Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial

Short title: NOACs in rheumatic atrial fibrillation

Raffaele De Caterina[1] and A. John Camm[2]

[1] Institute of Cardiology and Center of Excellence on Aging, G. d'Annunzio University – Chieti, and G. Monasterio Foundation – Pisa, Italy

[2] Division of Clinical Sciences, St George's University of London, London, UK

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Correspondence:
Raffaele De Caterina, MD, PhD
Institute of Cardiology, G. d'Annunzio University - Chieti-Pescara
C/o Ospedale SS. Annunziata
Via dei Vestini, 31
66013 Chieti
Tel.: +39-0871-41512
FAX: +39-0871-402817
E-mail: rdecater@unich.it

ABSTRACT

Patients at thromboembolic risk with non-valvular AF can now be managed either with a vitamin K antagonist (VKA) or with a fixed-dose of a non-VKA oral anticoagulant (NOAC), whilst patients with valvular AF have been restricted to VKAs on the basis of a potentially higher risk and different mechanism of thrombosis, and the lack of sufficient data on the efficacy of NOACs. The terms "non-valvular AF" and "valvular AF" have not been however consistently defined. "Valvular" AF has included any valvular disorder, including valve replacement and repair.

In AF with rheumatic mitral disease, observational studies strongly suggest that VKA treatment is valuable. These patients have not been included in NOAC trials, but there is also no stringent argument to have excluded them. This is at sharp variance from patients with mechanical valves, also excluded from the pivotal phase III trial comparing warfarin with NOACs, but in whom a single phase-II trial of dabigatran etexilate against VKA treatment was stopped prematurely because of increased rates of thromboembolism as well as increased bleeding associated with dabigatran. Until more data are available, such patients should be therefore managed with VKAs.

We here propose an open-label randomized trial of one of the NOACs against the best-of-treatment available in regions of the world in which rheumatic heart disease is still highly prevalent, aiming at showing the superiority of the NOAC used against current standard treatment.

Key words: valvular atrial fibrillation; valvular heart disease; rheumatic heart disease; thromboembolism; vitamin K antagonists; oral anticoagulants; non-vitamin K antagonist oral anticoagulants; NOACs; mitral stenosis; prosthetic valve; artificial valve; bioprosthetic valve; mechanical valve; stroke.

INTRODUCTION

Despite the same electrophysiologic abnormality, the risk of stroke and systemic embolism in atrial fibrillation (AF) ranges from <1%/year to >20%/year and can be assessed by simple clinical risk factors [1]. This has led to the gradual adoption of vitamin K antagonist (VKA) oral anticoagulation as a preventive strategy for most patients with AF, unless clearly identifiable to be at very-low-risk [2, 3]. The recent availability of non-VKA oral anticoagulants (NOACs) is likely to increase the number of AF patients treated with these drugs for stroke prevention in the future. In some such patients atrial appendage occlusion devices are now also a viable alternative [3].

All the pivotal trials comparing VKAs with the NOACs in AF have enrolled patients with so-called "non-valvular" AF and excluded patients at particularly high risk of thromboembolism, such as those with AF accompanying mitral stenosis or patients with mechanical prosthetic valves [4-7]. The reasons for not recruiting these patients in trials testing NOACs also included the possibility that the pathogenesis of thromboembolism may be substantially different from other types of AF. The distinction between "valvular" AF and "non-valvular" AF however still remains uncertain, with variable definitions adopted in the NOAC trials. This has led to therapeutic confusion, well illustrated by a recent web-based survey among over 500 Italian physicians mainly involved in the prescription of anticoagulants to AF patients. Here only 57.1% of the cardiologists and 67.9% of the internists agreed that the existing definitions of non-valvular AF (e.g. from guidelines) were sufficiently clear [8].

Because of this, we recently reviewed the literature related to the thromboembolic risk in AF in the presence of the various types of "valvular" heart diseases; definitions of the term in different trials with NOACs; and the use of the term in current and recent guidelines [9]. Specifically, we addressed the risk of thromboembolism in AF with or without various forms of valvular heart disease; and the qualitative type of thrombus forming in such conditions, as both have implications for treatment [9]. **Conclusions of this analysis were that some forms of "valvular" heart disease accompanied by AF are an area where further investigation for the use of NOACs is warranted. This seems to be the case for AF accompanying mitral stenosis.**

Thromboembolic risk in mitral stenosis, with or without atrial fibrillation

In the pre-surgery and pre-anticoagulant therapy era mitral stenosis was estimated to be responsible of 25% of all deaths from systemic embolism [10-12]. Up to 80% of patients with mitral stenosis and systemic embolism show AF on the ECG. One third of embolic events occur within 1 month of the onset of AF, and two thirds occur within 1 year [13].

