**Supplementary Tables**

## **Supplementary Table 1: ICD-10 codes**

|  |  |
| --- | --- |
|  | **ICD-10 codes** |
| ***Bleeding events*** | |
| **Gastrointestinal bleeding (specific search)** | K22.1, K22.3, K22.6*,* K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2, I85.0, I98.3 |
| **Gastrointestinal bleeding (sensitive search)** | C15, C15.3, C15.4, C15.5, C15.8, C15.9, C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, C21, C21.0, C21.1, C21.2, C21.8, D37.1, D37.2, D37.3, D37.4, D37.5, I85, I85.0, I85.1, I98.3, K29, K29.2, K29.3, K29.4, K29.5, K29.6, K29.7, K29.8, K29.9, K50, K50.0, K50.1, K50.8, K50.9, K51, K51.0, K51.2, K51.3, K51.4, K51.5, K51.8, K51.9, K55.0, K55.1, K55.8 K55.9, K57.1, K57.3, K57.5, K57.9, K22.1, K22.3, K22.6, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9, K29.0, K55.2, K62.5, K62.6, K63.1, K63.3, K92.0, K92.1, K92.2 |
| **Non-traumatic intracranial hemorrhage** | I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9 |
| **Traumatic intracranial hemorrhage** | S06.3, S06.4, S06.5, S06.6 |
| **Other bleeding** | D50.0, D62, H11.3, H35.6, H43.1, J94.2, M25.0, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N95.0, R04, R04.0, R04.1, R04.2, R04.8, R04.9, R31, R58 |
| ***Thrombotic events*** | |
| **Stroke** | I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8 |
| **TIA** | G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9 |
| **Myocardial infarct** | I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8 |
| **Deep venous thrombosis** | I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9 |
| **Pulmonary embolism** | I26, I26.0, I26.9 |
| **Other thrombosis** | H34.9, I63.6, I67.6, I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I76, I79.0, I79.1, I81, I82.0, I65, I65.0, I65.1, I65.2, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.8, I66.9, I67, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.6, I67.7, I67.8, I67.9, I68.8, G08, G95.1 |
| ***Treatment indication*** | |
| **Atrial fibrillation** | I48, I48.0, I48.1, I48.2, I48.3, I48.4, I48.9 |
| **Venous thromboembolism** | I26, I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9 |
| **Ischemic stroke** | G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, I69, I69.3, I69.8, 169.9 |
| **Mechanical heart valve** | Z95.2, Z95.3, Z95.4 |
| ***Comorbidities*** | |
| **Ischemic heart disease** | I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8 |
| **Heart failure** | I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.3, I50.4, I50.8, I50.9 |
| **Peripheral vascular disease** | I70, I70.0, I70.1, I70.2, I70.8, I70.9, I71, I71.0, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I72, I72.0, I72.1, I72.2, I72.3, I72.4, I72.8, I72.9, I73.0, I73.1, I73.8, I73.9, I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I77, I77.0, I77.1, I77.2, I77.3, I77.4, I77.5, I77.6, I77.8, I77.9 |
| **Cerebral accident** | I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.7, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6,I63.8, I63.9, I64, I64.0, I64.1, I64.2, I64.3, I64.4, I64.5, I64.6, I64.8, I64.9, G45, G45.0, G45.1, G45.2, G45.3, G45.4, G45.8, G45.9, G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8 |
| **Hemiplegia** | G81, G81.0, G81.1, G81.9, G82, G82.0, G82.1, G82.2, G82.3, G82.4, G82.5 |
| **Dementia** | F00, F00.0, F00.1, F00.2, F00.39, F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02, F02.0, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05, F05.0, F05.1, F05.8, F05.9, G30, G30.0, G30.1, G30.8, G30.9 |
| **Chronic lung disease** | J40, J41, J41.0, J41.1, J41.8, J42, J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9, J45, J45.0, J45.1, J45.8, J45.9, J46, J47, J60, J61, J62, J62.0, J62.8, J63, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.8, J64, J65, J66, J66.0, J66.1, J66.2, J66.8, J67, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3 |
| **Connective tissue disease** | D86, D86.0, D86.1, D86.2, D86.3, D86.8, D86.9, M05, M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9, M08, M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9, M09, M09.0, M09.1, M09.2, M09.8, M30, M30.0, M30.1, M30.2, M30.3, M30.8, M31, M31.0, M31.1, M31.2, M31.3, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M32, M32.0, M32.1, M32.2, M32.8, M32.9, M33, M33.0, M33.1, M33.8, M33.9, M34, M34.0, M34.1, M34.2, M34.8, M34.9, M35, M35.0, M35.1, M35.2, M35.3, M35.4, M35.5, M35.6, M35.7, M35.8, M35.9, M36, M36.0, M36.1, M36.2, M36.3, M36.4, M36.8 |
| **Peptic ulcer disease** | K22.1, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7, K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9 |
| **Mild liver disease** | B18, B18.0, B18.1, B18.2, B18.8, B18.9, K70.0, K70.1, K70.2, 70.3, K70.9, K71, K71.0, K71.1, K71.2, K71.3, K71.4, K71.5, K71.6, K71.7, K71.8, K71.9, K73, K73.0, K73.1, K73.2, K73.8, K73.9, K74, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.6, K76.1, K76.2, K76.3, K76.4, K76.8, K76.9 |
| **Moderate or severe liver disease** | B15.0, B16.0, B16.2, B19.0, K70.4, K72, K72.0, K72.1, K72.9, K76.6, I85, I85.0, I85.9, I86.4, I98.2 |
| **Moderate or severe renal disease** | I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, N00, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N1, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N03, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N07, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N11, N11.0, N11.1, N11.8, N11.9, N14, N14.0, N14.1, N14.2, N14.3, N14.4, N17, N17.0, N17.1, N17.2, N17.8, N17.9, N18, N18.0, N18.8, N18.9, N19, Q61, Q61.0, Q61.1, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q61.9 |
| **Diabetes mellitus without signs of end-organ damage** | E10.0, E10.1, E10.9, E11.0, E11.1, E11.9 |
| **Diabetes mellitus without end-organ damage** | E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8 |
| **Tumor** | C00-C75, C81-C85, C88, C90-C96 |
| **Metastasis** | C76-C80 |
| **HIV/AIDS** | B20, B20.0, B20.1, B20.2, B20.3, B20.4, B20.5, B20.6, B20.7, B20.8, B20.9, B21, B21.0, B21.1, B21.2, B21.3, B21.7, B21.8, B21.9, B22, B22.0, B22.1, B22.2, B22.7, B23, B23.0, B23.1, B23.2, B23.8, B24 |
| **Hypertension** | I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9 |
| **Bleeding or coagulation disorders** | D65, D66, D67, D68.0, D68.1, D68.2, D68.3, D68.4, D68.5, D68.6, D68.8, D68.9, D69.1, D69.3, D69.4, D69.5, D69.6 |

