

Inadequate anticoagulation by Vitamin K Antagonists is associated with Major Adverse Cardiovascular Events in patients with atrial fibrillation

Pastori, Daniele; Pignatelli, Pasquale; Saliola, Mirella; Carnevale, Roberto; Vicario, Tommasa; Del Ben, Maria; Cangemi, Roberto; Barillà, Francesco; Lip, Gregory Y.h.; Violi, Francesco

DOI:

[10.1016/j.ijcard.2015.08.054](https://doi.org/10.1016/j.ijcard.2015.08.054)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Pastori, D, Pignatelli, P, Saliola, M, Carnevale, R, Vicario, T, Del Ben, M, Cangemi, R, Barillà, F, Lip, GYH & Violi, F 2015, 'Inadequate anticoagulation by Vitamin K Antagonists is associated with Major Adverse Cardiovascular Events in patients with atrial fibrillation', *International Journal of Cardiology*, vol. 201, pp. 513-516. <https://doi.org/10.1016/j.ijcard.2015.08.054>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

After an embargo period, this document is subject to the terms of a Creative Commons Non-Commercial No Derivatives license.

Checked October 2015

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

Inadequate anticoagulation by warfarin is associated with major adverse cardiovascular events in patients with atrial fibrillation

Daniele Pastori, Pasquale Pignatelli, Mirella Saliola, Roberto Carnevale, Tommasa Vicario, Maria Del Ben, Roberto Cangemi, Francesco Barillà, Gregory Y.H. Lip, Francesco Violi

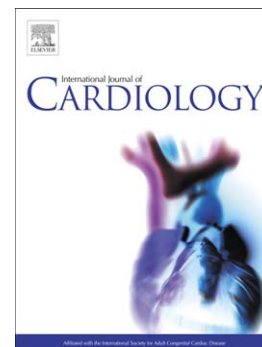
PII: S0167-5273(15)30285-0
DOI: doi: [10.1016/j.ijcard.2015.08.054](https://doi.org/10.1016/j.ijcard.2015.08.054)
Reference: IJCA 21006

To appear in: *International Journal of Cardiology*

Received date: 23 February 2015
Revised date: 3 July 2015
Accepted date: 2 August 2015

Please cite this article as: Pastori Daniele, Pignatelli Pasquale, Saliola Mirella, Carnevale Roberto, Vicario Tommasa, Del Ben Maria, Cangemi Roberto, Barillà Francesco, Lip Gregory Y.H., Violi Francesco, Inadequate anticoagulation by warfarin is associated with major adverse cardiovascular events in patients with atrial fibrillation, *International Journal of Cardiology* (2015), doi: [10.1016/j.ijcard.2015.08.054](https://doi.org/10.1016/j.ijcard.2015.08.054)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**INADEQUATE ANTICOAGULATION BY WARFARIN IS ASSOCIATED WITH MAJOR ADVERSE
CARDIOVASCULAR EVENTS IN PATIENTS WITH ATRIAL FIBRILLATION**

Daniele Pastori^{*(1)} MD, Pasquale Pignatelli^{*(1)} MD, Mirella Saliola⁽¹⁾ PhD, Roberto Carnevale^(1, 4)
PhD, Tommasa Vicario⁽¹⁾ MD, Maria Del Ben⁽¹⁾ MD, Roberto Cangemi⁽¹⁾ MD, Francesco Barilla⁽³⁾
MD, Gregory Y. H. Lip^{** (2)} MD, Francesco Violi^{** (1)} MD.

*equal contribution; **joint senior authors

Short title: Atrial fibrillation and Myocardial Infarction

⁽¹⁾ I Clinica Medica, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome.

⁽²⁾ University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK.

⁽³⁾ Department of the Heart and Great Vessels Attilio Reale, “Sapienza” University of Rome, Rome, Italy.

⁽⁴⁾ Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy.

Correspondence to

Professor Francesco Violi, I Clinica Medica, Viale del Policlinico 155, Roma, 00161, Italy. Phone: +39064461933; fax +390649970103; e-mail: francesco.violi@uniroma1.it

Disclosures: none

Funding: The study was supported by Sapienza University of Rome, Grant Code “Pignatelli Progetto Ricerca Sapienza 2011”.

