046
<i>Comorbidity Index</i>	4 [3-5]	3 [2-5]	4 [2-5]	0.167
Smoking Habit, n (%) 543				0.289
<i>Never Smoker</i>	304 (59.5)	142 (63.4)	181 (56.7)	
<i>Former Smoker</i>	236 (36.3)	74 (33.0)	123 (38.6)	
<i>Current Smoker</i>	23 (4.2)	8 (3.6)	15 (4.7)	

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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
CHA₂DS₂-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
<u>Undertreatment</u>			
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
<u>Overtreatment</u>			
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

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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

REPOSI (REgistro POliterate SIMI, Società Italiana di Medicina Interna) Investigators

Steering Committee: Pier Mannuccio Mannucci (*Chair, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano*), Alessandro Nobili (*co-chair, IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano*), Mauro Tettamanti, Luca Pasina, Carlotta Franchi (*IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano*), Francesco Perticone (*Presidente SIMI*), Francesco Salerno (*IRCCS Policlinico San Donato Milanese, Milano*), Salvatore Corrao (*ARNAS Civico, Di Cristina, Benfratelli, DiBiMIS, Università di Palermo, Palermo*), Alessandra Marengoni (*Spedali Civili di Brescia, Brescia*), Giuseppe Licata (*Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Medicina Interna e Cardioangiologia*), Francesco Violi (*Policlinico Umberto I, Roma, Prima Clinica Medica*), Gino Roberto Corazza, (*Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I*), Maura Marcucci (*Unità di Geriatria, Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico & Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italia*).

Clinical Data Monitoring and Revision: Tarek Kamal Eldin, Maria Pia Donatella Di Blanca (*IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano*).

Database Management and Statistics: Mauro Tettamanti, Codjo Djignefa Djade, Ilaria Ardoino, Laura Cortesi (*IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”, Milano*).

Investigators

Italian Hospitals

Domenico Prisco, Elena Silvestri, Caterina Cenci, Giacomo Emmi (*Azienda Ospedaliero Universitaria Careggi Firenze, Medicina Interna Interdisciplinare*);

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65

Gianni Biolo, Gianfranco Guarnieri, Michela Zanetti, Giovanni Fernandes (*Azienda Ospedaliera
Universitaria Ospedali Riuniti di Trieste, Trieste, Clinica Medica Generale e Terapia Medica*);

Massimo Vanoli, Giulia Grignani, Gianluca Casella, (*Azienda Ospedaliera della Provincia di Lecco,
Ospedale di Merate, Lecco, Medicina Interna*);

Mauro Bernardi, Silvia Li Bassi, Luca Santi, Giacomo Zaccherini (*Azienda Ospedaliera Policlinico
Sant'Orsola-Malpighi, Bologna, Semeiotica Medica Bernardi*);

Elmo Mannarino, Graziana Lupattelli, Vanessa Bianconi, Francesco Paciullo (*Azienda Ospedaliera
Santa Maria della Misericordia, Perugia, Medicina Interna, Angiologia, Malattie da Arteriosclerosi*);

Ranuccio Nuti, Roberto Valenti, Martina Ruvio, Silvia Cappelli, Alberto Palazzuoli (*Azienda
Ospedaliera Università Senese, Siena, Medicina Interna I*);

Teresa Salvatore, Ferdinando Carlo Sasso (*Azienda Ospedaliera Universitaria della Seconda
Università degli Studi di Napoli, Napoli, Medicina Interna e Malattie Epato-Bilio Metaboliche
Avanzate*);

Domenico Girelli, Oliviero Olivieri, Thomas Matteazzi (*Azienda Ospedaliera Universitaria Integrata
di Verona, Verona, Medicina Generale a indirizzo Immuno-Ematologico e Emocoagulativo*);

Mario Barbagallo, Lidia Plances, Roberta Alcamo (*Azienda Ospedaliera Universitaria Policlinico
Giaccone Policlinico di Palermo, Palermo, Unità Operativa di Geriatria e Lungodegenza*);

