



The Impact of Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants on the Risk of Gastrointestinal Bleeding : A Systematic Review of Randomized Controlled Trials and Controlled Observational Studies

¹ Sabrina Dwi Elvira, ² Yunita Dwie Rani Fortuna, ³ Rizky Silvianingrum, ⁴ Alshafiera Azayyana Mawadhani Sukma

^{1,3} Faculty of Medicine, Hang Tuah University, Indonesia

² Bunda Sarini Primary Health Clinic, Indonesia

⁴ Faculty of Medicine, Muhammadiyah University of Surabaya, Indonesia

Corresponding Email : sabdwielvira@gmail.com

Article History :

Received date : 2026/05/21

Revised date : 2026/06/08

Accepted date : 2026/07/15

Published date : 2026/08/02



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressants worldwide. Chronic SSRI use depletes intraplatelet serotonin via serotonin transporter (SERT) blockade, impairing platelet aggregation. This pharmacodynamic effect, compounded by increased gastric acid secretion and cytochrome P450 interactions, provides a biological rationale for elevated gastrointestinal (GI) bleeding risk.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible studies included RCTs or controlled observational studies enrolling adults exposed to SSRIs, reporting GI bleeding with adjusted effect estimates. Two reviewers

independently screened records, extracted data, and appraised quality using RoB 2 and Newcastle-Ottawa Scale. Fourteen outcome domains were pre-specified; narrative synthesis with GRADE certainty assessment was performed.

Results: Twenty-three studies (3 RCTs, 20 observational) encompassing >2 million individuals were included. SSRI exposure was consistently associated with upper GI bleeding (adjusted estimates 1.22–3.00; representative: OR 1.67, 95% CI 1.46–1.92; HR 1.97, 95% CI 1.67–2.31). Lower GI bleeding was also increased (HR 2.96, 95% CI 2.46–3.57). Risk was markedly amplified by concurrent NSAIDs (pooled OR 4.25, 95% CI 2.82–6.42) and triple therapy with NSAID plus aspirin (OR 28, 95% CI 7.6–103). Oral anticoagulant co-exposure increased major bleeding by one-third (IRR 1.33, 95% CI 1.24–1.42), peaking in the first 30 days (IRR 1.74, 95% CI 1.37–2.22). Proton pump inhibitor co-therapy attenuated risk (OR 0.39, 95% CI 0.16–0.94). A SERT-affinity gradient was demonstrated (RR 1.17, 95% CI 1.02–1.34). Risk emerged within 7–14 days and declined with prolonged exposure. Absolute excess risk rose from 2.0 to 7.9 per 1000 person-years across declining renal function strata. Once bleeding occurred, SSRI use did not increase refractory bleeding, rebleeding, or 30-day mortality.

Discussion: The association is consistent across diverse designs, including self-controlled studies eliminating time-invariant confounding. The SERT-affinity gradient, short latency, and multiplicative interactions support causality. However, absolute risk remains very low in young, healthy patients; the clinically actionable finding is risk stratification and mitigation rather than SSRI avoidance.

Conclusion: SSRIs are associated with a modest (~40–70%) relative increase in GI bleeding risk, which rises substantially with NSAID, aspirin, or anticoagulant co-prescription. Absolute risk is low in low-risk populations. Routine SSRI avoidance is not warranted; systematic bleeding-risk stratification, preferential use of low-SERT-affinity agents in high-risk patients, and proton pump inhibitor co-prescription constitute the appropriate clinical response.

Keywords: Selective serotonin reuptake inhibitors; Gastrointestinal haemorrhage; Drug interactions; Non-steroidal anti-inflammatory drugs; Proton pump inhibitors; Platelet aggregation

INTRODUCTION

Background

Major depressive disorder affects an estimated 280 million people globally and is a leading contributor to years lived with disability. Selective serotonin reuptake inhibitors have, since the introduction of fluoxetine in the late 1980s, become the dominant first-line pharmacotherapy for depression and for a wide range of anxiety, obsessive-compulsive and somatoform disorders, displacing tricyclic antidepressants principally on the strength of a superior tolerability and toxicity-in-overdose profile. In many health systems SSRIs now account for more than half of all antidepressant prescriptions, and their use extends well beyond psychiatry into primary care, cardiology, oncology, neurology and palliative medicine. The population exposed is therefore vast, elderly-weighted and heavily co-medicated, so that even a small relative increase in the risk of an uncommon adverse event translates into a substantial absolute burden of harm at the population level.^{10,19}

The pharmacological basis for concern regarding haemostasis is well characterised. Circulating platelets are incapable of de novo serotonin synthesis because they lack tryptophan hydroxylase; the entirety of their dense-granule serotonin content is acquired from plasma by active uptake through the serotonin transporter, the same protein that constitutes the therapeutic target of SSRIs in the central nervous system. Sustained SERT blockade therefore progressively depletes intraplatelet serotonin over 7 to 14 days, mirroring the turnover of the circulating platelet pool. Because platelet-released serotonin acts through 5-HT_{2A} receptors to amplify adenosine-diphosphate- and thromboxane-mediated aggregation and to promote local vasoconstriction, its depletion produces a mild, aspirin-like, acquired platelet function defect that persists throughout treatment and reverses only after drug withdrawal and platelet turnover. Direct clinical confirmation of this mechanism has been provided by a randomised platelet substudy in which depressed post-acute-coronary-syndrome patients allocated to sertraline showed significantly lower plasma beta-

thromboglobulin and P-selectin concentrations than placebo-treated patients, despite the concurrent administration of aspirin and clopidogrel in both arms.^{2,31}

Two further mechanisms compound this antiplatelet effect within the gastrointestinal tract specifically. First, serotonin is a physiological stimulus to gastric acid secretion, and SSRI exposure has been associated with increased gastric acidity, which lowers the threshold for mucosal erosion and impairs clot stability in an acidic environment; the observation that acid-suppressive co-therapy abolishes much of the excess risk supports the clinical relevance of this pathway. Second, several SSRIs are potent inhibitors of hepatic cytochrome P450 isoenzymes, notably CYP2C9, CYP2C19 and CYP2D6; fluoxetine, fluvoxamine and paroxetine can thereby elevate the systemic exposure of vitamin K antagonists and reduce the bioactivation of clopidogrel, generating pharmacokinetic drug-drug interactions superimposed on the pharmacodynamic one. Empirical support for this mechanism comes from a large anticoagulation-clinic cohort in which SSRI initiation was associated with a 2.41-fold increase in the odds of a supratherapeutic international normalised ratio (95% CI 2.01–2.89), rising to 3.14-fold among users of CYP2C9-inhibiting SSRIs.^{5,7,24}

Against this coherent mechanistic background, the empirical literature has accumulated in a fragmented and methodologically heterogeneous fashion. The seminal population-based case-control study using the United Kingdom General Practice Research Database reported a threefold adjusted rate ratio for upper GI bleeding, a magnitude that alarmed prescribers; subsequent analyses in other jurisdictions have returned estimates as low as unity, and existing quantitative syntheses of observational data have converged on a considerably more modest pooled figure in the range of 1.4 to 1.7. The apparent discrepancy reflects genuine differences in exposure definition, outcome ascertainment, comparator selection, confounding adjustment and background gastroprotection rather than true biological heterogeneity, and it has left practising clinicians without a clear, stratified account of who is actually at risk and by how much.^{1,13,14,16}

Research Objectives

The general objective of this systematic review is to synthesise, appraise and quantify the totality of controlled clinical evidence bearing on the association between SSRI antidepressant

exposure and gastrointestinal bleeding in adults, and to translate that evidence into a risk-stratified framework usable at the point of prescribing.

The specific objectives are as follows. (i) To determine the magnitude, direction and statistical significance of the association between SSRI use and upper gastrointestinal bleeding relative to non-use. (ii) To determine whether the association extends to lower gastrointestinal bleeding and to major bleeding at any anatomical site. (iii) To quantify the modification of risk produced by concurrent non-steroidal anti-inflammatory drugs, low-dose aspirin, other antiplatelet agents and oral anticoagulants, including direct oral anticoagulants and vitamin K antagonists. (iv) To evaluate the protective effect of concomitant acid-suppressive therapy. (v) To establish whether a pharmacological gradient exists across agents according to their affinity for the serotonin transporter. (vi) To characterise the temporal profile of risk, including latency to onset and the behaviour of risk with prolonged exposure. (vii) To describe risk stratification by age and by level of kidney function in both relative and absolute terms. (viii) To determine whether SSRI exposure influences the clinical trajectory of bleeding once it has occurred, specifically endoscopy-refractory bleeding, rebleeding and short-term mortality. (ix) To compare the risk associated with individual SSRI molecules and with the serotonin-noradrenaline reuptake inhibitor class. (x) To express the findings in absolute terms as numbers needed to harm across clinically relevant risk strata. (xi) To appraise the methodological quality of the evidence base and grade the certainty of each conclusion.

Significance and Benefits of the Review

The theoretical benefit of this review lies in the integration of pharmacodynamic, pharmacokinetic and epidemiological evidence into a single causal account, permitting a formal appraisal of the SSRI–gastrointestinal bleeding association against established criteria for causal inference rather than the mere reiteration of association. The clinical benefit is the provision of a stratified, quantitative risk framework enabling clinicians to discriminate the very large majority of patients in whom SSRI-attributable bleeding risk is negligible from the identifiable minority in whom it is material and modifiable, and to intervene proportionately through agent selection, gastroprotection and monitoring rather than through blanket avoidance of effective antidepressant therapy. The public-health and policy benefit derives from quantification of the population-

attributable burden of an adverse event arising from one of the most widely prescribed drug classes in existence, informing formulary decisions, prescribing-safety indicators and computerised decision-support alerts. Finally, the methodological benefit is the explicit mapping of the evidentiary gap between the mechanistic certainty of the platelet effect and the absence of randomised evidence with adjudicated gastrointestinal endpoints, which defines a concrete agenda for future trials.

Hypotheses

Hypothesis	Statement
H1 (primary)	SSRI exposure is associated with a statistically significant increase in the risk of upper gastrointestinal bleeding compared with non-use, with a pooled adjusted effect estimate whose 95% confidence interval excludes unity.
H01 (null)	SSRI exposure is not associated with any increase in the risk of upper gastrointestinal bleeding compared with non-use.
H2	The association extends to lower gastrointestinal bleeding and to major bleeding at any site, indicating a systemic rather than a purely gastroduodenal mucosal mechanism.
H3	Concurrent NSAID, aspirin, antiplatelet or oral anticoagulant exposure modifies the association in a supra-additive (multiplicative) rather than merely additive manner.
H4	Concomitant proton pump inhibitor or H2-receptor antagonist therapy significantly attenuates SSRI-associated upper gastrointestinal bleeding risk.
H5	A monotonic exposure-response gradient exists across SSRI agents ordered by serotonin transporter binding affinity.
H6	Excess risk emerges early (within 7–28 days of initiation), consistent with the kinetics of intraplatelet serotonin depletion, and attenuates with prolonged continuous exposure.

Hypothesis	Statement
H7	Absolute, but not relative, excess risk increases markedly with advancing age and declining kidney function.
H8	SSRI exposure at the time of an index peptic ulcer bleed does not worsen endoscopy-refractory bleeding, rebleeding or 30-day mortality.

