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TREATMENT OF ATRIAL FIBRILLATION IN NURSING HOMES: A PLACE FOR DIRECT ACTING ORAL ANTICOAGULANTS?

M. ALCUSKY, K.L. LAPANE

University of Massachusetts Medical School, Worcester, USA. Corresponding author: Matthew Alcusky, Post-doctoral fellow, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, Phone: 508-856-8965, Fax: (508) 856-8993, email: matthew.alcusky@umassmed.edu

Abstract: Atrial fibrillation affects ~1 in 6 long-term nursing home residents. After an ischemic stroke hospitalization, ~2/3 of nursing home residents receive skilled nursing care and functional independence continues to decline, a process often complicated by rehospitalization and stroke recurrence. Due to advanced age and multimorbidity, anticoagulation is indicated for essentially all nursing home residents with atrial fibrillation. Yet as the severity of cognitive and/or functional deficits increases, the net clinical benefit of anticoagulation becomes less certain. Therefore, nursing home residents are most likely to be in need of supportive clinical evidence regarding anticoagulation, but least likely to have risk/benefit information from trials. Approximately half of US nursing home residents with atrial fibrillation have been treated with warfarin historically. Trial evidence in ambulatory older adults supports a large relative risk reduction (~50%) for stroke with warfarin versus aspirin and generally comparable bleeding risk. However, nursing home residents have a complex confluence of multimorbidity and polypharmacy that distinguishes them from healthier, non-institutionalized trial populations. Exemplifying this distinction, maintaining nursing home residents treated with warfarin within the therapeutic range has been a challenge historically, increasing the risk of adverse events. The direct acting oral anticoagulants may be a preferred therapeutic option for an indeterminate fraction of nursing home residents with atrial fibrillation. A review of the literature on anticoagulant use in nursing homes underscores the need for evidence on the effectiveness and safety of the direct acting oral anticoagulants specific to clinically complex older adults..

Key words: Nursing homes, warfarin, direct acting oral anticoagulants, atrial fibrillation.

Introduction

The number of people with atrial fibrillation is on the rise, driven by increases in the prevalence of certain atrial fibrillation risk factors (e.g., obesity, diabetes) (1–3), population growth, and the overall aging of the population (4). For example, in the United States, ~ 6.1 million adults had diagnosed atrial fibrillation in 2010 (4), which is projected to increase to 12.1 million by 2050 (4). The age and sex-adjusted incidence of atrial fibrillation increased 21% from 1980 to 2000 (4). Ischemic stroke risk increases 5-fold in the presence of atrial fibrillation (5). Ischemic strokes caused by atrial fibrillation are more severe on average than other etiologies (6–8). In adults aged 80-89 years, atrial fibrillation is responsible for one in four strokes (4, 5). Ischemic stroke has devastating consequences for patients' functional independence, cognitive status, and quality of life (9–11), effects which are more severe at older ages (12). After a stroke, patients lose the equivalent of two activities of daily living (11) and quality of life is diminished (10). Incident stroke is associated with an acute decline in measures of global cognition, new learning, and verbal memory, and a sustained increase in the rate of incident cognitive impairment (9). Considering five out of six patients with atrial fibrillation are at least 65 years of age (13), improving atrial fibrillation management among older adults is imperative to reduce the burden of ischemic stroke.

This article reviews information regarding the use of anticoagulants in nursing homes. We review the importance of nursing homes as a segment of the healthcare industry. A summary of the evidence on anticoagulants is also provided. We then provide a review of what is known about anticoagulant use in nursing home settings. The information provided in this review highlights the "geriatric pharmacoparadox", coined because the understudied population of nursing home residents are most likely to be in need of supportive clinical evidence regarding anticoagulation, but least likely to have risk/benefit information from trials. The review highlights research gaps regarding the contemporary use of anticoagulants in nursing home residents.

