UCSF
UC San Francisco Previously Published Works

Title

Long-term functional outcomes and mortality after hospitalization for extracranial hemorrhage

Permalink

https://escholarship.org/uc/item/2zq7x0pv

Journal

Journal of Hospital Medicine, 17(4)

ISSN

1553-5592

Authors

Parks, Anna L
Jeon, Sun Y
Boscardin, W John
et al.

Publication Date

2022-04-01

DOI

10.1002/jhm.12799

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Hosp Med. Author manuscript; available in PMC 2023 April 01.

Published in final edited form as:

J Hosp Med. 2022 April ; 17(4): 235–242. doi:10.1002/jhm.12799.

Long-term functional outcomes and mortality after hospitalization for extracranial hemorrhage

Anna L. Parks, MD[1], **Sun Y. Jeon, MS PhD**[2], **W. John Boscardin, PhD**[2,4], **Michael A. Steinman, MD**[2], **Alexander K. Smith, MD, MPH, MAS**[2], **Kenneth E. Covinsky, MD, MPH**[2], **Margaret C. Fang, MD, MPH**[3], **Sachin J. Shah, MD, MPH**[3]

[1]Division of Hematology and Hematologic Malignancies, University of Utah, Salt Lake City, Utah

[2]Division of Geriatrics, University of California, San Francisco and San Francisco VA Medical Center, San Francisco, CA

[3]Division of Hospital Medicine, University of California, San Francisco, San Francisco, CA

[4]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA

Abstract

Background—The effects of extracranial hemorrhage (ECH), or bleeding outside the brain, are often considered transient. Yet there are few data on the long-term and functional consequences of ECH.

Objective—Define the association of ECH hospitalization with functional independence and survival in a nationally representative cohort of older adults.

Design—Longitudinal cohort study.

Setting—Data from the Health and Retirement Study from 1995 to 2016, a nationally representative, biennial survey of older adults.

Participants—Adults aged 66 and above with Medicare linkage and at least 12 months of continuous Medicare Part A and B enrollment.

Exposure—Hospitalization for ECH.

Main Outcomes and Measures—Adjusted odds ratios and predicted likelihood of independence in all activities of daily living (ADLs), independence in all instrumental activities of daily living (IADLs) and extended nursing home stay. Adjusted hazard ratio and predicted likelihood for survival.

Results—In a cohort of 6719 subjects (mean age 77, 59% women) with average follow-up time of 8.3 years (55,767 person-years), 736 (11%) were hospitalized for ECH. ECH was associated with a 15% increase in ADL disability, 15% increase in IADL disability, 8% increase in nursing

Corresponding Author Anna L. Parks, MD, Division of Hematology & Hematologic Malignancies, University of Utah, 30 N 1900 E, Salt Lake City, UT 84132, Anna.Parks@hsc.utah.edu, Phone: (801) 209-3969, Twitter handle : @annap_MD.

Declaration of interest: All authors declare no conflicts of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

home stays, and 4% increase in mortality. After ECH, subjects became disabled and died at the same annual rate as pre-ECH but never recovered to pre-ECH levels of function.

Conclusions—Hospitalization for ECH was associated with significant and durable declines in independence and survival. Clinical and research efforts should incorporate the long-term harms of ECH into decision-making and strategies to mitigate these effects.

Introduction

Bleeding, whether spontaneous or as a complication of invasive procedures or medications, is a major public health burden.[1–4] When assessing the effects of bleeding events, researchers and clinicians often focus on intracranial hemorrhage, uncommon but devastating. Yet extracranial hemorrhage (ECH)— defined as bleeding from any site other than intracranial, including gastrointestinal, genituourinary or nasophargyngeal —is a common and perilous reason for hospitalization in older adults. The risk of gastrointestinal bleeding, the most common form of ECH, is 2 per 1000 person-years and has a case fatality rate of 5%.[4] Risk of hospitalization for non-gastrointestinal extracranial bleeding (lung, joint, pericardial or peritoneal bleeding) is much lower (0.41 per 1000 person-years) but case fatality rate is similar to gastrointestinal bleeding (4%).[4] Though serious, the effects of ECH are often considered time-limited and reversible. For example, many decision models ignore ECH or assume that patients make a full recovery on the order of weeks.[5,6] Typical treatments for ECH can seem definitive, such as an endoscopy to stop the bleeding source or a transfusion to un-do its consequences. These treatments may produce short-term resolution of bleeding symptoms, but few studies have looked beyond short-term outcomes.[7,8] There are surprisingly few data on the long-term effects of extracranial bleeding on mortality and functional independence.

Functional disability has been shown among older adults who survive hospitalization, a third of whom acquire long-term deficits.[9] Although bleeding is a common cause of hospitalization, its specific long-term and functional impact is unknown. In addition to procedures, ECH hospitalizations can involve diet changes, procedural sedation, foley catheters, and bowel preparation for colonoscopy, all of which could contribute to acquired disability. Moreover, bleeding risk is closely tied to chronologic age, multimorbidity, and geriatric syndromes like falls, so patients may have diminished reserve, making it difficult to return to their prior level of functioning.[10] Understanding the lasting impact of ECH on morbidity and mortality is important for patients and caregivers when discussing expectations for recovery. Therefore, the primary objective of this study was to determine the association of ECH hospitalization with survival and functional independence in a nationally representative cohort of older adults.