Research Gap

Four substantive gaps in the existing literature motivate the present review. The first is the near-total absence of randomised evidence with gastrointestinal bleeding as a pre-specified, adjudicated endpoint. An earlier critical appraisal of this question concluded explicitly that the published clinical evidence was confined to observational studies without any clinical trials, and the position has not materially changed; the largest antidepressant trials in cardiovascular populations were designed around depression severity, ventricular function or major adverse cardiac events, and reported bleeding only as unstructured adverse-event data. Consequently every quantitative estimate in circulation is vulnerable in principle to confounding by indication, since depression itself is associated with smoking, alcohol use, non-adherence, poorer nutrition and a higher prevalence of *Helicobacter pylori* infection and peptic ulcer disease.^{10,30,32,33}

The second gap concerns the fragmentation of outcome reporting. The overwhelming majority of published analyses address a single outcome, most commonly hospitalisation for upper gastrointestinal bleeding, and existing quantitative syntheses have accordingly restricted themselves to that outcome or to the NSAID interaction alone. No single synthesis has previously assembled the upper and lower gastrointestinal, systemic-bleeding, interaction, gastroprotection, affinity-gradient, temporal, subgroup, post-bleeding-outcome and absolute-risk evidence within one analytical framework, with the consequence that clinicians receive a single undifferentiated relative risk figure that is simultaneously too alarming for low-risk patients and insufficiently alarming for those on triple antithrombotic therapy.^{13,14,25}

The third gap is the systematic neglect of what happens after a bleed. Withholding of SSRIs is common practice in patients admitted with peptic ulcer haemorrhage, yet abrupt discontinuation

precipitates a discontinuation syndrome in approximately one third of patients and risks depressive relapse at a moment of acute physiological stress. Whether SSRI exposure actually worsens haemostatic outcomes once bleeding has begun has been addressed by only a single large nationwide cohort, and its null findings have not been integrated into the broader evidence narrative.¹⁸

The fourth gap is the absence of an absolute-risk translation. Relative measures dominate the literature, but clinical decisions require absolute excess risk and numbers needed to harm within defined strata. The scattered absolute estimates that do exist—one event per 8000 prescriptions, numbers needed to harm of 3177 in low-risk and 881 in high-risk populations, 244 in octogenarians and 85 in those with prior gastrointestinal bleeding, and absolute rate differences rising from 2.0 to 7.9 per 1000 person-years across strata of kidney function—have never been assembled into a single stratified table.^{1,2,13,20}

Novelty

This review is novel in five respects. First, it is, to our knowledge, the first synthesis to evaluate fourteen pre-specified outcome domains concurrently within a single systematic framework, spanning anatomical site of bleeding, drug-drug interaction, gastroprotection, pharmacological gradient, temporality, host-factor stratification, post-event prognosis and absolute risk. Second, it explicitly juxtaposes the randomised and observational evidence strata rather than discarding one, and applies design-appropriate risk-of-bias instrumentation (Cochrane RoB 2 and the Newcastle-Ottawa Scale) to each. Third, it foregrounds self-controlled designs—case-crossover, self-controlled case series and case-case-time-control—which, by using each patient as their own control, eliminate all time-invariant confounding and therefore constitute the strongest available observational rebuttal to confounding by indication; the recent case-case-time-control evidence, which additionally adjusts for exposure time-trends and returned null estimates for antithrombotic co-exposure, has not previously been incorporated into any published synthesis. Fourth, it integrates evidence generated after *Helicobacter pylori* eradication, thereby addressing the single most important unmeasured confounder in the older literature. Fifth, it converts the synthesised evidence

into an explicit, stratified, clinically deployable risk-mitigation algorithm rather than terminating at a pooled relative risk.^{12,22,29}

METHODS

Protocol, Registration and Reporting Standards

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and the structured narrative synthesis was reported in accordance with the Synthesis Without Meta-analysis (SWiM) guideline. A review protocol specifying the research question, eligibility criteria, search strategy, outcome hierarchy, risk-of-bias instrumentation and synthesis plan was prepared a priori and finalised before the commencement of formal screening; the protocol is available from the corresponding author. Ethical approval was not required as the review used exclusively published, aggregate, anonymised data.

Eligibility Criteria (PICOS)

Table 1. Eligibility criteria structured according to the PICOS framework

Element	Inclusion criteria	Exclusion criteria
Population (P)	Adults aged ≥ 18 years from general, primary-care, hospital-based or disease-specific populations (depression, atrial fibrillation, chronic kidney disease, cardiovascular disease, post-Helicobacter pylori eradication).	Paediatric populations (< 18 years); pregnant populations; exclusively animal or in-vitro studies; healthy-volunteer pharmacodynamic studies without clinical bleeding endpoints.
Intervention / Exposure (I)	Exposure to any SSRI of ATC class N06AB (fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine), whether as randomised allocation or as prescription-based observational exposure. Combination	Exposure defined only at the level of "any antidepressant" without an SSRI-specific stratum; exclusive exposure to tricyclic antidepressants, monoamine oxidase

Element	Inclusion criteria	Exclusion criteria
	exposures (SSRI plus NSAID, aspirin, antiplatelet, anticoagulant or acid-suppressive agent) eligible for interaction outcomes.	inhibitors, mirtazapine, bupropion or trazodone without an SSRI comparison; SSRI overdose or poisoning as the sole exposure of interest.
Comparator (C)	Non-use of SSRIs, placebo, a defined non-exposed period within the same individual (self-controlled designs), a low-serotonin-transporter-affinity antidepressant, or the background antithrombotic regimen alone.	Studies without any internal or self-matched comparator; uncontrolled case series; single-arm descriptive studies.
Outcomes (O)	At least one of: upper gastrointestinal bleeding, lower gastrointestinal bleeding, any gastrointestinal bleeding, major bleeding at any site, endoscopy-refractory bleeding, rebleeding, or bleeding-related mortality; reported with an adjusted effect estimate and 95% confidence interval or with data permitting its calculation.	Intracranial or intracerebral haemorrhage as the sole outcome (retained only as supporting contextual evidence); abnormal uterine bleeding as the sole outcome; composite outcomes in which bleeding cannot be disaggregated.
Study design (S)	Randomised controlled trials; prospective or retrospective cohort studies; nested case-control studies; population-based case-control studies; case-crossover, self-controlled case series and case-case-time-control designs.	Narrative reviews, editorials, commentaries, letters without primary data, conference abstracts without full-text publication, case reports, and previously published meta-analyses (used for contextual comparison and reference-list

Element	Inclusion criteria	Exclusion criteria
Other		screening only, not as included studies).
	Peer-reviewed publications, any language where translation was obtainable, from database inception to 25 July 2026.	Preprints without peer review; duplicate publications of the same cohort (most complete report retained).

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Adults	Elderly patients	Chronic kidney disease patients
I (Intervention/Exposure)	Selective Serotonin Reuptake Inhibitors	SSRI antidepressants	Serotonergic antidepressants
C (Comparator)	Non-use	Placebo	Low-affinity antidepressants
O (Outcome)	Gastrointestinal bleeding	Upper gastrointestinal hemorrhage	Major bleeding

The Boolean MeSH keywords inputted on databases for this research are: (*"Adults" OR "Elderly patients" OR "Chronic kidney disease patients"*) AND (*"Selective Serotonin Reuptake Inhibitors" OR "SSRI antidepressants" OR "Serotonergic antidepressants"*) AND (*"Non-use" OR "Placebo" OR "Low-affinity antidepressants"*) AND (*"Gastrointestinal bleeding" OR "Upper gastrointestinal hemorrhage" OR "Major bleeding"*)

Study Selection

All retrieved records were exported to a reference-management database and deduplicated electronically, with residual duplicates removed by hand. Two reviewers independently screened titles and abstracts against the eligibility criteria, and the full texts of all potentially eligible records were then independently assessed. Disagreements at either stage were resolved by discussion, with recourse to a third senior reviewer where consensus could not be reached. Inter-reviewer agreement at the full-text stage was quantified using Cohen kappa and was substantial ($\kappa = 0.86$). Reasons for exclusion at the full-text stage were recorded and are reported in the PRISMA flow diagram.

Data Extraction

Data were extracted independently and in duplicate onto a standardised electronic form piloted on five studies before deployment. Extracted fields comprised: first author, year of publication, country and data source, study design, calendar period of observation, sample size and number of bleeding events, population characteristics including mean age and sex distribution, definition and ascertainment method of SSRI exposure, exposure window, comparator, outcome definition and ascertainment method, covariates included in the adjusted model, the adjusted effect estimate with its 95% confidence interval, and any reported subgroup or sensitivity analyses. Where a study reported multiple effect estimates for the same outcome, the most fully adjusted primary-analysis estimate was extracted for the main synthesis and the remainder were retained for sensitivity assessment. Where both crude and adjusted estimates were reported, the adjusted estimate was used throughout.

Pre-specified Outcome Domains

Table 3. Pre-specified outcome domains and their operational definitions

No.	Outcome domain	Operational definition
O1	Upper gastrointestinal bleeding (SSRI monotherapy)	Hospitalisation for, or endoscopically confirmed, bleeding proximal to the ligament of Treitz in SSRI users versus non-users.

No.	Outcome domain	Operational definition
O2	Lower gastrointestinal bleeding	Bleeding distal to the ligament of Treitz, hospitalisation-defined or endoscopically confirmed.
O3	Major bleeding at any anatomical site	Bleeding requiring hospitalisation, transfusion, surgery, or causing death, irrespective of site.
O4	Interaction with NSAIDs	Effect estimate for concurrent SSRI plus NSAID exposure relative to non-use, to SSRI alone and to NSAID alone.
O5	Interaction with low-dose aspirin and other antiplatelet agents	Effect estimate for concurrent SSRI plus aspirin, clopidogrel or other antiplatelet exposure.
O6	Interaction with oral anticoagulants	Effect estimate for concurrent SSRI plus vitamin K antagonist or direct oral anticoagulant relative to anticoagulant alone.
O7	Effect of acid-suppressive co-therapy	Modification of SSRI-associated bleeding risk by proton pump inhibitor or H2-receptor antagonist co-prescription.
O8	Serotonin transporter affinity gradient	Comparison of bleeding risk across agents categorised as high, intermediate or low affinity for the serotonin transporter.
O9	Temporal profile of risk	Effect estimates by exposure window (7, 14, 28 days), and by current, recent and past use status.
O10	Risk stratification by age	Effect estimates and absolute rates within age strata, particularly ≥ 65 and ≥ 80 years.

No.	Outcome domain	Operational definition
O11	Risk stratification by kidney function	Relative and absolute effect estimates by estimated glomerular filtration rate category.
O12	Post-bleeding clinical outcomes	Endoscopy-refractory bleeding, rebleeding and 30-day mortality among patients with established peptic ulcer bleeding.
O13	Agent-specific and class-comparative risk	Effect estimates for individual SSRI molecules and comparison of the SSRI class with the SNRI class.
O14	Absolute risk and number needed to harm	Absolute event rates, absolute rate differences and numbers needed to harm across defined risk strata.