Nursing homes as an important segment in the healthcare industry

The United States, like so many countries, is experiencing a "silver tsunami" owing to the aging of the population. By 2060, it is estimated that almost 1 in 4 Americans will be at least 65 years of age (currently 15%) (14, 15). During this time period, the number of Americans over 85 years of age is expected to triple to ~19.7 million, representing 4.7% of the total United States population (2.0% currently) (14). Given these shifts in the age distribution, the need for nursing home care is likely to increase. By 2040 nursing homes are expected to provide care for 7.3 million patients annually (16).

Currently, in the United States, on any given day ~1.4 million residents live in one of the ~16,000 nursing homes

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(17). By 2050, the demand for long-term care services is projected to nearly double. Among people aged at least 85 years, nursing home care accounts for the largest share of healthcare expenditures (18). This is because people in this age group often have a high disability rate and need help in activities of daily living (19, 20). In the United States, Medicaid (21) bears the brunt of most nursing home costs (e.g., $60 billion in 2016) (22). With a staggering $92,000 median annual per-resident nursing home cost coupled with annual expenditure growth rates at 3.5% (23), reducing acute and post-acute care expenditures, while striving for improved outcomes with pharmacotherapy, is imperative. Because most nursing home residents experience multimorbidity and have advanced age, virtually all nursing home residents with atrial fibrillation have indications for anticoagulation (CHA2DS2-VASc score >2) (24). Given the severity of cognitive and/or functional deficits of nursing home residents, the net clinical benefit of anticoagulation is often less certain compared with independent community dwelling older adults.

Changing landscape of anticoagulant use

There has been a dramatic change in the landscape of anticoagulation in the past 7 years. Until 2010, vitamin K antagonists were the only marketed oral anticoagulants (i.e., only warfarin in the US). Meta-analysis of clinical trials supports a 64% risk reduction for stroke and a 0.3% increased risk for serious extracranial hemorrhage with warfarin versus placebo in patients with atrial fibrillation (25). Anticoagulation is recommended for high risk patients (CHADS2 or CHA2DS2-VASc >2) with atrial fibrillation (24), but for warfarin users, concerns remain regarding time spent outside the therapeutic range. In 9 of 15 trials, the time in therapeutic range for warfarin was >65% (26). Yet, in the "real world", treated patients (26) including nursing home residents27 spent ~50% of time outside the therapeutic range, placing them at risk for adverse events (26).

Alternatives to warfarin— direct acting oral anticoagulants— have entered the market since 2010. In the United States, dabigatran was the first to be approved by the Food and Drug Administration in the fall of 2010, followed by rivaroxaban (2011), apixaban (2012), and edoxaban (2015). These 4 medications were approved for patients with atrial fibrillation based upon head to head Phase III clinical trial comparisons versus warfarin (28–31). Reviews of the trial and post-marketing observational evidence have indicated the direct acting oral anticoagulants are generally comparable in safety and effectiveness to warfarin, with a potentially lower risk of intracranial hemorrhage (32, 33). Unlike warfarin, the direct acting agents do not typically require strict monitoring (34–37). For these reasons, it comes as no surprise that direct acting oral anticoagulant use rose rapidly in the United States (38, 39), initially displacing warfarin (38) and subsequently expanding the number of treated community dwelling atrial fibrillation patients (40). Yet, clinicians caring for nursing home residents may be hesitant to extrapolate trial evidence to their patients.

Use of anticoagulants in nursing homes

Most nursing home residents with atrial fibrillation are high risk and qualify for anticoagulation (41, 42). Yet, historically, fewer than half of nursing home residents with atrial fibrillation were treated (41, 42) owing to high perceived bleeding risk (43, 44) labile anticoagulation with warfarin in nursing homes (~50% of time outside of therapeutic range) (27, 45, 46) and a high burden of complicating clinical factors (i.e., polypharmacy, comorbidities, cognitive impairment, functional limitations) (17, 47, 48). Only one-third of residents newly initiating warfarin for atrial fibrillation remain on treatment at 1-year, suggesting improvements are needed in pharmacologic management of these patients (49). Contemporary evidence remains scarce, as evaluations of anticoagulation practices in nursing homes were regional in scope, and were based on data before direct acting oral anticoagulants were approved by the Food and Drug Administration (27, 41, 42, 44–46, 49–51).

