

STATE-OF-THE-ART REVIEW

Implications of Frailty in Elderly Patients With Electrophysiological Conditions



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ABSTRACT

A growing number of complex older adults are referred for electrophysiological conditions and age alone is insufficient to guide management decisions such as implantable cardioverter-defibrillator (ICD) implantation or atrial fibrillation anticoagulation. The concept of frailty has emerged as a geriatric vital sign to gain insight into physiological reserve and prognostic risk beyond chronological age and comorbidities. To date, a number of published studies have evaluated frailty in patients with electrophysiological conditions. These studies collectively demonstrate that frail patients have an increased prevalence of atrial fibrillation, lower use of oral anticoagulation, higher risk of bleeding complications from oral anticoagulation, and higher risk of stroke and mortality. A paucity of studies have explored frailty in the setting of device implantation, with a signal suggesting that frail heart failure patients may have a lower likelihood of being considered for ICD and cardiac resynchronization therapy devices, and a higher risk of fatal and nonfatal events after ICD and cardiac resynchronization therapy implantation. Whether frailty modulates the risks and benefits of these devices is a critical knowledge gap for which further study is clearly warranted. (J Am Coll Cardiol EP 2016;2:288-94) © 2016 by the American College of Cardiology Foundation.

The burden of electrophysiological (EP) disease in older adults is continuously rising. Atrial fibrillation (AF) and sick sinus syndrome are regarded as “geriatric conditions,” whereas ventricular arrhythmias in failing hearts also affect the elderly in large numbers. Reflecting the advancing age of the general population, the prevalence of AF has reached 3 million in the United States and will continue to increase up to 7.5 million by 2050 (1). The implantation of permanent pacemakers has similarly increased by 56% over the past 10 years (2), and an international survey showed that virtually all 61 countries surveyed had steady increases in implantations of pacemaker and implantable cardioverter-defibrillator (ICD) devices (3). The

appropriateness of prophylactic ICD implantation in the very elderly remains a topic of great debate, with ethical and economical considerations, and widespread variability in practice.

As the EP practitioner is faced with a growing referral base of complex elderly patients, it has become clear that age alone is insufficient to characterize these patients and determine their eligibility for therapies such as ICD or AF anticoagulation. The concept of frailty has emerged as a means of better characterizing the resiliency of older adults beyond their age and comorbidities, in order to refine estimates of predicted risk and guide decisions for individualized care. Thus, the objective of this review is to define frailty for the EP practitioner and synthesize



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the current body of studies that have evaluated frailty using an objective measure in a population of older adults with EP conditions.

FRAILITY DEFINED

Frailty is a geriatric syndrome caused by subclinical impairments in multiple organ systems leading to loss of homeostatic reserve and resiliency. Under physiological stress, be it from illness or iatrogenesis, frail patients suffer a higher rate of fatal and nonfatal complications, functional decline, and disability (4). One of the central impairments is age-related loss of muscle mass and strength known as sarcopenia, which has been operationally defined by a number of phenotypic criteria: slow walking speed, weak muscle strength, unintentional weight loss, low physical activity, and exhaustion (Fried's scale) (5). Tools have been developed to objectively and rapidly quantify these phenotypic criteria and the interrelated domains of cognition, disability and mood in the clinical setting (Table 1) (6). These tools have been adopted in the fields of cardiac surgery, transcatheter valve implantation, heart failure, and ischemic heart disease, but they have yet to achieve meaningful penetration in the field of EP.

The utility of frailty in EP was highlighted by a joint consensus document from the French Societies of Cardiology and Gerontology, which recommended frailty assessment to help guide decisions about AF anticoagulation in the elderly. However, Hanon et al. (7) cautioned that there was a paucity of evidence and that further studies were needed before endorsing implementation of frailty scores. Since then, a number of studies have been published on the topic of frailty in AF and device implantation (Table 2), and there is an unmet need to synthesize the lessons learned from these studies for the practicing clinician and identify knowledge gaps for future research.