Giuseppe Licata, Luigi Calvo, Maria Valenti (*Azienda Ospedaliera Universitaria Policlinico P.
Giaccone di Palermo, Palermo, Medicina Interna e Cardioangiologia*);

Marco Zoli, Raffaella Arnò (*Azienda Ospedaliera Universitaria Policlinico S. Orsola-Malpighi,
Bologna, Unità Operativa di Medicina Interna Zoli*);

Franco Laghi Pasini, Pier Leopoldo Capecchi, Maurizio Bicchi (*Azienda Ospedaliera Universitaria
Senese, Siena, Unità Operativa Complessa Medicina 2*);

1 Giuseppe Palasciano, Maria Ester Modeo, Maria Peragine, Fabrizio Pappagallo, Stefania Pugliese,
2
3 Carla Di Gennaro (*Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Medicina*
4
5 *Interna Ospedaliera "L. D'Agostino", Medicina Interna Universitaria "A. Murri"*);
6
7 Alfredo Postiglione, Maria Rosaria Barbella, Francesco De Stefano (*Azienda Ospedaliera*
8
9 *Universitaria Policlinico Federico II di Napoli, Medicina Geriatrica Dipartimento di Clinica Medica*);
10
11 Maria Domenica Cappellini, Giovanna Fabio, Sonia Seghezzi, Margherita Migone De Amicis
12
13 (*Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Unità Operativa Medicina*
14
15 *Interna IA*);
16
17 Daniela Mari, Paolo Dionigi Rossi, Sarah Damanti, Barbara Brignolo Ottolini, Sarah Damanti
18
19 (*Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Geriatria*);
20
21 Gino Roberto Corazza, Emanuela Miceli, Marco Vincenzo Lenti, Donatella Padula (*Reparto 11,*
22
23 *IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I*);
24
25 Giovanni Murialdo, Alessio Marra, Federico Cattaneo (*IRCS Azienda Ospedaliera Universitaria San*
26
27 *Martino-IST di Genova, Genova, Clinica di Medicina Interna 2*);
28
29 Maria Beatrice Secchi, Davide Ghelfi (*Ospedale Bassini di Cinisello Balsamo, Milano, Divisione*
30
31 *Medicina*);
32
33 Luigi Anastasio, Lucia Sofia, Maria Carbone (*Ospedale Civile Jazzolino di Vibo Valentia, Vibo*
34
35 *Valentia, Medicina interna*);
36
37 Giovanni Davì, Maria Teresa Guagnano, Simona Sestili (*Ospedale Clinicizzato SS. Annunziata,*
38
39 *Chieti, Clinica Medica*);
40
41 Gerardo Mancuso, Daniela Calipari, Mosè Bartone (*Ospedale Giovanni Paolo II Lamezia Terme,*
42
43 *Catanzaro, Unità Operativa Complessa Medicina Interna*);
44
45 Maria Rachele Meroni (*Ospedale Luigi Sacco, Milano, Medicina 3°*);
46
47
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1 Paolo Cavallo Perin, Bartolomeo Lorenzati, Gabriella Gruden, Graziella Bruno, Cristina Amione,
2 Paolo Fornengo (*Dipartimento di Scienze Mediche, Università di Torino, Città della Scienza e della*
3 *Salute, Torino, Medicina 3*);
4
5 Rodolfo Tassara, Deborah Melis, Lara Rebella (*Ospedale San Paolo, Savona, Medicina I*);
6
7 Giuseppe Delitala, Vincenzo Pretti, Maristella Salvatora Masala (*Ospedale Universitario Policlinico*
8 *di Sassari, Sassari, Clinica Medica*);
9
10 Luigi Bolondi, Leonardo Rasciti, Ilaria Serio (*Policlinico Sant'Orsola-Malpighi, Bologna, Unità*
11 *Operativa Complessa Medicina Interna*);
12
13 Filippo Rossi Fanelli, Antonio Amoroso, Alessio Molfino, Enrico Petrillo (*Policlinico Umberto I,*
14 *Sapienza Università di Roma, Roma, Medicina Interna H*);
15
16 Giuseppe Zuccalà, Francesco Franceschi, Guido De Marco, Cordischi Chiara, Sabbatini Marta
17 (*Policlinico Universitario A. Gemelli, Roma, Roma, Unità Operativa Complessa Medicina d'Urgenza*
18 *e Pronto Soccorso*);
19
20 Giuseppe Romanelli, Claudia Amolini, Deborah Chiesa, Alessandra Marengoni (*Spedali Civili di*
21 *Brescia, Brescia, Geriatria*);
22
23 Antonio Picardi, Umberto Vespasiani Gentilucci, Paolo Gallo (*Università Campus Bio-Medico,*
24 *Roma, Medicina Clinica-Epatologia*);
25
26 Giorgio Annoni, Maurizio Corsi, Sara Zazzetta, Giuseppe Bellelli (*Università degli studi di Milano-*
27 *Bicocca Ospedale S. Gerardo, Monza, Unità Operativa di Geriatria*);
28
29 Franco Arturi, Elena Succurro, Mariangela Rubino, Giorgio Sesti (*Università degli Studi Magna*
30 *Grecia, Policlinico Mater Domini, Catanzaro, Unità Operativa Complessa di Medicina Interna*);
31
32 Paola Loria, Maria Angela Becchi, Gianfranco Martucci, Alessandra Fantuzzi, Mauro Maurantonio
33 (*Università di Modena e Reggio Emilia, Medicina Metabolica-NOCSAE, Baggiovara, Modena*);
34
35
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1 Giuseppe Delitala, Stefano Carta, Sebastiana Atzori (*Azienda Mista Ospedaliera Universitaria,*
2 *Sassari, Clinica Medica*);

