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Number needed to treat for net effect of anticoagulation in atrial fibrillation

Real-World vs. Clinical Trial Evidence

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Number needed to treat for net effect of anticoagulation in atrial fibrillation: Real-World *vs.* Clinical Trial Evidence

Short title: NNT_{net} in AF from Real-world *vs.* Clinical Trial

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What is already known about this subject:

- The measure of number needed to treat (NNT) is useful as it conveys both statistical and clinical significance.
- An assessment of the overall effects of treatment that integrated $NNT_{benefit}$ and NNT_{harm} was previously lacking.
- NNT for net effect has been recently introduced to amalgamate the combined benefit-and-harm effects of intervention.

What this study adds:

- NNT_{net} of anticoagulation therapy in atrial fibrillation at 1-year was 34 in a real-world cohort and 46 in a clinical trial population.
- NNT_{net} was better among patients with an excess baseline risk of stroke in both cohorts.
- The NNT_{net} approach in atrial fibrillation facilitates the overall care that considers the various risks and benefits of treatment among these patients.

Accepted Article

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Abstract

Background: The net benefit of oral anticoagulants (OACs) in atrial fibrillation (AF) is poorly understood. We aimed to determine the "NNT for net effect" (NNT_{net}) using Calculator of Absolute Stroke Risk (CARS) in anticoagulated patients with AF in real-world and clinical trial cohorts.

Methods: Post-hoc analysis of patient-level data from the real-world Murcia AF Project and the AMADEUS clinical trial. Baseline risk of stroke was determined using CARS. The risk of stroke and major bleeding events with OAC were determined using the number of respective events at 1-year. NNT_{net} was calculated as a reciprocal of the net effect of absolute risk reduction with OAC (NNT_{net}= 1 / (absolute risk reduction of stroke[ARR_{stroke}] - absolute risk increase of major bleeding[$ARI_{bleeding}$])).

Results: 3,511 patients were included (1,306 [37.2%] real-world patients and 2,205 [62.8%] clinical trial). The absolute 1-year stroke risk was similar across both cohorts. In the real-world cohort, OAC was associated with a 4.0% ARR_{stroke}, 25 $NNT_{benefit}$, 1.0% $ARI_{bleeding}$, 100 NNT_{harm} and 34 NNT_{net}. In the clinical trial cohort, OAC was associated with a 3.8% ARR_{stroke}, 27 $NNT_{benefit}$, 1.6% $ARI_{bleeding}$, 63 NNT_{harm} and 46 NNT_{net}. In both cohorts, the NNT_{net} was significantly lower in patients with an excess stroke risk of ≥2% by CARS.

Conclusion: Overall, the NNT_{net} approach in AF incorporates information regarding baseline risk of stroke and major bleeding, and relative effects of OAC with the potential to include multiple additional outcomes and weighting of events based on their perceived effects by individual patients.

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Introduction

Atrial fibrillation (AF) is a systemic condition that is characterised by an excess prothrombotic risk [1], and associated with significant morbidity and mortality[2–4]. Hence, a crucial element in the management of AF is stroke prevention with the use of oral anticoagulants (OACs). However, treatment with these agents contributes to an additional risk of bleeding. Therefore, the benefit of anticoagulation (*difference in stroke risk between pre- and post-treatment*) must be balanced against any potential risk of harm by adopting an individualised approach to risk assessments [5]. The results of these assessments should then be communicated to patients in an intuitive, simple and interpretable format to facilitate the clinician-patient shared decision-making process [6].

Recently, the Calculator of Absolute Stroke Risk (CARS) was proposed to allow a more precise estimation of personalised 1-year absolute risk of stroke in non-anticoagulated patients with AF [7]. This novel tool was developed using the nationwide Danish registry of 147,842 patients with AF and relied on similar clinical components as the widely adopted CHA_2DS_2-VASc score [8], but dealt with age as a continuous variable and accounts for the specific contribution of each risk factor. The authors reported that CARS had better predictive ability than the CHA_2DS_2-VASc score but the findings have not been externally validated.