The uptake of direct acting oral anticoagulants in nursing homes remains unknown. It is likely that the diffusion of direct acting oral anticoagulants to nursing home residents may be slower than in the community (which may be appropriate owing to the absence of evidence in a clinically complex population). There is a paucity of information regarding the safety and effectiveness of warfarin and direct acting oral anticoagulants in the oldest old, complicating the selection of a specific medication (52). The Birmingham Atrial Fibrillation Treatment of the Aged randomized clinical trial comparing warfarin to aspirin in community dwelling patients over 75 years of age constitutes the strongest evidence in support of the anticoagulation of older adults (53). The study reported a ~50% reduction in the rate of stroke and a comparable bleeding risk in those randomized to warfarin (53), however the time in therapeutic range was higher (67%) than is typical in nursing home residents. Even with the availability of direct acting oral anticoagulants, appropriately managed warfarin in older adults is expected to be the preferred regimen for certain patients, especially where frequent monitoring is viewed as beneficial. Beyond the decision to initiate anticoagulation, the question of if and when to discontinue therapy in the context of changes in a resident's clinical and functional status is also important. In Veterans at least 65 years of age treated with warfarin for atrial fibrillation, 16% continued anticoagulation after an incident dementia diagnosis and the rates of stroke and death were lower (with no excess rates of gastrointestinal bleeding) in those who persisted with warfarin compared with those who discontinued (54).

In the nursing home setting, concern about safe use of warfarin is warranted. Gurwitz et al documented that adverse events associated with warfarin therapy are common in the nursing home setting (27). The authors noted that most of

the warfarin-related adverse events were preventable with appropriate warfarin management at the prescribing and monitoring stages (27). Recent research has cautioned that practical advice on handling of warfarin treatment and drug interactions is needed because electronic alerts embedded within electronic medical records appeared to be insufficient to change practice (55).

Contemporary evidence for the treatment of atrial fibrillation is lacking in nursing homes. The frequency of warfarin use and the quality of monitoring may have changed since earlier evaluations were conducted. The availability of direct acting oral anticoagulants requiring less monitoring and having less potential for interactions may have increased the number of residents receiving oral anticoagulants. Moreover, shifts in anticoagulant utilization precipitated by the emergence of the direct acting agents may have improved outcomes for residents with atrial fibrillation. Yet in reality, we simply do not know.

Evidence from clinical trials should not be extrapolated to nursing home residents

Evidence on the safety and effectiveness of the direct acting oral anticoagulants specific to nursing home residents is needed. Decision-making in nursing homes is often complicated by the presence of cognitive impairment and functional limitations. Whether benefits of anticoagulation outweigh harms among residents with severe cognitive impairment and physical limitations is unknown. Advanced age, comorbid diseases, and polypharmacy increase risk for adverse events. Beyond the initial decision to treat, maintenance of warfarin within a narrow therapeutic range is challenging in nursing homes. Nursing home residents have been excluded from recent evaluations of anticoagulation practices (38, 39) and have not been identified in recently published trials (28–31).

Conclusions

The 2016 Joint Scientific Statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society (56) called for atrial fibrillation research on anticoagulant comparative effectiveness, adverse event risks by specific anticoagulant, consequences of non-adherence, and cessation of anticoagulation in older adults. One in three nursing home residents with atrial fibrillation have a history of stroke, placing them at increased risk of recurrent stroke (46). Yet fewer than 50% of nursing home residents with atrial fibrillation receive anticoagulation (41, 42, 45).