The ICD-10 codes used for the comorbidity variables were based on:

1. Thygesen SK, Christiansen CF, Christensen S, et al. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.
2. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a case definition to define hypertension using administrative data. Hypertension 2009;54:1423-8.

## **Supplementary Table 2: ATC codes for simultaneous drug use**

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| **Drug class** | **ATC codes** |
| **Antihistamines** | A02BA |
| **Antiplatelets** | B01AC |
| **NSAIDs** | M01A |
| **SSRI** | N06AB |
| **Statins** | C10AA |
| **Steroids** | H02AB |
| ***Hypertensive medications*** | |
| **a-blockers** | C02A, C02B, C02C |
| **b-blockers** | C07A, C07B |
| **Ca2+-blockers** | C08, C09BB, C09DB, C07FB |
| **Medications affecting the RAAS** | C09 |
| **Thiazides** | C03A, C09BA, C09DA, C07B, C07D, C08G |
| **Other diuretics** | C02L, C03B, C03D, C03EA, C03X, C07C, C07D |
| **Vasodilators** | C02D, C04, C05, C07E |

## **Supplementary Table 3: Origin of bleeding event identification in patients on oral anticoagulation.**

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| **Bleeding event origin** | **n (%)** |
| **Landspitali University hospital Iceland** | 482 (64%) |
| **Regional Hospitals** | 106 (14%) |
| **Cause of Death Registry** | 18 (2%) |
| **Endoscopy Database** | 146 (19%) |

## **Supplementary Table 4: Indications for oral anticoagulation in patients with gastrointestinal bleeding events.**

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| **Indication for oral anticoagulation** | **n (%)** |
| **Atrial fibrillation** | 550 (73%) |
| **Venous thromboembolism** | 96 (13%) |
| **Mechanical heart valve** | 20 (3%) |
| **Unknown** | 29 (4%) |

STROBE Statement—c STROBE Statement—checklist of items that should be included in reports of observational studies