The concept of "number needed to treat (NNT)" was first introduced in 1988 to help understand the effects of treatment in randomised controlled trials [9]. In the clinical setting, the measure of NNT is more meaningful than others such as relative risk or odds ratio as it conveys both statistical and clinical significance [10]. It can be specified as NNT for benefit ($NNT_{benefit}$) or NNT for harm (NNT_{harm}), to indicate on average, how many patients need to be treated to either a) achieve one additional beneficial event or prevent one adverse event or

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b) develop one additional adverse event, compared to a referent. Nonetheless, an assessment of the overall effects of treatment that integrated $NNT_{benefit}$ and NNT_{harm} was previously lacking. Recently, Li *et al.* introduced a new metric, termed "NNT for net effect" (NNT_{net}), to amalgamate the combined benefit-and-harm effects of intervention that may facilitate the overall management of patients with AF [11].

The use of CARS which provides a 1-year absolute risk of stroke which is needed for an assessment of the NNT_{net} of OAC in AF has not been studied. In our opinion, this will provide valuable information to clinicians and patients alike. Furthermore, many studies have reported differences in treatment outcomes between real-world and clinical trial data. Therefore, we aimed to evaluate the application of NNT_{net} to determine the benefits or harm of OAC therapy using CARS in patients with AF from real-world (Murcia AF Project) and clinical trial (AMADEUS [Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation] trial) cohorts.

Methods

In the present analysis, we included patient-level data from the Murcia AF Project and AMADEUS trial of those with a minimum follow-up of 1-year or stroke/major bleeding event prior to this. The design of both studies have previously been described [12,13]. In brief, the Murcia AF Project was an observational study from Spain that enrolled consecutive outpatients from May to December 2007 with non-valvular AF and who were on stable vitamin K antagonist (VKA) therapy (*i.e.* International Normalised Ratio [INR] of 2.0 to 3.0) during the preceding six months. The initial period of stable INR minimised heterogeneity, thus avoiding confounding factors due to differences in the quality of anticoagulation control at study entry. The reported time in therapeutic range was re-calculated after six months.

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Patients with rheumatic mitral or prosthetic heart valve, as well as those with any acute coronary syndrome, stroke, haemodynamic instability, and hospital admission or surgical intervention in the preceding six months, were excluded.

The AMADEUS trial was a multicentre, multinational, randomised, open-label non-inferiority study with blinded adjudication of outcomes comparing fixed-dose idraparinux and dose-adjusted VKA in patients with non-valvular AF. Recruitment took place from September 2003 to July 2005. Patients with an indication for OAC other than AF, transient AF caused by a reversible disorder, active bleeding or high-risk of bleeding, creatinine clearance of less than 10 mL/min, severe liver disease, poorly controlled hypertension, and recent or anticipated invasive procedure with potential for bleeding were excluded.

CHA_2DS_2-VASc and HAS-BLED scores were calculated as previously described [8,14]. In both cohorts, a complete medical history was recorded at inclusion and the parameters were used to calculate CARS [15]. All patients had sufficient information for CARS calculation. The online calculator for CARS utilised similar clinical parameters as the CHA_2DS_2-VASc score but evaluated the risk factors for stroke in a more dynamic manner by treating age as a continuous variable and assigning differing risk based on individual factors (*e.g.* hypertension and heart failure contributed to the risk of stroke differently). Patients were categorised into four groups according to their individual CARS: low risk (<1%), moderate risk (1 - 1.9%), high risk (2 - 10%) and very high risk (>10%). An average baseline 1-year risk of major bleeding in non-anticoagulated AF patients was estimated according to the presence of comorbidities using data from a previous report of a large prospective study of 182,678 Swedish patients with similar baseline demographics [16]. The risks of first stroke or major bleeding event with OAC were determined using the number of respective events at 1-year for each cohort.