Total word count: 4036

ABSTRACT

BACKGROUND: Time in therapeutic range (TTR) reflects the quality of anticoagulation and is inversely correlated with ischemic stroke in atrial fibrillation (AF) patients. Few data on the relationship between TTR and myocardial infarction (MI) are available. We investigated the association between TTR and Major Adverse Cardiovascular Events (MACE) in a cohort of anticoagulated AF patients.

METHODS: We calculated TTR for 627 AF patients on vitamin K antagonists, who were followed for a median of 30.8 months (1755 patients-year). The primary outcome was a combined endpoint of MACE including fatal/nonfatal MI and cardiovascular death.

RESULTS: Mean age was 73.3 (± 8.2) years, and 40.2% were women. **During follow-up, we recorded 67 events: 19 stroke/TIA (1.1%/year) and 48 MACE (2.9%/year): 24 MI and 24 cardiovascular deaths.** The cohort was categorized according to tertiles of TTR values: TTR 13-58%, 59-74%, and 75-100%. There was a significant increased rate of MACE across tertiles of TTR (Log-Rank test: $p < 0.001$). On Cox proportion hazard analysis, the 2nd vs. 1st tertile of TTR ($p = 0.002$, hazard ratio [HR] 0.347, confidence interval [CI] 95% 0.177-0.680), 3rd vs. 1st tertile of TTR ($p < 0.001$, HR 0.164, CI 95% 0.067-0.402), age ($p < 0.001$, HR 1.094, CI 95% 1.042-1.148), history of stroke/TIA ($p = 0.015$, HR 2.294, CI 95% 1.172-4.490) and smoking ($p = 0.003$, HR 3.450, CI 95% 1.532-7.769) predicted MACE.

CONCLUSION: TTR was an independent predictor of MACE in our cohort of AF patients. **Our findings suggest that a good anticoagulation control is necessary to reduce not only the risk of stroke but also that of MACE.**

KEYWORDS: atrial fibrillation, myocardial infarction, warfarin, anticoagulant drugs, cardiovascular diseases

INTRODUCTION

Non-valvular atrial fibrillation (AF) is a frequent cardiac arrhythmia and is known to be associated with a high risk of thromboembolic stroke[1]. A large number of AF patients have several risk factors of atherosclerosis, which accounts for an increased risk of atherosclerotic vascular complications[2]. In particular, peripheral artery disease, as assessed by ankle-brachial index, is detectable in about 20% of patients suffering from AF[3]. Furthermore, AF patients are also at higher risk of experiencing myocardial infarction (MI)[2, 4], with a risk ranging between 0.5% to 4%/year[4]. In a population-cohort study which included 1631 participants with AF, followed up for a median period of 4.5 years, the age-adjusted incidence rate of MI was 1.2 per 100 person-years, which was significantly higher compared to patients without AF, even after adjustment for traditional atherosclerotic risk factors and potential confounders[2]. Also, in a cohort of 1019 elderly AF patients we found a high rate of MI/vascular death (3,4%/year) during the follow-up[5].

Vitamin K antagonists (VKAs) are commonly used in heart disease[6], and in patients with AF to prevent ischemic stroke with an approximately risk reduction of 64%, and a reduction in all-cause mortality by 26%[7]. While previous studies consistently showed that warfarin decreases the risk of recurrent MI in patients who had suffered from acute coronary syndrome[8, 9], its effect on MI in AF is less clear. In a prospective cohort of AF patients without a clinical history of coronary heart disease, warfarin users had a 24% risk reduction of MI, compared to non-users, but the interplay between coagulation control and MI was unclear[2]. A retrospective analysis from SPORTIF III and V[10] trials showed that good anticoagulation control was associated with a significant reduction of MI in AF patients. Amongst warfarin treated patients (n>6,000) in the RE-LY trial, well controlled VKA with Time in Therapeutic Range (TTR) $\geq 65\%$ was associated with a lower MI rate compared to those patients with a TTR<65%[11].

However, the impact of warfarin on MI and other cardiovascular events in the 'real world' of AF is less certain. We therefore investigated the impact of anticoagulation quality, as assessed by TTR[12], on Major Adverse Cardiovascular Events (MACE) in a prospective study of AF patients.

Methods

Study design

This prospective single-center study included **627** patients with non-valvular AF who referred to our center for monitoring and management of antithrombotic therapies of the Department of Internal Medicine and Medical Specialties of Sapienza-University of Rome. All patients were treated with vitamin K antagonists, initially according to CHADS₂ score, and afterwards according to the CHA₂DS₂-VASc score[13]. Target INR value was 2.5 (range 2.0–3.0) and Time in Therapeutic Range (TTR) was used to assess the quality of anticoagulation[12]. TTR was calculated with the method described by Rosendaal[12], which uses linear interpolation of INR values to assign to each follow-up day a value of INR. Then, the percentage of days that the INR was in the therapeutic was calculated for each patient.