Correlation between the occurrence of embolism and mitral orifice dimensions or even the presence or absence of heart failure symptoms is not strict [12, 14, 15], and embolism can be the first manifestation of mitral

stenosis [11], or it can occur in patients with mild mitral stenosis, even before the development of dyspnea [10, 11, 13]. It is also controversial whether patients with mitral stenosis but *without* AF or a previous embolic event are at higher risk for embolic events. This has resulted in low-grade recommendations for oral anticoagulants in moderate-to-severe mitral stenosis even in the absence of AF in recent guidelines [16-18].
At the other extreme, patients with mitral stenosis and AF who have experienced an embolic event have recurrences at a rate of 15 to 40 events per 100 patient-months [14, 19-22], which is the highest rate of thromboembolism ever reported in AF.

Thrombi in mitral stenosis, even in the absence of AF, appear to have a much more frequent location out of the left atrial appendage, and being much more often "giant", even in recent literature [23-31]. Attempts have been made in finding predictors of its formation outside of or in addition to the classical risk factors [32-36], but with uncertain results.

The conclusion of this analysis is that AF with mitral stenosis, essentially on a rheumatic basis, is the form of AF with native valves with the highest risk of thromboembolism, probably related to the low-flow patterns occurring in the left atrium in such a condition, and with a frequent location of the thrombus outside of the left atrial appendage. In moderate and severe mitral stenosis thrombi may also occur in the absence of AF. The pathogenesis of thrombosis in such conditions is at the highest extreme of the spectrum of the low-flow patterns generally occurring in other forms of AF due to the lack of coordinated left atrial contraction, in this specific case exacerbated by the obstruction to LA emptying due to the presence of a stenotic mitral valve orifice. Such patients have never been randomized between alternative treatments, but there are also no speficic reasons, at sharp variance from intra-cardiac thrombi occurring, with or without AF, in the presence of mechanical heart valves, to hypothesize a differential response to various anticoagulants.

THE MAGNITUDE OF THE PROBLEM

Rheumatic fever is still the most common cause of acquired heart disease in children and young adults worldwide. Although the incidence of rheumatic fever has declined sharply in most developed areas of the world, the disease remains a major problem in many developing countries. In addition, there are fluctuations in the incidence of the disease over time, the reasons for which remain only partially understood. In many developing countries the incidence of acute rheumatic fever approaches or exceeds 100 per 100,000 [37]. As to *rheumatic heart disease*, of which mitral stenosis is a hallmark, the prevalence has been estimated at 0.6 per 1000 in the United States, but up to 21.0 per 1000 in Asia, 15.0 per 1000 in Africa, and 17.0 per 1000 in South America [37]. With an anticipated and conservative incidence of thromboembolism of at least 2 episodes per 100 patients/year in the overall population of patients with mitral stenosis (of any severity), with or

without AF, one can calculate that countries such as India, Pakistan, Egypt and other North African countries, Brazil and several Arab countries, accounting for at least 2 billion people worldwide, suffer an incidence of thromboembolic stroke due to this disease at least around 4.000.000 (4 million) per year. Experience with the use of vitamin K antagonists (VKAs) in conditions where such treatments are available shows that this is a largely preventable burden.

PROBLEMS WITH THE USE OF VITAMIN K ANTAGONISTS IN AREAS OF THE WORLD WITH HIGH PREVALENCE OF MITRAL STENOSIS

There are no randomized trials examining the efficacy of anticoagulation (essentially VKAs) in preventing embolic events specifically in patients with mitral stenosis. Current recommendations are only based on retrospective studies showing a 4- to 15-fold decrease in the incidence of embolic events with anticoagulation in these patients [14, 20]. Although with a high grade (Class I) because of the wide differential between treatment and no treatment, such recommendations are all level of evidence B in the case of mitral stenosis plus AF [17] (Class of recommendation and level of evidence not graded in the latest ESC Guidelines [18]).

As indicated above, in recent guidelines there are also low-grade recommendations for oral anticoagulants in moderate-to-severe mitral stenosis even *in the absence* of AF [16-18]. Specifically, current recommendations are Class IIb in the absence of AF [according to the presence of echocardiographic criteria of an enlarged left atrium and/or spontaneous echo-contrast (level of evidence B or C, respectively)] in the latest ACC/AHA Guidelines [17]; recommendation class IIa, level of evidence C in the latest ESC Guidelines [18].