3
4
5 Maria Grazia Serra, Maria Antonietta Bleve (*Azienda Ospedaliera "Cardinale Panico" Tricase, Lecce,*
6
7 *Unità Operativa Complessa Medicina*);

8
9
10 Laura Gasbarrone, Maria Rosaria Sajeve (*Azienda Ospedaliera Ospedale San Camillo Forlanini,*
11
12 *Roma, Medicina Interna 1*);

13
14
15 Antonio Brucato, Silvia Ghidoni, Paola Di Corato (*Azienda Ospedaliera Papa Giovanni XXIII,*
16
17 *Bergamo, Medicina 1*);

18
19
20 Giancarlo Agnelli, Emanuela Marchesini (*Azienda Ospedaliera Santa Maria della Misericordia,*
21
22 *Perugia, Medicina Interna e Cardiovascolare*);

23
24
25 Fabrizio Fabris, Michela Carlon, Francesca Turatto, Aldo Baritusso, Francesca Turatto (*Azienda*
26
27 *Ospedaliera Università di Padova, Padova, Clinica Medica I*);

28
29
30 Roberto Manfredini, Christian Molino, Marco Pala, Fabio Fabbian, Benedetta Boari, Alfredo De
31
32 Giorgi (*Azienda Ospedaliera - Universitaria Sant'Anna, Ferrara, Unità Operativa Clinica Medica*);

33
34
35 Giuseppe Paolisso, Maria Rosaria Rizzo, Maria Teresa Laieta (*Azienda Ospedaliera Universitaria*
36
37 *della Seconda Università degli Studi di Napoli, Napoli, VI Divisione di Medicina Interna e Malattie*
38
39 *Nutrizionali dell'Invecchiamento*);

40
41
42 Giovanbattista Rini, Pasquale Mansueto, Ilenia Pepe (*Azienda Ospedaliera Universitaria Policlinico*
43
44 *P. Giaccone di Palermo, Palermo, Medicina Interna e Malattie Metaboliche*);

45
46
47 Claudio Borghi, Enrico Strocchi, Valeria De Sando (*Azienda Ospedaliera Universitaria Policlinico S.*
48
49 *Orsola-Malpighi, Bologna, Unità Operativa di Medicina Interna Borghi*);

50
51
52 Carlo Sabbà, Francesco Saverio Vella, Patrizia Suppressa, Raffaella Valerio (*Azienda Ospedaliero-*
53
54 *Universitaria Consorziale Policlinico di Bari, Bari, Medicina Interna Universitaria C. Frugoni*);