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Ischaemic stroke was defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery due to an obstruction documented by imaging, surgery or autopsy. Major bleeding was defined according to the 2005 International Society on Thrombosis and Haemostasis (ISTH). All events in the AMADEUS trial were adjudicated by a central committee, who were blinded to treatment assignment [12].

The study protocol of the Murcia AF Project was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by the Ethics Committee from University Hospital Morales Meseguer. The AMADEUS trial received ethics approval for the main trial study and any ancillary analyses on the anonymised trial dataset. Patients from both studies gave informed consent to participation.

Statistical analyses

Continuous baseline variables were expressed using median and interquartile range (IQR), and tested for differences using the Kruskal-Wallis test. Categorical variables were expressed using absolute frequencies and percentages, and tested for differences using chi-squared test. Actual stroke and major bleeding risks at 1-year were determined as a percentage with 95% confidence intervals (CI). The relative risk reduction (RRR) or increase (RRI) was determined as the proportion of the change in absolute risk with OAC compared to baseline risk. The absolute risk reduction (ARR) and absolute risk increase (ARI) were calculated as the baseline estimated risk of stroke and bleeding, multiplied by the RRR or RRI, respectively. The $NNT_{benefit}$ and NNT_{harm} were derived from the reciprocal of the absolute risk reduction of stroke (ARR_{stroke}), *i.e.* $1/ARR_{stroke}$, and absolute risk increase of major bleeding ($ARI_{bleeding}$),*i.e.* $1/ARR_{bleeding}$, respectively. The NNT_{net} was calculated as the reciprocal of the net effect of absolute risk reduction with OAC ($NNT_{net}= 1/[ARR_{stroke} - ARI_{bleeding}]$). A

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sensitivity analysis was performed among the VKA-treated patients in the AMADEUS trial. Analyses were performed using SPSS software version 24.0 (SPSS Inc., Chicago, Illinois, United States).

Results

Of the original 1,361 and 4,576 patients from the real-world and AMADEUS trial, respectively, we included 3,511 patients with non-valvular AF: 1,306 (37.2%) real-world patients and 2,205 (62.8%) clinical trial participants. Baseline demographics for the real-world cohort are summarised in **Table 1**. Median age was 76 (IQR 70 - 81) years, with 51.7% females. Median CHA_2DS_2-VASc score was 4 (IQR 3 - 5) and HAS-BLED score 2 (IQR 2 - 3). Patients were classified according to their CARS risk profile as low risk <1% (3.5%), moderate risk 1 - 1.9% (9.9%), high risk 2 - 10% (67.5%) and very high risk >10% (19.1%).

Baseline demographics for the clinical trial cohort are summarised in **Table 2**. Median age was 71 (IQR 65 - 77) years, with 34.6% females. Participants were treated with either VKA (54.6%) or idraparinux (45.4%). Median CHA_2DS_2-VASc score was 3 (IQR 2 - 4) and HAS-BLED score 2 (IQR 1 - 2). Participants were classified according to their CARS risk profile as low risk<1% (5.0%), moderate risk 1 - 1.9% (18.8%), high risk 2 - 10% (54.4%) and very high risk>10% (21.8%). The absolute 1-year stroke risk according to CARS was very similar across both cohorts (**Figure 1**).

Ischaemic stroke risk at 1-year

In the real-world cohort, the baseline stroke risk at 1-year without OAC was 5.7% (95% CI 5.5 - 6.0). At 1-year, there were a total of 22 (1.7%) stroke events. The use of OAC was

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associated with a 4.0% ARR_{stroke} and 0.70 relative risk reduction of stroke (RRR_{stroke}). Accordingly, the $NNT_{benefit}$ with anticoagulation therapy to prevent one stroke event was 25 (**Table 3**).