Exclusion criteria were patients with prosthetic heart valves, severe valvulopathies, severe cognitive impairment, chronic infections (Human Immunodeficiency Virus infection, viral hepatitis), autoimmune systemic disease, active cancer and liver insufficiency (eg, cirrhosis).

Twelve patients were lost to follow-up (10 cancer, 1 hepatic cirrhosis, 1 valve replacement). At baseline, each patient provided written informed consent and patient's anthropometric data and medical history were recorded. Cardiovascular risk factors, such as arterial hypertension[14], diabetes mellitus[15] and heart failure[16] were defined according to currently used international definitions.

Endpoints

The primary outcome of the study was a combined endpoint of major adverse cardiovascular events (MACE) including fatal/nonfatal MI and cardiovascular death. Diagnosis of MI was made according to the European Society of Cardiology definition[17]. If a patient died within 4 weeks of MI, this event was recorded as fatal MI. Death was classified as vascular unless the central adjudication committee confirmed an unequivocal non-cardiovascular cause of death. Cardiovascular death included sudden death; progressive congestive heart failure; procedure related death. Only the first event that occurred during follow-up was used in the analysis. Moreover, the occurrence of ischemic stroke or transient ischemic attack (TIA) was recorded. Ischemic stroke was diagnosed on clinical manifestations and confirmed by radiological findings, and TIA was defined according to the Classification of Cerebrovascular Diseases III.[18]

We also registered the occurrence of hemorrhages during follow-up which were classified according to the **International Society of Thrombosis And Hemostasis** definition[19].

Adjudication of events during follow-up

Data on events were prospectively collected during follow-up. When an event occurred, a standardized form was filled in by the investigators. Details on events were registered, as well as death certificates, hospital discharge letter or copy of the medical records of hospitalization, and other clinical documentation (i.e. radiology and laboratory data) were also obtained from patients, or in case of death, from relatives of patients or from general practitioner. Adjudication of cardiovascular events was performed by an internal (FV, PP) and external (FB) committee who did not participate to the recruitment of patients and was unaware of the clinical and laboratory characteristics of any enrolled patient. Each member of the committee independently evaluated and adjudicated events in a blinded manner. In case of discordant evaluation or difficult adjudication of an event, the committee decided to award the event in a collegial way. The study

protocol was approved by the local ethical board of Sapienza-University of Rome and was conducted according to principles of the Declaration of Helsinki.

Statistical analyses

Categorical variables were reported as counts (percentage), continuous variables were expressed as mean \pm standard deviation (SD) or median and interquartile range (IQR), as appropriate. Independence of categorical variables was tested with the χ^2 test. The normal distribution of parameters was assessed by Kolmogorov–Smirnov test. Student unpaired t test and Pearson product-moment correlation analyses were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney U test and Spearman rank correlation test) were used for all the other variables. Group comparisons were performed using Fisher’s F-test (ANOVA) or Kruskal-Wallis test when needed. After dividing the AF population into tertiles according to TTR values, the cumulative incidence of MACE was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test.

Cox proportional hazards analysis was used to calculate the adjusted relative hazards of MACE by each clinical variable. In the multivariable analysis, all variables (listed in table 2) have been introduced in one step (forced entry procedure). Only p values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, SPSS Inc.).

Results

We included 627 AF patients treated with VKAs: mean age 73.3 (± 8.2) years, 40.2% were women. Median follow-up was 30.8 min 3.0- max 80.0 months, yielding 1755 patients-year of observation. Clinical characteristics of all patients included in the study are summarized in table 1.

During follow-up period, we recorded 67 events. Of these, 19 (3.0%, 1.1%/year) were cerebrovascular events (stroke/TIA) and 48 (7.6%, 2.7%/year) were MACE: the latter consisted of 24 MI and 24 CV deaths. In addition, 10 cardiac revascularizations occurred (not used for the analysis), and 18 non-cardiovascular deaths related to neoplastic disease.