1 Stefania Pugliese, Caterina Capobianco (*Azienda Ospedaliero-Universitaria Consorziale Policlinico*
2 *di Bari, Bari, Clinica Medica I Augusto Murri*);

3
4
5 Luigi Fenoglio, Christian Bracco, Alessia Valentina Giraudo, Elisa Testa, Cristina Serraino (*Azienda*
6
7 *Sanitaria Ospedaliera Santa Croce e Carle di Cuneo, Cuneo, S. C. Medicina Interna*);

8
9
10 Silvia Fargion, Paola Bonara, Giulia Periti, Marianna Porzio (*Fondazione IRCCS Cà Granda Ospedale*
11
12 *Maggiore Policlinico, Milano, Medicina Interna 1B*);

13
14
15 Flora Peyvandi, Alberto Tedeschi, Raffaella Rossio (*Fondazione IRCCS Cà Granda Ospedale*
16
17 *Maggiore Policlinico, Milano, Medicina Interna 2*);

18
19
20 Valter Monzani, Valeria Savojardo, Christian Folli, Maria Magnini (*Fondazione IRCCS Cà Granda*
21
22 *Ospedale Maggiore Policlinico, Milano, Medicina Interna Alta Intensità di Cura*);

23
24
25 Francesco Salerno, Alessio Conca, Giulia Gobbo, Alessio Conca (*IRCCS Policlinico San Donato e*
26
27 *Università di Milano, San Donato Milanese, Medicina Interna*);

28
29
30 Carlo L. Balduini, Giampiera Bertolino, Stella Provini, Federica Quaglia (*IRCCS Policlinico San*
31
32 *Matteo di Pavia, Pavia, Clinica Medica III*);

33
34
35 Franco Dallegri, Luciano Ottonello, Luca Liberale (*Università di Genova, Genova, Medicina Interna*
36
37 *1*);

38
39
40 Wu Sheng Chin, Laura Carassale, Silvia Caporotundo (*Ospedale Bassini, Cinisello Balsamo, Milano,*
41
42 *Unità Operativa di Geriatria*);

43
44
45 Giancarlo Traisci, Lucrezia De Feudis, Silvia Di Carlo (*Ospedale Civile Santo Spirito di Pescara,*
46
47 *Pescara, Medicina Interna 2*);

48
49
50 Nicola Lucio Liberato, Alberto Buratti, Tiziana Tognin (*Azienda Ospedaliera della Provincia di Pavia,*
51
52 *Ospedale di Casorate Primo, Pavia, Medicina Interna*);

1 Giovanni Battista Bianchi, Sabrina Giaquinto (*Ospedale "SS Gerosa e Capitano" di Lovere,*
2 *Bergamo, Unità Operativa Complessa di Medicina Generale, Azienda Ospedaliera "Bolognini" di*
3 *Seriate, Bergamo*);

4
5
6
7 Francesco Purrello, Antonino Di Pino, Salvatore Piro (*Ospedale Garibaldi Nesima, Catania, Unità*
8 *Operativa Complessa di Medicina Interna*);

9
10
11 Renzo Rozzini, Lina Falanga (*Ospedale Poliambulanza, Brescia, Medicina Interna e Geriatria*);

12
13 Giuseppe Montrucchio, Elisabetta Greco, Pietro Tizzani, Paolo Petitti (*Dipartimento di Scienze*
14 *Mediche, Università di Torino, Città della Scienza e della Salute, Torino, Medicina Interna 2 U.*
15 *Indirizzo d'Urgenza*);

16
17
18 Antonio Perciccante, Alessia Coralli (*Ospedale San Giovanni-Decollato-Andisilla, Civita Castellana*
19 *Medicina*);

20
21
22 Raffaella Salmi, Piergiorgio Gaudenzi, Susanna Gamberini (*Azienda Ospedaliera-Universitaria S.*
23 *Anna, Ferrara, Unità Operativa di Medicina Ospedaliera II*);