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| --- | --- | --- | --- | --- |
|  | **Item No.** | **Recommendation** | **Page  No.** | **Relevant text from manuscript** |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 1 | Population-based |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 | Causes of gastrointestinal bleeding (GIB) in patients on oral anticoagulants (OACs) are not well established. (…) A high proportion of GIB caused by colonic polyps and colorectal cancer among OAC patients indicates that OACs treatment may facilitate cancer diagnosis. The low proportion of ischemic colitis among those on OACs suggests that OACs provide a protective effect against ischemic colitis. OACs seem to increase the bleeding from angiodysplasia and mucosal erosive disease. |
| **Introduction** | | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 | The different aetiologies of gastrointestinal bleeding in the general population are well documented (Table 1). However, very limited data exist on the aetiology of GIB in patients using OACs. Further head-to-head comparisons of GIB events in non-OAC users might reveal the potential effects of OACs on the causes of GIB. |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 | The aim of the study was to examine the impact of oral anticoagulants on the causes of GIB … |
| **Methods** | | | |  |
| Study design | 4 | Present key elements of study design early in the paper | 4 | This was a retrospective nationwide study that included all individuals in Iceland with a prescription for OACs and were found to have a GIB event during 2014-2019. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 | Cases were found through a nationwide prescription database, GIB events were identified using ICD-codes, death registry or hospital endoscopy databases and confirmed by manual review of electronic medical records. Cases were compared to patients not on OACs from two prior Icelandic population-based studies on GIB. |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 4 | Data on all individuals that received a prescription for oral anticoagulants in Iceland were obtained from the Icelandic Medicine Registry (…) GIB events in patients with an OAC prescription were found by linking the patient’s personal identification number to their medical records. Bleeding events were identified by ICD-10 code search, endoscopy review and the cause of death registry. |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  *Case-control study*—For matched studies, give matching criteria and the number of controls per case | 5 | Exposed OAC UGIB 273 vs unexposed UGIB 258 Exposed OAC LGIB 391 vs unexposed LGIB 560 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4-5 | Data on all individuals that received a prescription for oral anticoagulants in Iceland were obtained from the Icelandic Medicine Registry in the period (…), Bleeding events were identified by ICD-10 code search, endoscopy review and the cause of death registry. The primary endpoint was any confirmed clinically relevant GIB event during the study period. Acute upper gastrointestinal bleeding (AUGIB) was defined as (…), The medical records of all patients with GIB events on OACs were searched for simultaneous PPI, NSAID, and antiplatelet therapy as they are available over the counter… |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4-5 | ICD-10 codes for any bleeding event, thromboembolic events, comorbidities, and indications for OACs were collected (…), Information was gathered from admission notes …. for simultaneous PPI, NSAID, and antiplatelet therapy |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5 | By having a population-based cohort. |
| Study size | 10 | Explain how the study size was arrived at |  | Population-based cohort and population based control. |

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| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6 | Continuous variables are presented as mean (standard deviation); categorical variables are presented as n (%). The Mann-Whitney test was used for comparison of continuous variables and the Fisher’s exact test was used for comparison of categorical variables. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 | …. with mixed effects logistic regression. Aetiologies with *n* > 10 were analysed. The variables corrected for were selected *a priori*. They included age, sex, Charlson Comorbidity Index, antiplatelet use and NSAID use. Additionally, the use of PPI was corrected for patients with upper GIB. |
| (*b*) Describe any methods used to examine subgroups and interactions |  |  |
| (*c*) Explain how missing data were addressed |  |  |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |  |  |
| (*e*) Describe any sensitivity analyses |  |  |
| **Results** | | | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 6 | A total of 12,005 individuals received 14,611 OACs prescriptions, as 2,626 patients had two or more OACs prescribed. Of 14,611 registered prescriptions, 752 bleeding events occurred in patients on anticoagulation. |
| (b) Give reasons for non-participation at each stage |  |  |
| (c) Consider use of a flow diagram |  |  |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6 | Table 2 (all anticoagulated patients), 3 (for upper bleeding) and 4 (for lower bleeding). |
| (b) Indicate number of participants with missing data for each variable of interest |  |  |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |  |  |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time | *6-7* | *Table 3-5* |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure |  |  |
| *Cross-sectional study—*Report numbers of outcome events or summary measures |  |  |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7 | Table 3-5 |
| (*b*) Report category boundaries when continuous variables were categorized |  |  |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |  |  |

Continued on next page

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| --- | --- | --- | --- | --- |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |  |  |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 8 | In the current nationwide study of gastrointestinal bleeding in OAC users and non-users, aetiology of bleeding was different between the two groups. Importantly, … |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 9 | Strengths of the study include (…) The current study also has several limitations … |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8-10 | The aetiology of gastrointestinal bleeding was found to be different in patients on anticoagulation compared to non-users. … |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 9 | Population-based but homogenous cohort (see strengths and limitations). |
| **Other information** | |  | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 1 | Acknowledgement: The writing and preparation of this paper (…) |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

hecklist of items that should be included in reports of observational studies