TTR and MACE

In the whole cohort, mean TTR was 66.8 ± 16.6 %. We found a significant difference of mean TTR in patients with and without MACE at follow-up (56.1 ± 17.6 vs. 67.7 ± 16.2 , respectively $p < 0.001$). This difference was also evident in patients who experienced cerebrovascular events (57.8 ± 20.8 vs. 67.1 ± 16.4 , $p = 0.016$). Similarly, all-cause mortality was associated with a significant lower TTR (59.4 ± 18.6 vs. 67.4 ± 16.4 of patients free from events, $p = 0.003$).

To investigate the relationship between TTR and MACE, we divided the cohort in three groups according to tertiles of TTR values. The first tertile of TTR included AF patients with poor anticoagulation control ($n = 205$, median TTR: 50% [min-max 13-58]); the second tertile those with moderate anticoagulation control ($n = 207$, median TTR: 67% [min-max 59-74]), and the third tertile those with optimal anticoagulation control group ($n = 215$, median TTR: 83% [min-max 75-100]).

AF patients with low TTR (i.e. $< 60\%$) spent most of their time below ($31.9 \pm 17.5\%$), than above the TTR ($19.5 \pm 15.7\%$, $p < 0.001$).

No differences among tertiles of TTR were found regarding clinical characteristics or concomitant therapies, with the exception of a lower prevalence of previous cardiac events in the third tertile (table 1).

Figure 1 shows the percentages of MACE for each tertile of TTR. A significantly increased incidence of MACE across tertiles of TTR **has been observed** (Log-Rank test: $p < 0.001$), with lowest rate of MACE in patients with good anticoagulation (i.e. high TTR, Figure 2).

On multivariable Cox regression analysis, we found that age, smoking and history of stroke/TIA were positively associated to MACE, whilst second and third tertile of TTR were inversely associated to MACE (Table 2).

Similar results were obtained after the exclusion of patients with previous cardiovascular events (Tertiles of TTR: global $p < 0.001$, HR 0.380, CI 95% 0.227-0.638).

TTR and hemorrhages

We registered 122 hemorrhages: 90 minor and 32 major, the latter consisting of 7 cerebral/subdural, 6 ocular, 9 muscular/articular, 8 gastrointestinal and 2 urinary. No differences regarding TTR were present between patients who bled or not (68.5 ± 16.0 vs. 66.4 ± 16.8 , respectively $p = 0.215$). Similar results were found when we considered only major hemorrhages ($p = 0.489$).

Discussion

The principal finding in this prospective cohort study of anticoagulated AF patients was that TTR is an independent predictor of MACE. The overall rate of MACE exceeded that of stroke, and AF patients with poor anticoagulation (i.e. TTR $< 60\%$) disclosed the highest incidence of MACE.

The rate of stroke/TIA of our population was similar to that reported by recent clinical trials with oral anticoagulants. Indeed, during the follow-up the annual event rate of cerebral ischemia was 1.1% which is consistent with previous reports showing that in AF patients treated with adjusted doses of VKAs stroke the incidence ranged from 1.1 to 4.4% per year [20].

Moreover, patients experiencing cerebrovascular events revealed a significantly lower TTR value compared to those free from events, reinforcing the need for a good anticoagulation control (such as TTR >70%) to protect patients from ischemic stroke.

The rate of cardiovascular events appears to be higher than that reported in recent interventional trials with the non-vitamin K oral anticoagulants (NOACs)[21]. Thus, the annual rate of MACE in our cohort was 2.7%, consistent with Roldàn et al.[22] who found a rate MI of 1.83%/year versus 1.66%/year of stroke; this was also consistent with a previous Italian study in high risk AF patients, which reported an annual MACE rate of 3.4%[23].

The present 'real world' study is the first to report that a good anticoagulation with VKAs is associated with a significant reduction of MACE amongst AF patients. The lowest rate of MACE was detected in AF patients with a TTR >75%, while the rate raised sharply with TTR<60%.

Our elderly AF population and atherosclerotic burden may account for this high rate of MACE. Thus, clinical history of our cohort was complicated more by coronary than cerebrovascular disease; indeed, we found that at least one atherosclerotic risk factor was detected in approximately 90% of patients.

Another possibility may be related to the different impact of VKAs on the pathophysiology of stroke and coronary events, which are largely dependent upon clotting or platelet activation, respectively[24]. Thus, it is possible that VKAs, which are able to reduce significantly thromboembolic stroke, would less favorably affect vascular events of athero-thrombotic origin, such as acute coronary syndromes. This was also evident from the results of a recent Cochrane analysis[25], including eight randomized trials and 9598 AF patients that showed how VKA significantly reduced the rate of ischemic stroke, but had less favorable effect in lowering the rate of myocardial infarction[25].