In the clinical trial cohort, the baseline stroke risk at 1-year without OAC was 5.1% (95% CI 4.9 - 5.3). At 1-year, there were a total of 29 (1.3%) stroke events. The use of OAC was associated with a 3.8% ARR_{stroke} and 0.75 RRR_{stroke}. Accordingly, the $NNT_{benefit}$ with anticoagulation therapy to prevent one stroke event was 27.

Major bleeding risk at 1-year

At 1-year, there were 43 (3.3%) major bleeding events in the real-world cohort. The use of OAC was associated with a 1.0% $ARI_{bleeding}$ and a 0.43 relative risk increase. Accordingly, the NNT_{harm} with anticoagulation therapy to contribute to one major bleeding event was 100 (**Table 3**).

At 1-year, there were 87 (3.9%) major bleeding events in the clinical trial cohort. The use of OAC was associated with a 1.6% $ARI_{bleeding}$ and a 0.70 relative risk increase. Accordingly, the NNT_{harm} with anticoagulation therapy to contribute to one major bleeding event was 63.

Number needed to treat for net effect

Balancing the effects of treatment, the NNT_{net} to provide an overall benefit of anticoagulation therapy was 34 in the real-world and 46 in the clinical trial (**Table 3**). In both cohorts, the NNT_{net} was significantly lower in patients with an excess stroke risk of ≥2% by CARS (**Table 4 and 5**). Among real-world patients with a very high (>10%) baseline stroke risk, the use of anticoagulation therapy was associated with an ARR_{stroke} of 10.9% while there was a

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corresponding $ARI_{bleeding}$ of 1.2%, generating an overall NNT_{net} of 11. Among similar clinical trial participants, the use of anticoagulation therapy was associated with an ARR_{stroke} of 11.0% while there was a corresponding $ARI_{bleeding}$ of 0.6%, generating an overall NNT_{net} of 10.

Sensitivity analysis

In a sensitivity analysis of the VKA group in clinical trial participants, the absolute and relative risks reduction in ischaemic stroke was near-identical compared to the overall cohort. However, the anticoagulation-mediated risk of bleeding was lower at 2.2% (95% CI 1.4 - 3.1), which led to a lower NNT_{net} of 26.

Discussion

In this study of patients with AF, we demonstrated the potential clinical applicability of the NNT for net benefit approach. We used CARS to show that the NNT_{net} of anticoagulation therapy at 1-year was 34 in a real-world cohort and 46 in a clinical trial population, and NNT_{net} was lower among patients with an excess baseline risk of stroke in both cohorts. Furthermore, the NNT: 1) to prevent one ischaemic stroke event was 25 (real-world) and 27 (clinical trial); and 2) to contribute to one major bleeding event was 100 (real-world) and 63 (clinical trial).

Our findings also confirm that CARS may be used as a means to determine the NNT_{net} for interventions in AF, and that the benefit of OAC therapy in terms of stroke prevention outweighs the potential risk of major bleeding in non-low-risk population cohorts by CHA_2DS_2-VASc score. Overall, the applicability of NNT_{net} is particularly relevant in AF as

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treatment with OAC confers a risk of serious harm and therefore the $NNT_{benefit}$ *vs.*NNT_{harm} need to be balanced. The difference in NNT_{net} between the real-world and clinical trial observed in our study were driven primarily by the increased risk of major bleeding with OAC in the latter cohort. This was likely due to the requirement that real-world patient cohort needed a period of stable INR for 6 months prior to enrolment. Additionally, it was likely that those with bleeding complications during this period were not included into the real-world study. Interestingly, the lack of bleeding events among low risk patients in the real-world cohort led to a lower NNT_{net} compared to higher risk groups.