Methods

Study population

We used data from 1995 to 2016 from the Health and Retirement Study (HRS) to examine the association of hospitalization for extracranial bleeding with functional status and death. The HRS is a nationally-representative, longitudinal cohort of over 43,000 Americans over

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

age 50 residing in the community or nursing homes with linked Medicare claims.[11] Subjects are interviewed every other year by phone, internet or in-person on topics related to health and function, work and retirement. Researchers interview proxies when participants cannot answer questions because of physical or cognitive impairment.[12,13]

We created a longitudinal cohort of all HRS participants aged 66 and older with Medicare claims linkage and at least 12 months of continuous Medicare Part A and B enrollment (Appendix Figure 1). Participants were enrolled when they first met inclusion criteria and censored at the time of disenrollment from Medicare part A or B, HRS drop out, or death. The HRS was approved by the institutional review board at the University of Michigan. The data used for this analysis are publicly available and contain no unique identifiers; the University of California, San Francisco, Committee on Human Research approved analysis of HRS data for this study and waived the requirement for patient consent (Institutional Review Board No. 16–19185).

Demographics and comorbidities

Information on participants' baseline sociodemographics and clinical characteristics was taken from the first HRS interview where participants met eligibility criteria. We also report time-varying clinical characteristics that contribute to bleeding risk and disability based on prior published studies: diagnosis of cancer, heart disease, hypertension, vascular disease, anemia, renal disease, atrial fibrillation, prior bleeding event, use of a walker, history of falls, or alcohol use.[14–18] We defined participants as having a specific comorbidity if, at any time point after cohort entrance, they self-reported a diagnosis in an HRS interview or met claims criteria at (Appendix Table 1), both of which correlate well with chart diagnoses and population estimates.[19,20] Falls were assessed using participants' answers to the HRS interview question, "Have you fallen down in the last 2 years?" Use of a walker was assessed using participants' answers to the HRS interview question, "Do you ever use equipment or devices such as a cane, walker or wheelchair when crossing a room?" Alcohol use was determined either using a claims diagnosis of alcohol use disorder or if participants reported drinking one or more alcoholic beverages per week.

Extracranial hemorrhage hospitalization

The primary exposure was hospitalization for extracranial bleeding. We defined hospitalization for ECH using a validated claims algorithm that has a positive predictive value of 89% to 99% compared with chart review (Appendix Table 2).[21,22] The algorithm incorporates claims for extracranial bleeding from upper and lower gastrointestinal, genitourinary, lung (epistaxis, hemoptysis), joint, pericardial and peritoneal sites. To identify current hemorrhagic events, the algorithm includes only hospitalizations with a primary discharge diagnosis related to bleeding. Hospitalizations associated with major trauma are excluded. We examined the first hospitalization for ECH for each participant. We report information on hospitalization characteristics, like endoscopic evaluation, admission to the ICU, blood transfusion, and discharge disposition.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Outcomes

We examined four outcomes: ADL (activity of daily living) independence, IADL (instrumental ADL) independence, extended nursing home stay, and death. We defined ADL independence as not needing assistance with any ADLs (walking across the room, dressing, bathing, eating, transferring to or from bed, and toileting).[23] We defined IADL independence as not needing assistance with any IADLs (preparing a hot meal, shopping for groceries, making telephone calls, taking medicines, and managing money).[24] We defined extended nursing home stay as self-report of spending ≥90 nights in a nursing home since the last interview.[25] ADL independence, IADL independence, and extended nursing home stays were measured at each biennial interview. We determined date of death using a combination of the National Death Index, Medicare enrollment files, and HRS surviving family member exit interviews.

Analysis

We conducted a longitudinal cohort study with the goal of determining three key measures for each study outcome: (1) the baseline outcome rate, (2) the association between ECH and the outcome, (3) and the association between ECH and change in baseline outcome rate. Participants entered the cohort when they first met inclusion criteria and were followed until censoring date as described above.

For ADL independence, IADL independence, and extended nursing home stay outcomes, we fit separate random-effects logistic regression models with repeated measures. Each outcome was modeled as a function of ECH, time in cohort, and the interaction between ECH and time in cohort, as well as time-invariant and time-varying confounders (modeling equation and visual representation in Appendix Text 1). We excluded observations with missing outcomes (1.2% with missing ADL outcome, 1.5% with missing IADL outcome, 1.0% with missing nursing home outcome). In exit interviews, next-of-kin reported dependence >90% of the time prior to death, so when exit interviews were missing, we imputed ADL and IADL status as dependent. For death, we fit a Gompertz survival model that modeled time to death as a function of the same dependent variables as described above (Appendix Text 2).[26] Gompertz is a parametric survival model; in this study, it is more useful than a semiparametric Cox model because it estimates a baseline hazard, and it is superior to other parametric models for mortality because it best reflects the observed mortality progression as age increases.[26] Compared to alternative models, the Gompertz model also demonstrated superior goodness-of-fit using the Akaike Information Criterion.[27] For all models, we defined confounders that contribute to bleeding, disability, and death a priori rather than using significance testing to determine which to include in the regression models, consistent with epidemiologic best practices.

