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ORIGINAL ARTICLE

Adherence and Quality of Life in Non-Valvular Atrial Fibrillation With Direct Oral Anticoagulants Versus Vitamin K Antagonists: A Systematic Review

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Abstract

Background: Direct anticoagulants (DOACs) and vitamin K antagonists (VKAs) differ in pharmacokinetic characteristics, intensity of required laboratory monitoring, and costs. These differences could affect patients' adherence to treatment and quality of life (QoL).

Objective: To assess whether patients with non-valvular atrial fibrillation (AF) using DOACs have better treatment adherence and QoL when compared to patients using VKAs.

Methods: We conducted a systematic review in Medline, Embase, LILACS, SciELO, CINAHL, and Cochrane Central, until June 9, 2021. We included studies that estimated and compared treatment adherence and QoL between DOACs and VKAs in adults with non-valvular AF. The methodological quality of the studies was assessed using the Joanna Briggs Institute (JBI) tools. The protocol was registered in the PROSPERO (CRD 42020165238).

Results: Sixteen studies, including 122,458 patients with non-valvular AF, evaluated adherence, and eleven studies, including 5,687 patients, assessed QoL. A variety of methods was used to measure adherence. Eleven studies showed no difference in adherence between DOACs and VKAs, while three studies favored VKAs over DOACs and two studies favored DOACs over VKAs. QoL was measured by specific (n = 3) or generic questionnaires (n = 8); results favored DOACs over VKAs in four studies, while in the other seven studies the results showed no difference between the groups. Meta-analyses were not performed due to high methodological heterogeneity among studies.

Conclusions: Available evidence regarding treatment adherence and QoL with DOACs and VKAs is characterized by methodological heterogeneity and conflicting findings.

Keywords: Atrial fibrillation; anticoagulants; medication adherence; quality of life; systematic review.

Introduction

Patients with atrial fibrillation (AF), the most frequent cardiac arrhythmia, have a five-fold higher risk of stroke. In the last decade, direct oral anticoagulants (DOACs) have emerged as an alternative to vitamin K antagonists (VKAs).[1] According to current guidelines, DOACs are recommended as first-line therapy for non-valvular AF patients. [2–4] Studies have shown similar efficacy and reduced rates of intracranial hemorrhage with DOACs when compared to warfarin, the leading representative of VKAs.[5–8]

DOACs advantages are related to the rapid onset of action, fewer drug or food interactions, fixed doses, and predictable pharmacokinetics that avoid the need for laboratory monitoring of anticoagulation.[9] However, due to their short half-life, missed doses or non-adherence to treatment increases the risk of thromboembolic events.[9]

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Due to the importance of patients' perspectives on their treatment, outcomes such as treatment adherence and health-related QoL have been considered in clinical practice.[10,11] The chronic use of oral anticoagulants can influence QoL, and poor adherence increases morbimortality and overall health care costs.[12] Previous systematic reviews have evaluated these outcomes in anticoagulated patients;[1,13,14] however, no review has systematically evaluated these outcomes comparing DOACs and VKAs, exclusively in patients with non-valvular AF.

This systematic review aims to evaluate the adherence and QoL in patients with non-valvular AF using DOACs compared to patients using VKAs.

Methods

This systematic review was conducted according to a protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) (42020165238). The reported results followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[15]

Eligibility criteria

Studies that compared patients using VKAs and DOACs (activated factor Xa inhibitors and factor IIa inhibitors) with ≥ 18 years and diagnosed with non-valvular AF were eligible. Studies that included valvular AF, or did not report their exclusion, were excluded. DOACs are contraindicated for patients with moderate to severe mitral stenosis or mechanical prostatic heart valve (valvular AF); in these cases, only VKAs are recommended.[2,4]

Information sources

Medline, Embase, LILACS, SciELO, CINAHL, and Cochrane Central Register of Controlled Trials databases were searched until June 9, 2021. The bibliography of selected studies was reviewed for retrieving further references.

Search strategy

The complete search strategies are presented in Chart S1. Outcome-related terms were not included to increase search sensitivity. No language or publication date restrictions were applied.