The revised CONSORT (Consolidated Standards of Reporting Trials) statements encouraged the reporting of NNT to promote the generalisability of results to different settings and interventions [17,18]. Nonetheless, this remains an under-utilised method of reporting in medical literature [19]. Moreover, studies that present NNT may only do so for $NNT_{benefit}$ or NNT_{harm}, but not both [20]. In this regard, we highlight the utility of a single metric, NNT_{net}, to provide an integrated assessment of the net effects of benefit-and-harm of intervention that may be extrapolated to assist with the decision-making process among individual patients. In the context of OAC prescription for the prevention of thromboembolism in AF, the NNT_{net} may simplify this process by providing a broad overview of the number of patients needed to treat for a net benefit, accounting for both ischaemic stroke and major bleeding. It may also be a valuable tool to assess the effects of other treatment with significant benefits and rarer complications, which would be expected to provide a low NNT_{net}.

An additional advantage of NNT_{net} is that it allows multiple outcomes to be assessed simultaneously and for each of these to be weighted separately [11]. Thus, taking into consideration not only the likelihood of events but also their severity and perceived effects by individual patients. In terms of OAC use among patients with AF, the outcomes of major

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bleeding (*excluding intra-cranial haemorrhage*) may not be of equal importance to stroke. Indeed, a previous study found that patients were willing to endure at least four major bleeds in order to prevent one stroke [21]. Weighting was not applied to this study as we did not have data on patient preferences.

Limitations

The findings from this study were based on a post-hoc analysis of the AMADEUS trial and a single tertiary-centre Caucasian population in the Murcia AF Project, and should therefore be interpreted with caution as it may be subject to bias. These results may not be valid for patients treated with non-vitamin K oral anticoagulants. Furthermore, the risk estimation of these cohorts using data from a different population was not ideal. As we censored the outcomes at 1-year, our results may not be applicable to periods of extended follow-up. Moreover, the CARS risk categories were based on arbitrary cut-offs. Despite the limitations above, it is important to highlight that the aim of this study was to investigate the application of the NNT_{net} approach in AF and as such, the concepts described in this study will be relevant to other situations. Future studies should evaluate the NNTnet approach in AF by accounting for competing risks (*e.g.* death).

Conclusions

Overall, the NNT_{net} approach in AF incorporates information regarding baseline risk of stroke and major bleeding, and relative effects of OAC with the potential to include multiple additional outcomes and weighting of events based on their perceived effects by individual patients. This simple and intuitive metric may be useful to improve communication and optimise the patient-centred management of AF.

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Conflict of interest statement:

WYD, JMRC, FM, GL and VR: None declared.

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Ethics approval: The study protocol of the Murcia AF Project was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by the Ethics Committee from University Hospital Morales Meseguer. The AMADEUS trial received ethics approval for the main trial study and any ancillary analyses on the anonymised trial dataset. Patients from both studies gave informed consent to participation.

Consent to participate: See above.

Consent for publication: See above.

Code availability: Not applicable.

Author contributions: WYD and GYHL contributed to study conception and design. WYD and JMRC contributed to data analysis, interpretation of data, and drafted the manuscript. FM, GL, VR and GYHL revised the manuscript critically for important intellectual content. All authors approved the final version of the submitted manuscript.

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Accepted Article

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Figure 1. Absolute stroke risk at 1-year in the Murcia AF Project and AMADEUS trial

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Table 1. Baseline characteristics stratified by CARS risk profile in the Murcia AF Project

