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Review

Impact of frailty models on the prescription of oral anticoagulants and on the incidence of stroke, bleeding, and mortality in older patients with atrial fibrillation: a systematic review

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ABSTRACT

Background: Frailty is common in older patients with atrial fibrillation (AF). Current guidelines recommend oral anticoagulant therapy (OAT) except in case of severe frailty or reduced life expectancy, but definitive evidence on which "frailty" tools may help to identify older AF patients expected to derive little or no benefit from OAT is still lacking. Some persistent uncertainties may derive from the different clinical implications that the two major models of frailty, namely the frail phenotype (FP) and the deficit accumulation model (DAM), underlie. We thus conducted a systematic review of published studies to examine the association of the presence of frailty, categorized according to the FP and DAM, with 1) OAT prescription and 2) incidence of clinical outcomes (all-cause mortality, stroke and/or systemic embolism and major or clinically relevant non-major bleeding) in patients receiving OAT.

Methods: Embase and MEDLINE were searched from inception until May 31st, 2022, for studies using a validated tool to identify frailty in subjects aged 65 years or older with a diagnosis of non-valvular AF; only studies on patients prescribed an OAT were considered eligible for the analyses involving clinical outcomes. The protocols for each review question have been registered in PROSPERO database (CRD42022308623 and CRD42022308628).

Findings: Twenty-three studies exploring the association between frailty and OAT prescription on a total of 504 719 subjects were included. Patients with increasing severity of DAM frailty showed consistently lower OAT prescription rates than non-frail patients, whereas use of OAT did not significantly differ between patients with the FP compared with non-frail subjects. Eleven studies exploring the association between frailty and clinical outcomes on a total of 41 985 individuals receiving oral anticoagulation were included. Compared with non-frail subjects, a higher risk of all-cause mortality and clinical outcomes could be observed for AF patients prescribed with OAT with severe frailty according to the DAM, with inconclusive findings for the FP. High levels of heterogeneity were observed in both groups of studies; therefore, a meta-analysis was not performed.

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Conclusions: Due to the great heterogeneity among different validated frailty measures, indiscriminately relying on "frailty" should not be regarded as the gold standard for clinical decision-making about stroke prevention in older AF patients. Present findings suggest that severe frailty according to the DAM is associated with less use of OAT and increased risk of all-cause mortality, thereby representing at the moment the most reasonable tool to efficiently recognize patients with limited life expectancy and for whom there is so far scant, if any, evidence of a clinical benefit of OAT.

1. Introduction

Oral anticoagulant therapy (OAT) is the standard of care for prevention of thromboembolic events in patients with non-valvular atrial fibrillation (AF) at high embolic risk, with direct oral anticoagulants (DOACs) being recommended over vitamin K antagonists (VKAs) (Kirchhof et al., 2016; Steffel et al., 2018) because of their well-demonstrated greater net clinical benefit in the general population as well as in older patients (Barco et al., 2013; Bo et al., 2017a; Malik et al., 2019). Notwithstanding these strong evidence-based recommendations, OAT and DOACs are still widely underused in the older population (Fohtung et al., 2017; Bo and Marchionni, 2020; Calsolaro et al., 2021; Shah et al., 2021; Wilkinson et al., 2021; Orlandi et al., 2022). Beyond clinical inertia, advanced age itself and limited life-expectancy, as well as a high burden of comorbidities, frailty and geriatric syndromes, and a perceived uncertain net clinical benefit are among the most reported reasons for not prescribing an OAT to older patients (Bo et al., 2017a; Fumagalli et al., 2017; Bo and Marchionni, 2020; Shah et al., 2021; Orlandi et al., 2022). Despite OAT underuse has long been regarded as a reflection of clinical inertia or malpractice rather than as the consequence of persistent uncertainties about its clinical benefit in some older and vulnerable patients, the latest 2021 European Heart Rhythm Association (EHRA) practical guide on the use of DOACs has acknowledged for the first time this gap of evidence in such patients stating that "*there may be no benefit to OAT in states of severe frailty or where life expectancy is likely to be limited*", thereby accepting the option of not prescribing (or de-prescribing) OAT for some "frail" older AF patients (Steffel et al., 2021). The clinical point thus seems to be the potential for harm and futility of OAT in older AF patients with limited life-expectancy, implicitly suggesting that severe "frailty" might be a reliable marker of poor short-term prognosis. Therefore, the knowledge gap concerns whether and which "frailty" tools may be able to identify older AF patients with a poor expected benefit of OAT in reason of their "severe frailty or reduced life expectancy" (Steffel et al., 2021). Still, the huge number of available frailty tools has generated confusion and led to inconsistent and often discordant conclusions, as it was well reflected by the previous apparently divergent European recommendations on the topic. Indeed, the 2018 EHRA practical guide on the use of DOACs in AF recommended to "*do not undertreat frail and elderly patients*" (Steffel et al., 2018; Steffel and Heidbuchel, 2018), and the 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF reinforced this recommendation, stating that "*frailty, comorbidities, and increased risk of falls do not outweigh the benefits of oral anticoagulant*" therapy, but failed to provide conclusive evidence on the net clinical benefit of OAT in frail patients (Hindricks et al., 2021).

Notably, a recent systematic review and meta-analysis on the management of AF for older people with frailty concluded that "*frailty is common and associated with adverse clinical outcomes [and] despite the majority of care for older people being provided in the community, there is a lack of evidence on the association between frailty, AF, anticoagulation, and clinical outcomes to guide optimal care in this setting*" (Wilkinson et al., 2019). We modestly argue that the "*lack of evidence on the association between frailty, AF, anticoagulation and clinical outcomes to guide optimal care in this setting*" might be ascribed to the pooling of studies using heterogeneous frailty tools identifying quite different patient phenotypes in the same meta-analysis. We thus hypothesized that reviewing OAT use, all-cause mortality and other adverse outcomes according to the different conceptualizations of frailty might provide useful information about current evidence on OAT prescription habits and benefits in patients with different frailty models.

1.1. Background and study hypothesis

Prescribing an OAT to older AF patients is often a troublesome decision, involving a global evaluation of their general health status and residual life-expectancy rather than deriving by simply counting variables within cardio-embolic and bleeding risk scores. Indeed, it has been consistently demonstrated that the presence of both comorbidities and geriatric syndromes, such as cognitive impairment and functional dependence, can influence against OAT prescription in older subjects (Bo and Marchionni, 2020; Shah et al., 2021; Polidori et al., 2022). Therefore, it is likely that physicians may sometimes perceive an OAT as "futile" or potentially harmful in patients with multi-morbidity and a high short-term risk of both cardiovascular and non-cardiovascular mortality (Bo and Marchionni, 2020). It is well recognized that the appropriate use of the multidimensional tools of geriatric medicine allows to weigh the net clinical benefit of different therapeutic strategies and is essential to offer the best medical care and, at the same time, to avoid harm and futility in older people (Stuck et al., 1993; Parker et al., 2018; Briggs et al., 2022) including those with AF (Polidori et al., 2022).

The use of the comprehensive geriatric assessment (CGA, including information on functional autonomy, cognitive and nutritional statuses, comorbidities, medications, and social support) and the CGA-derived Multidimensional Prognostic Index (MPI), which can reliably predict one-year mortality and adverse clinical outcomes in several clinical settings (Pilotto et al., 2008, 2010) has been recommended to guide OAT prescribing decisions in older AF patients. The MPI, as well as the MPI-like instruments which might be feasible in non-geriatric settings (Geriatric Care, "The Cologne experience") (Meyer and Polidori, 2019; Meyer et al., 2020), have been developed as prognostic indices and yield a continuous number, which means that these tools may be used for both correlation and prediction purposes. Moreover, the multidimensional nature of these tools allows to capture the overall patient's prognosis rather than just the physical one. Unfortunately, both the CGA and the MPI are perceived as complex and time-consuming, thereby limiting their use in daily clinical practice outside geriatric settings (Pilotto et al., 2010, 2020; Bo and Marchionni, 2020; Cruz-Jentoft et al., 2020; Alboni et al., 2021; Polidori et al., 2022).

In the quest for an easier alternative to this complex assessment, "frailty" became popular as a captivating surrogate, and it has been widely endorsed among cardiologists. However, since the seminal definition of frailty (Fried et al., 2001), the number of frailty tools available has been steadily growing. This, combined with the absence of a consensus on how to define and measure frailty, has posed significant challenges, and has generated a great deal of confusion both in research and clinical settings (Hoogendijk et al., 2019; Bo and Marchionni, 2020).

Despite the plethora of available tools to measure frailty, most of them derive from two main conceptual models. Frailty was originally conceptualized as an independent physical dimension, usually preceding the development of disability (Dent et al., 2019), although it was recognized that these conditions might sometimes coexist. Accordingly, Fried and colleagues defined frailty as a syndrome of progressive age-related deterioration in multiple physiological systems that results in an increased vulnerability to stressors and a higher risk of adverse

clinical outcomes. This syndrome can be diagnosed in the presence of at least three criteria among slow gait speed, low physical activity levels, unintentional weight loss, self-reported exhaustion, and muscle weakness (Fried et al., 2001). This Cardiovascular Health Study (CHS) derived "frail phenotype" (FP) identifies frailty as a single domain within a multidimensional health assessment, does not necessarily imply a high disease burden or the presence of functional dependence and it is closely connected with sarcopenia (Hoogendijk et al., 2019). The FP is associated with worsening mobility and autonomy, hospitalizations, and mortality over 7 years in community-dwelling older people (Fried et al., 2001), but there is some evidence that appropriate nutritional and physical interventions may delay or reverse the progression to disability of pre-frail and frail subjects (Ng et al., 2015). Patients with the FP may be at increased risk following cardiac surgery and cardiovascular interventions and of complications from medical treatments (Singh et al., 2014), thereby suggesting the opportunity of a tailored clinical approach in these patients. Since diagnosing the FP might be complex, several other easier tools have been proposed for its identification, including the Short Physical Performance Battery (SPPB) (Guralnik et al., 1994), the 5-meter gait speed (Hardy et al., 2007), and the simple FRAIL questionnaire (Morley et al., 2013).