IMPLICATIONS OF FRAILITY FOR AF CARE

One of the first observations made in the literature is that frail AF patients are significantly less likely to receive oral anticoagulation therapy (OAC) compared to their nonfrail counterparts. Perera et al. (8) prospectively applied the Edmonton Frail Scale in 220 older adults ≥ 70 years of age admitted to hospital with AF. Frail patients were 8-fold less likely to be discharged home on OAC therapy. Furthermore, frail patients were 3-fold more likely to suffer an embolic stroke or death during follow-up although this was not adjusted for OAC use given the relatively small sample size (8). Lefebvre et al. (9) retrospectively applied

the Canadian Study of Health and Aging Clinical Frailty Scale (CFS) (range 1 to 9) in 682 octogenarian patients with AF admitted to an academic hospital in Montreal, Canada. They discovered 3 independent predictors of anticoagulation approach: frailty, CHADS2 score, and HAS-BLED score. Interestingly, only severe frailty (CFS 7 to 9) was predictive of not receiving OAC whereas mild-to-moderate frailty (CFS 5 to 6) was not predictive. A CFS score of 6 or less was associated with an adjusted odds ratio (OR) of 3.41 for receiving OAC as compared to a CFS score of 7 to 9 (9).

Frewen et al. (10) applied the Fried frailty scale in a population-based cohort from Ireland and documented prevalent AF in 118 of 4,890 adults ≥ 50 years of age. In an age-adjusted model, frailty was surprisingly (and counterintuitively) associated with a lower likelihood of not receiving OAC (adjusted OR: 0.43; 95% confidence interval [CI]: 0.19 to 0.96). The authors acknowledged that their results contradicted those of Perera et al. (8), and hypothesized that frail patients may have greater comorbidity burden and hence higher stroke risk meriting OAC (10).

The ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry applied a modified version of the Fried frailty scale in a national sample of 10,130 adults with prevalent or incident AF (11,12). O'Brien et al. (13) reported that 1,330 (13.1%) patients had contraindications to OAC, and that those with contraindications were 3-fold more likely to be frail. Frailty was the third most often cited reason for not prescribing OAC, after prior bleeding event or high bleeding risk, and patient refusal. In frail patients, the physician's global assessment of stroke and bleeding risk was more often discordant with the objective CHADS2 and ATRIA scores (14). Steinberg et al. (15) more recently reported the frail patients were less likely to receive a prescription for the novel anticoagulant (novel oral anticoagulation therapy [NOAC]) drug dabigatran. Frail patients were also 50% less likely to be treated with a rhythm control strategy (16). Frailty was 1 of 4 risk factors for hospital admission in this AF population (adjusted hazard ratio: 1.20; 95% CI: 1.05 to 1.39); other risk factors were heart failure, increased heart rate, and AF symptom class (17). The ORBIT-AF group developed a risk model to predict major bleeding events in older adults receiving OAC (18). Although frailty was not selected for inclusion in the final model, unpublished data provided by the authors revealed that the prevalence of frailty was significantly greater in patients that experienced a major

ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation
CI	= confidence interval
CFS	= Clinical Frailty Scale
CRP	= C-reactive protein
CRT	= cardiac resynchronization therapy
EP	= electrophysiology
ICD	= implantable cardioverter-defibrillator
NOAC	= novel oral anticoagulation therapy
OAC	= oral anticoagulation therapy

TABLE 1 Assessment of Frailty and Interrelated Geriatric Domains

Criteria	Measurement Tool	Cutoff
Slowness	5-m gait speed*	≤0.83 m/s (slow) ≤0.50–0.65 m/s (very slow)
Weakness	Handgrip strength†	♂: ≤30 kg ♀: ≤20 kg
Physical inactivity	Physical activity questionnaire	♂: <383 kcal/week ♀: <270 kcal/week
Weight loss	Self-reported unintentional weight loss	>10 lbs or >5% in past year
Exhaustion	"Everything I did was an effort" "I could not get going"	"Moderate amount of time" or "Most of the time" (to either)
Cognition	Montreal Cognitive Assessment	Score <26 of 30
Mood	Geriatric Depression Scale (5 items)	Score ≥2 of 5
Disability	Katz Activities of Daily Living (6 items)	Score ≥1 of 6

Fried scale consists of slowness, weakness, physical inactivity, weight loss, and exhaustion, with ≥3/5 positive items required to classify a patient as frail. *Patient is asked to walk at a comfortable pace from 0-m start line to past 5-m finish line, cue to start and stop stopwatch is first footfall after start line and first footfall after finish line, repeated 3 times and average time is recorded. †Patient is asked to squeeze a handgrip dynamometer as hard as possible, repeated 3 times (with each hand and then with strongest hand) and maximum value is recorded.

bleeding complication as compared with those that did not (8% vs. 5%; $p = 0.005$).