Selection of studies

After removing duplicates, four peer reviewers independently analyzed titles and abstracts and identified eligible studies. The discrepancies were resolved by a third reviewer.

Data extraction

Data extraction was performed independently by three peer reviewers. The discrepancies were resolved by a fourth reviewer.

The following information was extracted: publication data, design, location, study period, study population and demographics of participants, sample size by exposure group, anticoagulants evaluated, the method used to measure outcomes, time of follow-up, and outcome measures results. Missing information was requested from the authors by email.

Outcomes

The evaluated outcomes were adherence and QoL. Eighty percent (80%) adhesion was considered the conventional threshold for 'good adherence.'[3,16] When studies reported crude and adjusted results, adjusted results were extracted.

Effect measures

We presented adherence as a percentage or mean of the adherence score with the standard deviation and QoL as the mean, median, or mean difference of the QoL score in absolute number or percentage, with the respective standard deviation or confidence interval (CI).

Risk of bias assessment

Two reviewers independently assessed the methodological quality of the studies included using the Joanna Briggs Institute (JBI) critical appraisal tools.[17] There are four possible answers for each criterion: 'yes,' 'no,' 'not clear,' or 'not applicable.' Discrepancies were resolved by consensus.

Considering the checklists do not propose scores to classify the methodological quality, we assigned one point to the items evaluated with 'yes' and zero to the items evaluated as 'no,' 'it is unclear' and 'not applicable.'

Data synthesis and analysis

Descriptive statistics were used to present the data by the outcome. We synthesized evidence narratively. Meta-analyses could not be performed due to the high methodological heterogeneity (especially interventions, settings, study designs, and outcome measures).

Results

Search results

A total of 18,271 abstracts were retrieved, of which 71 were inspected for eligibility criteria through the full article, with 24 studies included in the review. Figure 1 shows the selection process. The excluded studies and reasons are presented in Table S1.

Treatment adherence was assessed in 16 studies, including 122,458 patients with non-valvular AF (DOACs 56,749, VKAs 65,709). QoL was measured in 11 studies, including 5,687 (DOACs 3,329, VKAs 2,358). Three out 24 studies evaluated both outcomes simultaneously.[18–20]

Study characteristics

More than half of adherence[18,19,21–27] and QoL[18,19,28–31] studies were carried out in Europe. All studies were published between 2012 and 2021, of which 79.2% (n = 19) were published in the last five years. All the studies included were published in English, except three, which were published in Spanish,[19] Portuguese[25] and French.[26]

Risk of bias assessment

The detailed risk of bias assessment is presented in Tables S2-S4. For cross-sectional studies that measured adherence (n = 8), four[25,32–34] had low methodological quality. The main criteria that contributed to reducing the quality were lack of clarity in the definition of the sample inclusion criteria, lack of identification and strategies to deal with confounding, and adequate statistical analysis.

Five of the cohort studies (n = 8) had moderate[19–21,24,35] quality. The factors that contributed the most to the reduction in the methodological quality were differences between groups, incomplete follow-up, and strategies for dealing with incomplete follow-up.

All cohort studies that assessed QoL had moderate methodological quality (n = 4).[19,20,36,37] Of the cross-sectional studies (n = 6), the majority (n = 4) had low quality.[18,29,38,39] The criteria that contributed to the reduction in the methodological quality were the absence of identification and strategies to deal with confounding and inadequate statistical analysis.

The randomized clinical trial (RCT) was of moderate quality,[28] as it was not clear about the allocation concealment and blinding.

Treatment adherence

We categorized the studies according to the measurement methods and characteristics (Table S5). The following indirect methods were found: questionnaire (n = 8); administrative database (n = 5); reporting of missed doses (n = 2); and electronic monitoring of drug administration (MEMS) (n = 1). All studies that used the administrative dispensing method assessed the Proportion of Days Covered (PDC) formula to calculate adherence, and established a threshold of 80% for a compliant patient. The proportion of adherent participants in studies that used PDC[22–24,35,40] to assess adherence ranged from 42-81% in the DOACs group and 51-78% in the VKAs.