Almost concomitantly to the development of the FP, Rockwood et al. proposed a different approach to the concept of frailty, based on the CGA multidimensional evaluation. According to this "deficit accumulation model" (DAM), the more health deficits an individual presents (including functional limitations and disabilities, cognitive and sensory impairment, psycho-social variables, and number of diseases), the greater his/her risk for adverse outcomes (Mitnitski et al., 2001). Thus, frailty is intended in the DAM as the consequence of age-related health deficit accumulation, measured by a Frailty Index (FI), developed from the Canadian Study of Health and Aging (CSHA). This tool identifies older adults with frailty based on the proportion of deficits the subject presents among 70 evaluated items (with several shorter versions) (Jones et al., 2004). Frailty was classified as mild (FI-CGA 0–7), moderate (FI-CGA 7–13) and severe (FI-CGA $\geq$ 13) and higher FI scores are strongly associated with an increasing risk of short-term mortality and institutionalization, thus identifying patients with complex health status and high vulnerability to short-term adverse outcomes (Jones et al., 2004). The semi-quantitative Clinical Frailty Scale (CFS) originally stratified patients in seven categories (very fit, well, well with treated comorbidities, apparently vulnerable, mildly frail, moderately frail, and severely frail) according to a global "eye-ball" judgment of vulnerability ideally derived from a CGA. The CFS is highly correlated with FI scores and is significantly associated with an increased risk of death and institutionalization (Jones et al., 2004; Rockwood et al., 2005). The CFS was later modified in an inclusive 9-point scale (very fit, fit, managing well, very mild frailty, mild frailty, moderate frailty, severe frailty, very severe frailty, terminally ill, with scores $>$ 6 conventionally identifying patients with poor life-expectancy) (Rockwood and Theou, 2020). This version gained great popularity and was identified as the "frailty" scale in the recent EHRA practical guide (Steffel et al., 2021). However, since CFS scoring requires subjective clinical judgment, low inter-rater reproducibility might represent a major limitation to its more widespread use, especially among inexperienced raters (Shrier et al., 2021).

It is thus intuitive that considerations stemming from such divergent conceptualizations of "frailty" might generate confusion in the public. At odds with the FP, both the FI and the CFS do not identify frailty as a single domain within a multidimensional assessment, but rather provide a multidimensional evaluation of health status resulting from the interplay of disease burden, disability, cognitive and sensory impairment, and psycho-social variables (the FI) or by a trained and expert eye-ball geriatric evaluation (the CFS). Moreover, another relevant difference between these tools is that most FP models simply recognize the presence or absence of frailty (and, in some cases, pre-frailty) status, whereas some of the DAM tools may be used as continuous scales, thereby recognizing increasing severity levels of frailty. Not unexpectedly, the clinical implications that can be derived from these tools reflect more those provided by the MPI than those associated with the FP. Not surprisingly, patients identified as "frail" with such different tools show rather different prognoses. Indeed, 2-year all-cause mortality in older patients with severe frailty according to the FI/CFS (40–50%) (Jones et al., 2004) is remarkably higher than that reported for subjects with the FP (around 10%) (Fried et al., 2001), but it is almost superimposable to that observed in patients with severe disability (almost 50%) (Dunlay et al., 2015).

Moreover, several different validated "frailty" tools, based on hospital or administrative electronic databases, have been recently used to conduct studies on frailty. Most of these scores consider a large and heterogeneous number of acute and chronic health conditions (mainly cardiovascular), abnormal laboratory test results, indices of healthcare service or medical equipment use or a mix of signs and symptoms (Gilbert et al., 2018; Martinez et al., 2018; Steffel and Heidbuchel, 2018; Hohmann et al., 2019; Wilkinson et al., 2020, 2021; Kim et al., 2021; Lip et al., 2021; Orlandi et al., 2022).

Most of these tools rely on community- or hospital-based electronic health records including ICD-10 codes and resource use. Studies using these tools reported heterogeneous frailty prevalence figures (Steffel and Heidbuchel, 2018; Hohmann et al., 2019; Wilkinson et al., 2020, 2021; Lip et al., 2021). Notably, some of these frailty risk scores have shown a poor concordance with well validated frailty tools (Romero-Ortuno and Soraghan, 2014; Lopez et al., 2022; Soh et al., 2022). Whether these different tools identify the same patient phenotype and, more importantly, whether these scores may be used to measure biological age and residual life expectancy remains unsettled.

On the background of the divergent clinical implications of different frailty models, we hypothesized that in population studies investigating "frailty" in older AF people, severe frailty according to the DAM (i.e., a surrogate of poor health and reduced life-expectancy) rather than presence of the FP would predict less use of OAT and scant evidence of benefit from OAT in these patients. Accordingly, in the present systematic review we aimed to assess the available evidence on the use of "frailty" tools to guide clinical decision-making in older AF patients by answering two Review Questions (RQs): RQ #1) "is there an association between frailty and OAT prescription?" and RQ #2) "is there an association between frailty and clinical outcomes – including all-cause death, stroke or systemic embolism (SSE), and major or clinically relevant non-major bleeding (MB/CRNMB) – in patients receiving an OAT?". Notably, at odds with previous studies on this topic (Wilkinson et al., 2019), we explored these associations by categorizing frailty tools into the three main conceptualizations of frailty – namely, the frail phenotype (FP), the deficit accumulation model (DAM) and the hybrid models (HMs, which include elements from the FP and some measure of comorbidity), according to previous reports (Leng et al., 2014; Aguayo et al., 2017; Junius-Walker et al., 2018; Dent et al., 2019; Hoogendijk et al., 2019). We hypothesized that, compared with the FP, frailty tools based on the DAM would predict less use of OAT and lower benefit from OAT.

2. Materials and methods

The conduct and reporting of this review adhere to the general principles recommended by the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2009), the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Liberati et al., 2009). The protocols for each Review Question have been registered in the PROSPERO database (CRD42022308623 and CRD42022308628).

2.1. Eligibility criteria

Studies that used a validated measure to identify frailty in older

subjects (i.e., aged 65 years or older as study inclusion criteria, or with a mean or median sample age ≥70 years), with a diagnosis of non-valvular AF (thereby excluding AF patients with concomitant mechanical prosthetic valves and/or moderate to severe mitral stenosis, usually rheumatic) (Steffel et al., 2021) or atrial flutter, irrespective of its temporal pattern, were considered eligible for both RQs. For RQ #2, only studies involving patients with an OAT prescription (i.e., any VKA or DOAC at approved doses) were considered eligible. There was no restriction by country or study setting. Both prospective and retrospective observational studies, as well as experimental studies were considered eligible. Reviews, case reports, case series and conference proceedings were excluded but examined for additional relevant literature, followed by the reference list of both included full-text studies and relevant systematic reviews. Studies written in English, Italian and French languages were included.

2.2. Information sources, study selection and data extraction

We searched Embase and MEDLINE (Ovid interface) from inception until December 31st, 2021. A single search strategy suitable for both RQs was developed by two researchers (R.P. and E.B.) with input from the whole project team (Supplementary Table 1). As well, the International Clinical Trials Registry Platform Search Portal, Cochrane Trials and ClinicalTrials.gov were searched for ongoing or recently completed trials, and Cochrane Database of systematic reviews and PROSPERO were searched for ongoing or recently completed systematic reviews as sources of potentially relevant literature. As pertinent studies were identified, study reviewers checked for additional relevant cited and citing articles. The searches were re-run just before the final analyses on May 31st, 2022, and further studies were retrieved for inclusion.

Search outputs from different databases were imported in Mendeley Reference Manager and duplicate results were removed. To be considered duplicates, two or more citations had to share the same author, title, publication date, volume, issue, and start page information. The full-text versions of the citations were consulted when in doubt, by also checking the population sizes, methodology, and outcomes to determine whether the citations were duplicates.

The title and abstract of each unique article retrieved were systematically and independently screened for eligibility by two independent reviewers (R.P. and E.B.) to exclude obviously irrelevant results. Each remaining article from the first screening phase was then assessed against the eligibility criteria for each review question considering the full text. Screening stage and full-text review were performed on the web-tool Rayyan (HBKU Research Complex, Doha, Qatar; available from https://rayyan.qcri.org), where reasons for article exclusion were collated.

After the second phase, the full text of each included article was read thoroughly, and relevant information was collected in specifically developed spreadsheets for each RQ including i) identification of the study (article title, journal title, Authors, country(ies) and Institution(s) of the study, language, publication year), ii) methodological characteristics (study design, study objective/research hypothesis, demographic sample characteristics, length of follow-up, validated measure(s) of frailty adopted), iii) study sample characteristics (age, sex, ethnicity, prevalence of frailty) and iv) outcomes assessed (prevalence of OAT prescription for RQ #1 and incidence of SSE, MB/CRNMB and all-cause mortality for RQ #2). Statistical analyses with adjustments were also reported. If actual figures were unavailable, means and measures of dispersion were extrapolated from figures in the reports. Where frailty status was categorized, the specific frailty scale cut-off applied was used. Whenever possible, results from both intention-to-treat and per-protocol analyses were extracted. Data were extracted by two independent reviewers (R.P. and E.B.) for all included studies. Any disagreement ensued in any stage of the review process (i.e., screening, study inclusion, data extraction) was resolved through consensus and if consensus could not be found a third reviewer (M.B.) read the full text of the article for arbitration.

2.3. Risk of bias in individual studies

The Newcastle-Ottawa checklist was used by two authors (R.P. and E.B.) to independently assess the risk of bias on the domains of selection of the study groups, comparability of the groups, and ascertainment of outcome for each study included (Higgins et al., 2011; Wells et al., 2009). This tool evaluates one or more items for each domain and rates each item assigning a varying number of stars from a minimum of 0 stars to a maximum of 1–2 stars depending on the single item. Stars are pre-awarded in the Newcastle-Ottawa scale and are used to indicate quality elements. The number of stars assigned provides an overall measure of the study risk of bias with a higher number of stars identifying studies with lower risk of bias. For studies included in RQ #1, an adapted scale for cross-sectional studies was used (Herzog et al., 2013), and studies rated as satisfactory (5–6 stars), good (7–8 stars) or very good (9–10 stars) were considered as having a low risk of bias. Studies included in RQ #2 were assessed using the Newcastle-Ottawa scale version for cohort studies: 3 months for major bleeding and 6 months for stroke and systemic embolism and all-cause mortality were set as adequate lengths of follow-up (Hylek et al., 2007; Gomes et al., 2013) and a percentage of patients lost to follow-up lower than 10% was considered acceptable. Studies rated as satisfactory (5–6 stars) or good (7–9 stars) were considered as having a low risk of bias.