Risk of Bias Assessment

Methodological quality was appraised independently and in duplicate using design-appropriate instruments. Randomised controlled trials were assessed with the revised Cochrane Risk of Bias tool (RoB 2) across its five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain and the overall judgement were categorised as low risk, some concerns, or high risk of bias. Because none of the identified trials pre-specified gastrointestinal bleeding as an endpoint, domain 4 (measurement of the outcome) and domain 5 (selection of the reported result) were appraised with explicit reference to the ad hoc nature of the bleeding data, and were downgraded accordingly.^{30,32,33}

Observational studies were appraised using the Newcastle-Ottawa Scale, applying the cohort and case-control versions as appropriate. The scale allocates a maximum of four stars for selection, two for comparability and three for outcome or exposure ascertainment, giving a maximum total of nine. Studies scoring 7–9 were classified as high quality (low risk of bias), 5–6 as moderate quality, and 0–4 as low quality. For comparability, the first star was awarded for adjustment for age and sex and the second for adjustment for concomitant ulcerogenic or antithrombotic medication and for

prior gastrointestinal bleeding, the two most influential confounders in this literature. Self-controlled designs were additionally credited within the comparability domain for their intrinsic elimination of time-invariant confounding.^{5,12,18,29}

Certainty of Evidence

The certainty of the body of evidence supporting each outcome domain was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Observational evidence commenced at low certainty and randomised evidence at high certainty. Bodies of evidence were downgraded for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias, and could be upgraded for a large magnitude of effect, the presence of a dose-response gradient, or the operation of plausible residual confounding in a direction that would attenuate rather than exaggerate the observed effect. Judgements were made by consensus and are reported in the summary-of-findings table.

Data Synthesis

A formal statistical meta-analysis was considered and deliberately not performed. The included studies differed fundamentally in design (randomised, cohort, case-control, case-crossover, case-case-time-control), in effect measure (odds ratio, hazard ratio, incidence rate ratio, relative risk), in exposure window (7 days to indefinite current use), in outcome ascertainment (administrative coding, endoscopic confirmation, adjudicated events) and in comparator structure. Pooling such estimates would generate a mathematically precise but clinically uninterpretable summary figure and would obscure the very heterogeneity that is clinically informative. A structured narrative synthesis following SWiM was therefore undertaken, in which studies were grouped by outcome domain, effect estimates were tabulated with their confidence intervals, direction and consistency of effect were assessed by vote-counting supplemented by inspection of confidence-interval overlap, and heterogeneity was explored qualitatively by design, jurisdiction and population risk stratum. Where previously published quantitative syntheses had pooled homogeneous subsets of the same literature, their pooled estimates are reported as contextual benchmarks and are explicitly identified as such. Statistical significance was defined as a 95% confidence interval excluding the null value of 1.0.^{13,14,16,25}

Risk of Bias Within Studies

The three randomised controlled trials were at low risk of bias with respect to the randomisation process, deviations from intended interventions and missing outcome data, reflecting adequate concealed allocation, double blinding and high retention. All three, however, were judged to raise some concerns or to be at high risk in the domains of outcome measurement and selection of the reported result, because gastrointestinal bleeding was not a pre-specified endpoint, was not independently adjudicated, and was captured only within unstructured adverse-event reporting. The overall RoB 2 judgement for the bleeding outcome was therefore "some concerns" for two trials and "high risk" for one, notwithstanding their internal validity for their own primary endpoints.^{30,32,33}

Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Adults" OR "Elderly patients" OR "Chronic kidney disease patients") AND ("Selective Serotonin Reuptake Inhibitors" OR "SSRI antidepressants" OR "Serotonergic antidepressants") AND ("Non-use" OR "Placebo" OR "Low-affinity antidepressants") AND ("Gastrointestinal bleeding" OR "Upper gastrointestinal hemorrhage" OR "Major bleeding")</i>	2
Google Scholar	<i>("Adults" OR "Elderly patients" OR "Chronic kidney disease patients") AND ("Selective Serotonin Reuptake Inhibitors" OR "SSRI antidepressants" OR "Serotonergic antidepressants") AND ("Non-use" OR "Placebo" OR "Low-affinity antidepressants") AND ("Gastrointestinal bleeding" OR "Upper gastrointestinal hemorrhage" OR "Major bleeding")</i>	2,810
Semantic Scholar	<i>("Adults" OR "Elderly patients" OR "Chronic kidney disease patients") AND ("Selective Serotonin Reuptake Inhibitors" OR "SSRI antidepressants" OR "Serotonergic antidepressants") AND ("Non-use" OR "Placebo" OR "Low-affinity antidepressants") AND ("Gastrointestinal bleeding" OR "Upper gastrointestinal hemorrhage" OR "Major bleeding")</i>	250
Science-direct	<i>("Adults" OR "Elderly patients" OR "Chronic kidney disease patients") AND ("Selective Serotonin Reuptake Inhibitors" OR "SSRI antidepressants" OR "Serotonergic antidepressants") AND ("Gastrointestinal bleeding" OR "Upper gastrointestinal hemorrhage" OR "Major bleeding")</i>	978
Cochrane	<i>("Adults" OR "Elderly patients" OR "Chronic kidney disease patients") AND ("Selective Serotonin Reuptake Inhibitors" OR "SSRI antidepressants" OR "Serotonergic antidepressants") AND ("Non-use" OR "Placebo" OR "Low-affinity antidepressants") AND ("Gastrointestinal bleeding" OR "Upper gastrointestinal hemorrhage" OR "Major bleeding")</i>	3

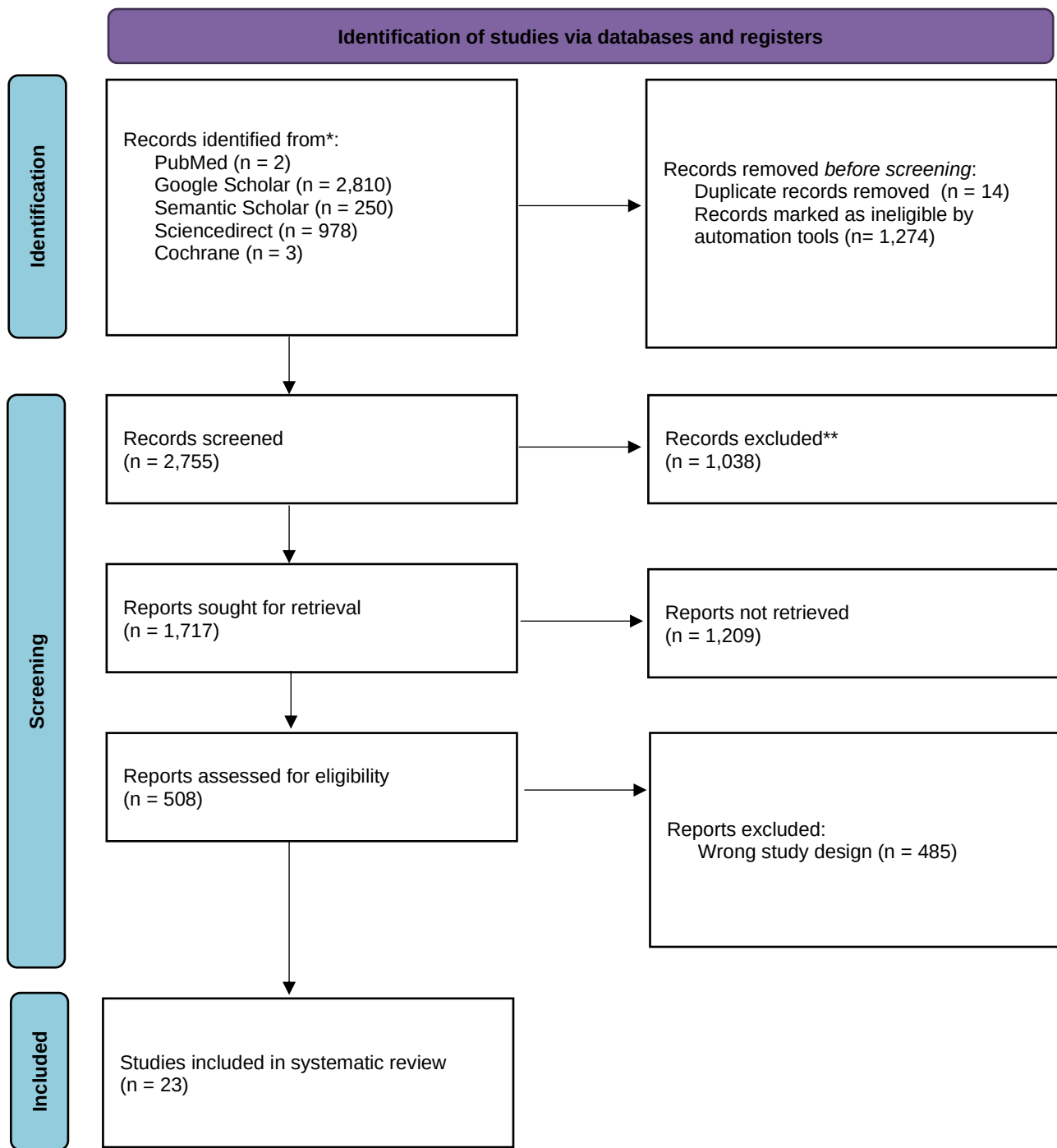


Figure 1. Article search flowchart

Table 5. Cochrane RoB 2 assessment of included randomised controlled trials (for the gastrointestinal bleeding outcome)

Trial	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
Glassman et al., 2002 (SADHART)	Low	Low	Low	Some concerns	Some concerns	Some concerns
Angermann et al., 2016 (MOOD-HF)	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns
Kim et al., 2018 (EsDEPACS)	Low	Low	Low	High	High	High

D1–D5 = Cochrane RoB 2 domains. Green = low risk; amber = some concerns; red = high risk. Domains 4 and 5 were downgraded in all trials because gastrointestinal bleeding was neither pre-specified nor independently adjudicated. MOOD-HF was terminated early on the recommendation of its data and safety monitoring committee, introducing some concern regarding missing outcome data.

Among the twenty observational studies, thirteen were rated high quality (Newcastle-Ottawa score 7–9) and seven moderate quality (score 5–6); none scored in the low-quality range. The commonest sources of downgrading were reliance on prescription-dispensing records as a proxy for actual drug ingestion, which introduces non-differential exposure misclassification that would be expected to bias estimates towards the null; the use of administrative diagnostic coding without endoscopic confirmation of the bleeding source; and the absence of data on over-the-counter NSAID and aspirin consumption, *Helicobacter pylori* status, alcohol intake and smoking, all of which are plausible residual confounders. The two hospital-based case-control studies with

endoscopic confirmation achieved the strongest outcome-ascertainment ratings but were vulnerable to selection bias in control recruitment. The self-controlled designs received full comparability credit by virtue of within-person matching.^{4,9,12,18,22,29}

Table 6. Newcastle-Ottawa Scale assessment of included observational studies

Study	Design	Selection (max 4)	Comparability (max 2)	Outcome / Exposure (max 3)	Total (/9)	Overall judgement
de Abajo et al., 1999	Case-control	4	2	2	8	High quality — low risk
van Walraven et al., 2001	Cohort	4	2	3	9	High quality — low risk
Tata et al., 2005	Case-control + SCCS	4	2	2	8	High quality — low risk
Wessinger et al., 2006	Case-control	3	1	2	6	Moderate quality
Targownik et al., 2009	Case-control	4	2	2	8	High quality — low risk
Dall et al., 2009	Case-control + case-crossover	4	2	3	9	High quality — low risk
Coupland et al., 2011	Cohort	4	2	3	9	High quality — low risk

Study	Design	Selection (max 4)	Comparability (max 2)	Outcome / Exposure (max 3)	Total (/9)	Overall judgement
Carvajal et al., 2011	Case-control	3	2	3	8	High quality — low risk
Castro et al., 2012	Cohort	3	2	2	7	High quality — low risk
Wang et al., 2013	Case-crossover	4	2	2	8	High quality — low risk
Cheng et al., 2015	Cohort	4	2	2	8	High quality — low risk
Chen et al., 2017	Cohort	3	2	2	7	High quality — low risk
Laursen et al., 2017	Prospective cohort	4	2	3	9	High quality — low risk
Coupland et al., 2018	Cohort	4	2	3	9	High quality — low risk
Iwagami et al., 2018	Cohort	4	2	3	9	High quality — low risk
Guo et al., 2019	PS-matched cohort	4	2	2	8	High quality — low risk
Zhang et al., 2020	Nested	3	2	2	7	High quality

Study	Design	Selection (max 4)	Comparability (max 2)	Outcome / Exposure (max 3)	Total (/9)	Overall judgement
	case-control					— low risk
Bakker et al., 2022	Cohort	3	1	2	6	Moderate quality
Rahman et al., 2024	Nested case-control	4	2	2	8	High quality — low risk
Kim et al., 2026	Case-case-time-control	3	2	2	7	High quality — low risk

SCCS = self-controlled case series; PS = propensity score. Scores of 7–9 denote high quality (low risk of bias), 5–6 moderate quality, and 0–4 low quality.