The potential of VKAs in reducing the thromboembolic burden in mitral stenosis is however considerably hampered by the inability of achieving good quality of anticoagulation. In the setting of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE)-W trial, comparing the efficacy of warfarin with the combination of aspirin plus clopidogrel in non-valvular AF, a post-hoc analysis evaluated times in therapeutic range (TTRs) of patients on VKAs. Here TTRs for patients under warfarin were used to calculate the mean TTR for each of 526 centers and 15 countries participating in the trial [38]. Proportional-hazards analysis, with and without adjustment for baseline variables, was performed, with patients stratified by TTR quartile and country. A wide variation in TTRs was found between centers, with mean TTRs for centers in the 4 quartiles of 44%, 60%, 69%, and 78%. For patients at centers with TTR above the study median warfarin had a marked benefit, reducing vascular events by >2-fold (relative risk, 2.14; 95% confidence interval, 1.61 to 2.85; P<0.0001). However, for patients at centers below the median TTR (65%) no treatment benefit was demonstrated, as measured by relative risk for vascular events of clopidogrel plus aspirin versus warfarin (relative risk, 0.93; 95% confidence interval, 0.70 to 1.24; P=0.61). Mean TTR also varied between countries from 46% to 78%, and relative risk (clopidogrel plus aspirin versus warfarin) varied from 0.6 to 3.6 (a 5-fold difference!). A population-average model predicted that TTR of

58% would be needed to be confident that patients would benefit from being on warfarin. Below this level there appears to be little benefit of warfarin over antiplatelet therapy [38]. Below this TTR level, among the 15 countries participating in ACTIVE-W, were countries such as South Africa (46.3%) Brazil (47.1%), Russia (53.4%) and Poland (55.3%).

Similarly, an analysis of the RE-LY trial was carried out to assess efficacy and safety of dabigatran compared with warfarin for stroke prevention in AF at different levels of international normalized ratio (INR) control, assessed as each centre's mean TTR (cTTR) in the warfarin population [39]. The authors found that for all vascular events, non-hemorrhagic events, and death, advantages of dabigatran were greater at sites with poor INR control than at those with good INR control (albeit the interaction between quality of INR control and such outcomes was not formally statistically significant), overall pointing to the plausible hypothesis that local standards of care affect the relative benefits with the use of new treatment alternatives. From this analysis, countries with cTTR below the level of 58% (the threshold conservatively derived from the previous analysis [38]), included Taiwan (44%), Mexico (47%), Peru (48%), Romania (49%), India (49%), Colombia (53%), Russia (53%), Brazil (54%), China (55%), Korea (55%), Greece (56%), Thailand (56%), Malaysia (56%), and Poland (57%) [39] (**Figure 1**).

There is a wide overlap of poor quality of anticoagulation, as obtained from center-derived information and taken as an approximation of the country quality of anticoagulation, and the distribution of rheumatic heart disease and mitral stenosis in the world. Recently published data from the Global Rheumatic Heart Disease Registry (the REMEDY study) [40] show that oral anticoagulants (VKAs) were prescribed in 69.5% of patients with rheumatic heart disease and an indication for anticoagulation. Prescription was relatively high (91.6%) in patients with a mechanical valve, intermediate (68.6%) of patients with AF, and very low (20.3%) in those with mitral stenosis in sinus rhythm with either dilated left atrium or left atrial thrombus (high-risk mitral stenosis in sinus rhythm). Independent of prescriptions, however, of the patients on OACs for the recognized indications, 12.2% had had no INR monitoring, whereas 34.1% had only one to three INR tests in the 6 months preceding enrollment in the registry. The INR at enrolment was subtherapeutic in 32.7%, therapeutic in 28.3%, and above the therapeutic range in 17.7%, with no INR testing on the remainder of 21.4%. Sixty percent of participants were unaware of the therapeutic range of INR [40]. Estimates of anticoagulation quality are likely even over-optimistic, as derived from centers involved in clinical trials, with likely high motivation, probably overestimating the average anticoagulation quality in such countries.

This information reliably tells us that in vast areas of the world where mitral stenosis is an important cause of stroke and systemic embolism, treatment with VKAs, with the well-known barriers to its optimization, is not a trustable and reliable treatment for stroke prevention. Alternative treatments, such as aspirin, possibly being given in such countries, are likely to be here reasonable alternative to badly controlled VKAs and remain a possible standard of therapy, despite their well-known inferiority compared with well-controlled VKA therapy [41].

THE PROPOSAL

On the basis of these considerations, we believe it would be highly desirable to test the hypothesis of a superiority of any of the NOACs so far tested in AF in the setting of moderate/severe mitral stenosis, with or without concomitant AF, compared with "standard therapy", consisting of the local treatment protocols, with either aspirin, or other antiplatelet agents—as single agent or in combination—or locally used VKAs.