Three studies (De Breucker et al. [19], Maes et al. [20], Denoel et al. [21]) applied the Identification of Seniors at Risk frailty questionnaire in older adults who were hospitalized with AF. Based on their cutoff of Identification of Seniors at Risk score ≥2, 84% of patients were frail but this was not predictive of OAC use. The proportion of patients receiving OAC ranged from 50% to 61%. In multivariable models, risk factors for not receiving OAC were: prescription of antiplatelet agent (OR: 5.3; 95% CI: 3.8 to 7.5), ethanol abuse (OR: 4.0; 95% CI: 1.4 to 13.3), and ≥90 years of age (OR: 2.0; 95% CI: 1.2 to 3.4). The geriatric characteristics of cognitive impairment, malnutrition, depression, falls, and functional dependence were not found to be independent risk factors [19–21]. However, frailty seemed to be a risk factor for not being therapeutic on OAC, with only 21% of patient in target range.

Thus, the evidence demonstrates that frail patients are 2 to 8 times less likely to receive OAC therapy for stroke prevention in AF, despite the fact that they are at higher risk of subsequent stroke and mortality. An analysis from 5,888 participants in the Cardiovascular Health Study showed that frailty (as measured by slow gait speed) was an independent risk factor for stroke-related mortality, including cardioembolic and non-cardioembolic strokes [22]. This "treatment paradox" may be explained by clinicians not prescribing OAC in frail patients for fear of bleeding complications. That said, there has yet to be a published study proving that frail patients are at higher risk of bleeding or other complications when treated with OAC.

In addition to the link between frailty and AF treatment, there is epidemiological and translational data to support a link between frailty and AF co-prevalence. Polidoro et al. [23] applied a modified version of the Searle frailty scale in adults 56 to 96 years of age admitted to an internal medicine ward in Italy. In this cross-sectional study, the investigators enrolled 70 patients with AF and 70 without, and found that AF was associated with a 4-fold increase in frailty (adjusted OR: 4.09, 95% CI: 1.51 to 11.07) after adjusting for age, sex, cardiovascular disease, and risk factors [23].

Beyond advanced age, frailty and AF share common risk factors at the pathophysiological level. Frailty and AF are both associated with low-grade inflammation, as evidenced by up-regulation of inflammatory cytokines such as interleukin-6 and an accompanying rise in C-reactive protein (CRP) [24–26]. Cross-sectional studies have shown that patients with prevalent AF have higher levels of CRP than age-matched controls [27,28]. Longitudinal studies have shown that individuals with high levels of CRP are at risk for developing de novo incident AF [29]. Acute systemic inflammation is thought to play a role in triggering AF in settings such as cardiac surgery, sepsis, and critical care [30–32]. Similarly, acute and chronic inflammatory states exert adverse effects on muscle, such that CRP (and other inflammatory makers) are consistently correlated with frailty and sarcopenia [24,33–35].

Another common risk factor between frailty and AF is impairment in cardiac autonomic control as evidenced by decreased HRV [36,37]. Studies have shown that decreased HRV often precedes episodes of paroxysmal AF and, in an analysis from the Framingham Heart Study, that it may be predictive of incident AF [35]. Low-frequency oscillation was the HRV parameter that best predicted new-onset AF in a middle-aged Finnish cohort [38]. Similarly, decreased HRV has garnered interest as a candidate biomarker for frailty. The rationale being that the healthy cardiovascular system is characterized by a dynamic complexity that is charged with detecting and adapting to various changes in order to maintain homeostasis—the high variability in our basic heart rate is proof of this concept. As we age, clinical and subclinical impairments in cardiovascular physiology render the system less dynamic and complex, and thus heart rate less variable [39].