Evidence to inform anticoagulant treatment decisions among the ~240,000 American nursing home residents with atrial fibrillation is needed (17, 45). Clinical trials of direct acting oral anticoagulants will not likely be conducted in nursing homes despite the evidence needed to inform the difficult treatment decisions facing residents and their providers. In the absence of the "gold-standard" study design, observational research using large databases of real-world patients is well-suited to handle treatment effect heterogeneity and to inform decisions made for an individual patient. Evidence on key parameters (e.g., use, dosing, safety, effectiveness) of direct acting oral anticoagulants and contemporary evidence on warfarin specific to the nursing home setting are needed to identify changes in anticoagulant use patterns, to quantify their impact, and to improve resident-centered decision-making (57) regarding anticoagulation in nursing homes.

The quality of medication decisions in the nursing home environment depends upon the quality of communication between on-site clinicians (e.g., nurses, nurse practitioners), off-site physicians, consultant pharmacists, social workers, the patient and their family (57, 58). This review highlights the need for evidence to inform a shared decision-making process and address the dilemma facing all clinicians caring for very old, clinically complex patients: Will initiating an anticoagulant cause harm without the potential for substantial benefit? Is withholding an anticoagulant (proven effective in younger, less frail patients) more judicious? Will this resident benefit from aggressive pharmacologic management of atrial fibrillation? If so, which specific anticoagulant will increase the probability of benefit while reducing risk? The time has come to address the information needs for a growing segment of the population neglected by the evidence.

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References

1. Geiss LS, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, Albright AL, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. JAMA. 2014 Sep 24;312(12):1218-26.
2. Fryar C. Prevalence of Overweight, Obesity, and Extreme Obesity among Adults Aged 20 and over: United States, 1962–1962 through 2011–2014.; 2016. https://www.cdc.gov/nchs/data/hestat/obesity_adult_13_14/obesity_adult_13_14.htm accessed August 24, 2017.
3. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA. 2016 Jun 7;315(21):2284-91.
4. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119-125.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991 Aug;22(8):983-8.
6. Tu HT, Campbell BC, Christensen S, Desmond PM, De Silva DA, Parsons MW, et al; EPITHET-DEFUSE Investigators. Worse stroke outcome in atrial fibrillation is explained by more severe hypoperfusion, infarct growth, and hemorrhagic transformation. Int J Stroke. 2015;10:534–540.
7. Sandercock P, Bamford J, Dennis M, Burn J, Slattery J, Jones L, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project). BMJ. 1992;305:1460–1465.
8. Henninger N, Goddeau RP, Karmarkar A, Helenius J, McManus DD. Atrial Fibrillation Is Associated with a Worse 90-Day Outcome Than Other Cardioembolic Stroke Subtypes. Stroke. 2016;47(6):1486-1492.
9. Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B,