Key elements for this trial would be:

1. An open-label design, increasing feasibility
2. A comparison with the standards of care for thromboembolic prophylaxis, which may consist of antiplatelet agents (aspirin in most cases); or VKAs, but in which case the quality of INR control is to be expected as being poor
3. A superiority design, which we consider rational on the basis of the considerations highlighted above
4. To be conducted in countries, such as Mexico, Brazil, Egypt, South Africa, India, China, etc., where centers exist recruiting large numbers of patients with rheumatic heart disease, and where a possibility exists of patient follow-up
5. Ideally with one of the NOACs available for once-daily use, considering the importance of practical aspects of long-term treatments in countries where difficulties in ensuring patients' education to the importance of therapeutic adherence are higher than in developed countries
6. Ideally with the same dosages of the NOACs used in pivotal trials in AF.

While most of the above points are self-explicatory, the issue of the choice of the appropriate NOAC dosing requires some further reasoning and explanation.

Besides the obvious advantage of the widest documentation of efficacy and safety, the following elements of knowledge argue for keeping the same "standard" NOAC dosing schemes already adopted and tested in the large 4 pivotal AF trials against warfarin in "non-valvular" AF [4-7]:

(a) despite the clearly higher thromboembolic risk of mitral stenosis compared with classical "non-valvular" AF, there has never been a clear demonstration that a higher intensity of anticoagulation with VKAs is here warranted. Indeed, current guidelines [2, 3, 42, 43] and standard practice continue to recommend the same 2.0-3.0 INR for atrial fibrillation accompanying mitral stenosis, similarly to other types of AF;

(b) for anticoagulation in atherothrombotic prophylaxis, such as post-myocardial infarction, the higher anticoagulation intensity (3.0-4.5 or similar) previously recommended and used in some trials [44-47] has never itself been demonstrated to be more effective (or more advantageous), than the standard 2.0-3.0 intensity [48];

(c) wherever a higher intensity VKA therapy is used, specifically in some settings of mechanical valve antithrombotic prophylaxis (e.g., with an unfavorable – tricuspid, mitral or pulmonary – mechanical valve position, in the presence of a medium- or high-thrombogenicity mechanical valve, or in the presence of comorbidities), its rationale is relatively weak [18, 49], and indeed not adopted in the ACC/AHA Guidelines [50];

(d) in conditions of mechanical heart valves, the attempts of using one NOAC (dabigatran etexilate) in the RE-ALIGN study [51] at dosages (220 mg B.I.D.) higher than those used in "non-valvular" AF in the RE-LY trial [4] has certainly resulted in much and prohibitively higher rates of bleeding, without any evidence of increased efficacy [51].

Therefore, on the background of a "standard" anticoagulation intensity used in mitral stenosis for VKAs, and of the considerable bleeding risk entailed by higher-than-standard NOAC dosing, we would strongly advise to use, in an advocated trial in mitral stenosis, the same NOAC dosages used in the pivotal "non-valvular" AF trials.

STATISTICAL CONSIDERATIONS AND CALCULATION OF SAMPLE SIZE

In the Apixaban VErsus acetylsalicylic acid to Reduce the Risk Of Embolic Stroke (AVERROES) trial [52], which was a comparison of the factor Xa inhibitor apixaban with aspirin in patients with AF at a raised risk of stroke, but who were considered not suitable candidates or were unwilling to receive VKA therapy, apixaban proved significantly superior to aspirin for preventing stroke and systemic embolism (hazard ratio with apixaban, 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001), therefore with a 55% reduction of the primary endpoint.

- Considering that some of the patients recruitable in this study may also receive VKA therapy, which is likely to be not well controlled anyhow for the considerations highlighted above, we hypothesize a more conservative hazard ratio of the NOAC vs the local standard-of-care of 0.70 (30% relative risk reduction in the primary endpoint of stroke and systemic embolism). Calculations of sample size will allow variations of this estimate up to 0.80.
- We hypothesize to recruit patients with moderate or severe mitral stenosis [standard echo criteria of a mitral valve area <1.5 cm^2 (measured by planimetry and the pressure-half-time method, which are complementary)], according to current guidelines [18, 50]. In such patients the rate of stroke is to be considered in the order of 5-10 per 100 patients/year, since including also patients without AF.
- We hypothesize recruiting in at least two countries (e.g., Mexico and South-East China), where we have preliminarily inquired the feasibility and willingness of local doctors to participate.