IMPLICATIONS OF FRAILTY FOR DEVICE IMPLANTATION

Use of ICDs for primary prevention in older adults remains controversial and polarizing within the EP

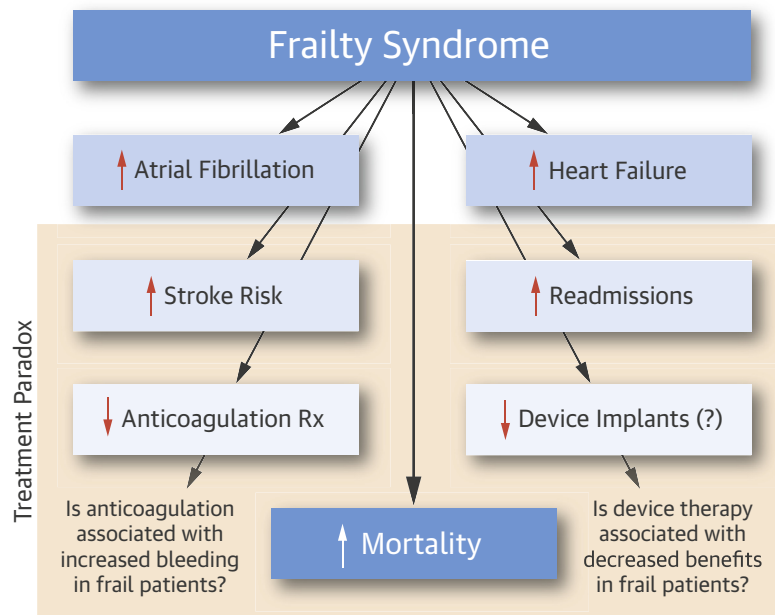
TABLE 2 Reviewed Studies

First Author (Year) (Ref. #)	Population (n)	Frailty Scale	Frailty-Related Findings
Atrial fibrillation			
Lefebvre et al. (2015) (9)	Inpatients ≥ 80 yrs of age, AF (682)	Canadian Study of Health and Aging Clinical Frailty Scale	Nonfrail to moderately frail patients were more likely to receive OAC than severely frail patients (OR: 3.41)*
Denoe et al. (2014) (21)	Older adults admitted with chronic AF, age ≥ 75 yrs (142)	ISAR scale	Frailty prevalence 84% (ISAR score ≥ 2); Among patients with an indication for OAC, 61% received it
Maes et al. (2014) (20)	Frail older adults admitted with AF and CHADS ≥ 2 , ≥ 75 yrs of age (773)	ISAR scale	Among frail AF patients, 50% received OAC and 21% had therapeutic INR; Factors associated with OAC underuse were age ≥ 90 , antiplatelet therapy, ethanol abuse
Frewen et al. (2013) (10)	Community-dwelling adults in Ireland, ≥ 50 yrs of age (4,890)	Fried scale	AF prevalence 3% overall; Frailty associated with less nontreatment of AF (OR: 0.43)
Polidoro et al. (2013) (23)	Older adults admitted to hospital, mean 79 yrs of age (140)	Searle scale (modified)	Frailty independently associated with prevalent AF (AF: 89% frail vs. no AF: 67% frail)
De Breucker et al. (2010) (19)	Older adults admitted with chronic AF, mean 84 yrs of age (111)	ISAR scale	Frailty prevalence 90% (ISAR score ≥ 2); Among all patients, 49% were not receiving OAC on admission despite similar CHADS2 scores
Perera et al. (2009) (8)	Older adults admitted with AF, ≥ 70 yrs of age (220)	Edmonton frail scale	Frailty prevalence 64%; frailty associated with not receiving OAC on admission and discharge; frailty predictive of embolic stroke (RR: 3.5) and mortality (RR: 2.8)
O'Brien et al. (2014) (13)	Outpatients with incident or prevalent AF, median 75 yrs of age (10,130)	Modified Fried scale	Among patients with a physician-documented contraindication to OAC (n = 1,330), 17.6% were due to "frequent falls/frailty"
Steinberg et al. (2014) (17)	Outpatients with incident or prevalent AF, median 75 yrs of age (9,484)	Modified Fried scale	Frailty predictive of all-cause hospitalization (HR: 1.20)
Steinberg et al. (2014) (17)	Outpatients with incident or prevalent AF, median 75 yrs of age (10,094)	Modified Fried scale	Frailty associated with a higher provider-assessed bleeding and stroke risk versus objective calculated risk estimates
Steinberg et al. (2013) (16)	Outpatients with incident or prevalent AF, median 75 yrs of age (10,061)	Modified Fried scale	Frailty prevalence higher in rate control group versus rhythm control group (6.8% vs. 3.5%); frailty associated with not receiving a rhythm control strategy
Steinberg et al. (2013) (16)	Outpatients with incident or prevalent AF, median 75 yrs of age (9,974)	Modified Fried scale	Frailty prevalence higher in no dabigatran group versus dabigatran group (6.0% vs. 3.5%); frailty associated with not receiving NOAC