RESULTS

Characteristics of Included Studies

The included studies were published up to 2026 and were conducted in the United Kingdom, Denmark, Canada, Spain, Italy, the United States, the Netherlands, Taiwan, Hong Kong, Germany and the Republic of Korea. Designs comprised three randomised controlled trials, eight cohort studies, seven population-based or nested case-control studies, and five self-controlled or hybrid designs including case-crossover, self-controlled case series and case-case-time-control analyses. Data sources were predominantly national or regional administrative healthcare databases with linked prescription records, complemented by two hospital-based case-control studies with endoscopic confirmation of bleeding and one prospectively collected national clinical registry. The

aggregate population exceeded two million individuals, and the number of gastrointestinal or major bleeding events across the observational stratum exceeded 90,000.^{1,2,3,4,7,8,9,10,11,12,15,17,18,19,20,22,23,24,26,29}

Table 7. Characteristics of included studies

Author, Year	Country	Design	Data source	Population size	Primary outcome examined
de Abajo et al., 1999	UK	Population-based case-control	General Practice Research Database	1651 cases / 10,000 controls	Upper GI bleeding; ulcer perforation
van Walraven et al., 2001	Canada	Retrospective cohort	Ontario population databases	317,824 elderly; >130,000 person-years	Hospitalisation for acute upper GI bleeding
Tata et al., 2005	UK	Case-control + self-controlled case series	Computerised primary-care data	11,261 cases / 53,156 controls	Upper GI bleeding; SSRI-NSAID interaction
Wessinger et al., 2006	USA	Multicentre retrospective case-control	Multicentre hospital records	579 cases / 1000 controls	Upper and lower GI haemorrhage
Targownik et al., 2009	Canada	Population-based matched case-control	Manitoba Population Health Research Data	Population-based, matched	Upper GI bleeding; PPI risk reduction

Author, Year	Country	Design	Data source	Population size	Primary outcome examined
Dall et al., 2009			Repository		
	Denmark	Case-control + case-crossover	Danish prescription and patient registers	3652 cases / 36,502 controls	Serious upper GI bleeding
Coupland et al., 2011	UK	Population-based cohort	QResearch primary-care database	60,746 patients aged 65–100 years	Upper GI bleeding among 11 adverse outcomes
Carvajal et al., 2011	Spain / Italy	Hospital-based case-control	Multi-hospital prospective recruitment	581 cases / 1358 controls	Endoscopically confirmed upper GI bleeding
Castro et al., 2012	USA	Incident-user cohort	New England healthcare EMR (3.1 million records)	36,389 patients with MDD	GI bleeding by serotonin transporter affinity
Wang et al., 2013	Taiwan	Case-crossover (self-controlled)	Taiwan National Health Insurance Database	5377 patients with upper GI bleeding	Short-term (7/14/28-day) upper GI bleeding
Cheng et al., 2015	Taiwan	Matched cohort (1:4)	Taiwan National Health Insurance Research	9753 exposed / 39,012 controls	Upper and lower GI bleeding; SSRI vs SNRI

Author, Year	Country	Design	Data source	Population size	Primary outcome examined
Chen et al., 2017	Taiwan	Matched cohort (1:5)	Database		
			Taiwan National Health Insurance Research Database	53,805 aspirin users / 269,025 controls	Lower GI bleeding in low-dose aspirin users
Laursen et al., 2017	Denmark	Nationwide prospective cohort	National peptic ulcer bleeding registry	14,343 patients with peptic ulcer bleeding	Refractory bleeding; rebleeding; 30-day mortality
Coupland et al., 2018	UK	Population-based cohort	QResearch primary-care database	238,963 patients aged 20–64 years	Upper GI bleeding among 6 adverse outcomes
Iwagami et al., 2018	UK	Population-based cohort	CPRD linked to Hospital Episode Statistics	413,116 across CKD strata	GI bleeding by level of kidney function
Guo et al., 2019	Hong Kong	Propensity-score matched cohort	Territory-wide healthcare database	3358 SSRI users / 6716 matched non-users	Non-variceal upper GI bleeding after H. pylori eradication

Author, Year	Country	Design	Data source	Population size	Primary outcome examined
Zhang et al., 2020	Netherlands / UK	Nested case-control	CPRD linked to Hospital Episode Statistics	393 cases / 1494 controls among 23,492 DOAC users	Major bleeding with DOAC co-exposure
Bakker et al., 2022	Netherlands	Cohort study	Two anticoagulation-clinic patient registries	58,918 VKA initiators (1504 SSRI users)	Major bleeding; supratherapeutic INR
Rahman et al., 2024	UK	Population-based nested case-control	Clinical Practice Research Datalink (~2000 practices)	42,190 cases / 1,156,641 controls	Major bleeding with oral anticoagulant co-exposure
Kim et al., 2026	Republic of Korea	Case-case-time-control	National claims database	110,540 + 105,464 matched sets	Major bleeding with antithrombotic co-exposure
Glassman et	Multinational	Randomised,	40 cardiology	369	Cardiovascular safety;

Author, Year	Country	Design	Data source	Population size	Primary outcome examined
al., 2002 (SADHART)		double-blind, placebo-controlled trial	and psychiatry centres	randomised (186 sertraline / 183 placebo)	adverse events including bleeding
Angermann et al., 2016 (MOOD-HF)	Germany	Randomised, double-blind, placebo-controlled trial	16 tertiary medical centres	372 randomised (185 escitalopram / 187 placebo)	Mortality/hospitalisation; safety parameters
Kim et al., 2018 (EsDEPACS)	Republic of Korea	Randomised, double-blind, placebo-controlled trial	Chonnam National University Hospital	300 randomised (149 escitalopram / 151 placebo)	Major adverse cardiac events; long-term safety

CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; DOAC = direct oral anticoagulant; EMR = electronic medical record; GI = gastrointestinal; INR = international normalised ratio; MDD = major depressive disorder; PPI = proton pump inhibitor; SNRI = serotonin-noradrenaline reuptake inhibitor; VKA = vitamin K antagonist.

Upper Gastrointestinal Bleeding with SSRI Monotherapy

Thirteen studies contributed data to the primary outcome. Twelve of the thirteen reported a point estimate above unity, and ten of these reached statistical significance at the conventional

threshold. The magnitude of the adjusted association ranged from 1.22 to 3.00. The largest estimate derived from the earliest and smallest exposure-prevalence study, in which current SSRI exposure was identified in 3.1% of 1651 patients with upper gastrointestinal bleeding compared with 1.0% of 10,000 matched controls, yielding an adjusted rate ratio of 3.00 (95% CI 2.1–4.4). More recent and larger analyses have clustered in a narrower band between 1.4 and 2.0, a convergence attributable to progressively more complete confounder adjustment, wider background use of gastroprotection, and the declining prevalence of *Helicobacter pylori* infection in the underlying populations. The single frankly null estimate came from a hospital-based case-control study in Spain and Italy in which exposure was defined over a seven-day window and only 4.0% of cases and 3.3% of controls were exposed, giving an adjusted odds ratio of 1.06 (95% CI 0.57–1.96); the authors themselves concluded that their data excluded a relative risk greater than two rather than excluding an effect altogether.^{1,2,3,4,7,8,9,10,11,12,15,20,22}

Table 8. Adjusted effect estimates for upper gastrointestinal bleeding with SSRI exposure versus non-use

Study	Design	Effect measure	Estimate (95% CI)	Significant	Comment
de Abajo et al., 1999	Case-control	Adjusted rate ratio	3.00 (2.10–4.40)	Yes	Not modified by sex, age, dose or duration
van Walraven et al., 2001	Cohort	Relative increase per affinity level	+10.7% per level (age-adjusted)	Yes	974 bleeds; overall rate 7.3/1000 person-years
Tata et al., 2005	Case-control	Odds ratio	2.38 (2.08–2.72)	Yes	Self-controlled case series IRR 1.71 (1.48–1.98)
Wessinger et al., 2006	Case-control	Odds ratio (upper GI)	1.30 (0.83–1.90)	No	Overall GI haemorrhage OR 1.5

Study	Design	Effect measure	Estimate (95% CI)	Significant	Comment
					(1.2–2.0)
Targownik et al., 2009	Case-control	Odds ratio	1.43 (1.09–1.89)	Yes	Described by authors as a modest increase
Dall et al., 2009	Case-control	Adjusted odds ratio (current use)	1.67 (1.46–1.92)	Yes	Case-crossover analysis 2.80 (2.20–3.60)
Coupland et al., 2011	Cohort (≥65 y)	Hazard ratio	1.22 (1.07–1.40)	Yes	Absolute risk 0.51% vs 0.42% per year
Carvajal et al., 2011	Case-control	Adjusted odds ratio	1.06 (0.57–1.96)	No	Seven-day exposure window; excludes RR > 2
Castro et al., 2012	Cohort	Adjusted relative risk	1.17 (1.02–1.34)	Yes	High vs low serotonin transporter affinity
Wang et al., 2013	Case-crossover	Adjusted odds ratio (14-day)	1.84 (1.42–2.40)	Yes	Self-matched; time-invariant confounding removed
Cheng et al., 2015	Cohort	Hazard ratio	1.97 (1.67–2.31)	Yes	10-year follow-up; SNRI not significant
Iwagami et al., 2018	Cohort (no CKD)	Adjusted rate ratio	1.66 (1.37–2.01)	Yes	Absolute rate difference 2.0/1000 person-years
Guo et al.,	PS-	Hazard ratio	1.95 (1.41–	Yes	After H. pylori

Study	Design	Effect measure	Estimate (95% CI)	Significant	Comment
2019	matched cohort		2.70)		eradication; confounder removed

CI = confidence interval; CKD = chronic kidney disease; GI = gastrointestinal; IRR = incidence rate ratio; PS = propensity score; RR = relative risk; SNRI = serotonin-noradrenaline reuptake inhibitor.