24
25
26 Andrea Semplicini, Lucia Gottardo (*Ospedale SS. Giovanni e Paolo, Venezia, Medicina Interna 1*);

27
28
29 Gianluigi Vendemiale, Gaetano Serviddio, Roberta Forlano (*Ospedali Riuniti di Foggia, Foggia,*
30 *Medicina Interna Universitaria*);

31
32
33 Cesare Masala, Antonio Mammarella, Valeria Raparelli (*Policlinico Umberto I, Roma, Medicina*
34 *Interna D*);

35
36
37 Francesco Violi, Stefania Basili, Ludovica Perri (*Policlinico Umberto I, Roma, Prima Clinica Medica*);

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5
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8
9

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12
13

14 Roberto Corinaldesi, Roberto De Giorgio, Mauro Serra, Valentina Grasso, Eugenio Ruggeri
15
16 (*Dipartimento di Scienze Mediche e Chirurgiche, Unità Operativa di Medicina Interna, Università*
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18
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27
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31
32

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35
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13
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15 Antonio Cittadini, Michele Arcopinto, Andrea Salzano, Emanuele Bobbio, Alberto Maria Marra,

16
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18 Domenico Sirico (*Azienda Policlinico Universitario Federico II di Napoli, Napoli, Medicina Interna e*
19 *Riabilitazione Cardiologica*);

20
21
22
23 Guido Moreo, Francesco Scopelliti, Francesca Gasparini, Melissa Cocca (*Clinica San Carlo Casa di*
24 *Cura Polispecialistica, Paderno Dugnano, Milano, Unità Operativa di Medicina Interna*).

25 26 27 28 29 30 **Spanish Hospitals**

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36 Muela Molinero Alberto (*Hospital de Leon*);

37
38
39 Abad Requejo Pedro, Lopez Pelaez Vanessa, Tamargo Lara (*Hospital del Oriente de Asturias,*
40 *Arriondas*);

41
42
43 Corbella Viros Xavier, Formiga Francesc (*Hospital Universitario de Bellvitge*);

44
45
46 Diez Manglano Jesus, Bejarano Tello Esperanza, Del Corral Behamonte Esther, Sevil Puras Maria
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50 Manuel Romero (*Hospital Infanta Elena Huelva*);

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53 Pinilla Llorente Blanca, Lopez Gonzalez-Cobos Cristina, Villalba Garcia M. Victoria (*Hospital*
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2 Gonzalez Becerra Concepcion, Fernandez Moyano Antonio, Mercedes Gomez Hernandez, Manuel

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4 Poyato Borrego (*Hospital San Juan De Dios Del Aljarafe, Sevilla*);

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6
7 Pacheco Cuadros Raquel, Perez Rojas Florencia, Garcia Olid Beatriz, Carrascosa Garcia Sara
8
9
10 (*Hospital Virgen De La Torre De Madrid*);

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12 Gonzalez-Cruz Cervellera Alfonso, Peinado Martinez Marta (*Hospital General Universitario De*
13
14 *Valencia*);