The Morisky Medication Adherence Scale (MMAS-8) was used in four studies,[18,20,26,34] followed by the Morisky-Green Scale (n = 2).[19,27] The short-form Adherence to Refills and Medications Scale (ARMS) was applied in one study.[41] Others adopted both the Brief Medication Questionnaire (BMQ) and the Measurement of Treatment Adherence (MAT).[25]

For questionnaires, six studies[18,19,25–27,34] reported the outcome as the proportion of adherents, with the percentage of adherents of 76.3% (1103/1446) in the DOACs group as compared to 74.3% (823/1107) in the VKAs group.

Two studies assessed adherence by the number of doses missed.[32,33] One of the studies[32] found a less mean number of missed doses in the warfarin group (0.2) than dabigatran users (0.4) (p = 0.007). The other study did not find any difference between groups.[33]

The only study that used MEMS found a more significant difference in the proportion of adherents in patients using VKAs (97.9%) as compared to DOACs users (95.8%) (p = 0.003).[21]

The 12 studies that measured the proportion of adherent patients[18,19,21–27,34,35,40] showed an overall adherence rate of 66.8%. In the DOACs group, the rate was 71.6%, and in the VKAs, 62.8%. (a percentage obtained through the ratio between the number of adherent patients in each anticoagulant class and the total number of patients included in the studies). Adherence results varied between anticoagulants, with a significant difference in five studies,[19,21,25,32,40] with three favorable to VKAs.[21,25,32] Among

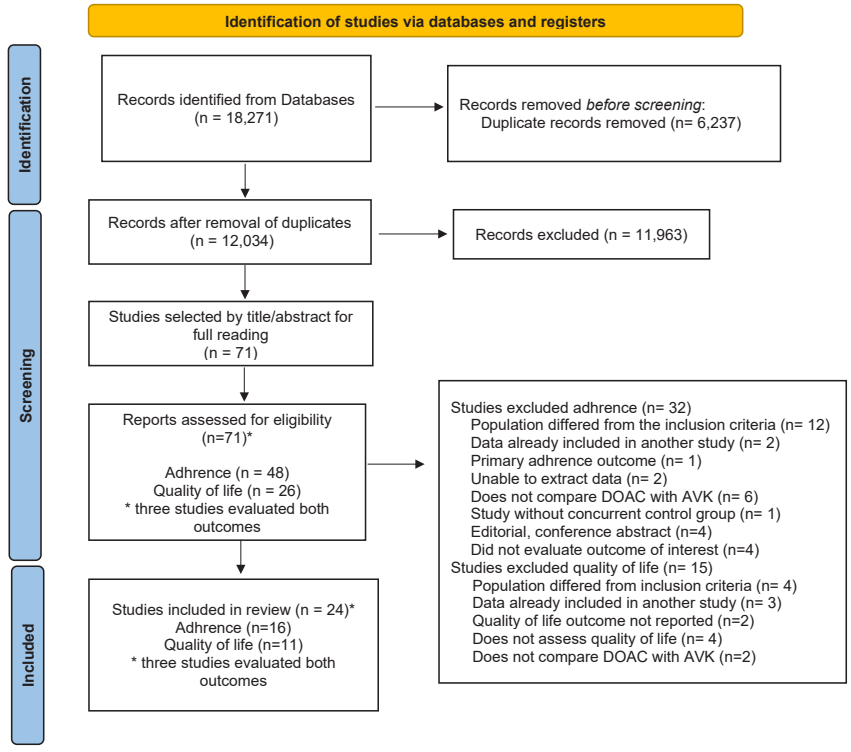

Figure 1 – Flowchart of the selection process for eligible studies.

studies that showed better adherence in the VKAs group, different measurement methods were used (MEMS,[21] missed doses[32] and questionnaires[25]).

Quality of life (QoL)

Table S6 presents the characteristics and results of the studies analyzed. Three studies adopted specific[19,20,38] questionnaires, while eight[18,28–31,36,36,37] used generic questionnaires.