In contrast with previous findings[10], we found no association between TTR value and the occurrence of bleeding. The relative small number of major hemorrhages may account for this different result.

What are the clinical implications? Maintaining AF in good anticoagulation, is a fundamental objective to reduce not only the risk of thrombo-embolic related vascular events, but also the incidence of MACE, so reinforcing the need for a more appropriate and constant monitoring of anticoagulation in AF. The overall high rate of MACE in the real world of AF patients treated with VKAs indicates that oral anticoagulants alone may not counteract sufficiently outcomes from coronary origin, and other anti-atherosclerotic regimens should be considered to further reduce the risk of MACE. This is even more important considering that, despite the study was conducted in a specialized center for the monitoring of anti-thrombotic therapies, about one third of AF patients still had an inadequate TTR; this is in keeping with a previous finding reporting difficulty in achieving and maintaining adequate adherence to therapy with warfarin and a constant and effective anticoagulation in AF[26]. Finally, it remains to be established if the rate of MACE may be differently affected by NOACs.

Limitations. This study is limited by its observational cohort design and residual confounding is likely, although we have attempted to adjust for comorbidities on multivariate analysis. Our data refer to an elderly AF population with multiple atherosclerotic risk factors and a clinical history often complicated by coronary heart disease and, thereby, cannot be extrapolated to a younger AF population. Moreover, all patients were recruited from a single center.

Conclusions. We found that TTR was an independent predictor of MACE in our cohort of AF patients, **suggesting that a good anticoagulation control is necessary to reduce not only the risk of stroke but also that of MACE.**

Authorship

D. Pastori, P. Pignatelli, F. Violi contributed to the concept and design of the study, analysis and interpretation of data and writing of the manuscript; M. Saliola: data collection, R. Carnevale: data collection, critical writing or revising of the manuscript, T. Vicario: data collection, R. Cangemi: analysis and interpretation of data, M. Del Ben: critical writing or revising of the manuscript, F. Barillà: critical writing or revising of the manuscript, G. Y. H. Lip: critical writing or revising the intellectual content. All authors have read and approved the final version of the manuscript to be published.

Table 1. Baseline characteristics of whole cohort and according to tertiles of Time in Therapeutic Range (TTR).

	Overall	Tertiles of TTR			p value
		1 st 13-58%	2 nd 59-74%	3 rd 75-100%	
<i>Age (years)</i>	73.3±8.2	72.9±8.7	73.1±7.9	73.9±8.0	0.365
<i>Persistent/Permanent AF</i>	54.2	51.7	57.0	54.0	0.556
<i>Women (%)</i>	40.2	39.5	39.1	41.9	0.825
<i>Body Mass Index (kg/m²)</i>	27.4±4.4	27.5±4.7	27.4±4.6	27.2±4.0	0.832
<i>Smoking (%)</i>	8.1	8.3	9.7	6.5	0.494
<i>CHA₂DS₂-VASc score</i>	3.0 [2.0-4.0]	4.0 [2.5-5.0]	4.0 [2.0-4.0]	3.0 [2.0-4.0]	0.247
<i>Hypertension (treated, %)</i>	94.7	91.7	96.6	95.8	0.057
<i>Diabetes mellitus (%)</i>	20.6	23.9	19.8	18.1	0.326
<i>History of MI/cardiac revascularization (%)</i>	22.3	26.8	25.1	15.3	0.009
<i>Heart failure (%)</i>	15.3	17.6	14.5	14.0	0.545
<i>History of stroke/TIA (%)</i>	14.2	17.1	15.0	10.7	0.142
<i>Antiplatelet (%)</i>	10.2	11.2	13.0	6.5	0.063
<i>Statins (%)</i>	47.2	49.8	47.3	44.7	0.577

ACE: Angiotensin Converting Enzyme, AF: Atrial Fibrillation, ARBs: Angiotensin Receptor Blockers,

MI: Myocardial Infarction, TIA: Transient Ischemic Attack, TTR: Time in Therapeutic Range

Table 2. Cox proportional hazard analysis of factors associated to Major Adverse Cardiovascular Events (MACE).