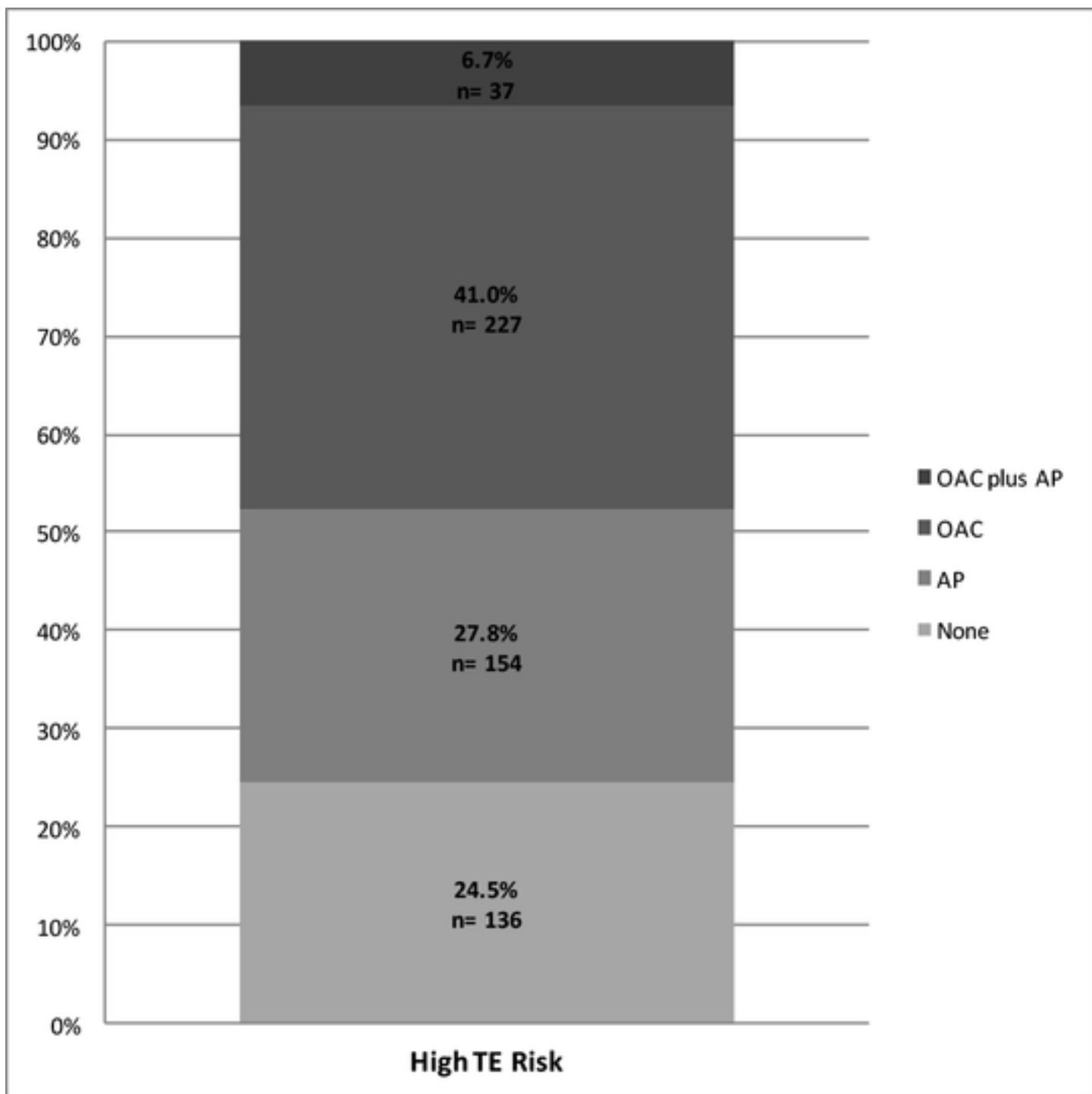
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16
17 Ruiz Cantero Alberto, Albarracín Arraigosa Antonio, Godoy Guerrero Montserrat, Barón Ramos
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19
20 Miguel Ángel (*Hospital De La Serrania De Ronda*);