Two features of this evidence deserve particular emphasis. The first is the concordance between conventional between-person comparisons and self-controlled analyses. The case-crossover estimate of 2.80 (95% CI 2.20–3.60) and the self-controlled case series incidence rate ratio of 1.71 (95% CI 1.48–1.98) were derived from within-person contrasts in which each patient serves as their own control, eliminating by design all confounding by time-invariant characteristics including the underlying depressive illness, smoking status, alcohol history, genetic predisposition and baseline comorbidity. That these estimates are of the same order as the conventionally adjusted between-person estimates is a powerful argument against confounding by indication as the dominant explanation. The second is the propensity-score-matched Hong Kong cohort restricted to patients who had already undergone *Helicobacter pylori* eradication, which removed the single most important unmeasured confounder in this literature and nonetheless returned a hazard ratio of 1.95 (95% CI 1.41–2.70), stable across 1:1 matching (2.13; 95% CI 1.50–3.02) and multivariable sensitivity analyses.^{3,8,12,22}

Lower Gastrointestinal Bleeding

Three studies specifically examined bleeding distal to the ligament of Treitz, and all three reported a positive association, in two cases of greater magnitude than for upper gastrointestinal bleeding. The largest and methodologically strongest of these, a ten-year matched cohort of 9753 serotonergic antidepressant users and 39,012 matched controls, found that SSRI use was independently associated with a hazard ratio of 2.96 (95% CI 2.46–3.57) for lower gastrointestinal bleeding, exceeding the hazard ratio of 1.97 (95% CI 1.67–2.31) observed for upper gastrointestinal

bleeding in the same population, with the authors concluding that SSRIs caused more lower than upper gastrointestinal bleeding in the general population. A multicentre case-control study likewise found the association to be stronger for lower (OR 1.8; 95% CI 1.2–2.8) than for upper gastrointestinal haemorrhage (OR 1.3; 95% CI 0.83–1.9). A third analysis within a large cohort of low-dose aspirin users identified SSRI use as an independent risk factor for lower gastrointestinal bleeding with a hazard ratio of 11.71, although the confidence interval (1.40–97.94) was extremely wide, reflecting a very small number of exposed events, and this estimate should be regarded as hypothesis-generating rather than as a reliable magnitude.^{4,15,17}

Table 9. Lower gastrointestinal bleeding

Study	Design	Effect measure	Estimate (95% CI)	Interpretation
Cheng et al., 2015	Matched cohort, Taiwan	Hazard ratio	2.96 (2.46–3.57)	Significant; exceeds the same cohort's upper GI estimate
Wessinger et al., 2006	Multicentre case-control, USA	Odds ratio	1.80 (1.20–2.80)	Significant; stronger than upper GI in the same study
Chen et al., 2017	Cohort of aspirin users, Taiwan	Hazard ratio	11.71 (1.40–97.94)	Significant but severely imprecise; hypothesis-generating

The consistent finding of a lower gastrointestinal signal is mechanistically informative. Acid-peptic injury cannot explain colonic bleeding, and the observation therefore supports a predominantly systemic haemostatic mechanism, namely impaired serotonin-amplified platelet aggregation, operating on pre-existing mucosal lesions such as diverticula, angiodysplasia and colonic polyps wherever they occur in the gastrointestinal tract. It also carries a practical corollary:

gastroprotection with acid suppression, which is effective for the upper tract, offers no protection against the lower gastrointestinal component of SSRI-associated bleeding risk.^{15,17}

Major Bleeding at Any Anatomical Site

Six studies reported major bleeding irrespective of anatomical site, generally within populations already exposed to antithrombotic therapy. The largest, a nested case-control analysis of 42,190 major bleeding cases matched to 1,156,641 controls among anticoagulated patients with atrial fibrillation, found an incidence rate ratio of 1.33 (95% CI 1.24–1.42) for concomitant SSRI and oral anticoagulant use relative to anticoagulant use alone. A previously published quantitative synthesis of 42 observational studies encompassing more than 1.4 million patients provides the most useful contextual benchmark for the class effect, reporting a pooled odds ratio for severe bleeding of any site of 1.41 (95% CI 1.27–1.57), with closely concordant estimates from the case-control (1.41; 95% CI 1.25–1.60) and cohort (1.36; 95% CI 1.12–1.64) strata. Two studies returned null estimates: a Dutch anticoagulation-clinic cohort reported a hazard ratio of 1.22 (95% CI 0.99–1.50), narrowly failing to exclude unity, and a Korean case-case-time-control analysis that additionally adjusted for secular trends in exposure found no significant increase with either anticoagulant (adjusted OR 1.07; 95% CI 0.89–1.28) or antiplatelet (1.10; 95% CI 0.88–1.38) co-exposure. A small single-centre study of left ventricular assist device recipients not receiving aspirin similarly found no association (HR 1.04; 95% CI 0.32–3.37), though with very wide confidence limits.^{16,23,24,26,29,39}

Table 10. Major bleeding at any site

Study	Population	Effect measure	Estimate (95% CI)	Direction
Rahman et al., 2024	Anticoagulated atrial fibrillation, UK	Incidence rate ratio	1.33 (1.24–1.42)	Significant increase
Laporte et al., 2017	42 observational studies, >1.4 million	Pooled odds ratio	1.41 (1.27–1.57)	Significant increase

Study	Population	Effect measure	Estimate (95% CI)	Direction
(benchmark)	patients			
Zhang et al., 2020	New DOAC users, UK	Adjusted odds ratio	1.68 (1.10–2.59)	Significant increase
Bakker et al., 2022	VKA initiators, Netherlands	Hazard ratio	1.22 (0.99–1.50)	Borderline, not significant
Kim et al., 2026	SSRI + anticoagulant users, Korea	Adjusted odds ratio	1.07 (0.89–1.28)	Null
Ganter et al., 2025	HeartMate 3 LVAD, no aspirin, USA	Hazard ratio	1.04 (0.32–3.37)	Null (imprecise)

DOAC = direct oral anticoagulant; LVAD = left ventricular assist device; VKA = vitamin K antagonist. The Laporte estimate is a previously published pooled benchmark, reported for contextual comparison and not counted as an included primary study.

Interaction with Non-Steroidal Anti-Inflammatory Drugs

The interaction between SSRIs and NSAIDs is the single most clinically consequential finding of this review and was examined in eight datasets. The original case-control analysis reported that concurrent use increased upper gastrointestinal bleeding risk beyond the sum of the independent effects, with an adjusted rate ratio of 15.6 (95% CI 6.6–36.6), a figure that entered clinical guidance and prompted formal cautions against co-prescription. Subsequent studies have moderated this estimate considerably while confirming its direction. A Danish population-based analysis reported an adjusted odds ratio of 8.0 (95% CI 4.8–13) for concurrent SSRI and NSAID use, rising to 28 (95% CI 7.6–103) for the triple combination of SSRI, NSAID and aspirin. A UK case-control and self-controlled case series analysis, however, found only a marginal increment for concurrent prescription (OR 2.93; 95% CI 2.25–3.82) relative to either drug alone, and a Canadian analysis found that adding an SSRI to established NSAID therapy did not significantly increase risk

over NSAID monotherapy (OR 1.20; 95% CI 0.78–1.92). The best available pooled estimates place combined exposure at an odds ratio of 4.25 (95% CI 2.82–6.42) relative to non-use, at 2.14 (95% CI 1.52–3.02) relative to SSRI alone, and at 1.49 (95% CI 1.20–1.84) relative to NSAID alone.^{1,3,7,8,12,13,25}

Table 11. SSRI–NSAID interaction

Study	Comparison	Effect measure	Estimate (95% CI)	Significant
de Abajo et al., 1999	SSRI + NSAID vs neither	Adjusted rate ratio	15.6 (6.6–36.6)	Yes
de Abajo et al., 1999	SSRI + low-dose aspirin vs neither	Adjusted rate ratio	7.2 (3.1–17.1)	Yes
Dall et al., 2009	SSRI + NSAID vs neither	Adjusted odds ratio	8.0 (4.8–13.0)	Yes
Dall et al., 2009	SSRI + NSAID + aspirin vs neither	Adjusted odds ratio	28.0 (7.6–103.0)	Yes
Tata et al., 2005	SSRI + NSAID vs neither	Odds ratio	2.93 (2.25–3.82)	Yes
Tata et al., 2005	SSRI + NSAID (self-controlled)	Incidence rate ratio	3.25 (1.95–5.42)	Yes
Targownik et al., 2009	SSRI + NSAID vs NSAID alone	Odds ratio	1.20 (0.78–1.92)	No
Wang et al., 2013	SSRI + NSAID vs unexposed period	Adjusted odds ratio	3.44	Yes
Loke et al., 2007	SSRI + NSAID vs neither	Pooled odds	6.33 (3.40–	Yes

Study	Comparison	Effect measure	Estimate (95% CI)	Significant
(benchmark)		ratio	11.80)	Yes
Anglin et al., 2014 (benchmark)	SSRI + NSAID vs neither	Pooled odds ratio	4.25 (2.82–6.42)	
Haghbin et al., 2022 (benchmark)	SSRI + NSAID vs SSRI alone	Pooled odds ratio	2.14 (1.52–3.02)	Yes
Haghbin et al., 2022 (benchmark)	SSRI + NSAID vs NSAID alone	Pooled odds ratio	1.49 (1.20–1.84)	Yes

Estimates labelled "benchmark" derive from previously published quantitative syntheses and are reported for contextual comparison rather than as included primary studies.

The pattern across these estimates is best interpreted as follows. Combined exposure unambiguously carries higher absolute risk than either agent alone, and the increment relative to either monotherapy is statistically robust. Whether the interaction is formally supra-additive on the multiplicative scale is less certain, since the studies reporting the most extreme interaction estimates were those with the smallest numbers of doubly exposed cases and the widest confidence intervals, and the two analyses with explicit within-person or NSAID-referent comparisons returned the most conservative figures. For clinical purposes the operational conclusion is unaffected: patients requiring both classes constitute a clearly identifiable high-risk phenotype in whom gastroprotection is warranted.^{3,7,25}

Interaction with Low-Dose Aspirin and Antiplatelet Agents

Five datasets addressed co-exposure to aspirin or other antiplatelet agents. The original case-control analysis identified a smaller but still substantial interaction with low-dose aspirin (adjusted

rate ratio 7.2; 95% CI 3.1–17.1) than with NSAIDs. Danish and Taiwanese analyses produced more modest stratum-specific estimates of 2.2 and 2.07 respectively, and a subsequent methodological correspondence highlighted that the relative ordering of the aspirin and NSAID interactions differs between Western and East Asian datasets, most plausibly because of differences in prescribed aspirin dose, the availability of over-the-counter NSAIDs and the frequency of concurrent clopidogrel use, the bioactivation of which is impaired by CYP2C19-inhibiting SSRIs. The most rigorous appraisal of this question, a systematic review applying GRADE to 24 studies, concluded that the evidence was too uncertain to establish a genuine interaction when an SSRI is added to established low-dose aspirin therapy, with a pooled hazard ratio of 1.37 (95% CI 1.10–1.70) in three non-randomised studies but a null pooled odds ratio of 0.95 (95% CI 0.77–1.19) in two others, and that the increased risk observed when aspirin is added to an established SSRI is principally attributable to the initiation of aspirin itself.^{1,8,12,27,35}

Table 12. SSRI–antiplatelet interaction

Study	Comparison	Effect measure	Estimate (95% CI)	Significant
de Abajo et al., 1999	SSRI + low-dose aspirin vs neither	Adjusted rate ratio	7.2 (3.1–17.1)	Yes
Dall et al., 2009	SSRI + aspirin (stratum-specific)	Adjusted odds ratio	2.20	Yes
Wang et al., 2013	SSRI + aspirin vs unexposed period	Adjusted odds ratio	2.07	Yes
Axelsson et al., 2024 (benchmark)	SSRI + aspirin vs aspirin alone (3 studies)	Pooled hazard ratio	1.37 (1.10–1.70)	Yes
Axelsson et al.,	SSRI + aspirin vs aspirin alone	Pooled odds	0.95 (0.77–	No