Of the studies with specific instruments, two[20,38] used the Duke Anticoagulation Satisfaction Scale (DASS). In both studies, total mean scores in the three domains evaluated (limitations, inconvenience and psychological impact) were lower for users of DOACs, indicating better QoL than VKAs. However, only Cabbar *et al*. demonstrated a significant difference between groups (DOACs 75.19±18.52 vs VKAs 90.12±17.28; $p < 0.001$).[38]

One study used the AF QoL instrument (AF-QoL 18) and demonstrated better QoL in patients using dabigatran as compared to VKAs (50.6 vs. 42.8; $p < 0.001$).[20]

Modifications of the Medical Outcomes Study Form 36 (SF-36) were used in four studies.[28–30,39] Ng *et al*.[39] demonstrated better measures in the eight domains evaluated for patients using VKAs, without statistical significance.

Two studies[29,30] showed better health conditions for DOACs when compared to VKAs. Apsite *et al*.[29] demonstrated a favorable difference to DOACs in the physical functioning ($p = 0.012$) and social ($p = 0.026$) domains. At the same time, Cabbar *et al.* found a relevant difference between groups in all domains ($p < 0.05$).[38] van Miert *et al.* [28] showed no significant difference between groups in the SF-36 domains, comparing the mean difference in the score at baseline and after one year of follow-up.

Four studies[18,31,36,37] evaluated the outcome by the EuroQol 5-dimension questionnaire (EQ-5D). Two studies[18,31] used the EQ-5D questionnaire with three response levels (EQ5D-3L), showing better health status for patients using DOACs, without statistical significance ($p = 0.29$).

For measurement of the utility score, two studies adopted EQ5D comparing dabigatran to warfarin. Ho *et al*.[36] found a utility score of 0.77±0.17 for the dabigatran group and 0.74±0.16 for VKAs. Monz *et al*.[37] found a utility score of 0.77 (IC 95% 0.75- 0.80) for dabigatran and 0.78 (IC 95% 0.76- 0.81) for VKAs. Both studies did not find statistical significance.

Three studies[18,36,37] reported data from the visual analog scale (VAS); the mean score reported by patients in the VKAs group ranged from 65.0 to 73.9, and from 67.1 to 72.8 in the DOACs group. The difference between groups was not significant in any of the studies.

Discussion

Studies included in this review that reported the proportion of adherents showed that three out of ten patients did not adhere to the treatment. This finding corroborates a systematic review of non-compared studies that evaluated adherence to oral anticoagulants in AF patients, which found 30% of non-adherents.[14]

Adherence to anticoagulants differed among studies, depending on the measurement method. The assessment through questionnaires is considered adequate to monitor adherence in clinical practice.[42] However, there is a potential for memory bias and social desirability,[43,44] overestimating the adherence to treatments.

Retrospective studies on pharmacy dispensing records and PDC have important limitations since drug dispensing does not mean that the patient is taking the drug. Furthermore, temporary interruptions due to medical reasons are not identified, being considered non-adherence, especially in the case of VKAs. Due to dose variability, interruptions are more frequent with VKAs, making it difficult to calculate a reliable PDC. They may underestimate the proportion of adherents in this group of patients.[24] Hence, since the dose calculation is less certain for VKAs, the PDC measures and gaps are less confident in VKAs-treated patients. Comparisons between VKAs and DOACs risk differential misclassification in favor of DOACs.

Stephenson *et al*.[20] reported higher adherence rates with PDC when compared to questionnaires. It should be noted that these methods have different perspectives. PDC provides a broad view of adherence over a period; on the other hand, questionnaires are restricted to a short recall time.[20]

The studies that assessed adherence by PDC are cohort, methodologically more adequate than cross-sectional studies to verify the factors associated with non-adherence. However, it is not possible to state that PDC is a better method than the questionnaires. There is no "gold standard" to measure adherence; all forms have strengths and limitations.[45]

Our data do not confirm the hypothesis that DOACs can improve adherence, given their characteristics, such as predictable pharmacokinetics, that avoid the need for laboratory monitoring and fewer interactions with foods and drugs. .