2.4. Outcomes

For RQ #1, the primary outcome was the prescription of any OAT (i.e., any VKA or DOAC at approved doses) according to the three frailty conceptualizations (DAM, FP and HMs). For RQ #2, the primary outcomes were all-cause mortality, as well as the incidences of SSE, and MB/CRNMB (both assessed with a standardized definition, e.g., TIMI [Thrombolysis In Myocardial Infarction] and ISTH [International Society on Thrombosis and Haemostasis] criteria), according to the three frailty conceptualizations (DAM, FP and HMs).

Two authors (R.P. and E.B.) extracted odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data. OR for frail versus non-frail subjects were used; when the reverse was reported by the Authors then an inverse OR was calculated. Adjusted association measures were preferred because they account for confounding variables and are considered more reliable. After the Chi-squared test and the I^2 statistic, performed using RevMan 5.3 software, studies were not found to be adequately homogeneous, thus data were not synthesized using a meta-analysis technique but only a narrative synthesis of study results was performed.

3. Results

3.1. RQ #1: Frailty and prescription of oral anticoagulant therapy

3.1.1. Study selection and characteristics

The identification of studies for RQ #1 is summarized in Fig. 1a. The search strategy identified 10 136 studies, of which 140 were retrieved for full-text review. Eligibility criteria were met in 24 studies, but two studies analyzed the same population derived from the Systematic Assessment of Geriatric Elements in Atrial Fibrillation (SAGE-AF) study and were considered together (Mailhot et al., 2020; Saczynski et al., 2020); therefore, twenty-three studies were finally included in the review. These were all observational studies, of which 17 were cohort studies (12 prospective and 5 retrospective), with a total of 504 719 participants. Fifteen studies were based in hospital (Bo et al., 2015; Denoël et al., 2014; Doucet et al., 2008; Ekerstad et al., 2018; Ferguson et al., 2017; Gullón et al., 2019; Induruwa et al., 2017; Lefebvre et al., 2016; Nguyen et al., 2016a; Pilotto et al., 2016; Requena Calleja et al., 2019; Tan et al., 2022; Wojszel and Kasiukiewicz, 2020), three studies

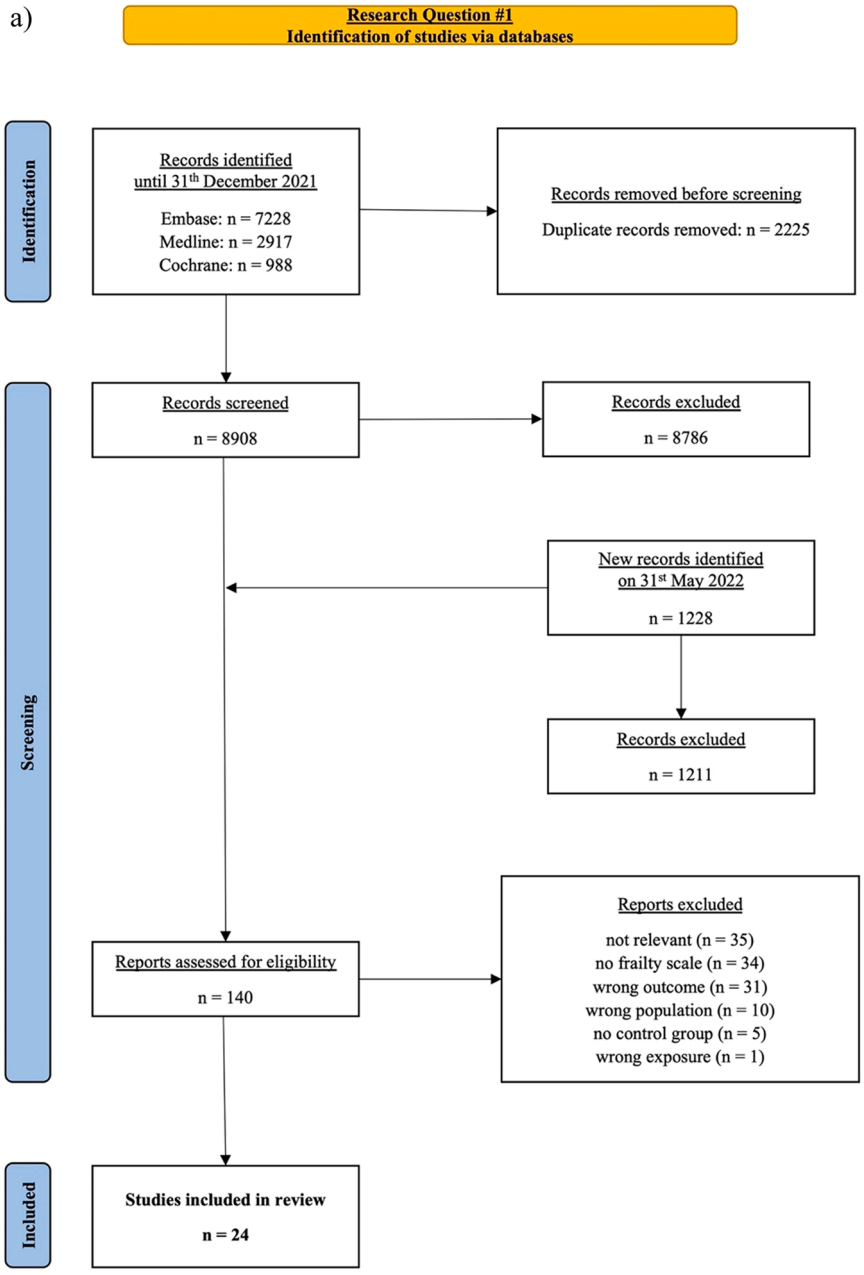

Fig. 1. PRISMA diagram of included studies for Review Question #1 (a) and Review Question #2 (b).

involved outpatients (Akishita et al., 2022; Madhavan et al., 2019; Mailhot et al., 2020; Saczynski et al., 2020), three included both in-patients and outpatients (Gugganig et al., 2021; Kim et al., 2017; Sanghai et al., 2022), one study was community-based (Wilkinson et al., 2021) and one involved nursing home residents (Campitelli et al., 2021). Eleven studies were conducted in Europe, three in Australia, three in Canada, three in the United States, one in Japan, one in Singapore and one in South Korea (Table 1a).

3.1.2. *Risk of bias within studies*

Overall, the risk of bias was considered low for all included studies (Supplementary Table 2a), even if a higher risk of bias was identified in six studies in terms of comparability mainly due to the lack of control for confounding factors (i.e., a multivariate analysis was not performed) (Denoël et al., 2014; Doucet et al., 2008; Ferguson et al., 2017; Gugganig et al., 2021; Kim et al., 2017; Pilotto et al., 2016).

3.1.3. *Participant characteristics*

The mean age ranged from a minimum of 72.0 ± 16.0 (Ferguson et al., 2017) to a maximum of 86.1 ± 5.1 years (Ekerstad et al., 2018). Female participants varied from 27.3% (Gugganig et al., 2021) to 68.4% (Wojszel and Kasiukiewicz, 2020), excluding the study by Sanghai et al. conducted among US Veterans in which female patients represented 2.1% of the study sample (Sanghai et al., 2022).

3.1.4. *Assessment of frailty*

Among the 23 studies included, seventeen different validated measures of frailty were used. In the study by Tan et al. two different frailty tools were adopted; hence it was considered twice for the analysis. Nine studies adopted frailty tools derived from the DAM, of which three were electronic tools, eight studies used different tools to assess the FP and seven studies used HMs. The most adopted tools were the CFS, the Edmonton Frailty Scale, Fried's FP criteria and the FRAIL scale, three