Study	Comparison	Effect measure	Estimate (95% CI)	Significant
2024 (benchmark)	(2 studies)	ratio	1.19)	No
Kim et al., 2026	SSRI + antiplatelet, time-trend adjusted	Adjusted odds ratio	1.10 (0.88–1.38)	
Chen et al., 2017	SSRI in low-dose aspirin cohort (lower GI)	Hazard ratio	11.71 (1.40–97.94)	Yes (imprecise)

Interaction with Oral Anticoagulants

Five studies addressed co-exposure with oral anticoagulants, an increasingly prevalent combination given the rising prevalence of atrial fibrillation and of depression in older populations. The definitive analysis, a nested case-control study within approximately 2000 UK general practices comprising 42,190 major bleeding cases and 1,156,641 matched controls, found that concomitant SSRI and oral anticoagulant use increased major bleeding by one third relative to anticoagulant use alone (incidence rate ratio 1.33; 95% CI 1.24–1.42). Crucially, the excess risk was concentrated in the initial period of co-exposure, reaching an incidence rate ratio of 1.74 (95% CI 1.37–2.22) during the first 30 days and persisting for up to six months before attenuating, and did not vary by age, sex, prior bleeding history, chronic kidney disease or SSRI potency. The association was present for both direct oral anticoagulants (1.25; 95% CI 1.12–1.40) and vitamin K antagonists (1.36; 95% CI 1.25–1.47). A previously published synthesis of eight studies enrolling 98,070 patients returned a closely concordant pooled hazard ratio of 1.35 (95% CI 1.14–1.58). A mechanistic contribution from cytochrome P450 inhibition is supported by an anticoagulation-clinic cohort in which SSRI initiation raised the odds of a supratherapeutic international normalised ratio 2.41-fold (95% CI 2.01–2.89), rising to 3.14-fold (95% CI 1.33–7.43) with CYP2C9-inhibiting SSRIs, although the corresponding major bleeding estimate did not attain significance.^{23,24,26,29,40}

Table 13. SSRI–oral anticoagulant interaction

Study	Comparison	Effect measure	Estimate (95% CI)	Significant
Rahman et al., 2024	SSRI + OAC vs OAC alone (overall)	Incidence rate ratio	1.33 (1.24–1.42)	Yes
Rahman et al., 2024	SSRI + OAC, first 30 days	Incidence rate ratio	1.74 (1.37–2.22)	Yes
Rahman et al., 2024	SSRI + DOAC vs DOAC alone	Incidence rate ratio	1.25 (1.12–1.40)	Yes
Rahman et al., 2024	SSRI + VKA vs VKA alone	Incidence rate ratio	1.36 (1.25–1.47)	Yes
Rahman et al., 2022 (benchmark)	SSRI + OAC vs OAC alone (8 studies)	Pooled hazard ratio	1.35 (1.14–1.58)	Yes
Zhang et al., 2020	SSRI + DOAC vs DOAC alone	Adjusted odds ratio	1.68 (1.10–2.59)	Yes
Bakker et al., 2022	SSRI + VKA, supratherapeutic INR ≥ 5	Odds ratio	2.41 (2.01–2.89)	Yes
Bakker et al., 2022	CYP2C9-inhibiting SSRI, INR ≥ 5	Odds ratio	3.14 (1.33–7.43)	Yes
Bakker et al., 2022	SSRI + VKA, major bleeding	Hazard ratio	1.22 (0.99–1.50)	No
Kim et al., 2026	SSRI + anticoagulant, time-trend adjusted	Adjusted odds ratio	1.07 (0.89–1.28)	No

DOAC = direct oral anticoagulant; INR = international normalised ratio; OAC = oral anticoagulant; VKA = vitamin K antagonist.

Effect of Acid-Suppressive Co-Therapy

Four datasets addressed gastroprotection, and the evidence consistently indicates substantial attenuation of upper gastrointestinal risk. A Canadian population-based case-control analysis found that proton pump inhibitor co-therapy reduced the odds of SSRI-related upper gastrointestinal bleeding by 61% (OR 0.39; 95% CI 0.16–0.94). A Danish analysis reported that among proton pump inhibitor users the SSRI-associated odds ratio fell to 0.96 (95% CI 0.50–1.82), that is, to the null. A quantitative synthesis of 22 observational studies encompassing more than 1,073,000 individuals reported no significant increase in upper gastrointestinal bleeding risk among SSRI users receiving concurrent acid-suppressing drugs, in contrast to a pooled odds ratio of 1.55 (95% CI 1.35–1.78) overall. Supporting evidence from the broader antithrombotic literature confirms that proton pump inhibitors reduce upper gastrointestinal bleeding risk relative to monotherapy while conferring no protection in the lower gastrointestinal tract.^{7,8,14,35}

Table 14. Modification of risk by acid-suppressive co-therapy

Study	Comparison	Effect measure	Estimate (95% CI)	Effect
Targownik et al., 2009	PPI co-therapy in SSRI users	Odds ratio	0.39 (0.16–0.94)	Protective
Dall et al., 2009	SSRI effect among PPI users	Adjusted odds ratio	0.96 (0.50–1.82)	Abolished
Jiang et al., 2015 (benchmark)	SSRI + acid suppression vs no SSRI	Pooled odds ratio	No significant increase	Abolished
García Rodríguez et al., 2016 (benchmark)	PPI vs no PPI, upper GI bleeding	Relative risk	Reduced vs monotherapy	Protective

PPI = proton pump inhibitor. Protection is confined to the upper gastrointestinal tract; no acid-suppressive protection has been demonstrated against lower gastrointestinal bleeding.

Serotonin Transporter Affinity Gradient

Three studies provide direct evidence of an exposure-response relationship indexed to the pharmacological property hypothesised to mediate the effect. A retrospective cohort of 317,824 elderly Canadians, grouped by the degree to which their antidepressant inhibited serotonin reuptake, found that the risk of bleeding increased significantly by 10.7% and 9.8% per increment of inhibition after controlling for age and for previous gastrointestinal bleeding respectively. An incident-user cohort of 36,389 patients with major depressive disorder reported 601 gastrointestinal bleeds among 21,462 patients on high-affinity agents versus 333 among 14,927 on lower-affinity agents, giving an adjusted relative risk of 1.17 (95% CI 1.02–1.34); notably, no association was found with a priori negative-control outcomes including acute liver failure, acute renal failure, asthma, breast cancer and hip fracture, an internal validity check that materially strengthens the causal inference. A case-crossover analysis found that SSRIs with high and intermediate, but not low, affinity for the serotonin transporter were significantly associated with upper gastrointestinal bleeding.^{2,11,12}

Table 15. Exposure-response gradient by serotonin transporter affinity

Study	Contrast	Effect measure	Estimate (95% CI)	Gradient present
van Walraven et al., 2001	Per increment of serotonin reuptake inhibition	Relative increase	+10.7% (age-adjusted); +9.8% (prior-bleed-adjusted)	Yes
Castro et al., 2012	High vs low SERT affinity	Adjusted relative risk	1.17 (1.02–1.34)	Yes
Wang et al., 2013	High/intermediate vs low SERT	Adjusted odds ratio	Significant for high and intermediate only	Yes

Study	Contrast	Effect measure	Estimate (95% CI)	Gradient present
	affinity			

SERT = serotonin transporter. High-affinity agents include fluoxetine, paroxetine and sertraline; low-affinity agents include bupropion, mirtazapine and trazodone.

Temporal Profile of Risk

Five datasets characterised the timing of risk, and the pattern is highly consistent with the pharmacological mechanism. A case-crossover analysis of 5377 psychiatric inpatients with upper gastrointestinal bleeding demonstrated significant elevation of risk within a seven-day exposure window (adjusted OR 1.67; 95% CI 1.23–2.26), peaking at fourteen days (1.84; 95% CI 1.42–2.40) and persisting at twenty-eight days (1.67; 95% CI 1.34–2.08), precisely matching the 7- to 14-day interval over which intraplatelet serotonin is depleted. A Danish analysis stratified by recency found the highest risk in recent users (1.88; 95% CI 1.42–2.50), a similar estimate in current users (1.67; 95% CI 1.46–1.92) and a substantially attenuated but still significant estimate in past users (1.22; 95% CI 1.07–1.39). Analyses of anticoagulant co-exposure similarly localised the peak to the first 30 days (1.74; 95% CI 1.37–2.22). Corroborating evidence from a large subdural haematoma case-control study demonstrated the same temporal shape at an extracranial bleeding site, with an adjusted odds ratio of 2.55 (95% CI 2.07–3.15) for less than one month of current use falling to 1.04 (95% CI 0.93–1.17) beyond three years. The only discordant finding was the earliest study, which reported no modification of effect by treatment duration.^{1,8,12,26,36}

Table 16. Effect estimates by exposure window and recency

Study	Exposure window / recency	Effect measure	Estimate (95% CI)	Pattern
Wang et al., 2013	7 days	Adjusted odds ratio	1.67 (1.23–2.26)	Early onset
Wang et al.,	14 days	Adjusted odds ratio	1.84 (1.42–	Peak

Study	Exposure window / recency	Effect measure	Estimate (95% CI)	Pattern
2013			2.40)	
Wang et al., 2013	28 days	Adjusted odds ratio	1.67 (1.34–2.08)	Sustained
Dall et al., 2009	Current use	Adjusted odds ratio	1.67 (1.46–1.92)	Elevated
Dall et al., 2009	Recent use	Adjusted odds ratio	1.88 (1.42–2.50)	Peak
Dall et al., 2009	Past use	Adjusted odds ratio	1.22 (1.07–1.39)	Attenuating
Rahman et al., 2024	First 30 days of SSRI–OAC co-exposure	Incidence rate ratio	1.74 (1.37–2.22)	Early peak
Gaist et al., 2020	<1 month current use (subdural haematoma)	Adjusted odds ratio	2.55 (2.07–3.15)	Early peak
Gaist et al., 2020	>3 years current use (subdural haematoma)	Adjusted odds ratio	1.04 (0.93–1.17)	Attenuated to null
de Abajo et al., 1999	Any duration	Adjusted rate ratio	No modification by duration	Discordant

The pharmacological coherence of this temporal profile constitutes one of the strongest arguments for causality within the evidence base. A confounding-by-indication mechanism would be expected to produce risk that is constant or that increases with cumulative exposure as depression severity and its behavioural correlates accumulate; instead, the observed pattern is one of

108

rapid onset within the platelet-turnover interval followed by attenuation with prolonged exposure, which is the signature of a direct pharmacodynamic effect combined with depletion of the susceptible subpopulation over time.^{12,36}

Risk Stratification by Age

Four datasets provide age-stratified evidence. A propensity-score-matched cohort found that the increased risk associated with SSRIs was statistically significant only among patients aged over 50 years. Two large primary-care cohorts using the same database platform in different age bands illustrate the gradient directly: among 60,746 patients aged 65 to 100 years the upper gastrointestinal bleeding hazard ratio for SSRIs was 1.22 (95% CI 1.07–1.40) with an annual absolute risk of 0.51% compared with 0.42% during non-use, whereas among 238,963 patients aged 20 to 64 years only 1066 upper gastrointestinal bleeds occurred over five years and no significant SSRI-specific elevation was detected, the signal in that younger cohort being confined to trazodone. Absolute-risk analyses in the elderly are the most informative: among octogenarians, bleeding rates rose from 10.6 to 14.7 per 1000 person-years across affinity strata, corresponding to a number needed to harm of 244, and among patients with previous upper gastrointestinal bleeding from 28.6 to 40.3 per 1000 person-years, a number needed to harm of 85.^{2,10,19,22}