Devices			
Dominguez-Rodriguez et al. (2015) (49)	Older adults scheduled for CRT-D implantation, ≥ 70 yrs of age (102)	Fried scale	Frailty prevalence 28%; frailty predictive of increased decompensated HF episodes after CRT-D implantation (HR: 4.55)
Green et al. (2016) (47)	Older adults undergoing primary prevention ICD implantation, ≥ 65 yrs of age (83,792)	Adjusted Clinical Groups System (based on ICD-9 codes)	Frailty prevalence 10%; frailty predictive of increased 1-year mortality (22% if frail vs. 12% overall)
Hess et al. (2013) (11)	Outpatients with incident or prevalent AF, median 75 yrs of age (10,096)	Modified Fried scale	Frailty was independently associated with not receiving evidence based therapies for HF, including ICDs (OR: 0.75)
AF = atrial fibrillation; CRT-D = cardiac resynchronization therapy with defibrillator; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; ICD-9 = International Classification of Diseases, Ninth Revision; INR = international normalized ratio; ISAR = identification of seniors at risk; OAC = oral anticoagulation therapy; OR = odds ratio; RR = relative risk.			

community, particularly at the extremes of age (>80 to 90 years of age) (40). Those in favor of restricting use state that frail patients have a higher risk of death from competing noncardiac causes (41,42) and this may mitigate the benefits of ICD. A combined analysis of 4 clinical trials showed that 75% of patients had multiple comorbidities and that the benefits of ICD were inversely proportional to the number of comorbidities (43). Similarly, observational data has shown that the benefits of ICD were nullified in the highest-risk subset of older adults with predicted risk of mortality $>20\%$ at 1 year (unlikely to be included in clinical trials) (31). Conversely, those *not* in favor of restricting devices on the basis of frailty state that the vast majority of frail heart failure patients survive >2 years (44), and that above 75 years of age, the effectiveness of ICD is backed by subgroup analyses from

large-scale clinical trials (45) and the absolute risk of procedural complications is low ($\leq 4.5\%$) (46).

The interaction between frailty status and ICD effectiveness has yet to be defined since frailty was not historically measured or recorded in clinical trials. Some have argued that the healthy-candidate bias resulting from unmeasured differences in frailty have inflated the reported benefits of ICD implantation in older adults (33). Observational studies have provided data on the prognostic implications of frailty in this setting. A retrospective study of 83,792 Medicare patients undergoing ICD implantation for primary prevention ascertained frailty via a panel of 99 International Classification of Diseases, Ninth Revision codes representing malnutrition, dementia, visual impairment, decubitus ulcer, incontinence, weight loss, lack of social support, difficulty walking, and

CENTRAL ILLUSTRATION Effect of Frailty on Prevalence, Prognosis, and Therapy for Electrophysiology Conditions