	p value	HR	CI 95.0%	
2nd vs. 1st tertile of TTR*	0.002	0.347	0.177	0.680
3rd vs. 1st tertile of TTR*	<0.001	0.164	0.067	0.402
Persistent/Permanent AF	0.744	0.906	0.500	1.641
Female sex	0.525	0.806	0.415	1.565
Age	<0.001	1.094	1.042	1.148
Hypertension (treated)	0.377	0.576	0.169	1.960
Diabetes	0.344	1.410	0.692	2.874
Heart Failure	0.106	1.753	0.887	3.463
History of Stroke/TIA	0.015	2.294	1.172	4.490
History of MI/Cardiac revascularization	0.336	1.384	0.714	2.681
Antiplatelet	0.805	0.881	0.323	2.402
Smoking	0.003	3.450	1.532	7.769
Statins	0.165	1.573	0.830	2.981

*Global p value: p<0.001.

AF: Atrial Fibrillation, CI: Confidence Interval, HR: Hazard Ratio, MI: Myocardial Infarction, TIA:

Transient Ischemic Attack, TTR: Time in Therapeutic Range

Figure Legend

Figure 1. Percentages of MACE according to tertiles of time in therapeutic range.

Figure 2. Kaplan-Meier curves estimate of survival free from MACE according to tertiles of time in therapeutic range. Black line: first tertile, dark grey line: second tertile, light grey line: third tertile (Log-Rank test, $p < 0.001$).

ACCEPTED MANUSCRIPT

References

- [1] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke; a journal of cerebral circulation*. 1991;22:983-8.
- [2] Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA internal medicine*. 2014;174:107-14.
- [3] Violi F, Davi G, Hiatt W, Lip GY, Corazza GR, Perticone F, et al. Prevalence of peripheral artery disease by abnormal ankle-brachial index in atrial fibrillation: implications for risk and therapy. *Journal of the American College of Cardiology*. 2013;62:2255-6.
- [4] Polimeni L, Perri L, Saliola M, Basili S, Violi F. The risk of myocardial infarction in patients with atrial fibrillation: an unresolved issue. *Internal and emergency medicine*. 2010;5:91-4.
- [5] Pastori D, Pignatelli P, Angelico F, Farcomeni A, Del Ben M, Vicario T, et al. Incidence of myocardial infarction and vascular death in elderly patients with atrial fibrillation taking anticoagulants: relation to atherosclerotic risk factors. *Chest*. 2015;147:1644-50.
- [6] De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. *Thrombosis and haemostasis*. 2013;110:1087-107.
- [7] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Annals of internal medicine*. 2007;146:857-67.
- [8] Testa L, Zoccai GB, Porto I, Trotta G, Agostoni P, Andreotti F, et al. Adjusted indirect meta-analysis of aspirin plus warfarin at international normalized ratios 2 to 3 versus aspirin plus clopidogrel after acute coronary syndromes. *The American journal of cardiology*. 2007;99:1637-42.
- [9] Rothberg MB, Celestin C, Fiore LD, Lawler E, Cook JR. Warfarin plus aspirin after myocardial infarction or the acute coronary syndrome: meta-analysis with estimates of risk and benefit. *Annals of internal medicine*. 2005;143:241-50.
- [10] White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Archives of internal medicine*. 2007;167:239-45.
- [11] Clemens A, Fraessdorf M, Friedman J. Cardiovascular outcomes during treatment with dabigatran: comprehensive analysis of individual subject data by treatment. *Vascular health and risk management*. 2013;9:599-615.
- [12] Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thrombosis and haemostasis*. 1993;69:236-9.
- [13] European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *European heart journal*. 2010;31:2369-429.
- [14] Mancia G, Fagard R, Narkiewicz K, Redan J, Zanchetti A, Bohm M, et al. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *Journal of hypertension*. 2013;31:1925-38.
- [15] Authors/Task Force M, Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *European heart journal*. 2013;34:3035-87.
- [16] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European journal of heart failure*. 2012;14:803-69.