	Real-World			
CARS risk profile	Low (n = 46)	Moderate (n = 129)	High (n = 881)	Very high (n = 250)
Age (years), median (IQR)	54 (52 - 55)	63 (61 - 65)	77 (73 - 81)	77 (73 - 82)
Age groups (years), n (%)				
18 - 39	0 (0)	0 (0)	0 (0)	0 (0)
40 - 54	28 (60.9)	1 (0.8)	2 (0.2)	1 (0.4)
55 - 64	18 (39.1)	86 (66.7)	8 (0.9)	16 (6.4)
65 - 74	0 (0)	42 (32.6)	275 (31.2)	63 (25.2)
≥75	0 (0)	0 (0)	596 (67.7)	170 (68.0)
Female sex, n (%)	9 (19.6)	40 (31.0)	501 (56.9)	125 (50.0)
BMI (kgs/m^2), median (IQR)	29 (26 - 33)	29 (27 - 33)	29 (26 - 33)	30 (27 - 33)
eGFR, median (IQR)	81 (66 - 92)	81 (66 - 93)	70 (57 - 84)	70 (57 - 86)
Comorbidities, n (%)				
Anaemia	5 (10.9)	13 (10.1)	160 (18.2)	59 (23.6)
Coronary artery disease	6 (13.0)	34 (26.4)	160 (18.2)	41 (16.4)
Diabetes mellitus	2 (4.3)	17 (13.2)	256 (29.1)	67 (26.8)
Heart failure	15 (32.6)	32 (24.8)	297 (33.7)	60 (24.0)
Hypertension	24 (52.2)	87 (67.4)	758 (86.0)	199 (79.6)
Prior thromboembolism	0 (0)	0 (0)	7 (0.8)	249 (99.6)
Vascular disease	8 (17.4)	36 (27.9)	189 (21.5)	55 (22.0)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TIA, transient ischaemic attack.

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Table 2. Baseline characteristics stratified by CARS risk profile in the AMADEUS trial

	Clinical Trial			
CARS risk profile	Low (n = 111)	Moderate (n = 415)	High (n = 1199)	Very high (n = 480)
Age (years), median (IQR)	52 (48 - 55)	62 (59 - 65)	74 (70 - 78)	73 (66 - 78)
Age groups (years), n (%)				
18 - 39	2 (1.8)	0 (0)	1 (0.1)	0 (0)
40 - 54	81 (73.0)	7 (1.7)	19 (1.6)	0 (0)
55 - 64	28 (25.2)	282 (68.0)	36 (3.0)	77 (16.0)
65 - 74	0 (0)	126 (30.4)	562 (46.9)	204 (42.5)
≥75	0 (0)	0 (0)	581 (48.5)	199 (41.5)
Female sex, n (%)	13 (11.7)	80 (19.3)	489 (40.8)	180 (37.5)
BMI (kgs/m^2), median (IQR)	31 (26 - 34)	29 (27 - 33)	28 (25 - 31)	27 (25 - 30)
eGFR, median (IQR)	64 (52 - 79)	74 (58 - 90)	88 (75 - 95)	89 (79 - 95)
Comorbidities, n (%)				
Anaemia	4 (6.3)	11 (4.7)	84 (13.7)	36 (12.7)
Coronary artery disease	18 (16.2)	138 (33.3)	386 (32.2)	157 (32.7)
Diabetes mellitus	9 (8.1)	64 (15.4)	269 (22.4)	87 (18.1)
Heart failure	46 (41.4)	134 (32.3)	268 (22.4)	88 (18.3)
Hypertension	84 (75.7)	320 (77.1)	935 (78.0)	334 (69.6)
Prior thromboembolism	0 (0)	0 (0)	42 (3.5)	480 (100)
Vascular disease	18 (16.2)	138 (33.3)	386 (32.2)	157 (32.7)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TIA, transient ischaemic attack.

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Table 3. Number needed to treat in the Murcia AF Project and AMADEUS trial

	Real-World	Clinical Trial
Ischaemic stroke risk at 1-year		
Baseline risk without anticoagulation (%)	5.7% (95% CI 5.5 - 6.0)	5.1% (95% CI 4.9 - 5.3)
Anticoagulation-mediated risk (%)	1.7% (95% CI 1.1 - 2.6)	1.3% (95% CI 0.8 - 1.8)
Relative risk reduction	0.70	0.75
Absolute risk reduction (%)	4.0%	3.8%
$NNT_{benefit}$	25	27
Major bleeding risk at 1-year		
Baseline risk without anticoagulation (%)*	2.3%	2.3%
Anticoagulation-mediated risk (%)	3.3% (95% CI 2.4 - 4.4)	3.9% (95% CI 3.1 - 4.8)
Relative risk increase	0.43	0.70
Absolute risk increase (%)	1.0%	1.6%
NNT_{harm}	100	63
NNT_{net}	34	46

*Baseline risk without anticoagulation was estimated according to the presence of comorbidities using data from Friberg *et al.* [16]

CI, confidence interval; NNT, number needed to treat.