Sample size calculation

Assuming an alpha error of 0.05; a beta error of 0.20 (statistical power of 0.80); a dropout/withdrawal rate of 5% per year; a NOAC/standard of care groups ratio of 1:1; using a log-rank test, the overall sample sizes that would be required with various combinations of stroke rates (from 5% to 10%), NOAC efficacy over the standard of care (hazard ratios 0.70; 0.75; 0.80); and study duration (1 to 3 years), are reported in **Table 1**. The sample size of each group corresponds to the overall sample size (in **Table 1**) divided by two.

CONCLUSIONS

A randomized trial of one of the NOACs against the best-of-treatment available in regions of the world in which rheumatic heart disease is still highly prevalent, aiming at showing the superiority of the NOAC used against current standard treatment, appears feasible and highly desirable.

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FIGURE LEGEND

Figure 1: Country distribution of the mean time in therapeutic range (TTR) in the RE-LY trial. Source: Ref. [39], redrawn.

	Study Duration: 1 year					
Stroke rate x100 py	**5**	**6**	**7**	**8**	**9**	**10**
HR: 0.70	2940	2520	2100	1890	1680	1470
HR: 0.75	3990	3570	3150	2730	2310	2100
HR: 0.80	6930	5742	4892	4254	3734	3318

	Study Duration: 2 years					
Stroke rate x100 py	**5**	**6**	**7**	**8**	**9**	**10**
HR: 0.70	1580	1390	1162	1044	926	812
HR: 0.75	2152	1938	1726	1482	1270	1164
HR: 0.80	3732	3110	2668	2334	2050	1822

	Study Duration: 3 years					
Stroke rate x100 py	**5**	**6**	**7**	**8**	**9**	**10**
HR: 0.70	1144	990	848	744	684	594
HR: 0.75	1554	1372	1242	1086	940	846
HR: 0.80	2652	2210	1894	1684	1498	1346

Table 1. Overall sample size computation (py = person-years).

Figure

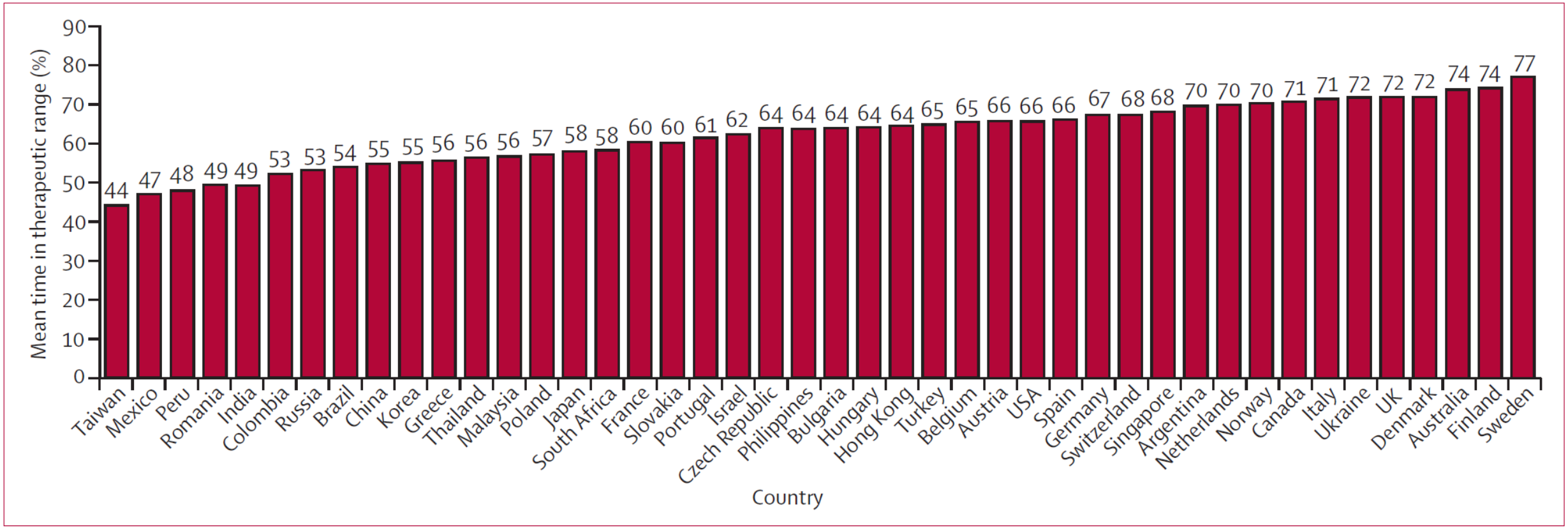

Figure 1: **Country distribution of mean time in therapeutic range in the RE-LY trial**