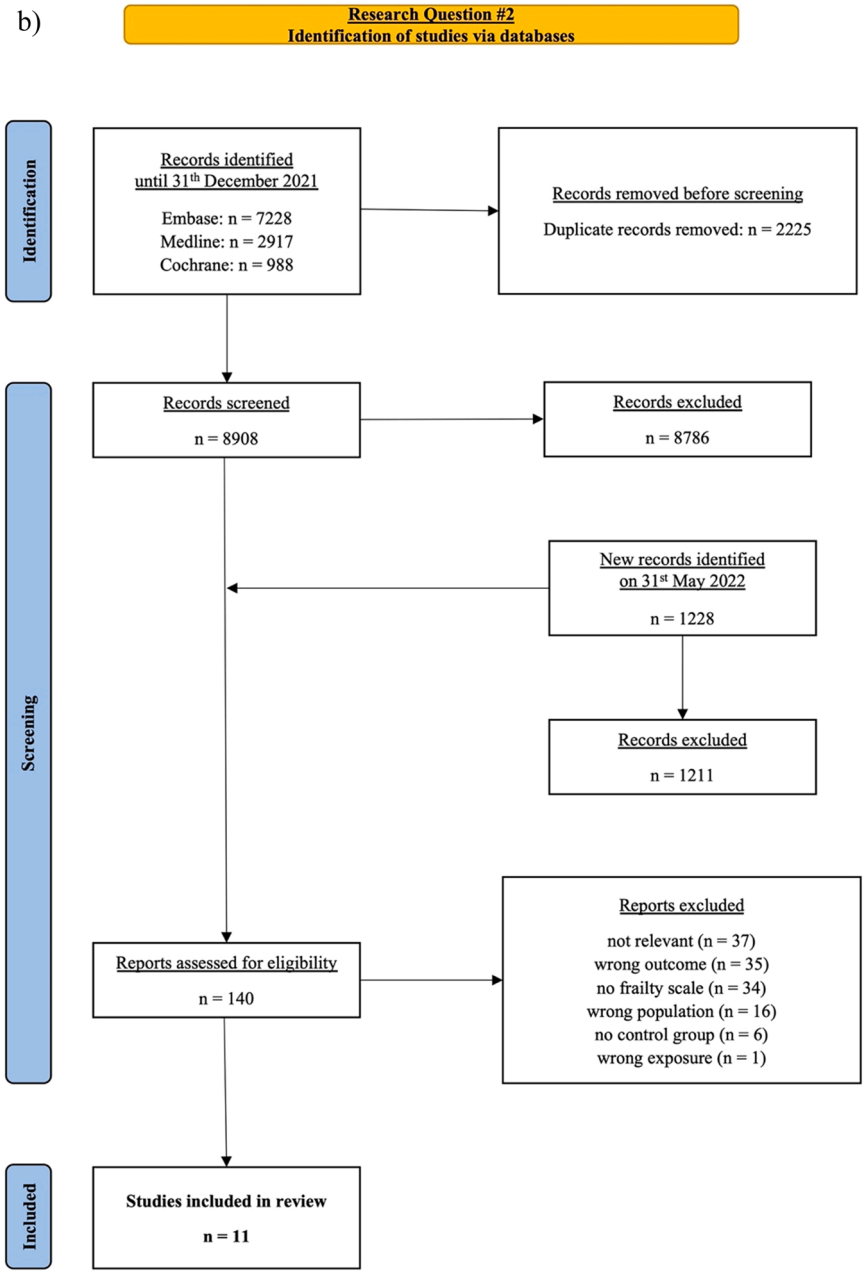

Fig. 1. (*continued*).

studies each. Overall, the prevalence of frailty varied from 5.9% (Madhavan et al., 2019) to 89.5% (Wilkinson et al., 2021) (Table 2a; Supplementary Table 3a).

3.1.5. *Deficit accumulation model frailty and oral anticoagulation*

Of the nine studies adopting a frailty tool derived from the DAM, five studies involved hospitalized patients, two enrolled a mixed population of inpatients and outpatients, one was community-based and one involved nursing home residents.

Seven studies reported aORs for the association between frailty and OAT prescription; although five of them were clinically and methodologically similar (Campitelli et al., 2021; Induruwa et al., 2017; Lefebvre et al., 2016; Orlandi et al., 2022; Sanghai et al., 2022), they were statistically heterogeneous (X^2 369,7, $p < 0{,}00001$; I^2 99%); hence meta-analysis was not performed. However, all these studies showed that older subjects with increasing severity of frailty according to the DAM were less frequently prescribed an OAT than not-frail people after multivariate analysis. Of the remaining two studies reporting aORs, the study by Wilkinson et al. showed that people with any degree of frailty (mild, moderate and severe) assessed with an electronic tool in a community-based population had higher odds of OAT prescription than those without frailty (pooled aOR 0.68 [95% CI 0.5–0.85]) (Wilkinson et al., 2021); the other one was a small study reporting an aOR for the association between severe frailty and prescription of OAT and showed that severely frail older subjects had lower odds of OAT prescription than those with mild or moderate frailty and those without frailty (aOR 0.27 [95% CI 0.08–0.94]) (Wojszel and Kasiukiewicz, 2020). Furthermore, one study showed no association between OAT prescription and frailty at univariate analysis, but no measure of effect was reported (Gugganig et al., 2021) and the last one was a small study using a brief screening tool with limited predictive validity (Identifying Seniors at Risk – ISAR tool) and reported an unadjusted OR (1.12 [95% CI 0.50–2.96]) (Denoël et al., 2014).

Notwithstanding these limitations, a clear trend towards less

Table 1
Summary of included studies for Review Question #1 (a) and Review Question #2 (b).

a)

Study	Study design	Setting	Country	Number of centers	Age criteria	n
Akishita et al. (2022)	Prospective cohort	Ambulatory patients	Japan	Multi (1 273)	≥ 75	2 951
Bo et al. (2015)	Cross-sectional	Geriatric and Internal Medicine inpatients	Italy	Multi (3)	≥ 65	550
Campitelli et al. (2021)	Retrospective cohort	Nursing Home residents	Canada	Multi (registry)	> 65	36 466
Denoël et al. (2014)	Cross-sectional	Patients admitted to the ED	Belgium	Single	≥ 75	142
Doucet et al. (2008)	Prospective cohort	Geriatric inpatients	France	Multi (2)	> 65	209
Ekerstad et al. (2018)	Prospective cohort	Inpatients	Sweden	Single	≥ 75	408
Ferguson et al. (2017)	Prospective cohort	Cardiologic inpatients	Australia	Single	≥ 18	137
Gugganig et al. (2021)	Prospective cohort	Mixed (inpatients, outpatients, direct contact with the GP)	Switzerland	Multi (14)	≥ 65	2 369
Gullón et al. (2019)	Prospective cohort	Internal Medicine inpatients	Spain	Multi (64)	> 75	557
Induruwa et al. (2017)	Cross-sectional	Medical inpatients	England	Single	≥ 75	419
Kim et al. (2017)	Retrospective cohort	Geriatric inpatients and outpatients	Republic of Korea	Single	≥ 65	365
Lefebvre et al. (2016)	Cross-sectional	Inpatients	Canada	Multi (3)	≥ 80	682
Madhavan et al. (2019)	Prospective cohort	Outpatients	US	Multi (174, registry)	≥ 18	9 479
Mailhot et al. (2020) Saczynski et al. (2020)	Prospective cohort	Ambulatory patients	US	Multi (7)	≥ 65	1 244
Nguyen et al. (2016a)	Prospective cohort	Geriatric, Internal Medicine and Cardiology inpatients	Australia	Single	≥ 65	302
Orlandi et al. (2022)	Cross-sectional	ED or hospital discharged patients (with new diagnosis of NVAF)	Canada	Multi (administrative database)	≥ 20	75 796
Perera et al. (2009)	Prospective cohort	Geriatric, Internal Medicine and Cardiology inpatients	Australia	Single	≥ 70	220
Pilotto et al. (2016)	Retrospective cohort	Recently discharged inpatients with AF diagnosis and MPI-SVaMA performed	Italy	Single	> 75	1 827
Requena Calleja et al. (2019)	Prospective cohort	Internal Medicine inpatients	Spain	Multi (64)	≥ 65	596
Sanghai et al. (2022)	Retrospective cohort	Mixed (US Veterans Affairs beneficiaries inpatients and outpatients)	US	Multi (registry)	n.s.	308 664
Tan et al. (2022)	Cross-sectional	Internal Medicine and Cardiologic inpatients	Singapore	Single	≥ 65	150
Wilkinson et al. (2021)	Retrospective cohort	Community (GP)	England	Multi (384, registry)	≥ 65	61 177
Wojszel and Kasiukiewicz (2020)	Cross-sectional	Subacute Geriatric inpatients	Poland	Single	n.s.	95

ED: Emergency Department; GP: General Practitioner; MPI-SVaMA: Multidimensional Prognostic Index – *Scheda di Valutazione Multidimensionale dell'Anziano e dell'Adulto*; NVAF: non-valvular atrial fibrillation, US: United States.

b)

Study	Study design	Setting	Country	Number of centers	Age criteria	n
Bo et al. (2017b)	Prospective cohort	Geriatric and Internal Medicine inpatients	Italy	Multi (3)	≥ 65	452
de Simone et al. (2020)	Retrospective cohort	Hospital (inpatients/outpatients not specified)	Italy	Single	≥ 80	731
Doucet et al. (2008)	Prospective cohort	Geriatric inpatients	France	Multi (2)	> 65	209
Gugganig et al. (2021)	Prospective cohort	Mixed (inpatients, outpatients, direct contact with GP)	Switzerland	Multi (14)	≥ 65	2 369
Gullón et al. (2019)	Prospective cohort	Internal Medicine inpatients	Spain	Multi (64)	> 75	557
Kusano et al. (2021)	Prospective cohort	Community (GP)	Japan	Multi (510, registry)	n.s.	5 717
Madhavan et al. (2019)	Prospective cohort	Outpatients	US	Multi (174, registry)	≥ 18	9 479
Ohta et al. (2021)	Retrospective cohort	Inpatients	Japan	Single	n.s.	120
Wang et al. (2021)	Prospective cohort	Outpatients	US	Multi (7)	≥ 65	1 244
Wilkinson et al. (2020)	Post-hoc sub-analysis of RCT	Outpatients	Multi (46)	Multi (1393)	≥ 21	20 867
Yamamoto et al. (2019)	Retrospective cohort	Mixed (inpatients and outpatients)	Japan	Single	n.s.	240

GP: General Practitioner; n.s.: not specified, RCT: Randomized Clinical Trial, US: United States.

prescription of OAT in DAM assessed severely frail AF patients compared with non-frail patients emerged (Table 3).

3.1.6. *Frail phenotype and oral anticoagulation*

Of the eight studies included that adopted a frailty tool according to the FP, six studies included hospitalized patients and two involved outpatients.

Only three studies reported aORs for the association between frailty and prescription of OAT but were clinically and methodologically different; therefore, meta-analysis was not performed (Gullón et al., 2019; Madhavan et al., 2019; Mailhot et al., 2020). Among them, only the study by Madhavan et al. involving outpatients showed a lower odds of OAT prescription in frail subjects than those without frailty (despite a very low prevalence of frail subjects), whereas the other two showed no difference according to frailty status after multivariate analysis. The remaining five studies had small sample sizes (min 137 max 596 participants); among them, four studies showed no association between OAT prescription and frailty at univariate analysis (Doucet et al., 2008; Ferguson et al., 2017; Tan et al., 2022) and only one study reported a reduced OAT prescription in frail older subjects at univariate analysis (Requena Calleja et al., 2019).

In summary, with the only exception of the study by Madhavan et al., no difference was observed in OAT prescription between persons with and without the FP (Table 3).