We used the method of recycled predictions to illustrate the regression model results because it allows one to compare the population predicted outcome rate under different scenarios.[28,29] For each outcome, we used the regression model results (Appendix Tables 3 **&** 4) to calculate and plot the predicted outcome probability over time for the entire cohort in two scenarios: (1) a population where none experience an ECH and (2) a population where all experience an ECH at 5.2 years, the median time to ECH in this cohort. We

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

performed all analyses using SAS 9.4 (Cary, NC) and STATA (Version 16.1, College Station, TX). We report all results with 95% confidence intervals. STROBE statement checklist can be found in Appendix Table 5.

Results

Cohort characteristics

Our cohort consisted of 6719 subjects with an average follow-up time of 8.3 years, resulting in 55,767 person-years of observation. There were 736 (11%) participants hospitalized for ECH between 1995 and 2016. Mean age was 77 years, and 59% were women (Table 1). Eighty-one percent identified as White, 12% as Black, and 14% were proxy interviews. Hypertension (65%) was the most common comorbid condition, followed by vascular disease (37%) and heart disease (37%). One-third of participants had a history of falls, and one-quarter used alcohol. At baseline, 15% reported needing assistance with at least one ADL, 23% reported needing assistance with at least one IADL, and 4% lived in a nursing home.

The overwhelming majority of diagnoses associated with participants' hospital admissions were related to upper and lower gastrointestinal bleeding (Table 2). Ninety-one percent of ECH occurred at a gastrointestinal site, 5% occurred at a genitourinary site, and the remaining 4% were classified as occurring at other sites. Median length of stay was 5 days (IQR 3,7). One-hundred-sixty-four patients (21%) were admitted to the ICU. Thirty-two percent underwent upper endoscopy, 13% underwent colonoscopy, and 17% underwent both during hospitalization. Fifty-nine percent received a transfusion during admission. Nearly three-quarters (71%) were discharged home, 16% were discharged to skilled-nursing facilities, 4% died, and the remainder were discharged to other locations (e.g. acute care facilities, long-term care hospitals, hospice).

Longitudinal functional outcomes after ECH hospitalization

Figure 1 depicts two predicted probability curves for ADL independence: one curve showing a population where none experience an ECH (blue curve) and a second curve showing a population where all experience an ECH at 5.2 years (red curve), the median time to ECH in this cohort. These curves graphically represent three key findings based on the full model results (Appendix Table 3) and described in detail in the following sections— (1) baseline rate of function loss (blue curve throughout follow-up and red curve prior to 5.2 years), (2) change in function associated with ECH (difference between blue and red curves at 5.2 years), and (3) change in baseline rate of function loss following ECH (difference between red and blue curve slope after 5.2 years).

For ADLs, the baseline population likelihood of ADL independence declined by an average of 3.1% per year (95% CI −3.1% to −3.3%). Assuming hospitalization for ECH at 5.2 years, ECH was associated with a drop in ADL independence from 68% to 53% (−15%, 95% CI −11% to −18%). Following ECH, the baseline rate of ADL disability did not change, meaning that subjects returned to the same annual rate of loss of ADL independence.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The baseline rate of IADL independence declined by an average of 3.4% per year (95% CI −3.3% to −3.5%) (Appendix Figure 2). IADL independence declined abruptly from 61% to 45% after hospitalization for ECH at 5.2 years (−15%, 95% CI −10% to −19%). After ECH, the baseline rate of IADL disability did not change.

Finally, the baseline rate of independence from a long-term nursing home stay declined by 1.9% per year (95% CI −1.6% to −2.1%) (Appendix Figure 3). Assuming an ECH at 5.2 years, the likelihood of no long-term nursing home stay decreased from 89% to 81% (−7.8%, 95% CI −4.6% to −9.4%). ECH did not affect the baseline rate of freedom from a nursing home stay; that is, subjects returned to the same annual rate of having a long-term nursing home stay.

Longitudinal mortality outcomes

Figure 2 depicts two population survival curves: one assuming no ECH hospitalizations (blue curve) and the second assuming everyone had an ECH hospitalization at 5.2 years (red curve), the median time to ECH in this cohort. This figure graphically represents three key findings based on the full model results (Appendix Table 4)—(1) baseline mortality rate (blue curve throughout follow-up and red curve prior to 5.2 years), (2) change in mortality associated with ECH (difference between blue and red curve at 5.2 years), and (3) change in baseline mortality rate following ECH (difference between red and blue curve slope after 5.2 years).

Absent ECH hospitalizations, the average annual decline in the predicted survival was −4.3% per year (95% CI −3.9% to −4.6%). With an ECH at 5.2 years, ECH hospitalization was associated with a reduction in predicted survival from 78% to 74% (−4.0%, 95% CI −2.1% to −5.3%). ECH was not associated with a change in the baseline mortality rate following hospitalization.