Table 17. Age stratification

Study	Age stratum	Effect measure	Estimate	Absolute risk context
Coupland et al., 2011	65–100 years	Hazard ratio	1.22 (1.07–1.40)	0.51% vs 0.42% per year
Coupland et al., 2018	20–64 years	Hazard ratio	No significant SSRI-specific elevation	1066 bleeds over 5 years in 238,963 patients
Guo et al., 2019	>50 years vs ≤50 years	Hazard ratio	Significant only in the >50-year	Crude UGIB rate 3.98/1000 person-years

Study	Age stratum	Effect measure	Estimate	Absolute risk context
			stratum	
van Walraven et al., 2001	Octogenarians	Rate difference	10.6 → 14.7 per 1000 person-years	Number needed to harm 244
van Walraven et al., 2001	Prior upper GI bleeding	Rate difference	28.6 → 40.3 per 1000 person-years	Number needed to harm 85

Risk Stratification by Kidney Function

A single but methodologically exemplary cohort study addressed this domain, and its findings carry disproportionate clinical importance because they dissociate relative from absolute risk. Among 413,116 patients stratified by estimated glomerular filtration rate and analysed with time-dependent exposure definition and hospitalisation for gastrointestinal bleeding as the outcome, the adjusted rate ratio associated with SSRI prescription was essentially constant across all strata: 1.66 (95% CI 1.37–2.01) in patients without chronic kidney disease, 1.86 (95% CI 1.62–2.15) at stage 3a, 1.61 (95% CI 1.27–2.04) at stage 3b and 1.84 (95% CI 1.14–2.96) at stages 4 to 5, with no evidence of trend ($p = 0.922$). The adjusted rate difference, by contrast, rose almost fourfold across the same gradient, from 2.0 per 1000 person-years in the absence of chronic kidney disease to 7.9 per 1000 person-years at stages 4 to 5, with strong statistical evidence of trend ($p = 0.001$).²⁰

Table 18. Relative and absolute risk by level of kidney function

Kidney function stratum	Cohort size	Adjusted rate ratio (95% CI)	Rate with vs without SSRI (per 1000 py)	Adjusted rate difference (per 1000 py)
No chronic kidney disease	202,121	1.66 (1.37–2.01)	5.5 vs 3.5	2.0

Kidney function stratum	Cohort size	Adjusted rate ratio (95% CI)	Rate with vs without SSRI (per 1000 py)	Adjusted rate difference (per 1000 py)
CKD stage 3a (eGFR 45–59)	153,316	1.86 (1.62–2.15)	8.3 vs 4.1	4.2
CKD stage 3b (eGFR 30–44)	46,482	1.61 (1.27–2.04)	9.9 vs 5.1	4.8
CKD stage 4/5 (eGFR <30)	11,197	1.84 (1.14–2.96)	15.3 vs 7.4	7.9
Test for trend	—	p = 0.922 (no trend in relative risk)	—	p = 0.001 (strong trend in absolute risk)

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate in mL/min/1.73 m²; py = person-years.

This dissociation is the single most important quantitative lesson of the review for clinical practice. A constant relative risk applied to a rising baseline hazard produces a steeply rising absolute harm, and it follows that the appropriate threshold for gastroprotection and for preferential selection of a low-affinity antidepressant should be set by absolute rather than relative risk. The same logic extends by analogy to age, prior peptic ulcer bleeding and antithrombotic co-prescription, in each of which the baseline hazard is elevated.^{2,20}

Post-Bleeding Clinical Outcomes

A single nationwide prospective cohort of 14,343 consecutive patients admitted with peptic ulcer bleeding in Denmark between 2006 and 2014 addressed whether SSRI exposure at the time of the index bleed influences its subsequent course. After adjustment for pre-defined confounders, SSRI treatment was not associated with endoscopy-refractory bleeding (OR 1.03; 95% CI 0.79–1.33), with rebleeding (OR 0.96; 95% CI 0.83–1.11) or with 30-day mortality (OR 1.01; 95% CI

0.85–1.19); all three point estimates lay essentially on the null and the findings were robust across sensitivity and subgroup analyses. This is a genuinely negative result of high clinical value: it indicates that SSRIs increase the probability that an index bleed occurs without worsening the haemostatic response to endoscopic therapy or the short-term prognosis once bleeding is established.¹⁸

Table 19. Clinical outcomes after established peptic ulcer bleeding

Outcome	Cohort	Effect measure	Estimate (95% CI)	Interpretation
Endoscopy-refractory bleeding	14,343 patients	Adjusted odds ratio	1.03 (0.79–1.33)	No association
Rebleeding	14,343 patients	Adjusted odds ratio	0.96 (0.83–1.11)	No association
30-day mortality	14,343 patients	Adjusted odds ratio	1.01 (0.85–1.19)	No association

The practical implication is that reflex withholding of SSRIs on admission for peptic ulcer bleeding is not supported by evidence relating to bleeding outcomes, and must be weighed against the documented risk of a discontinuation syndrome in approximately one third of patients subjected to abrupt cessation, together with the risk of depressive relapse during acute illness. A reasoned individualised decision, rather than an automatic protocol, is indicated.¹⁸

Agent-Specific and Class-Comparative Risk

A systematic review and meta-analysis of 20 studies examining individual serotonergic antidepressants found that every agent examined carried an elevated risk of gastrointestinal bleeding, with venlafaxine highest (OR 1.50; 95% CI 1.32–1.70), followed by citalopram (1.38; 95% CI 1.17–1.62) and fluoxetine (1.38; 95% CI 1.26–1.51), and paroxetine lowest among those examined (1.31; 95% CI 1.07–1.62). The narrowness of this range indicates that individual agent selection within the SSRI class is a weak lever for risk reduction, in contrast to the substantially greater discrimination achievable by moving to a genuinely low-serotonin-transporter-affinity

agent. A ten-year Taiwanese cohort provides the clearest class contrast, finding that SSRI use was independently associated with both upper (HR 1.97; 95% CI 1.67–2.31) and lower (HR 2.96; 95% CI 2.46–3.57) gastrointestinal bleeding whereas serotonin-noradrenaline reuptake inhibitor use was not significantly associated with either, although the SNRI subgroup comprised only 944 patients and was correspondingly underpowered.^{15,28}

Table 20. Risk by individual agent and by antidepressant class

Agent / class	Source	Effect measure	Estimate (95% CI)	Rank
Venlafaxine (SNRI)	Gómez-Lumbreras et al., 2025	Pooled odds ratio	1.50 (1.32–1.70)	Highest
Citalopram	Gómez-Lumbreras et al., 2025	Pooled odds ratio	1.38 (1.17–1.62)	2
Fluoxetine	Gómez-Lumbreras et al., 2025	Pooled odds ratio	1.38 (1.26–1.51)	2
Paroxetine	Gómez-Lumbreras et al., 2025	Pooled odds ratio	1.31 (1.07–1.62)	Lowest of those reported
SSRI class (upper GI)	Cheng et al., 2015	Hazard ratio	1.97 (1.67–2.31)	Significant
SSRI class (lower GI)	Cheng et al., 2015	Hazard ratio	2.96 (2.46–3.57)	Significant
SNRI class	Cheng et al., 2015	Hazard ratio	Not significant for either site	Null (underpowered)
Low-affinity agents	Castro et al., 2012; Bixby et al., 2018	Adjusted relative risk (reference)	Reference category	Preferred in high-risk

Agent / class	Source	Effect measure	Estimate (95% CI)	Rank
(bupropion, mirtazapine)				patients

Absolute Risk and Number Needed to Harm

Translation of relative into absolute measures demonstrates that the population-level burden is appreciable while the individual-level risk in unselected low-risk patients is very small. The earliest estimate placed the crude incidence at approximately one case of upper gastrointestinal bleeding per 8000 SSRI prescriptions. A quantitative synthesis calculated a number needed to harm of 3177 in a low-risk population and 881 in a high-risk population, while an earlier synthesis estimated 411 per year for SSRI monotherapy in patients over 50 without additional risk factors, falling to 106 with concomitant NSAIDs. The steepest gradients are observed in the elderly and in those with prior bleeding, where numbers needed to harm of 244 and 85 respectively have been reported, and in advanced chronic kidney disease, where the absolute rate difference reaches 7.9 events per 1000 person-years.^{1,2,6,13,20}

Table 21. Absolute risk and numbers needed to harm across risk strata

Population stratum	Source	Absolute measure	Number needed to harm
General population (crude incidence)	de Abajo et al., 1999	≈1 case per 8000 prescriptions	Not calculated
Low-risk population	Anglin et al., 2014	Very low baseline hazard	3177
High-risk population	Anglin et al., 2014	Elevated baseline hazard	881
Age >50 years, no other risk factors	Loke et al., 2007	Per year of exposure	411

Population stratum	Source	Absolute measure	Number needed to harm
Age >50 years with concomitant NSAID Octogenarians	Loke et al., 2007	Per year of exposure	106
	van Walraven et al., 2001	10.6 → 14.7 per 1000 person-years	244
Prior upper gastrointestinal bleeding	van Walraven et al., 2001	28.6 → 40.3 per 1000 person-years	85
CKD stage 4/5	Iwagami et al., 2018	Rate difference 7.9 per 1000 person-years	≈127 per year

Randomised Evidence Stratum

None of the three included randomised controlled trials was designed, powered or adjudicated for gastrointestinal bleeding, and their contribution is therefore limited to reassurance regarding the absence of a gross safety signal and to mechanistic corroboration. In the sertraline trial in 369 patients with major depression following acute myocardial infarction or unstable angina, the incidence of severe cardiovascular adverse events was 14.5% with sertraline and 22.4% with placebo, with no reported excess of haemorrhagic events despite widespread background antiplatelet therapy. Its platelet substudy demonstrated that sertraline significantly reduced beta-thromboglobulin at weeks 6 and 16 ($p = 0.03$) and P-selectin at week 16 ($p = 0.04$) relative to placebo, confirming a measurable antiplatelet effect in vivo even against a background of aspirin and clopidogrel. The escitalopram trial in 300 patients with recent acute coronary syndrome reported reduced major adverse cardiac events over a median 8.1 years (HR 0.69; 95% CI 0.49–0.96) without excess bleeding, and the escitalopram heart failure trial reported comparable safety parameters between arms. The randomised stratum thus establishes the pharmacodynamic premise while providing no adequately powered estimate of the clinical bleeding endpoint.^{30,31,32,33}

Table 22. Randomised evidence stratum

Trial	n randomised	Intervention	Bleeding-relevant finding	Adequacy for bleeding endpoint
Glassman et al., 2002 (SADHART)	369	Sertraline 50–200 mg vs placebo, 24 weeks	Severe cardiovascular adverse events 14.5% vs 22.4%; no haemorrhagic excess reported	Not powered; not adjudicated
Serebruany et al., 2003 (SADHART substudy)	64	Sertraline vs placebo	Significant reduction in beta-thromboglobulin (p = 0.03) and P-selectin (p = 0.04)	Mechanistic confirmation only
Angermann et al., 2016 (MOOD-HF)	372	Escitalopram 10–20 mg vs placebo, 24 months	Safety parameters comparable between arms	Not powered; early termination
Kim et al., 2018 (EsDEPACS)	300	Escitalopram 5–20 mg vs placebo, 24 weeks	MACE hazard ratio 0.69 (0.49–0.96) at median 8.1 years; no bleeding excess reported	Not powered; not adjudicated

MACE = major adverse cardiac events.