Table 2
Sample characteristics of the included studies for Review Question #1 (a) and Review Question #2 (b).

a) Study	Mean (SD) or median (IQR) age [% ≥ 75 years old]	Female sex (%)	Frailty model	Frailty tool	Frailty cut-off	Frailty prevalence
Akishita et al. (2022)	[100]	42.3	Hybrid	Kihon Checklist	≥ 8: frail 4–7: pre-frail	36.2 (frail) 31.3 (pre-frail)
Bo et al. (2015)	81.7 (6.8) [84.7]	55.6	Hybrid	GFI	≥ 4: frail	77.5
Campitelli et al. (2021)	[55.8]	61.0	Deficit accumulation	FI[1]	> 30% of deficits: frail 20–30% of deficits: pre-frail	48.8 (frail) 35.6 (pre-frail)
Denoël et al. (2014)	[100]	n.s.	Deficit accumulation	ISAR	≥ 2: frail	84.0
Doucet et al. (2008)	84.7 (7)	60.8	Frail phenotype	TUGT	n.s.	49.3
Ekerstad et al. (2018)	86.1 (5.1) [100]	55.8	Frail phenotype	FRESH	≥ 2: frail	n.s.
Ferguson et al. (2017)	72 (16)	36.5	Frail phenotype	SHARE-FI	n.s.	63.0
Gugganig et al. (2021)	73 (8)	27.3	Deficit accumulation	FI	≥ 0.25: frail 0.1–0.24 pre-frail	10.6 (frail) 60.7 (pre-frail)
Gullón et al. (2019)	85.2 (5.2)	54.8	Frail phenotype	FRAIL Scale	≥ 3: frail	46.7
Induruwa et al. (2017)	[100]	54.9	Deficit accumulation	9-items CFS	≥ 5: frail	67.3
Kim et al. (2017)	79.4 (6.5) [73.4]	48.2	Hybrid	KLoSHA-FI	≥ 0.35: frail 0.2–0.34: pre-frail	48.2 (frail) 18.6 (pre-frail)
Lefebvre et al. (2016)	[100]	60.4	Deficit accumulation	9-items CFS	≥ 7: frail	25.2
Madhavan et al. (2019)	75.0 (67.0–82.0)	42.6	Frail phenotype	Fried's criteria[2]	≥ 3: frail	5.9
Mailhot et al. (2020)	76.0 (7.0)	48.8	Frail phenotype	Fried's criteria	≥ 3: frail ≥ 3: frail 1–2: pre-frail	13.8 13.8 (frail) 53.0 (pre-frail)
Saczynski et al. (2020)	75.5 (7.1)					
Nguyen et al. (2016a)	84.7 (7.1) [73.4]	50.0	Hybrid	R-EFS	≥ 8: frail	53.3
Orlandi et al. (2022)	75 (64–84) [51.8]	44.7	Deficit accumulation	HFRS[3]	> 15: high risk of frailty 5–15: intermediate risk of frailty	4.7 (high risk of frailty) 17.9 (intermediate risk of frailty)
Perera et al. (2009)	82.7 (6.3)	54.0	Hybrid	M-EFS	n.s.	64
Pilotto et al. (2016)	84.4 (7.1)	64.3	Hybrid	MPI-SVaMA	< 0.34: mildly frail 0.34–0.47 moderately frail ≥ 0,48 highly frail	34.7 (moderately frail) 26.7 (highly frail)
Requena Calleja et al. (2019)	84.9 (5.2)	52.9	Frail phenotype	FRAIL Scale	≥ 3: frail	51.2
Sanghai et al. (2022)	77.7 (9.6) [60.0]	2.1	Deficit accumulation	VA-FI	> 0.2 frail > 0.11–0.2: pre-frail	35.5 (frail) 32.1 (pre-frail)
Tan et al. (2022)	79.4 (7.1)	52.0	Frail phenotype	FRAIL Scale	≥ 3: frail 1–2: pre-frail	29.3 (frail) 50.0 (pre-frail)
			Hybrid	EFS	≥ 12: severely frail 10–11: moderately frail 8–9: mildly frail 6–7: vulnerable	13.3 (severely frail 17.3 (moderately frail) 19.3 (mildly frail) 22.7 (vulnerable)
Wilkinson et al. (2021)	79.7 (73.3–85.5) [69.2]	45.8	Deficit accumulation	eFI[4]	> 0.36: severely frail 0.24–0.36: moderately frail 0.12–0.24: mildly frail	23.0 (severely frail) 33.2 (moderately frail) 33.3 (mildly frail)
Wojszel and Kasiukiewicz (2020)	83.1 (5.7)	68.4	Deficit accumulation	7-items CFS	≥ 6: severely frail	29.5 (severely frail)

CFS: Clinical Frailty Scale; FI: Frailty Index; eFI: 30-items electronic Frailty Index; FRESH: Frail Elderly Support Research; GFI: Groningen Frailty Indicator; HFRS: Hospital Frailty Risk Score; IQR: Interquartile Range; ISAR: Identification of Senior At Risk; KLoSHA-FI: Korean Longitudinal Study on Health and Aging – Frailty Index; M-EFS: Modified Edmonton Frailty Scale; MPI-SVaMA: Multidimensional Prognostic Index – *Scheda di Valutazione Multidimensionale dell'Anziano e dell'Adulto*; R-EFS: Reported Edmonton Frailty Scale; n.s.: not specified; SD: standard deviation; SHARE-FI: Survey of Health, Ageing and Retirement in Europe – Frailty Index; TUGT: Timed Up and Go Test; VA-FI: 30-items Veteran Affairs – Frailty Index.

[1] 72 items on Resident Assessment Instrument Minimum Dataset (RAI-MDS) 2.0.

[2] Using the American Geriatric Society's Geriatric Evaluation and Management Tool for Frailty (AGS-GEMT).

[3] Based on 109 International Classification of Diseases 10th revision codes.

[4] From every Electronic Health Record (EHR) preceding December 2015.

3.1.7. *Hybrid models frailty and oral anticoagulation*

Of the seven studies adopting HMs for the evaluation of frailty, five studies were conducted in hospital settings, one study involved outpatients and another one a mixed population of inpatients and outpatients.

Since the four studies reporting aORs for the association between frailty and OAT prescription were clinically and methodologically similar but statistically heterogeneous (X^2 28,0, $p < 0{,}00001$; I^2 89%), meta-analysis was not performed (Bo et al., 2015; Nguyen et al., 2016a; Perera et al., 2009; Tan et al., 2022). Only the study by Perera et al. showed a lower odds of OAT prescription in frail subjects than those without frailty, whereas the other three did not show significantly different odds of OAT prescription in frail vs non-frail patients after multivariate analysis.

Of the remaining three studies, two studies showed no association between OAT prescription and frailty (Akishita et al., 2022; Kim et al., 2017) and one reported a reduced OAT prescription in frail older subjects (Pilotto et al., 2016), both at univariate analysis.

At a glance, a weak trend showing no difference in OAT prescription between frail patients and non-frail AF subjects was observed,

b)

Study	Mean (SD) or median (IQR) age [% ≥ 75 years old]	Female sex (%)	Frailty model	Frailty tool	Frailty cut-off	Frailty prevalence (%)
Bo et al. (2017b)	81.6 (6.6) [85.0]	54.9	Hybrid	GFI	≥ 4: frail	75.4
de Simone et al. (2020)	84.9 (4.1)	58.9	Hybrid	R-EFS	≥ 4: frail	n.s.
Doucet et al. (2008)	84.7 (7.0)	60.8	Frail phenotype	TUGT	n.s.	49.3
Gugganig et al. (2021)	73.0 (8.0)	27.3	Deficit accumulation	FI	≥ 0.25: frail 0.1–0.24: pre-frail	10.6 (frail) 60.7 (pre-frail)
Gullón et al. (2019)	85.2 (5.2)	54.8	Frail phenotype	FRAIL questionnaire	≥ 3: frail	46.7
Kusano et al. (2021)	73.9 (9.5) [50.9]	35.2	Deficit accumulation[1]	Japanese LTCI	n.s.	12.1
Madhavan et al. (2019)	75.0 (67.0–82.0)	42.6	Frail phenotype	Fried's criteria[2]	≥ 3: frail	5.9
Ohta et al. (2021)	77.7 (9.5) [67.5]	40.0	Frail phenotype	Fried's criteria	≥ 3: frail 1–2: pre-frail	28.3 (frail) 60.0 (pre-frail)
Wang et al. (2021)	75.3 (7)	47.9	Frail phenotype	Fried's criteria	≥ 3: frail 1–2: pre-frail	13.3 (frail) 53.0 (pre-frail)
Wilkinson et al. (2020)	[58.7][3]	38.1	Deficit accumulation	FI	≥ 0.36 severely frail 0.24–0.35 mildly-moderately frail 0.12–0.23 pre-frail	1.7 (severely frail) 17.8 (mildly-moderately frail) 59.1 (pre-frail)
Yamamoto et al. (2019)	76.1 (10.0)	42.9	Deficit accumulation	9-items CFS	≥ 5: frail	50.0

CFS: Clinical Frailty Scale; FI: 40-items Frailty Index; GFI: Groningen Frailty Indicator; LTCI: Long-Term Care Insurance; R-EFS: Reported Edmonton Frailty Scale; TUGT: Timed Up and Go Test.

[1] Even if this Japanese tool was compared only with the Fried's criteria, it was included among the Deficit Accumulation Model because of its characteristics.

[2] Using the American Geriatric Society's Geriatric Evaluation and Management Tool for Frailty (AGS-GEMT).

[3] % ≥ 70 years old.

notwithstanding a significant heterogeneity of HM frailty tools adopted (Table 3).

3.2. RQ #2: Frailty and incidence of all-cause mortality, SSE, MB/CRNMB in AF patients receiving oral anticoagulation

3.2.1. Study selection and characteristics

The identification of studies for RQ #2 is summarized in Fig. 1b. The search strategy identified 10,136 studies, of which 140 were retrieved for full-text review. Eligibility criteria were met in 11 studies and were included in the review. Ten studies were observational studies (of which 7 were prospective studies and 3 retrospective studies) and one study was a post-hoc analysis of the randomized controlled trial ENGAGE AF-TIMI 48 by Wilkinson et al., with a total of 41 985 participants (Wilkinson et al., 2020). Four studies involved hospitalized patients (Bo et al., 2017b; Doucet et al., 2008; Gullón et al., 2019; Ohta et al., 2021), three studies outpatients (Madhavan et al., 2019; Wang et al., 2021; Wilkinson et al., 2020), three studies both inpatients and outpatients (de Simone et al., 2020; Gugganig et al., 2021; Yamamoto et al., 2019) and one study was community-based and conducted on general practices (Kusano et al., 2021). Five studies were conducted in Europe, three in Japan, two in the United States and one was an international study involving 46 countries (Table 1b).