Sensitivity analyses

We tested the robustness of our primary result with three sensitivity analyses. First, because intercurrent hospitalizations unrelated to ECH in the two-year period between interviews could affect disability trajectory, we adjusted for hospitalization for causes other than ECH in our regression. Secondly, because overall illness trajectory following ECH hospitalization could also affect disability trajectory, we adjusted for the time between ECH hospitalization and subsequent HRS interview. We found that our primary result was consistent when we controlled for these potential biases (full results in Appendix Table 6). Finally, we examined how ECH-associated disability compares with disability from hospitalization for other reasons; to do so, we used the same cohort to analyze the association between hospitalization for any reason other than ECH with functional independence. Compared to ECH, non-ECH hospitalization was associated with similar predicted likelihood of ADL disability immediately after the event, but disability accelerated more after non-ECH hospitalization.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Discussion

In this nationally representative cohort, we demonstrate that ECH was associated with persistent, increased risk of death and disability. ECH confers a 4% excess mortality risk. Survivors experience a substantial loss of independence that does not remit over time: 15% increase in ADL disability, 15% increase in IADL disability, and 8% increase in long-term nursing home stays. Compared to the baseline rate, this is akin to accelerating loss of ADL independence by 4.0 years, IADL independence by 3.8 years, move to a nursing home by 3.4 years, and death by an additional year.

These results build on research of the outcomes following ECH. Our finding that ECH is associated with a 4% increase in mortality corroborates the case fatality rates reported in studies of gastrointestinal bleeding, the predominant form of ECH.[4,30–32] We found that almost 1 in 10 bleeding hospitalizations was for a non-gastrointestinal bleeding event. Although epistaxis and hematuria do not always require the same intensity of care as gastrointestinal bleeding and are sometimes characterized as “nuisance bleeding,” we demonstrate that hospitalization for these additional sites of extracranial bleeding can have important long-term consequences. We expanded the current literature by showing that ECH survivorship is associated with increased ADL and IADL dependence and prolonged nursing home stays, all of which have profound implications for patients, caregivers and the healthcare system.

The association of ECH with functional dependence, prolonged nursing home use, and mortality has implications for the care of patients at-risk for ECH and those hospitalized ECH. ECH seems to follow the well-established observation that hospitalization for any reason is associated with disability in older adults.[9] Although ECH shares some characteristics with other medical hospitalizations, these results provide an estimate of ECH-specific disability that is important for shared decision-making. Furthermore, these results demonstrate that, in absolute terms, ECH is associated with substantial disability on a population level.

Prevention of the morbidity and mortality associated with ECH can occur at multiple levels. Pre-hospitalization, recognition of the severity of ECH should prompt quality improvement initiatives to address modifiable risk factors for bleeding like inappropriate combination of antiplatelet and anticoagulant medications.[33] Consideration should be given to care pathways that divert low-risk patients with ECH to observation, novel hospital-at-home models, non-invasive testing such as CT angiography, or expedited outpatient management.[34,35] In the hospital, evidence-based interventions to prevent hospital-acquired disability, such as units dedicated to older patients, should be employed.[36] These results can also be used to guide expectations for recovery and independent community living following ECH.

These results also inform the risk-benefit tradeoff of medications known to increase the risk of hemorrhage. ECH is a common side-effect of widely used medications like anticoagulants and antiplatelets and the most common reason for Emergency Department visits due to medication harm in the U.S.[37] Even low-dose direct acting anticoagulants increase the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

absolute risk of ECH by 1.5%/year in older adults with atrial fibrillation.[38] Principally, the findings counteract the perception that extracranial hemorrhages are reversible with time-limited impact. While it is commonly appreciated that thromboses, such as stroke, myocardial infarction, and venous thromboembolism, are major threats to independence, these results demonstrate hospitalization for ECH, while seemingly transient, is associated with substantial long-term disability and death. That hemorrhage may result in the same outcomes we seek to avoid by using anticoagulants and antiplatelets should prompt efforts to integrate hemorrhage into clinical decision-making vis-à-vis its effect on function. Further, the study findings support measuring long-term functional outcomes in clinical trials in addition to clinical events.

The study design and data have limitations that are important to consider when interpreting the results. The biennial assessment period means that functional changes within that interval might be missed. Nevertheless, because episodes of disability strongly predict chronic impairment, the long-term trajectory presented is revealing.[39] We used claims-based definitions for bleeding that have been previously validated and have good positive predictive value, but hospital records were not obtained to independently validate these outcomes.[21,22] We evaluated only inpatient bleeding episodes and only those that were documented as the primary reason for hospitalization; thus, our results only apply to a subset of bleeding events significant enough to merit hospitalization yet not occurring in the context of other illnesses. We were not able to determine whether bleeding events occurred on anticoagulant or antiplatelet medications because Medicare Part D prescription data are only available for 2006 onward. However, because medication-related bleeding events are more severe and patients taking anticoagulant and antiplatelet medications often have multimorbidity, we anticipate that bleeding hospitalizations due to medications would have an even greater impact on survival and function.[40,41] Whether and how medications affect ECH-related disability should be a focus of future studies. We accounted for patient characteristics that are associated with ECH, death and disability, and sensitivity analyses controlling for non-ECH hospitalization and time from ECH to HRS interview confirmed out primary result. Nevertheless, we cannot exclude the possibility that unmeasured confounders contribute to these declines rather than ECH. In addition, Medicare claims data lack the granularity needed to examine hemorrhage severity, such as the degree of organ dysfunction or acute interventions, that might produce differing long-term outcomes.