Wadley VG. Trajectory of Cognitive Decline After Incident Stroke. JAMA. 2015 Jul 7;314(1):41-51.
10. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, Elkind MS. Quality of life declines after first ischemic stroke. The Northern Manhattan Study. Neurology. 2010 Jul 27;75(4):328-34.
11. Dhamoon MS, Moon YP, Paik MC, Sacco RL, Elkind MS. Trajectory of functional decline before and after ischemic stroke: the Northern Manhattan Study. Stroke. 2012 Aug;43(8):2180-4.
12. Russo T, Felzani G, Marini C. Stroke in the very old: a systematic review of studies on incidence, outcome, and resource use. J Aging Res. 2011;2011:108785..
13. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001 May 9;285(18):2370-5.
14. OECD (2009), OECD Factbook 2009: Economic, Environmental and Social Statistics, OECD Publishing, Paris.
15. U.S. Census Bureau, Population Division. Table 3: Projections of the Population by Sex and Selected Age Groups for the United States: 2015 to 2060 (NP2014-T3) Released December, 2014. Accessed September 15, 2017.
16. American Health Care Association. LTC Patient Projections. https://www.ahcancal.org/research_data/Pages/LTC-Patient-Projections.aspx.
17. Harris-Kojetin L, Sengupta M, Parl-Lee E, Valverde R. Long-term care services in the United States: 2013 overview. Hyattsville, MD: National Center for Health Statistics; 2013.
18. Hartman M, Catlin A, Lassman D, Cylus J, Heffler S. U.S. health spending by age, selected years through 2004. Health Aff. 2008;27(1).
19. Houser A, Fox-Grage W, Ujvari K. Across the States: Profiles of Long-Term Services and Supports. AARP. 2012. Available at: http://www.aarp.org/content/ dam/aarp/research/public_policy_institute/ltc/2012/across-the-states-2012-full-report-AARP-ppi-ltc.pdf. Accessed May 5, 2016.
20. Feder J, Komissar H. The importance of federal financing to the nation's long-term care safety net. Washington, DC: Georgetown University; 2012.
21. Reaves EL, Musumeci M. Medicaid and Long-Term Services and Supports: A Primer. Kaiser Family Foundation. December, 2015. from http://files.kff.org/attachment/report-medicaid-and-long-term-services-and-supports-a-primer. Accessed September 1, 2017.
22. Medicaid and CHIP Payment and Access Commission.Total Medicaid Spending by State and Category. from https://www.macpac.gov/publication/total-medicaid-benefit-spending-by-state-and-category/. Accessed September 12, 2017.
23. Genworth Financial, Inc. 2016 Cost of Care. https://www.genworth.com/dam/Americas/US/PDFs/Consumer/corporate/cost-of-care/179703_CofC_Annual_060316.pdf. Accessed September 1, 2017.
24. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014 Dec 2;64(21):e1-76.
25. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857-67.
26. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008 Nov;1(2):84-91.
27. Gurwitz JH, Field TS, Radford MJ, Harrold LR, Becker R, Reed G, DeBellis K, Moldoff J, Verzier N. The safety of warfarin therapy in the nursing home setting. Am J Med. 2007 Jun;120(6):539-44.
28. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.
29. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92.
30. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369(22):2093-104
31. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.
32. Sardar P, Chatterjee S, Wu WC, Lichstein E, Ghosh J, Aikat S, et al. New oral anticoagulants are not superior to warfarin in secondary prevention of stroke or transient ischemic attacks, but lower the risk of intracranial bleeding: insights from a meta-analysis and indirect treatment comparisons. PLoS One. 2013 Oct 25;8(10):e77694.
33. Raschi E, Bianchin M, Ageno W, De Ponti R, De Ponti F. Risk-Benefit Profile of Direct-Acting Oral Anticoagulants in Established Therapeutic Indications: An Overview of Systematic Reviews and Observational Studies. Drug Saf. 2016 Dec;39(12):1175-1187. Review.
34. Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim; 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022512s000lbl.pdf. Accessed June 25, 2017.
35. Xarelto [package insert]. Leverkusen, Germany: Janssen; 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022406s000lbl.pdf. Accessed June 25, 2017.
36. Eliquis [package insert]. Princeton, New Jersey: Bristol Myers Squibb; 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf. Accessed September 1, 2017.