3.2.2. Risk of bias within studies

Overall, the included studies were all at low risk of bias, except for the study by Doucet et al., which was at higher risk for comparability and assessment of incidence of mortality and SSE (Doucet et al., 2008). A higher risk of bias was identified in terms of comparability in four studies mainly due to the lack of control for confounding factors (i.e., a multivariate analysis was not performed) (de Simone et al., 2020; Doucet et al., 2008; Gullón et al., 2019; Kusano et al., 2021) and adequacy of follow-up of cohorts in two studies (Doucet et al., 2008; Gullón et al., 2019) (Supplementary Table 2b).

3.2.3. Participant characteristics

The mean age of participants ranged from a minimum of 73.0 ± 8.0 years (Gugganig et al., 2021) to a maximum of 85.2 ± 5.2 years (Gullón et al., 2019). Female participants were between 27.3% (Gugganig et al., 2021) and 60.8% (Bo et al., 2017b). The prevalence of frailty varied from 5.9% (Madhavan et al., 2019) to 75.4% (Bo et al., 2017b). Mean length of follow-up ranged from 3 (Doucet et al., 2008) to 33.6 months (Wilkinson et al., 2020) (Table 2b).

3.2.4. Assessment of frailty

Among the eleven studies included in the review, eight different validated measures of frailty were used. Four studies adopted frailty tools derived from the DAM (that by Kusano et al. adopted an electronic tool), five studies used different tools to assess the FP and two studies used HMs. The most used tools were Fried's FP criteria and the 40-item FI (Table 2b; Supplementary Table 3b). A meta-analysis was not performed: the methodological, clinical, and statistical differences across observational studies and the inconsistency in the reporting of outcomes precluded a statistical synthesis of the results of included studies (reported in Table 4).

3.2.5. Deficit accumulation model frailty and outcomes

Among the four studies adopting a DAM frailty tool, two studies involved a mixed population of inpatients and outpatients, one study included outpatients only and one was a general practice community-based study.

The study by Gugganig et al. reported adjusted hazard ratios (aHRs) showing that among OAT-treated older patients, those with frailty were at higher risk for both MB and all-cause death compared with non-frail subjects, but no measure of efficacy was reported about the association between frailty and the incidence of SSE (Gugganig et al., 2021). The study by Kusano et al. reported aHRs showing that frail older patients on OAT were at higher risk for all-cause death than non-frail patients, but no association was found with SSE and MB (at multivariate and univariate analysis, respectively) (Kusano et al., 2021). The study by Yamamoto et al. reported HRs showing that frail older patients on OAT were at higher risk for SSE, MB and all-cause death (with no difference in incidence of cardiac death) at univariate analysis. A multivariate analysis was conducted only on the incidence of a composite outcome and confirmed that frail subjects were at higher risk than non-frail patients (Yamamoto et al., 2019). Eventually, the post-hoc analysis of the

Table 3
Studies reporting the association between frailty and anticoagulation status by frailty model (RQ #1).

Study	n	Association frailty-OAC prescription	Measure of efficacy after multivariate analysis (if performed)	Adjustment (s)
Deficit accumulation				
Campitelli et al. (2021)	36 466	Less use	aRR 0.95 (0.92–0.98)	age, sex, cognitive impairment, components of CHA_2DS_2-VASc and HAS-BLED, concurrent medication use
Denoël et al. (2014)	142	No difference	OR 1.12 (0.50–2.96)	
Gugganig et al. (2021)	2 369	No difference	n.a.	
Induruwa et al. (2017)	419	Less use	aOR 0.77 (0.70–0.85)	age, sex, components of CHA_2DS_2-VASc and HAS-BLED
Lefebvre et al. (2016)	682	Less use	aOR 0.29 (0.16–0.54)	age, falls history, $CHADS_2$, HAS-BLED, length of hospital stay, use of antiplatelet/ NSAIDs/corticosteroids
Orlandi et al. (2022)	75 796	Less use	aOR 0.61 (0.58–0.64)	frailty, female sex, age, anemia, thrombocytopenia, cancer, end-stage liver disease, excess alcohol, falls history, chronic kidney disease, catheter ablation, calendar year
Sanghai et al. (2022)	308 664	Less use	aOR 0.66 (0.64–0.68)	sex, race, marital status, depression, current smoking, heart failure, vascular disease, hypertension, diabetes, intracranial bleeding, gastrointestinal bleeding, anemia, stroke, excess alcohol, Veteran Act entitlement, chronic kidney disease stage, medication count, BMI, admission 4 weeks prior, use of antiplatelet/statin/ beta blocker/ACEI/ARB
Wilkinson et al. (2021)	61 177	More use	aOR 2.51 (2.33–2.71) severely frail aOR 2.34 (1.18–2.50) moderately frail aOR 1.84 (1.72–1.96) mildly frail	age, sex, smoking, indices of multiple deprivation, general practice identifier, oral anticoagulation, and antiplatelet prescription
Wojszel and Kasiukiewicz (2020)	95	Less use	aOR 0.27 (0.08–0.94) severely frail	anemia, albumin < 35 g/L, CHA_2DS_2-VASc, HAS-BLED ≥ 3
Frail phenotype				
Doucet et al. (2008)	209	No difference	n.a.	
Ekerstad et al. (2018)	408	No difference	n.a.	
Ferguson et al. (2017)	137	No difference	n.a.	
Gullón et al. (2019)	557	No difference	aOR 0.93 (0.54–1.49)	sex, age, AF subtype, history of acute coronary syndrome, CHA_2DS_2-VASc, HAS-BLED, Charlson Comorbidity Index, ADL dependence (Katz), cognitive impairment (SPMSQ), sarcopenia, fall history
Madhavan et al. (2019)	9 479	Less use	aOR 0.69 (0.56–0.84)	age, sex, education, BMI, history of chronic obstructive pulmonary disease, peripheral artery disease, stroke/ transient ischemic attack and congestive heart failure, eGFR, hematocrit, AF subtype, rate vs rhythm control, use of digoxin, CHA_2DS_2-VASc, ORBIT score, EHRA score, HAS-BLED, functional status
Mailhot et al. (2020)	1 244	No difference	aOR 0.66 (0.31–1.42)	CHA_2DS_2-VASc, age, education, race, marital status, HAS-BLED, history of asthma/chronic obstructive pulmonary disease and acute coronary syndrome, vision impairment, hearing impairment, social support, depression, anxiety, falls history in the previous 6 months
Saczynski et al. (2020)		No difference	aOR 0.69 (0.35–1.36)	age, cognitive impairment, social isolation, visual impairment, hearing impairment, depression, CHA_2DS_2-VASc, HAS-BLED, AF subtype, quality of life, use of antiplatelet, congestive heart failure, provider type
Requena Calleja et al. (2019)	596	Less use	n.a.	
Tan et al. (2022)	150	No difference	OR 0.61 (0.37–1.01)	
Hybrid				
Akishita et al. (2022)	2 951	No difference	n.a.	
Bo et al. (2015)	550	No difference	aOR 0.80 (0.41–1.57)	age, AF subtype, CHA_2DS_2-VASc, HAS-BLED, Charlson Comorbidity Index, ADL dependence (Katz), cognitive impairment (SPMSQ), depression (GDS), malnutrition (MNA-SF), discharge to a facility, contraindication to OAT
Kim et al. (2017)	365	No difference	n.a.	
Nguyen et al. (2016a)	302	No difference	aOR 0.66 (0.40–1.11)	age, history of/predisposition to bleeding, eGFR, congestive heart failure
Perera et al. (2009)	220	Less use	aOR 0.12 (0.06–0.23)	age > 75 years, CCS, sex, herbal medications, admission ward, malnutrition, medication count, cognitive impairment (MMSE), ADL dependence (Katz), excess alcohol, excessive falls risk, anemia, history of adverse reaction to warfarin and aspirin, stroke and hemorrhagic stroke, major bleeding episodes, cancer, thrombocytopenia, uncontrolled hypertension, diabetes, congestive heart failure
Pilotto et al. (2016)	1 827	Less use	n.a.	
Tan et al. (2022)	150	No difference	aOR 0.89 (0.64–1.25)	age, chronic kidney disease, ADL dependence (Barthel)

ACEI: angiotensin-converting enzyme inhibitors; ADL: Activity Daily Living; AF: atrial fibrillation; ARB: angiotensin II receptor blockers; BMI: Body Mass Index; eGFR: estimated glomerular filtration rate; GDS: Geriatric Depression Scale; MMSE: Mini-Mental State Examination; MNA-SF: Mini Nutritional Assessment – Short Form; NSAID: non-steroidal anti-inflammatory drugs; SPMSQ: Short Portable Mental State Questionnaire.