In summary, the results of our study show that hospital admission for ECH is associated with increased mortality, loss of functional independence, and prolonged nursing home stays. This should prompt better recognition and incorporation of the enduring harms of bleeding into both patient care and research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Funding:

Dr. Parks reports funding from the National Institute on Aging (R03AG074074, T32-AG000212); Dr. Fang reports funding from the National Heart, Lung, And Blood Institute (K24HL141354); Dr. Steinman reports funding from the National Institute on Aging (K24AG049057); Dr. Smith reports funding from the National Institute on Aging (K24AG068312); Dr. Covinsky reports funding from the National Institute on Aging (P30AG044281); Dr. Shah reports funding from the National Center for Advancing Translational Sciences (KL2TR001870).

References

1. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. BMC Med. 2006;4(1):22. doi:10.1186/1741-7015-4-22 [PubMed: 16987411]
2. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding Risks With Aspirin Use for Primary Prevention in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(12):826–835. doi:10.7326/M15-2112 [PubMed: 27064261]
3. Lin KJ, De Caterina R, Rodríguez LAG. Low-Dose Aspirin and Upper Gastrointestinal Bleeding in Primary Versus Secondary Cardiovascular Prevention. Circ Cardiovasc Qual Outcomes. 2014;7(1):70–77. doi:10.1161/CIRCOUTCOMES.113.000494 [PubMed: 24254886]
4. Selak V, Kerr A, Poppe K, et al. Annual Risk of Major Bleeding Among Persons Without Cardiovascular Disease Not Receiving Antiplatelet Therapy. JAMA. 2018;319(24):2507. doi:10.1001/jama.2018.8194 [PubMed: 29946729]
5. Eckman MH, Wise RE, Naylor K, et al. Developing an Atrial Fibrillation Guideline Support Tool (AFGuST) for Shared Decision Making. Curr Med Res Opin. 2015;31(4):603–614. doi:10.1185/03007995.2015.1019608 [PubMed: 25690491]
6. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med. 2009;151(5):297–305. doi:10.7326/0003-4819-151-5-200909010-00003 [PubMed: 19721017]
7. Mullady DK, Wang AY, Waschke KA. AGA Clinical Practice Update on Endoscopic Therapies for Non-Variceal Upper Gastrointestinal Bleeding: Expert Review. Gastroenterology. 2020;159(3):1120–1128. doi:10.1053/j.gastro.2020.05.095 [PubMed: 32574620]
8. Niikura R, Nagata N, Yamada A, et al. Efficacy and Safety of Early vs Elective Colonoscopy for Acute Lower Gastrointestinal Bleeding. Gastroenterology. 2020;158(1):168–175.e6. doi:10.1053/j.gastro.2019.09.010 [PubMed: 31563627]
9. Covinsky KE, Palmer RM, Fortinsky RH, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. J Am Geriatr Soc. 2003;51(4):451–458. doi:10.1046/j.1532-5415.2003.51152.x [PubMed: 12657063]
10. Kaplan RC, Heckbert SR, Koepsell TD, et al. Risk Factors for Hospitalized Gastrointestinal Bleeding Among Older Persons. J Am Geriatr Soc. 2001;49(2):126–133. doi:10.1046/j.1532-5415.2001.49032.x [PubMed: 11207865]
11. Juster FT, Suzman R. An Overview of the Health and Retirement Study. J Hum Resour. 1995;30:S7–S56. doi:10.2307/146277
12. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). Int J Epidemiol. 2014;43(2):576–585. doi:10.1093/ije/dyu067 [PubMed: 24671021]
13. Fisher GG, Ryan LH. Overview of the Health and Retirement Study and Introduction to the Special Issue. Work Aging Retire. 2018;4(1):1–9. doi:10.1093/workar/wax032 [PubMed: 29423243]
14. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395–401. doi:10.1016/j.jacc.2011.03.031 [PubMed: 21757117]
15. Parks AL, Fang MC. Scoring Systems for Estimating the Risk of Anticoagulant-Associated Bleeding. Semin Thromb Hemost. 2017;43(5):514–524. doi:10.1055/s-0037-1598061 [PubMed: 28359135]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

16. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151(3):713–719. doi:10.1016/j.ahj.2005.04.017 [PubMed: 16504638]
17. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093–1100. doi:10.1378/chest.10-0134 [PubMed: 20299623]
18. Covinsky KE, Pierluissi E, Johnston CB. Hospitalization-Associated Disability: "She Was Probably Able to Ambulate, but I'm Not Sure." JAMA. 2011;306(16):1782–1793. doi:10.1001/jama.2011.1556 [PubMed: 22028354]
19. Bush TL, Miller SR, Golden AL, Hale WE. Self-report and medical record report agreement of selected medical conditions in the elderly. Am J Public Health. 1989;79(11):1554–1556. doi:10.2105/AJPH.79.11.1554 [PubMed: 2817172]
20. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol. 2004;57(10):1096–1103. doi:10.1016/j.jclinepi.2004.04.005 [PubMed: 15528061]
21. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20(6):560–566. doi:10.1002/pds.2109 [PubMed: 21387461]
22. Graham DJ, Reichman ME, Wernecke M, et al. Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation. JAMA Intern Med. 2016;176(11):1662–1671. doi:10.1001/jamainternmed.2016.5954 [PubMed: 27695821]
23. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. The Gerontologist. 1970;10(1):20–30. doi:10.1093/geront/10.1_part_1.20 [PubMed: 5420677]
24. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179–186. [PubMed: 5349366]
25. Li Q, Zheng NT, Temkin-Greener H. Quality of End-of-Life Care of Long-Term Nursing Home Residents with and without Dementia. J Am Geriatr Soc. 2013;61(7):1066–1073. doi:10.1111/jgs.12330 [PubMed: 23772891]
26. Olshansky SJ, Carnes BA. Ever since Gompertz. Demography. 1997;34(1):1–15. [PubMed: 9074828]
27. The Akaike information criterion: Background, derivation, properties, application, interpretation, and refinements - Cavanaugh - 2019 - WIREs Computational Statistics - Wiley Online Library. Accessed January 16, 2022. https://wires.onlinelibrary.wiley.com/doi/abs/10.1002/wics.1460
28. Bieler GS, Brown GG, Williams RL, Brogan DJ. Estimating model-adjusted risks, risk differences, and risk ratios from complex survey data. Am J Epidemiol. 2010;171(5):618–623. doi:10.1093/aje/kwp440 [PubMed: 20133516]
29. Graubard BI, Korn EL. Predictive margins with survey data. Biometrics. 1999;55(2):652–659. doi:10.1111/j.0006-341x.1999.00652.x [PubMed: 11318229]
30. Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. Am J Gastroenterol. 2012;107(8):1190–1195; quiz 1196. doi:10.1038/ajg.2012.168 [PubMed: 22688850]
31. Lanas A, García-Rodríguez LA, Polo-Tomás M, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol. 2009;104(7):1633–1641. doi:10.1038/ajg.2009.164 [PubMed: 19574968]
32. Vora P, Pietila A, Peltonen M, Brobert G, Salomaa V. Thirty-Year Incidence and Mortality Trends in Upper and Lower Gastrointestinal Bleeding in Finland. JAMA Netw Open. 2020;3(10):e2020172. doi:10.1001/jamanetworkopen.2020.20172 [PubMed: 33034641]
33. Schaefer JK, Errickson J, Li Y, et al. Adverse Events Associated With the Addition of Aspirin to Direct Oral Anticoagulant Therapy Without a Clear Indication. JAMA Intern Med. Published online April 19, 2021. doi:10.1001/jamainternmed.2021.1197

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

34. Levine DM, Ouchi K, Blanchfield B, et al. Hospital-Level Care at Home for Acutely Ill Adults: A Randomized Controlled Trial. Ann Intern Med. 2020;172(2):77–85. doi:10.7326/M19-0600 [PubMed: 31842232]

35. García-Blázquez V, Vicente-Bártulos A, Olavarria-Delgado A, et al. Accuracy of CT angiography in the diagnosis of acute gastrointestinal bleeding: systematic review and meta-analysis. Eur Radiol. 2013;23(5):1181–1190. doi:10.1007/s00330-012-2721-x [PubMed: 23192375]

36. Landefeld CS, Palmer RM, Kresevic DM, Fortinsky RH, Kowal J. A randomized trial of care in a hospital medical unit especially designed to improve the functional outcomes of acutely ill older patients. N Engl J Med. 1995;332(20):1338–1344. doi:10.1056/NEJM199505183322006 [PubMed: 7715644]

37. Budnitz DS, Shehab N, Lovegrove MC, Geller AI, Lind JN, Pollock DA. US Emergency Department Visits Attributed to Medication Harms, 2017–2019. JAMA. 2021;326(13):1299–1309. doi:10.1001/jama.2021.13844 [PubMed: 34609453]

38. Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation | NEJM. Accessed June 30, 2021. https://www-nejm-org.ucsf.idm.oclc.org/doi/full/10.1056/NEJMoa2012883

39. Gill TM, Kurland BF. Prognostic Effect of Prior Disability Episodes among Nondisabled Community-living Older Persons. Am J Epidemiol. 2003;158(11):1090–1096. doi:10.1093/aje/kwg237 [PubMed: 14630605]

40. Fang MC, Go AS, Chang Y, et al. Death and Disability from Warfarin-Associated Intracranial and Extracranial Hemorrhages. Am J Med. 2007;120(8):700–705. doi:10.1016/j.amjmed.2006.07.034 [PubMed: 17679129]