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Frailty is associated with an increased prevalence of atrial fibrillation and heart failure. Although frail patients are more likely to suffer fatal and nonfatal events, they are less likely to be treated with anticoagulation therapy for atrial fibrillation and implantable cardioverter-defibrillator or cardiac resynchronization device therapy for heart failure. Further research is needed to elucidate the risks and benefits of these therapeutic interventions in frail patients and accordingly determine whether this treatment paradox is justified (or not).

falls (47). Frail patients were found to have a 22% risk of mortality at 1 year compared to 12% overall; risk was magnified in the presence of concomitant dementia, diabetes, and chronic obstructive pulmonary disease. The likelihood of being referred for ICD appears (somewhat indirectly) to be decreased in frail heart failure patients. An analysis from the ORBIT-AF registry showed a decreased use of therapies including but not limited to ICD among patients with AF and comorbid heart failure (OR: 0.75; 95% CI: 0.59 to 0.95) (11).

The type of device being implanted and the desired goals of therapy are highly relevant to decision making in this challenging group of patients. Cardiac resynchronization therapy (CRT) may have a meaningful impact (and hence logical indication) in frail patients because it seeks to improve the patient-centered outcomes of functional status and quality of life (48). Dominguez-Rodriguez et al. (49) applied the Fried frailty scale in 102 elderly patients ≥ 70 years of age that underwent CRT with defibrillator implantation for nonischemic cardiomyopathy.

Twenty-nine patients were identified as frail (28%). Frailty was a strong predictor of the primary endpoint of decompensated heart failure over 1 year of follow-up after CRT with defibrillator implantation (hazard ratio: 4.55; 95% CI: 1.73 to 12.01) (49). In our experience, the improvement in physical function observed after CRT implantation often leads to improvements in gait speed and frailty scores (i.e., “de-frails” patients). Prophylactic ICD therapy does not necessarily have the same effect because its desired effect is prevention of sudden cardiac death, which occurs in a minority of patients and is superseded by death from non-arrhythmogenic causes in most frail elders.

KNOWLEDGE GAPS

The studies identified were skewed toward AF, with fewer studies addressing device implantation, and no studies directly addressing other aspects of EP such as permanent pacemakers, left atrial appendage occluder devices, and ablation procedures. Only

1 study addressed the use of NOACs, and it remains to be seen whether the practitioner's hesitancy in prescribing vitamin K antagonists to frail elders will carry over with the newer (more stable) agents. The relationship between frailty status and OAC or NOAC related bleeding complications is a critical knowledge gap that has yet to be addressed. If there exists such a relationship, then frailty may foreseeably be integrated in bleeding risk scores (e.g., HAS-BLED) to improve discrimination. To date, risk scores have only considered chronological age (50,51), whereas advanced biological age (i.e., frailty) may ultimately be more predictive. The studies reviewed are subject to the usual limitations associated with observational data, and ultimately, an adequately powered randomized trial is needed to demonstrate the effect of frailty on treatment risk or response.

CONCLUSIONS AND RECOMMENDATIONS

This review has highlighted the relevance of frailty in predicting risk and guiding treatment decisions for older adults with EP conditions (**Central Illustration**). The main findings can be summarized as follows: 1) a substantial proportion of older adults with AF and device-eligible heart failure have objective evidence of frailty; 2) frailty appears to be an important patient-related predictor for anticoagulation approach in AF and possibly for ICD use in chronic heart failure; and 3) frailty is a major risk factor for death and readmission in patients with AF and those with chronic heart failure undergoing ICD or CRT implantation.

As the field of EP continues to expand, complex elderly patients are increasingly being referred such that the concept of frailty is directly relevant to clinical practice. Frailty is associated with a higher

prevalence of AF and seems to be a decisive factor in the management of this population. Frail patients fare worse than their nonfrail elderly and are less aggressively treated; whether this "treatment paradox" is justified or not remains to be elucidated—studies are needed to clarify the relationship between frailty status and treatment-related benefits and risks. Unfortunately, this data cannot be extrapolated from randomized clinical trials since frailty was not objectively measured in these protocols. Moving forward, integration of frailty measures in trial protocols is strongly recommended to enable comparative-effectiveness research.