Table 4
Studies reporting the association between frailty and stroke and systemic embolism (a), major bleeding and/or clinically relevant non major bleeding (b) and all-cause mortality (c) by frailty model (RQ #2).

a) Study	n	Association frailty-stroke/SSE	Measure of efficacy after multivariate analysis (if performed)	Adjustment (s)
Deficit accumulation				
Gugganig et al. (2021)	2 369	n.s.		
Kusano et al. (2021)	5 717	No difference	aHR 1.50 (0.90–2.50)	sex, age, eGFR, AF subtype, history of ischemic stroke, use of anti-dementia medications
Wilkinson et al. (2020)	20 867	Higher risk[1]	aHR 2.30 (1.17–4.52) severely frail aHR 1.84 (1.31–2.59) mildly-moderately frail	sex, age, race, and region
Yamamoto et al. (2019)	240	Higher risk	n.s.[2]	
Frail phenotype				
Doucet et al. (2008)	209	No difference	n.a.	
Gullón et al. (2019)	557	No difference	n.a.	
Madhavan et al. (2019)	9 479	No difference	aHR 0.96 (0.63–1.46)	age, race, sex, education, payor/insurance, smoking, history of cancer, hypertension, osteoporosis, diabetes, hypothyroidism, gastrointestinal bleeding, obstructive sleep apnea, dyslipidemia, anemia, cognitive impairment, chronic obstructive pulmonary disease, peripheral vascular disease, stroke/transient ischemic attack, congestive heart failure, valvular disease, coronary artery disease, intraventricular conduction, left atrial disease, height, heart rate, blood pressure, BMI, eGFR, hematocrit, AF subtype, AF management strategy, prior cardioversions, catheter ablation of AF, functional status
Ohta et al. (2021)	120	n.s.		
Wang et al. (2021)	1 244	n.s.		
Multidimensional				
Bo et al. (2017b)	452	No difference	n.s.	n.s.
de Simone et al. (2020)	731	No difference	HR 2.10 (0.85–5.21)	

AF: atrial fibrillation; BMI: Body Mass Index; eGFR: estimated glomerular filtration rate.
[1] However, interaction by treatment group was not significant.
[2] Multivariate analysis was performed only for composite outcome (stroke and/or systemic embolism, major bleeding, and all-cause mortality) and showed a higher risk.

ENGAGE AF-TIMI 48 conducted by Wilkinson et al. reported aHRs showing that increasing severity of frailty in older patients on OAT was associated with higher risks for SSE, MB, and all-cause death (Wilkinson et al., 2020). Still, severe frailty was observed only in 1.7% of participants.

In summary, a clear trend of a higher risk of the outcomes of interest (including all-cause mortality) in AF patients receiving OAT considered frail according to the DAM compared to non-frail patients receiving OAT was observed.

3.2.6. *Frail phenotype and outcomes*

Five studies adopted a frailty tool according to the FP. Three studies involved hospitalized patients and two studies included outpatients. Only the study by Madhavan et al. reported aHRs for every outcome according to frailty status, notwithstanding a very low prevalence of frail subjects. This study showed no difference in the incidence of SSE and no interaction between frailty and OAT (Madhavan et al., 2019).

Adjusted HRs by Ohta et al. showed a greater risk of MB in frail patients with OAT than in non-frail subjects, but an analysis on the association between the presence of frailty and SSE incidence and all-cause mortality was not performed (Ohta et al., 2021). The analyses by Wang et al., on the other hand, showed that frail older patients on OAT were at higher risk for death and MB/CRNMB (with no difference in the incidence of MB only) than non-frail subjects, but analysis on the association with SSE was not performed (Wang et al., 2021).

Finally, the studies by Doucet et al. (2008) and Gullón et al. (2019) found no difference in the clinical outcomes of interest between frail and non-frail AF patients receiving OAT at univariate analysis, apart from a higher risk of all-cause death at 1 year in frail patients. In both studies no multivariate analysis was performed.

Briefly, scant evidence of a higher risk of bleeding and all-cause mortality was observed in AF patients receiving OAT presenting with the FP than in non-frail subjects.

3.2.7. *Hybrid models frailty and outcomes*

Only two studies adopted HMs for the evaluation of frailty, involving hospitalized patients and a mixed population of inpatients and outpatients, respectively. Bo et al. reported aORs showing a greater all-cause mortality in frail patients on OAT than in non-frail patients, but no association with SSE and MB was observed (Bo et al., 2017b).

De Simone et al. noted a greater incidence of MB among frail patients on OAT with no association with SSE at univariate analysis and no analysis performed on the association with all-cause death (de Simone et al., 2020). In summary, no clear trend emerged for clinical outcomes of interest between frail and non-frail AF patients on OAT evaluated by HMs.

b)

Study	n	Association frailty-MB/ CRNMB	Measure of efficacy after multivariate analysis (if performed)	Adjustment(s)
Deficit accumulation				
Gugganig et al. (2021)	2 369	Higher risk	aHR 2.68 (1.40–5.12) VKA aHR 2.52 (1.34–4.73) DOAC[1]	age, sex, type of oral anticoagulation, use of antiplatelet, AF subtype, education, smoking
Kusano et al. (2021)	5 717	No difference	n.a.	
Wilkinson et al. (2020)	20 867	Higher risk[2]	aHR 2.86 (1.72–4.76) severely frail aHR 1.79 (1.36–2.37) mildly-moderately frail	sex, age, race, and region
Yamamoto et al. (2019)	240	Higher risk	n.s.[3]	
Frail phenotype				
Doucet et al. (2008)	209	No difference	n.a.	
Gullón et al. (2019)	557	No difference	n.a.	
Madhavan et al. (2019)	9 479	No difference[4]	n.s.	n.s.
Ohta et al. (2021)	120	Higher risk	aHR 1.85 (1.17–2.91)	chronic kidney disease, dyslipidemia
Wang et al. (2021)	1 244	Higher risk[5]	aHR 2.83 (1.55–5.17)	age, sex, race, education, history of bleeding, HAS-BLED, systolic blood pressure, use of anticoagulation and antiplatelet
Multidimensional				
Bo et al. (2017b)	452	No difference	n.s.	n.s.
de Simone et al. (2020)	731	Higher risk	aHR 3.56 (95% CI n.s.)	eGFR

AF: atrial fibrillation; eGFR: estimated glomerular filtration rate.

[1] Multivariate analysis performed by type or oral anticoagulant therapy.

[2] However, interaction by treatment group was not significant.

[3] Multivariate analysis was performed only for composite outcome (stroke and/or systemic embolism, major bleeding, and all-cause mortality) and showed a higher risk.

[4] No interaction frailty-OAT

[5] If considering both major and clinically relevant non major bleeding (if considering only major bleeding: no difference).

4. Discussion

Our systematic review demonstrates a great level of heterogeneity among studies on frailty and OAT in older AF patients in terms of study design, sample size, setting, frailty tool adopted and outcomes. Moreover, we found a high variability among frailty tools, implying potential serious problems in case these instruments would be used to guide clinical decision-making. Our findings are in keeping with, and add on, the conclusions by Wilkinson et al., that available data do not allow and should discourage the indiscriminate use of "frailty" to guide optimal care for AF in older patients (Wilkinson et al., 2019).

However, our review moved a step further: the analysis of frailty tools categorized into the main conceptualizations of frailty – DAM and FP – seems to suggest that each model may guide decision-making in different clinical situations by describing different phenotypes. Even if for the RQ #1 no meta-analysis was performed for methodological, clinical, and statistical heterogeneity, a clear trend could be observed: compared with people without frailty, severely frail patients identified according to the DAM showed consistently lower OAT prescription rates, whereas in subjects with the FP no differences in OAT prescription were observed compared to non-frail patients. Findings from studies adopting HM frailty tools were much more heterogeneous. Therefore, patients with moderate to severe frailty according to the FI/CFS are often denied OAT. Similarly, for RQ #2, no meta-analysis was performed for methodological, clinical, and statistical heterogeneity. Few studies considered the impact of frailty on clinical outcomes in patients receiving OAT and only 11 studies were included. However, compared with non-frail subjects, a trend to a higher risk for all-cause mortality and clinical outcomes could be observed for patients with severe frailty according to the DAM, with inconclusive findings in the other models. Therefore, in keeping with the study hypothesis, our systematic review demonstrated a trend suggesting that identification of severe frailty according to the DAM, but not identification of the FP, is associated with a reduced prescription of OAT and a higher risk for all-cause mortality and clinical outcomes.

Frailty has become a high-priority theme in cardiovascular (CV) medicine as a consequence of the increasing age and complexity of patients. However, due to a lack of consensus, there is widespread confusion on the best tool to be used according to different purposes in various clinical settings, including stable and subclinical CV disease, heart failure, coronary syndromes, cardiac surgery, trans-catheter aortic valve replacement (TAVR) and AF (Afilalo et al., 2014). Irrespective from the tool adopted, most studies consistently demonstrated that frail patients compared with non-frail subjects have a worse prognosis, including a higher all-cause and CV mortality, as well as a higher risk of adverse clinical outcomes (Veronese et al., 2017; Wilkinson et al., 2019; Marinus et al., 2021; Akishita et al., 2022; He et al., 2022; Shrauner et al., 2022; Proietti et al., 2022). Moreover, cognitive and functional impairment are more prevalent in frail than in fit persons (Mone et al., 2022a, 2022b). A basic principle when managing "frailty" in the CV setting is that there will never be a gold standard test for frailty, but rather the best tool should be adopted according to the specific clinical scenario (Afilalo et al., 2014; Hoogendijk et al., 2019).

There are many scenarios in daily clinical practice in which frailty assessment can provide valuable prognostic information and assist the clinicians in defining optimal care pathways for their patients. Ideally, frailty is not a reason to withhold care but rather represents an opportunity to provide care in a more patient-centered approach. However, guidelines on AF have focused their attention on the appropriate selection of older patients who can derive a clear benefit from OAT, using cardioembolic risk scores which can reliably identify persons at very low risk of ischemic stroke or systemic embolism. Still, as a matter of fact, the most common clinical uncertainties in this setting concern the decision of withholding OAT in patients perceived to have a short life-expectancy and therefore at risk of futile or potentially harmful treatment despite their intrinsic high risk of ischemic stroke or systemic embolism (Bo and Marchionni, 2020; Calsolaro et al., 2021). Actually, if an older subject's life expectancy is substantially shorter than the lag time to benefit from a preventive intervention, administering that intervention exposes that patient to the immediate risks of that intervention (further increased by the presence of comorbidities and functional limitations) with a small chance to survive long enough to get any benefit from it (Lee et al., 2013). Incidence of SSE among older long-term care residents has been reported to range from 0.13% to 0.26% over 30 days (1.43–3.08%/year) in those not prescribed OAT, whereas the monthly incidence of bleeding among those receiving OAT ranged from 0.22% to 0.28% (2.61%–

c)