41. Shah SJ, Fang MC, Jeon SY, Gregorich SE, Covinsky KE. Geriatric Syndromes and Atrial Fibrillation: Prevalence and Association with Anticoagulant Use in a National Cohort of Older Americans. J Am Geriatr Soc. 2021;69(2):349–356. doi:10.1111/jgs.16822 [PubMed: 32989731]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

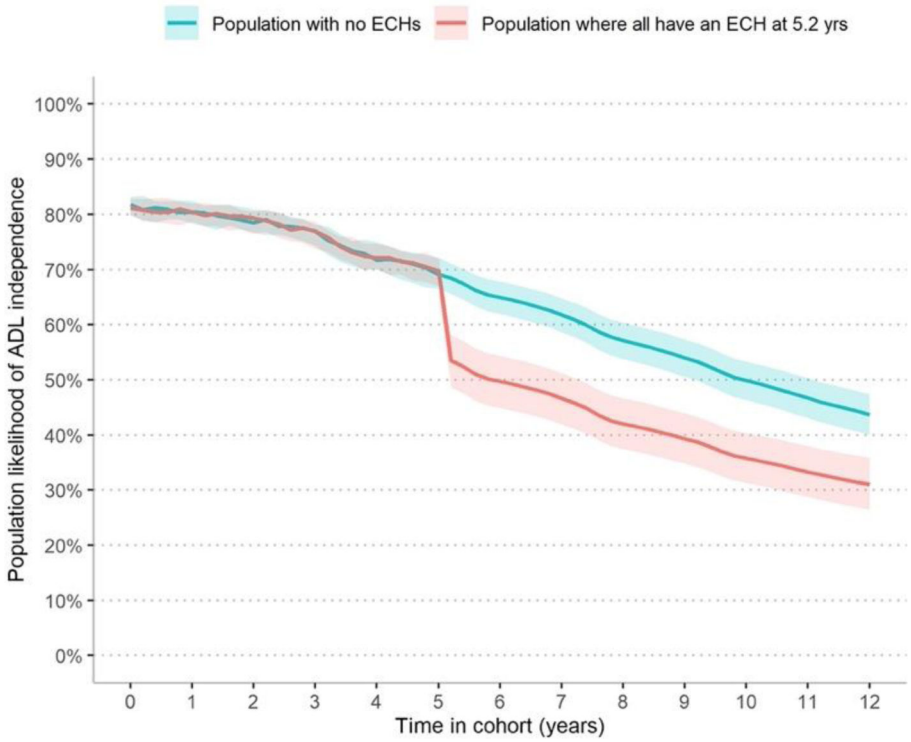

Figure 1. Longitudinal likelihood of ADL independence and association with extracranial hemorrhage

Legend- ADL, activity of daily living; ECH, extracranial hemorrhage.

This graph is produced from the regression model results (Appendix Text 1, Appendix Table 3).The blue line represents the predicted likelihood of the outcome assuming no one has an ECH, and the red line represents the predicted likelihood of the outcome assuming all have an ECH at 5.2 years, the median time to ECH in the cohort. The blue line represents the predicted loss of independence where there are no ECH admissions in the cohort (i.e., the baseline rate of function loss). The red line represents a scenario where everyone in the population has an ECH: (1) the red line from 0 to 5.2 years represents the baseline rate of function loss pre-ECH; (2) at 5.2 years, the difference between the blue and red lines represents the change in function associated with ECH (3) after 5.2 years, the red line describes the change in baseline rate of function loss post-ECH. Functional trajectory is displayed through 12 years, the 75th percentile of follow up time.

The analysis is based on 6719 participants; we excluded 333 person waves (1.2%) with missing ADL outcome data, 400 person-waves (1.5%) with missing IADL outcome data, 268 person-waves (0.98%) with missing nursing home outcome data.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