We recommend that the basic frailty assessment include a 5-m gait speed, and if feasible, timed chair stands and balance (to calculate the short physical performance battery) (52) as well as handgrip strength and questions about weight loss, physical activity, and exhaustion (to calculate the Fried score). These frailty assessment tools have been validated in patients with various forms of cardiovascular disease (6), including the EP conditions covered in this review. Additional geriatric domains may be added, including activities of daily living and assessment of cognitive function, although these should not be equated with frailty because they represent interrelated yet distinct concepts. With this information, the EP practitioner will be better equipped for risk prediction and patient selection in this challenging population.

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REFERENCES

1. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009;104:1534-9.
2. Greenspon AJ, Patel JD, Lau E, et al. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol* 2012;60:1540-5.
3. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009—a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* 2011;34:1013-27.
4. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm—issues and controversies. *J Gerontol A Biol Sci Med Sci* 2007;62:731-7.
5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-56.
6. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;63:747-62.
7. Hanon O, Assayag P, Belmin J, et al. Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of atrial fibrillation in elderly people. *Arch Cardiovasc Dis* 2013;106:303-23.
8. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age Ageing* 2009;38:156-62.
9. Lefebvre MD, St-Onge M, Glazer-Cavanagh M, et al. The effect of bleeding risk and frailty status on anticoagulation patterns in octogenarians with atrial fibrillation: The FRAIL-AF study. *Can J Cardiol* 2015;32:169-76.
10. Frewen J, Finucane C, Cronin H, et al. Factors that influence awareness and treatment of atrial fibrillation in older adults. *Qjm* 2013;106:415-24.
11. Hess PL, Kim S, Piccini JP, et al. Use of evidence-based cardiac prevention therapy among outpatients with atrial fibrillation. *Am J Med* 2013;126:625-32.e1.
12. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J* 2011;162:606-12.e1.