Study	n	Follow-up (months)[1]	Association frailty-mortality	Measure of efficacy after multivariate analysis (if performed)	Adjustment(s)
Deficit accumulation					
Gugganig et al. (2021)	2 369	24	Higher risk	aHR 14.52 (5.03–41.90) VKA aHR 32.34 (7.04–148.50) DOAC[2]	age, sex, type of oral anticoagulation, use of antiplatelet, AF subtype, education, smoking
Kusano et al. (2021)	5 717	24 (6)	Higher risk	aHR 2.09 (1.42–3.08)	age, sex, body weight, AF subtype, excess alcohol, eGFR, history of ischemic stroke, coronary artery disease, congestive heart failure, dyslipidemia, major bleeding, cancer, frailty, use of antidementia medication, antiplatelet combination, under dose of rivaroxaban
Wilkinson et al. (2020)	20 867	33.6	Higher risk[3]	aHR 4.97 (3.42–7.23) severely frail aHR 3.13 (2.48–3.95) mildly-moderately frail	age, sex, race, and region
Yamamoto et al. (2019)	240	9.2 (1.5–25.5)	Higher risk	n.s.[4]	
Frail phenotype					
Doucet et al. (2008)	209	3	No difference	n.a.	
Gullón et al. (2019)	557	12	Higher risk	n.a.	
Madhavan et al. (2019)	9 479	30.6 (22.0–35.8)	No difference[5]	n.s.	n.s.
Ohta et al. (2021)	120	17.0	n.s.		
Wang et al. (2021)	1 244	12	Higher risk	aHR 3.87 (1.96–7.65)	age, sex, race, education
Multidimensional					
Bo et al. (2017b)	452	9.9 (2.0)	Higher risk	aOR 2.77 (95% CI n.s.)	n.s.
de Simone et al. (2020)	731	28.1 (13.6)	n.s.		

[1] Duration of follow-up was expressed by mean (SD) or median (25°–75° percentiles) where available. Otherwise, stated follow-up time was reported.
[2] Multivariate analyses performed by type of oral anticoagulant therapy.
[3] However, interaction by treatment group was not significant.
[4] Multivariate analysis was performed only for composite outcome (stroke and/or systemic embolism, major bleeding, and all-cause mortality) and showed a higher risk. No difference was observed at univariate analysis for cardiac death.
[5] No interaction frailty-OAT.

3.31%/year) (Kapoor et al., 2022). In a study including hospitalized multimorbid older AF patients, Calsolaro et al. reported that the cumulative incidence of SSE was 2.2% in those receiving OAT and 2.4% in those untreated, the latter having a dramatic shorter survival compared with anticoagulated patients (5.6 vs 15 months, respectively) (Calsolaro et al., 2021). Similarly, among 123 227 patients with incident or prevalent AF (median age 75.2 years, average follow-up 3.2 years), those who were not prescribed an OAT had a lower incidence of stroke (5.2%) and experienced a higher overall mortality (48.8%) than anticoagulated patients (Calderon et al., 2022). These studies suggest that most practicing physicians correctly recognize patients with limited life expectancy and often do not prescribe OAT to them. However, subjective assessment and chronological age are inadequate proxies of biological age in the geriatric population, and mortality indices that incorporate comorbid conditions and functional status could help clinicians improve prediction of life expectancy (Lee et al., 2013; Beard et al., 2016). Therefore, the first issue in delivering effective patient-centered care in the context of AF is how physicians can assess the global health status and residual life expectancy of older patients (World Health Organization, 2015).

Unfortunately, our results do not support the indiscriminate and interchangeable use of "frailty" instruments to assist physicians in this clinical decision-making task. Although frailty tools are still generally not used in everyday cardiology clinical practice, pooled electronic health-related data sets are increasingly pervasive in several clinical settings. However, most of them have not formally demonstrated to be able to identify AF patients expected to derive a poor benefit from an OAT due to their limited residual life-expectancy. The CGA and the CGA-derived MPI have been adopted in several clinical settings and have been recommended to help guide decisions about anticoagulation in older AF patients (Pilotto et al., 2008, 2010, 2020; Bibas et al., 2016; Cruz-Jentoft et al., 2020). Notably, CGA-based prescription of OAT in older AF patients has been independently associated with significant benefit on mortality, not fully accounted for by a reduction of stroke incidence and fatality, but rather reflecting the reduced life-expectancy in those who are intentionally denied OAT in reason of their complex comorbidities and poor health status (Ashburner et al., 2017; Bo et al., 2016, 2017b; Giustozzi et al., 2019; Calsolaro et al., 2021). Notwithstanding, these tools are scarcely used outside the geriatric setting, and their simplified versions for non-geriatricians almost invariably lose some of their power (Polidori et al., 2022).

Whilst there is evidence that the CGA and the CGA-derived MPI may

reliably predict one-year mortality and adverse clinical outcomes in several clinical settings (Stuck et al., 1993; Pilotto et al., 2008, 2010; ; Parker et al., 2018; Briggs et al., 2022), including those with AF (Polidori et al., 2022), our results suggest that frailty tools are not the same when used for clinical decision making about OAT prescription in complex, older AF patients. However, by demonstrating that severe frailty according to DAM is associated with a reduced use of OAT and an increased all-cause mortality, our review provides some support to the recent EHRA practical guide statement (Steffel et al., 2021). Indeed, since the frailty tool to be used in this scenario should identify a surrogate of "*poor health and functional status associated with limited life expectancy*", tools derived from the FP, which is not associated with a higher risk of short-term mortality, are not suitable for this purpose, whereas both the FI and the semi-quantitative CFS, which identify individuals at high risk of all-cause mortality and institutionalization, might be considered reasonable options. Accordingly, our review has demonstrated that there is scant evidence, if any, of a net benefit of OAT in patients with severe frailty according to the FI/CFS, who are those most frequently denied an OAT (Lefebvre et al., 2016; Nguyen et al., 2016b; Induruwa et al., 2017; Papakonstantinou et al., 2018; Shinohara et al., 2019; Yamamoto et al., 2019; Guo et al., 2020), whereas there is some more consistent, yet observational, evidence of a benefit from OAT in older AF subjects with the FP (Martinez et al., 2018; Gullón et al., 2019; Madhavan et al., 2019; Wilkinson et al., 2019; Mailhot et al., 2020; Hindricks et al., 2021; Lip et al., 2021). However, a not negligible limitation of the CFS is its eye-ball subjective assessment of health status and expected survival, that could hinder its inter-rater agreement (Jones et al., 2004; Rockwood et al., 2005). Also, the classification tree recently proposed to assist with the routine CFS scoring does not appear fit for usual cardiology practice (Theou et al., 2021). Despite these limitations, our findings provide some evidence for the use of the CFS as the only handy frailty tool for everyday cardiology clinical practice, as suggested by its graphical representation in the recent 2021 EHRA practical guide on the use of DOACs (Steffel et al., 2021).

4.1. Strengths and limitations of the present systematic review

To our knowledge, this is the first systematic review to summarize current evidence for OAT management in older AF people according to different frailty models. We used a robust search strategy, pre-specified the methods of the review in a published protocol and performed an assessment of the risk of bias for all included studies.

However, we had to deal with a great amount of heterogeneity in terms of study design, setting and outcomes. A wide range of frailty measures was used, and the specific frailty scale cut-offs applied by single study Authors were used, therefore introducing additional heterogeneity, and making meta-analysis not performable.

Moreover, frailty was often diagnosed in an acute hospital setting, despite guidance suggests that frailty assessment is best performed in the community. Most studies excluded patients with cognitive or severe sensory impairment due to the necessity for informed consent, and so they may not be fully representative of the entire older population. Some studies required participants to complete a physical task, which may exclude those with advanced frailty and/or disability. Altogether, these limitations further strengthen our findings by suggesting that most unfit and frail patients might have been excluded in some observational studies. In addition, adjusted estimates were reported and considered for narrative synthesis where available, even if the choice of confounders for adjustment widely varied among studies.

Finally, considering clinical outcomes individually as it was the case in studies included for RQ #2 does not allow to estimate the net clinical benefit of OAT, which is represented by the balance between ischemic stroke risk, hemorrhagic risk and competing causes of death. As already seen in previous studies, the net clinical benefit of anticoagulation decreases with advancing age, being strongly associated with competing risks of death and it is only modestly affected by the age-related increase in ischemic stroke risk. Thus, failing to account for competing risks likely overestimates the net clinical benefit of anticoagulation (Shah et al., 2019).

5. Conclusions

Our findings suggest that indiscriminately relying on tools identifying "frailty" should not be regarded as the gold standard for making decisions on OAT prescription in older AF patients. By recognizing that "*there may be no benefit to OAC in states of severe frailty or where life expectancy is likely to be limited*", the Authors of the 2021 EHRA practical guide endorsed a true holistic approach to the "patient affected by AF" as opposed to the approach to the "AF disease", implying that the assessment of life-expectancy in frail patients may guide optimal, patient-centered care avoiding futility and potential harm from medical treatments. Therefore, we need tools that are feasible in clinical practice across settings, as multidimensional frailty can only be captured by multidimensional assessments. Accordingly, our findings provide evidence that patients with severe frailty according to the DAM are less prescribed with OAT and at higher risk of all-cause mortality despite the use of OAT, suggesting that these scales (namely, the FI and CFS), notwithstanding their inherent limitations, might be useful tools to rapidly recognize patients with limited life expectancy and for whom there is so far scant, if any, evidence of benefit from OAT.

Pragmatic prospective trials including comprehensive multidimensional assessment in older AF in-patients are urgently needed to provide adequate evidence to assist clinical decision-making in everyday clinical practice.

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Data availability

All Authors had all access to the data in this work and approved the submission of the present manuscript. All material in this assignment is Authors' own work and does not involve plagiarism. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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R.P., E.B., M.C.P. and M.B. contributed to the conception and design of the study; R.P. and E.B. developed the search strategy, then independently screened all articles against the eligibility criteria for each RQ and extracted relevant information from all included articles; R.P. and E. B. performed statistical analysis and independently assessed the risk of bias for all included articles; R.P., E.B. and M.B. wrote the main manuscript text; R.P., E.B., M.C.P. and M.B. contributed to the revision and approval of the final manuscript.

Conflicts of interest

The authors of this manuscript declare they have no conflict of interest to disclose.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101761.

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