- [17] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Journal of the American College of Cardiology*. 2012;60:1581-98.
- [18] Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke; a journal of cerebral circulation*. 1990;21:637-76.
- [19] Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of thrombosis and haemostasis : JTH*. 2005;3:692-4.
- [20] Lip GY, Hart RG, Conway DS. Antithrombotic therapy for atrial fibrillation. *Bmj*. 2002;325:1022-5.
- [21] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-62.
- [22] Roldan V, Marin F, Manzano-Fernandez S, Fernandez H, Gallego P, Valdes M, et al. Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? *Thrombosis and haemostasis*. 2013;109:956-60.
- [23] Cangemi R, Pignatelli P, Carnevale R, Corazza GR, Pastori D, Farcomeni A, et al. Cholesterol-adjusted vitamin E serum levels are associated with cardiovascular events in patients with non-valvular atrial fibrillation. *International journal of cardiology*. 2013;168:3241-7.
- [24] Violi F, Loffredo L. Thromboembolism or atherothromboembolism in atrial fibrillation? *Circulation Arrhythmia and electrophysiology*. 2012;5:1053-5.
- [25] Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *The Cochrane database of systematic reviews*. 2007:CD006186.
- [26] Colonna P, Abrignani MG, Colivicchi F, Verdecchia P, Alunni G, Bongo AS, et al. [ANMCO statement on prevention of thromboembolism in atrial fibrillation and role of the new oral anticoagulants]. *Giornale italiano di cardiologia*. 2013;14:295-322.