37. Savaysa [package insert]. Tokyo, Japan: Daiichi Sankyo, Inc; 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed September 1, 2017.
38. Patel PA, Zhao X, Fonarow GC, Lytle BL, Smith EE, Xian Y, Bhatt DL, Peterson ED, Schwamm LH, Hernandez AF. Novel Oral Anticoagulant Use Among Patients With Atrial Fibrillation Hospitalized With Ischemic Stroke or Transient Ischemic Attack. Circ Cardiovasc Qual Outcomes. 2015 Jul;8(4):383-92.
39. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ,et al.; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Factors associated with non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with new-onset atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II). Am Heart J. 2017 Jul;189:40-47.
40. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. Am J Med. 2015;128(12):1300-1305e5.
41. Abel Latif AK, Peng X, Messinger-Rapport BJ. Predictors of anticoagulation prescription in nursing home residents with atrial fibrillation. J Am Med Dir Assoc. 2005;6(2):128-131.
42. Ghaswalla PK, Harpe SE, Slattum PW. Warfarin use in nursing home residents: Results from the 2004 national nursing home survey. Am J Geriatr Pharmacother. 2011;10(1).
43. McGrath ER, Go AS, Chang Y, Borowsky LH, Fang MC, Reynolds K, et al. Use of Oral Anticoagulant Therapy in Older Adults with Atrial Fibrillation After Acute Ischemic Stroke. J Am Geriatr Soc. 2017;65(2):241-248.
44. Monette J, Gurwitz JH, Rochon PA, Avorn J. Physician attitudes concerning warfarin for stroke prevention in atrial fibrillation: Results of a survey of long-term care practitioners. J Am Geriatr Soc. 1997;45(9):1060-1065.
45. McCormick D, Gurwitz JH, Goldberg RJ, Becker R, Tate JP, Elwell A, et al. Prevalence and quality of warfarin use for patients with atrial fibrillation in the long-term care setting. Arch Intern Med. 2001 Nov 12;161(20):2458-63.
46. Gurwitz JH, Monette J, Rochon PA, Eckler MA, Avorn J. Atrial fibrillation and stroke prevention with warfarin in the long-term care setting. Arch Intern Med. 1997 May 12;157(9):978-84. PubMed PMID: 9140268.
47. Bernstein AB, Remsburg RE. Estimated Prevalence of People with Cognitive Impairment: Results from Nationally Representative Community and Institutional Surveys. Gerontologist. 2007;47(3):350-354.
48. Dwyer LL, Han B, Woodwell DA, Rechtsteiner EA. Polypharmacy in nursing home residents in the United States: Results of the 2004 National Nursing Home Survey. Am J Geriatr Pharmacother. 2010;8(1):63-72.
49. Patel AA, Reardon G, Nelson WW, Philpot T, Neidecker M V. Persistence of warfarin therapy for residents in long-term care who have atrial fibrillation. Clin Ther. 2013;35(11):1794-1804.
50. Quilliam BJ, Lapane KL. Clinical correlates and drug treatment of residents with stroke in long-term care. Stroke. 2001;32(6):1385-1393.
51. Quilliam BJ, Lapane KL, Eaton CB, Mor V. Effect of antiplatelet and anticoagulant agents on risk of hospitalization for bleeding among a population of elderly nursing home stroke survivors. Stroke. 2001;32(10):2299-2304.
52. Stöllberger C, Brooks R, Finsterer J, Pachofszky T. Use of Direct-Acting Oral Anticoagulants in Nonagenarians: A Call for More Data. Drugs and Aging. 2016;33(5):315-320.
53. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al.; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493-503.
54. Orkaby AR, Ozonoff A, Reisman JI, Miller DR, Zhao S, Rose AJ. Continued Use of Warfarin in Veterans with Atrial Fibrillation After Dementia Diagnosis. J Am Geriatr Soc. 2017;65(2):249-256.
55. Teruel RS, Thue G, Fylkesnes SI, Sandberg S, Kristoffersen AH. Warfarin monitoring in nursing homes assessed by case histories. Do recommendations and electronic alerts affect judgements? Scand J Prim Health Care. 2017 Sep;35(3):299-306.
56. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge gaps in cardiovascular care of the older adult population. Circulation. 2016;133(21):2103-2122.
57. Tjia J, Gurwitz JH, Briesacher BA. Challenge of changing nursing home prescribing culture. Am J Geriatr Pharmacother. 2012 Feb;10(1):37-46.

58. Tjia J, Mazor KM, Field T, Meterko V, Spenard A, Gurwitz JH. Nurse-Physician Communication in the Long-Term Care Setting: Perceived Barriers and Impact on Patient Safety. J Patient Satisf. 2009;5(3):145-152.