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Table 4. Number needed to treat stratified by CARS risk profile in the Murcia AF Project

	Real-World			
CARS risk profile	Low	Moderate	High	Very high
Ischaemic stroke risk at 1-year				
Baseline risk without anticoagulation (%)	0.7% (95% CI 0.6 - 0.7)	1.5% (95% CI 1.5 - 1.6)	3.8% (95% CI 3.7 - 3.9)	15.8% (95% CI 15.4 - 16.1)
Anticoagulation-mediated risk (%)	0% (95% CI 0 - 0)	0% (95% CI 0 - 0)	1.2% (95% CI 0.6 - 2.2)	4.9% (95% CI 2.4 - 8.7)
Relative risk reduction	1.00	1.00	0.68	0.69
Absolute risk reduction (%)	0.7%	1.5%	2.6%	10.9%
$NNT_{benefit}$	143	67	39	10
Major bleeding risk at 1-year				
Baseline risk without anticoagulation (%)*	2.1%	2.1%	3.6%	5.5%
Anticoagulation-mediated risk (%)	0% (95% CI 0 - 0)	1.6% (95% CI 0.2 - 5.6)	3.0% (95% CI 1.9 - 4.3)	6.7% (95% CI 3.7 - 11.0)

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Relative risk increase	-1.00	-0.24	-0.17	0.22
Absolute risk increase (%)	-2.1%	-0.5%	-0.6%	1.2%
NNT_{harm}	-48	-200	-167	84
NNT_{net}	36	50	32	11

*Baseline risk without anticoagulation was estimated according to the presence of comorbidities using data from Friberg *et al.* [16]

CI, confidence interval; NNT, number needed to treat.

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Table 5. Number needed to treat stratified by CARS risk profile in the AMADEUS trial

	Clinical Trial			
CARS risk profile	Low	Moderate	High	Very high
Ischaemic stroke risk at 1-year				
Baseline risk without anticoagulation (%)	0.6% (95% CI 0.6 - 0.7)	1.5% (95% CI 1.5 - 1.5)	3.3% (95% CI 3.2 - 3.4)	13.9% (95% CI 13.7 - 14.1)
Anticoagulation-mediated risk (%)	0% (95% CI 0 - 0)	0.7% (95% CI 0 - 1.5)	1.0% (95% CI 0.4 - 1.6)	2.9% (95% CI 1.4 - 4.4)
Relative risk reduction	1.00	0.53	0.70	0.79
Absolute risk reduction (%)	0.6%	0.8%	2.3%	11.0%
$NNT_{benefit}$	167	125	44	10
Major bleeding risk at 1-year				
Baseline risk without anticoagulation (%)*	0.5%	2.1%	3.6%	3.6%
Anticoagulation-mediated risk (%)	0.9% (95% CI 0 - 2.7)	1.9% (95% CI 0.6 - 3.3)	4.8% (95% CI 3.6 - 6.1)	4.2% (95% CI 2.4 - 6.0)

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Relative risk increase	0.80	-0.10	0.33	0.17
Absolute risk increase (%)	0.4%	-0.2%	1.2%	0.6%
NNT_{harm}	250	-500	84	167
NNT_{net}	500	100	91	10

*Baseline risk without anticoagulation was estimated according to the presence of comorbidities using data from Friberg *et al.* [16]

CI, confidence interval; NNT, number needed to treat.

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