Adherence to anticoagulation remains a challenge, regardless of the drug used.[46] Our results suggest that frequent patient follow-up may be necessary to verify adherence and assess individual patient treatment barriers. A study showed that implementing an anticoagulation clinic with patient education, measuring medication adherence, monitoring adverse events, assessing any change in medicines, and reviewing laboratory tests during the visit, reduced thromboembolic and hemorrhagic events by 49% and 42%, respectively.[47] These reductions were achieved regardless of the class of oral anticoagulant used.

There are generic and specific instruments regarding the QoL measurement, an important health care outcome.[48,49] out of three studies that used specific questionnaires, two demonstrated a statistically significant difference in favor of DOACs.[19,38] On the other hand, no difference was found in the RCT.[28] In previous studies with AF patients and venous thromboembolism or patients who underwent electrical cardioversion, the pharmacological groups did not differ.[1,50]

The literature demonstrates anticoagulant therapy initiation leads to decreasing QoL, with improvements occurring after long-term use. Likewise, worse QoL is found in patients with less than one year of treatment.[51,52] Lesser perception of QoL during the first month in VKAs users can be explained by changes in lifestyle, frequent consultations needed to monitor anticoagulation, and difficulties in achieving adequate levels of International Normalized Ratio (INR).[50] These lifestyle modifications and reducing intake of vitamin K-rich foods can reduce the perception of QoL.[53]

The difficulty in keeping INR levels close to the recommended goals has been associated with increased anxiety and poorer QoL.[54] Besides, DOACs have a lower risk of bleeding, do not bring important lifestyle changes, and do not need laboratory monitoring. Therefore, it is likely that DOACs can be associated with better QoL, considering that characteristics of this therapeutic class can bring convenience to patients.[53] However, in most studies the results showed no difference between the groups.

This systematic review was comprehensive, including several databases and a sensitive search strategy. We focused on studies with non-valvular AF patients, exclusively; studies that included patients with valvular

AF, or did not report their exclusion, were not analyzed. However, there are some limitations. First, it was not possible to conduct meta-analysis, due to the high heterogeneity among the studies. We found differences in population characteristics, sociocultural variations, measurement methods, follow-up periods, and length of oral anticoagulant use. Second, only studies that assessed adherence during treatment were included. Studies evaluating primary adherence and discontinuation were not analyzed. Third, using data from pharmacy dispensing records may overestimate compliance, as a patient is only considered non-compliant when no dispensing has taken place. The patient may discontinue treatment even in possession of the drug. Therefore, the adherence percentages may be lower than those we found in these studies. Fourth, the impact of the cost of DOACs on adherence to treatment was not considered. The acquisition costs of DOACs are higher, compared to VKAs, which is a barrier to adherence[46, 55, 56] and cause some clinical implications, as the suspension of therapy due to economic restrictions, even when transient, puts the patient at risk of thromboembolic events.[46] Studies conducted in the USA demonstrate significantly higher pharmacy costs with DOACs when compared with warfarin, but lower hospital, outpatient, and total healthcare costs.[57–59] Finally, most studies were carried out in Europe and North America; data extrapolation should be carried out with caution to other populations.

Based on existing studies, the lack of robust evidence, and external validation of the results obtained, it is not possible to state that DOACs provide better adherence and QoL than VKAs; therefore, the choice of ACO must be individualized for each patient.

Conclusion

Due to the considerable methodological heterogeneity between studies and conflicting findings, we cannot conclude that DOACs provide better adherence and QoL in all stages of treatment when compared to VKAs. Well-designed prospective comparative studies are needed to assess these outcomes, considering factors associated with non-adherence and poorer QoL.

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Author Contributions

Conception and design of the research: Zortea V, Curvello KD, Pizzol TSD. Acquisition of data: Zortea V, Curvello KD, Pilger D, Douros A, Leal LF, Sempé TS, Pizzol TSD. Analysis and interpretation of the data: Zortea V, Curvello KD, Sempé TS, Pizzol TSD. Writing of the manuscript: Zortea V, Pizzol TSD. Critical revision of the manuscript for intellectual content: Zortea V, Curvello KD, Pilger D, Douros A, Leal LF, Sempé TS, Pizzol TSD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Erratum

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