13. O'Brien EC, Holmes DN, Ansell JE, et al. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 2014;167:601-9.e1.
14. Steinberg BA, Kim S, Thomas L, et al. Lack of concordance between empirical scores and physician assessments of stroke and bleeding risk in atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Circulation* 2014;129:2005-12.
15. Steinberg BA, Holmes DN, Piccini JP, et al. Early adoption of dabigatran and its dosing in US patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. *J Am Heart Assoc* 2013;2:e000535.
16. Steinberg BA, Holmes DN, Ezekowitz MD, et al. Rate versus rhythm control for management of atrial fibrillation in clinical practice: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 2013;165:622-9.
17. Steinberg BA, Kim S, Fonarow GC, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2014;167:735-42.e2.
18. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015.
19. De Breucker S, Herzog G, Peppersack T. Could geriatric characteristics explain the under-prescription of anticoagulation therapy for older patients admitted with atrial fibrillation? A retrospective observational study. *Drugs Aging* 2010;27:807-13.
20. Maes F, Dalleur O, Henrard S, et al. Risk scores and geriatric profile: can they really help us in anticoagulation decision making among older patients suffering from atrial fibrillation? *Clin Interv Aging* 2014;9:1091-9.
21. Denoel P, Vanderstraeten J, Mols P. Could some geriatric characteristics hinder the prescription of anticoagulants in atrial fibrillation in the elderly? *J Aging Res* 2014;2014:693740.
22. Longstreth WT Jr., Bernick C, Fitzpatrick A, et al. Frequency and predictors of stroke death in 5,888 participants in the Cardiovascular Health Study. *Neurology* 2001;56:368-75.
23. Polidoro A, Stefanelli F, Ciacciarelli M, Pacelli A, Di Sanzo D, Alessandri C. Frailty in patients affected by atrial fibrillation. *Arch Gerontol Geriatr* 2013;57:325-7.
24. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med* 2002;162:2333-41.
25. Cesari M, Penninx BW, Pahor M, et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2004;59:242-8.
26. Schaap LA, Pluijm SM, Deeg DJ, et al. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. *J Gerontol A Biol Sci Med Sci* 2009;64:1183-9.
27. Balouch MA, Kolek MJ, Darbar D. Improved understanding of the pathophysiology of atrial fibrillation through the lens of discrete pathological pathways. *Glob Cardiol Sci Pract* 2014;2014:24-36.
28. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;104:2886-91.
29. Aviles RJ, Martin DO, Apperson-Hansen C, et al. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;108:3006-10.
30. Kanji S, Williamson DR, Yaghi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. *J Crit Care* 2012;27:326.e1-8.
31. Christian SA, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. *J Crit Care* 2008;23:532-6.
32. Bramer S, van Straten AH, Soliman Hamad MA, Berrekouw E, Martens EJ, Maessen JG. The impact of new-onset postoperative atrial fibrillation on mortality after coronary artery bypass grafting. *Ann Thorac Surg* 2010;90:443-9.
33. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor- α with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci* 2002;57:M326-32.
34. Chang SS, Weiss CO, Xue QL, Fried LP. Association between inflammatory-related disease burden and frailty: results from the Women's Health and Aging Studies (WHAS) I and II. *Arch Gerontol Geriatr* 2012;54:9-15.
35. Singh JP, Larson MG, Levy D, Evans JC, Tsuji H, Benjamin EJ. Is baseline autonomic tone associated with new onset atrial fibrillation?: Insights from the framingham heart study. *Ann Noninvasive Electrocardiol* 2004;9:215-20.
36. Chaves PH, Varadhan R, Lipsitz LA, et al. Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women. *J Am Geriatr Soc* 2008;56:1698-703.
37. Varadhan R, Chaves PH, Lipsitz LA, et al. Frailty and impaired cardiac autonomic control: new insights from principal components aggregation of traditional heart rate variability indices. *J Gerontol A Biol Sci Med Sci* 2009;64:682-7.
38. Perkiomaki J, Ukkola O, Kiviniemi A, et al. Heart rate variability findings as a predictor of atrial fibrillation in middle-aged population. *J Cardiovasc Electrophysiol* 2014;25:719-24.
39. Kaplan DT, Furman MI, Pincus SM, Ryan SM, Lipsitz LA, Goldberger AL. Aging and the complexity of cardiovascular dynamics. *Biophys J* 1991;59:945-9.
40. Barra S, Providencia R, Paiva L, Heck P, Agarwal S. Implantable cardioverter-defibrillators in the elderly: rationale and specific age-related considerations. *Europace* 2015;17:174-86.
41. Shmilyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. *Ageing Res Rev* 2013;12:719-36.
42. Goldfarb M, Sheppard R, Afialo J. Prognostic and Therapeutic Implications of Frailty in Older Adults with Heart Failure. *Curr Cardiol Rep* 2015;17:92.
43. Steinberg BA, Al-Khatib SM, Edwards R, et al. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. *J Am Coll Cardiol HF* 2014;2:623-9.
44. Cacciatore F, Abete P, Mazzella F, et al. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest* 2005;35:723-30.
45. Kong MH, Al-Khatib SM, Sanders GD, Hasselblad V, Peterson ED. Use of implantable cardioverter-defibrillators for primary prevention in older patients: a systematic literature review and meta-analysis. *Cardiol J* 2011;18:503-14.
46. Tsai V, Goldstein MK, Hsia HH, Wang Y, Curtis J, Heidenreich PA. Influence of age on perioperative complications among patients undergoing implantable cardioverter-defibrillators for primary prevention in the United States. *Circ Cardiovasc Qual Outcomes* 2011;4:549-56.
47. Green AR, Leff B, Wang Y, et al. Geriatric conditions in patients undergoing defibrillator implantation for prevention of sudden cardiac death: prevalence and impact on mortality. *Circ Cardiovasc Qual Outcomes* 2016;9:23-30.
48. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
49. Dominguez-Rodriguez A, Abreu-Gonzalez P, Jimenez-Sosa A, et al. The impact of frailty in older patients with non-ischaemic cardiomyopathy after implantation of cardiac resynchronization therapy defibrillator. *Europace* 2015;17:598-602.
50. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet* 1996;348:423-8.
51. Poli D, Antonucci E, Testa S, Tassetto A, Ageno W, Palareti G. Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. *Circulation* 2011;124:824-9.
52. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85-94.

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