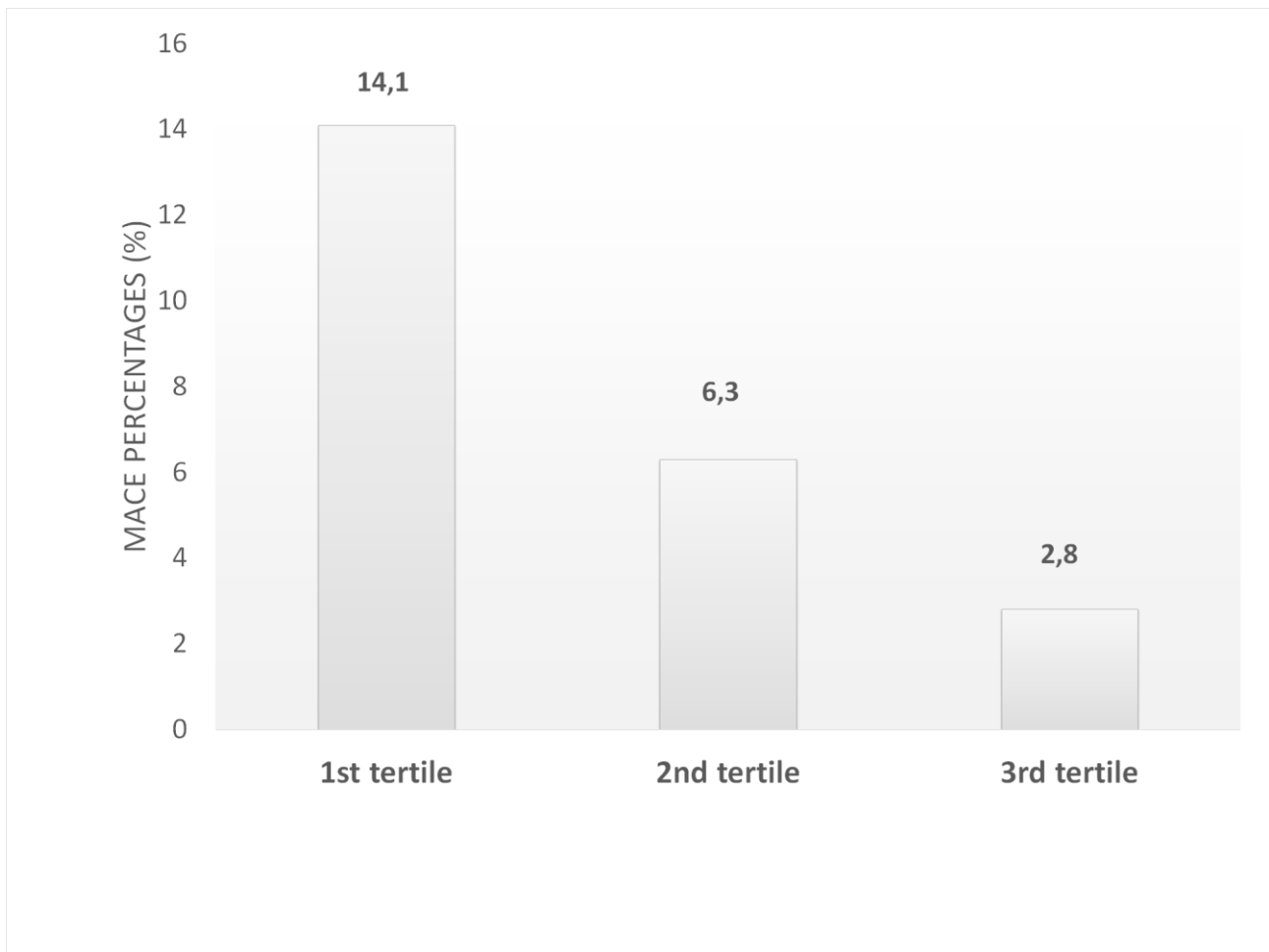


Figure 1

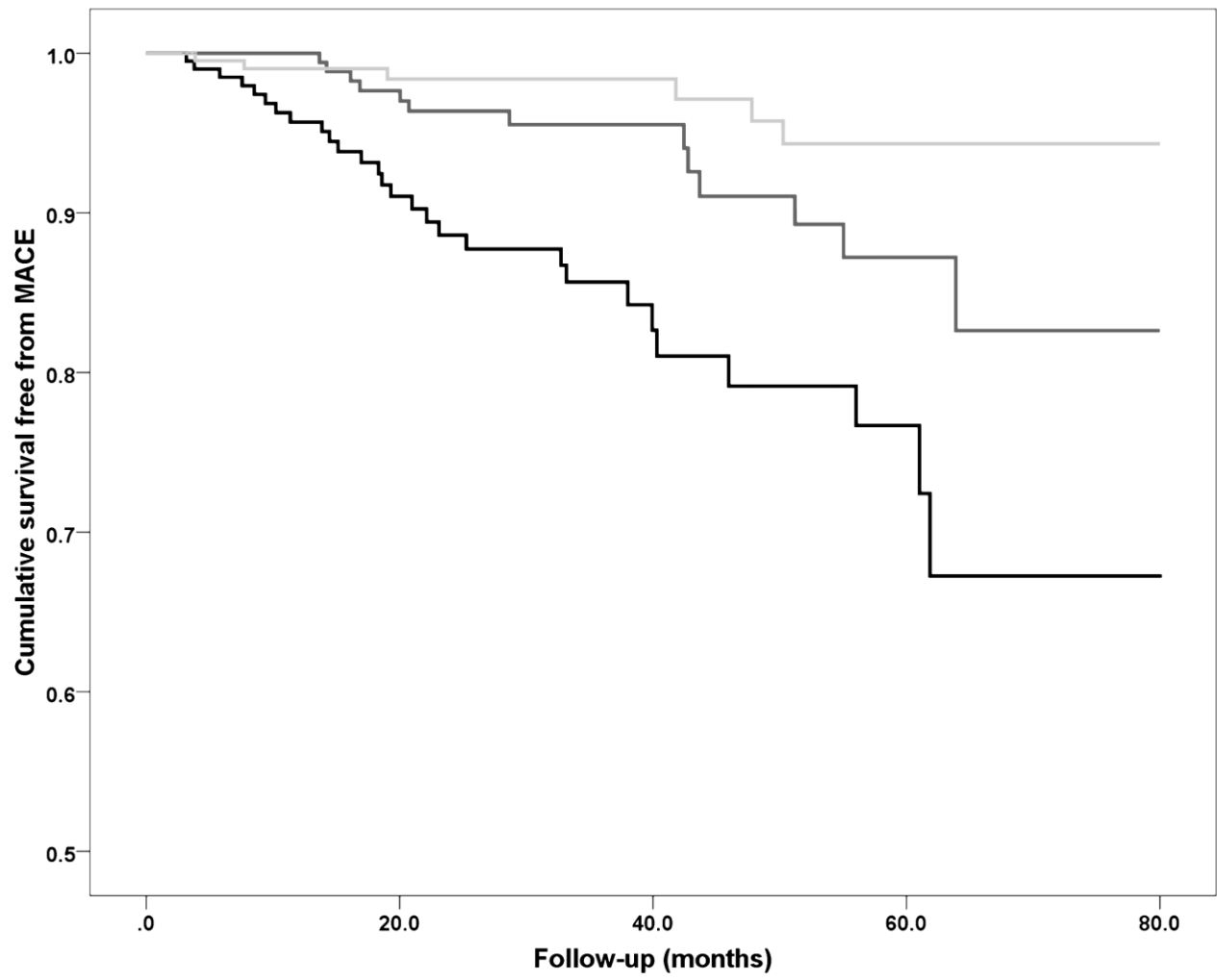


Figure 2