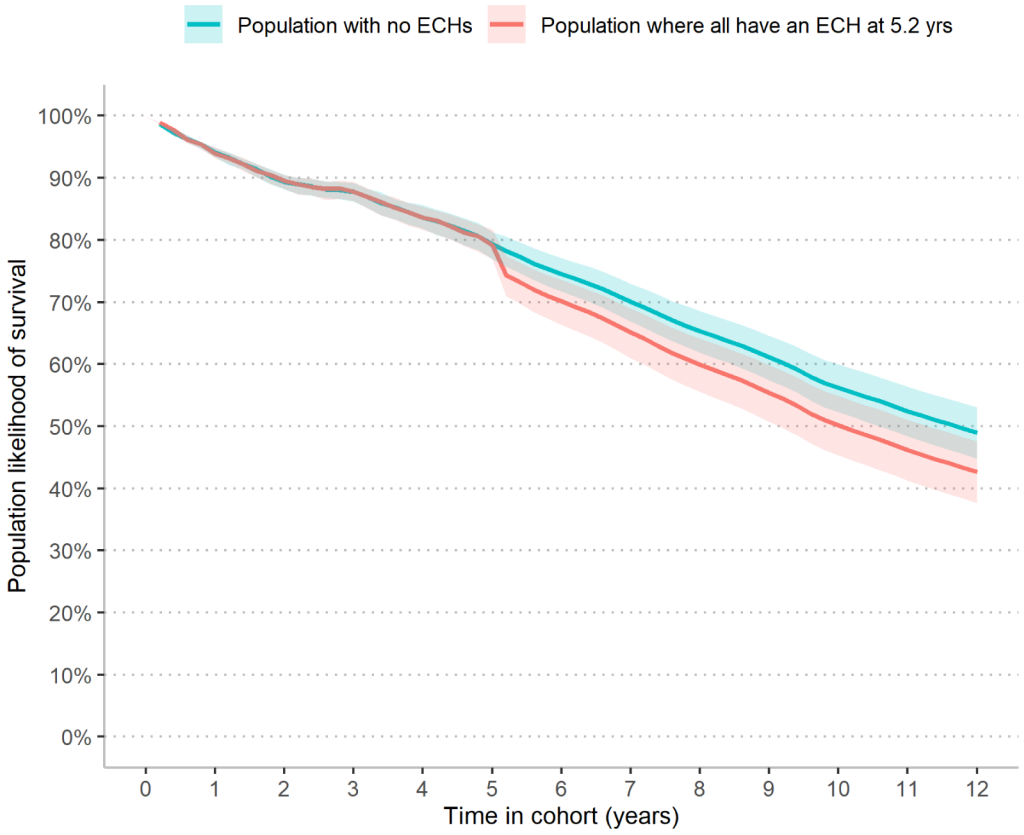

Figure 2. Longitudinal likelihood of mortality and association with extracranial hemorrhage

Legend ECH, extracranial hemorrhage.

This graph is produced from the regression model results (Appendix Text 2, Appendix Table 4).The blue line represents the predicted likelihood of the outcome assuming no one has an ECH, and the red line represents the predicted likelihood of the outcome assuming all have an ECH at 5.2 years, the median time to ECH in the cohort. The blue line represents the predicted survival where there are no ECH admissions in the cohort (i.e., the baseline mortality rate). The red line represents a scenario where everyone in the population has an ECH: (1) the red line from 0 to 5.2 years represents the baseline survival rate pre-ECH; (2) at 5.2 years, the difference between the blue and red lines represents the mortality associated with ECH (3) after 5.2 years, the red line describes the change in baseline mortality rate post-ECH. Survival trajectory is displayed through 12 years, the 75th percentile of follow up time.

The analysis is based on 6719 participants; none were missing mortality data.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Baseline cohort characteristics

Sociodemographics	**Cohort (n=6719)**
Age, years, median (IQR)	77 (74, 83)
Women, (%)	3897 (58)
Married or partnered, (%)	3493 (52)
Lives alone, (%)	2150 (32)
Greater than high school education, (%)	3964 (59)
Race, (%)	
White	5442 (81)
Black	806 (12)
Other	67 (1)
Hispanic ethnicity, (%)	336 (5)
Proxy interview, (%) *	940 (14)
Medical comorbidities	
Cancer (excluding minor skin cancer), n (%)	1142 (17)
Heart disease, (%)	2486 (37)
Hypertension, (%)	4300 (64)
Vascular disease, (%) **	2486 (37)
Anemia, (%)	1008 (15)
Renal disease, (%)	269 (4)
Atrial fibrillation, (%)	538 (8)
Prior bleeding event, (%)	47 (1)
Alcohol use, (%)	1680 (25)
Function and community dwelling	
ADL disability, (%)	1008 (15)
IADL disability, (%)	1545 (23)
Nursing home residence, (%)	269 (4)
Use of walker, (%)	1411 (21)
Falls, (%)	2217 (33)

Abbreviations – IQR=interquartile range, ADL=activities of daily living, IADL=instrumental activities of daily living

Comorbidity definitions by Medicare claims and self-report of physician diagnosis can be found in Appendix Table 1

* Proxy interview defined as next-of-kin interview when participants cannot answer questions because of physical or cognitive impairment

** Vascular disease defined as acute myocardial infarction or ischemic heart disease

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Bleeding hospitalization characteristics

Bleeding hospitalization characteristics	ECH admission (n=763)
Site of bleeding, n (%)	
Gastrointestinal	696 (91)
Genitourinary	39 (5)
Other *	28 (4)
Procedures during admission, n (%)	
Upper endoscopy	246 (32)
Colonoscopy	98 (13)
Both	126 (17)
Neither	293 (38)
Packed red blood cell transfusion, n (%)	450 (59)
Intensive Care Unit admission, n (%)	164 (21)
Length of stay, median (IQR)	5 (3,7)
Discharge location, n (%)	
Home	538 (71)
Skilled nursing facility	120 (16)
Deceased	32 (4)
Others **	73 (10)

Abbreviations- RBC= red blood cell, ICU= intensive care unit, LOS= length of stay, IQR=interquartile range

* Other bleeding sites include epistaxis (1%), hemoptysis, hemoperitoneum, hemopericardium, hemarthrosis, unspecific hemorrhage (<1%)

** Other discharge locations include long-term care hospital, hospice, transfer to other acute care hospital