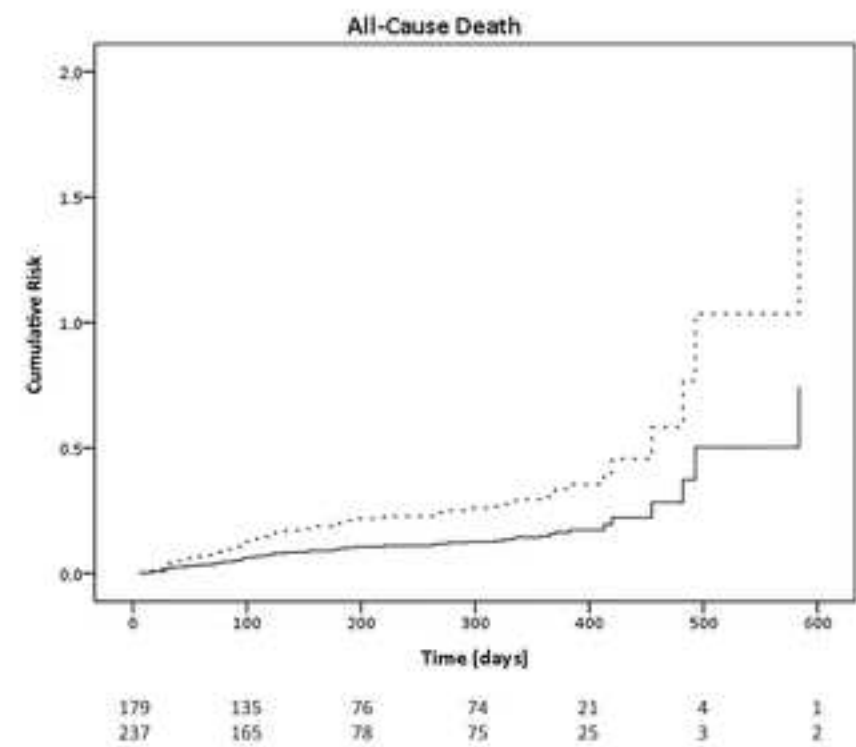
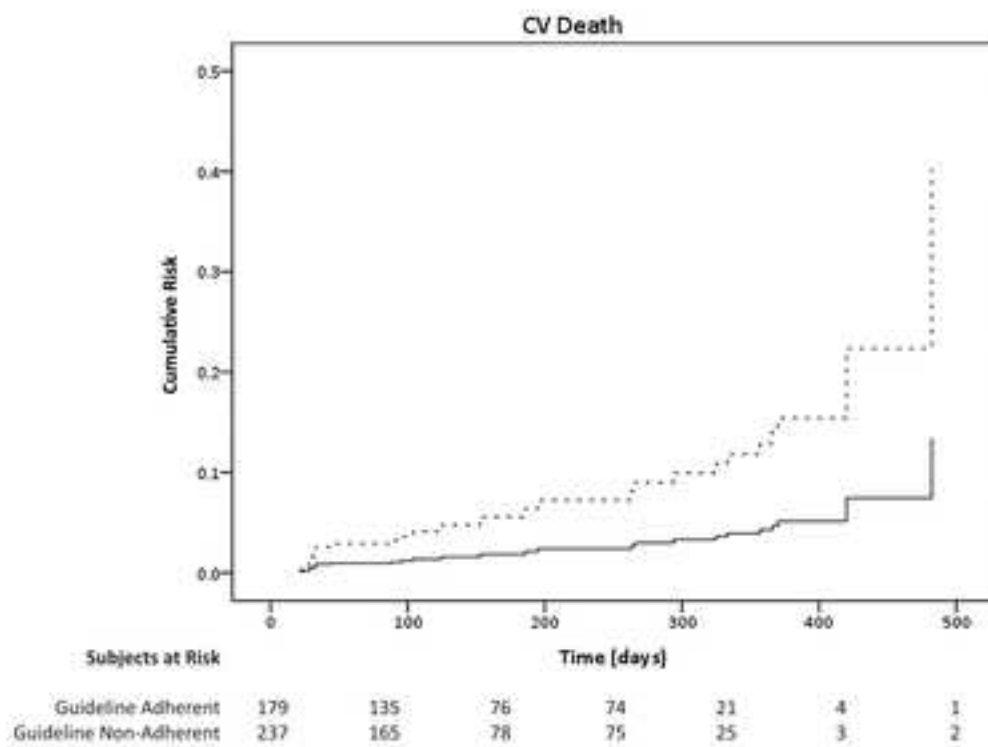
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23 Machin Jose Manuel (*Hospital Universitario De Guadalajara*);

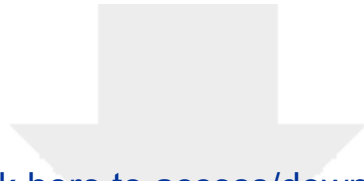
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26 Novo Veleiro Ignacio, Alvela Suarez Lucía (*Hospital Universitario De Santiago De Compostela*);

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Supplementary Material

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