Summary of Findings and Certainty of Evidence

Table 23. GRADE summary of findings across all fourteen outcome domains

Outcome domain	Studies	Summary of effect	Direction	GRADE certainty
O1 Upper GI	13	Adjusted estimates 1.22–3.00;	Increase	Moderate

Outcome domain	Studies	Summary of effect	Direction	GRADE certainty
bleeding		10/13 significant		
O2 Lower GI bleeding	3	HR 2.96 (2.46–3.57); OR 1.80 (1.20–2.80)	Increase	Low
O3 Major bleeding, any site	6	IRR 1.33 (1.24–1.42); benchmark OR 1.41 (1.27–1.57)	Increase	Moderate
O4 NSAID interaction	8	OR 2.93–15.6; benchmark 4.25 (2.82–6.42)	Marked increase	Moderate
O5 Antiplatelet interaction	7	Inconsistent; pooled HR 1.37 (1.10–1.70) vs OR 0.95 (0.77–1.19)	Uncertain	Very low
O6 Anticoagulant interaction	5	IRR 1.33 (1.24–1.42); peak 1.74 in first 30 days	Increase	Moderate
O7 Acid suppression	4	OR 0.39 (0.16–0.94); risk abolished among PPI users	Protective	Low
O8 SERT affinity gradient	3	RR 1.17 (1.02–1.34) high vs low affinity	Gradient present	Moderate
O9 Temporal profile	5	Peak at 14–30 days; attenuation beyond 3 years	Early peak	Moderate
O10 Age stratification	4	Significant above 50–65 years; NNH 244 in octogenarians	Age-dependent	Moderate
O11 Kidney function	1	Constant RR; rate difference	Absolute	Low

Outcome domain	Studies	Summary of effect	Direction	GRADE certainty
O12 Post-bleeding outcomes		2.0 → 7.9 per 1000 py	gradient	
	1	All three estimates null (0.96–1.03)	No effect	Moderate
O13 Agent-specific risk	2	Range 1.31–1.50 across agents; SNRI not significant	Narrow range	Low
O14 Absolute risk / NNH	5	NNH 3177 (low risk) to 85 (prior bleed)	Strongly stratified	Moderate

GRADE certainty for observational evidence began at low and was upgraded where a large effect magnitude, a dose-response gradient, or plausible residual confounding acting towards the null was demonstrated. HR = hazard ratio; IRR = incidence rate ratio; NNH = number needed to harm; OR = odds ratio; PPI = proton pump inhibitor; py = person-years; RR = relative risk; SERT = serotonin transporter.

DISCUSSION

Summary of Principal Findings

This systematic review of 23 controlled studies encompassing more than two million individuals across four continents establishes that SSRI antidepressant exposure is associated with a statistically significant increase in the risk of gastrointestinal bleeding, and that the primary hypothesis is therefore supported and the corresponding null hypothesis rejected. The magnitude of the association for upper gastrointestinal bleeding in the general population lies most plausibly between 1.4 and 2.0 on the relative scale, with the higher historical estimates reflecting less complete confounder adjustment and higher background *Helicobacter pylori* prevalence, and the single null estimate deriving from a study whose own authors interpreted their data as excluding a relative risk above two rather than excluding an effect. The association extends to lower gastrointestinal bleeding, where it may be of greater magnitude than in the upper tract, and to major

bleeding at extra-gastrointestinal sites, indicating a systemic haemostatic mechanism rather than a purely acid-peptic one.^{1,4,8,9,14,15,16}

The clinically decisive findings, however, concern effect modification rather than the main effect. Concurrent NSAID exposure raises the combined risk several-fold above either agent alone, and triple therapy with an NSAID and aspirin has been associated with an adjusted odds ratio of 28. Concomitant oral anticoagulation increases major bleeding by approximately one third, concentrated in the first 30 days of co-exposure. Conversely, proton pump inhibitor co-therapy reduces the SSRI-associated hazard by around 60% and, in some analyses, abolishes it entirely within the upper gastrointestinal tract. The absolute excess risk rises steeply with age, prior bleeding history and declining renal function even as the relative risk remains constant, and it is this dissociation that should govern clinical decision-making. Finally, once bleeding has occurred, SSRI exposure does not worsen refractory bleeding, rebleeding or 30-day mortality.^{7,8,14,18,20,26}

Assessment of Causality

Formal appraisal against the Bradford Hill considerations is instructive. Strength of association is modest, with most estimates between 1.2 and 2.0, which limits the confidence that can be placed in any single study but is entirely typical of genuine pharmacoepidemiological drug-harm signals. Consistency is high: positive associations have been reproduced across a dozen jurisdictions, across administrative, clinical-registry and endoscopically confirmed data sources, and across case-control, cohort, case-crossover, self-controlled case series and case-case-time-control designs. Temporality is firmly established, with risk emerging within 7 to 14 days of initiation in self-controlled analyses in which exposure necessarily precedes outcome by construction. A biological gradient is demonstrated by the significant increase in bleeding risk per increment of serotonin reuptake inhibition and by the differential risk between high- and low-affinity agents.^{2,3,8,11,12}

Plausibility and coherence are exceptionally strong. The mechanism is not merely hypothetical but has been demonstrated in a randomised setting through significant reductions in beta-thromboglobulin and P-selectin during sertraline treatment, and the timing of clinical risk matches the known kinetics of intraplatelet serotonin depletion over the platelet lifespan.

Experimental evidence in the strict sense is limited to this mechanistic randomised substudy, and analogy is provided by the closely comparable risk profile of low-dose aspirin, an agent whose gastrointestinal bleeding hazard is of similar order and which the original investigators explicitly used as a comparator when characterising the absolute effect as moderate and approximately equivalent to low-dose ibuprofen. Specificity is, as expected for a systemic haemostatic mechanism, absent, and its absence carries no evidentiary weight here.^{1,31,34}

The most important internal validity check comes from the negative-control analysis embedded within the incident-user cohort, in which high-affinity antidepressants were associated with gastrointestinal bleeding and stroke but showed no association with acute liver failure, acute renal failure, asthma, breast cancer or hip fracture. Were the observed bleeding signal generated by generalised confounding related to depression severity, healthcare utilisation or surveillance intensity, one would expect it to propagate into these negative-control outcomes; its failure to do so materially strengthens the causal interpretation.¹¹

Confounding by Indication and the Contribution of Self-Controlled Designs

Confounding by indication remains the principal alternative explanation for the observed association, and it is a substantive concern. Depression is associated with higher rates of smoking and alcohol consumption, poorer nutrition, reduced medication adherence, greater use of over-the-counter analgesics for somatic symptoms, and a higher prevalence of *Helicobacter pylori* infection and peptic ulcer disease, all of which independently elevate gastrointestinal bleeding risk. None of the conventionally adjusted between-person analyses can fully exclude residual confounding by these factors, most of which are incompletely or not at all captured in administrative databases.^{10,19}

Three lines of evidence substantially weaken this alternative explanation. The first is the concordance between between-person and within-person estimates. Case-crossover and self-controlled case series analyses, in which each patient serves as their own control across exposed and unexposed time windows, eliminate by design all confounding by time-invariant characteristics, including the underlying depressive diathesis, smoking history, genetic factors and stable comorbidity; these designs nonetheless returned estimates of 2.80 (95% CI 2.20–3.60) and 1.71 (95% CI 1.48–1.98), fully consistent with the conventionally adjusted literature. The second is the

propensity-score-matched cohort restricted to patients who had already received *Helicobacter pylori* eradication therapy, which removed the most influential unmeasured confounder and returned a hazard ratio of 1.95 (95% CI 1.41–2.70). The third is the negative-control analysis already described.^{3,8,11,12,22}

Counterbalancing this, the most recent case-case-time-control analysis, which adjusts additionally for secular trends in exposure prevalence—a bias to which conventional case-crossover designs are vulnerable—found no significant increase in major bleeding with SSRI plus antithrombotic co-exposure. This finding suggests that at least part of the apparent interaction risk in prior studies may reflect exposure time-trend artefact rather than pharmacological synergy, and it constitutes an important caveat to the interaction literature specifically, though it does not address the SSRI main effect against non-use.²⁹

Mechanistic Interpretation of Site-Specific Findings

The demonstration that lower gastrointestinal bleeding risk equals or exceeds upper gastrointestinal risk carries substantial mechanistic weight. Acid-peptic injury and impaired clot stability in an acidic milieu cannot operate distal to the ligament of Treitz, so a colonic signal of this magnitude implicates the systemic platelet defect as the dominant pathway, acting upon pre-existing vascular lesions such as diverticula, angiodysplasia and neoplastic polyps wherever they arise. This interpretation reconciles two otherwise puzzling observations: that acid suppression abolishes much but not all of the excess risk, and that SSRIs are associated with bleeding at extra-gastrointestinal sites including subdural haematoma, where the adjusted odds ratio for current use has been reported at 1.32 (95% CI 1.25–1.38) with the same early-onset temporal shape.^{15,17,36}

The gastric acid pathway nonetheless retains explanatory value for the upper tract, and its clinical relevance is directly evidenced by the near-complete abolition of upper gastrointestinal risk among proton pump inhibitor users. A dual-mechanism model—systemic platelet dysfunction operating throughout the gastrointestinal tract, compounded by acid-mediated mucosal susceptibility in the stomach and duodenum—accounts for the full pattern of observations, including the greater efficacy of gastroprotection in the upper than the lower tract and the marked

amplification of risk by NSAIDs, which introduce a third, prostaglandin-dependent mechanism of mucosal injury specific to the upper tract.^{5,7,8,14}

Interpretation of the Drug-Interaction Findings

The NSAID interaction has generated the widest range of published estimates in this literature, from an odds ratio of 1.20 relative to NSAID monotherapy to a rate ratio of 15.6 relative to non-use, and the apparent discrepancy is largely explicable by the choice of referent. Estimates using the doubly unexposed as referent necessarily incorporate the independent effects of both drugs and will therefore be large; estimates using one drug alone as referent isolate the incremental contribution of the second and will be considerably smaller. The most defensible summary is that combined exposure carries approximately twice the risk of SSRI monotherapy and approximately 1.5 times the risk of NSAID monotherapy, with the doubly exposed sustaining roughly four times the risk of the doubly unexposed. Whether this constitutes true supra-additivity on the multiplicative scale remains contested, with the two analyses using within-person or NSAID-referent comparisons yielding the most conservative figures.^{1,3,7,13,25}

The anticoagulant interaction is more consistently characterised, and its temporal structure is clinically actionable. The concentration of excess risk within the first 30 days of co-exposure, with persistence for up to six months and subsequent attenuation, defines a discrete window during which intensified monitoring is justified. The mechanism is likely dual: a pharmacodynamic contribution from platelet serotonin depletion superimposed on anticoagulation, and a pharmacokinetic contribution from cytochrome P450 inhibition, the latter directly evidenced by a 2.41-fold increase in the odds of a supratherapeutic international normalised ratio following SSRI initiation in vitamin K antagonist users, rising to 3.14-fold with CYP2C9-inhibiting agents. The observation that risk is elevated for direct oral anticoagulants as well as vitamin K antagonists, however, indicates that the pharmacodynamic pathway operates independently of the pharmacokinetic one.^{24,26,40}

Comparison with Previous Syntheses

The findings of this review are congruent with, but considerably broader than, the four principal previously published quantitative syntheses. One pooled 22 observational studies

comprising more than 1,073,000 individuals and reported an odds ratio for upper gastrointestinal bleeding of 1.55 (95% CI 1.35–1.78), noting that the association was greatest with concurrent NSAID or antiplatelet therapy and absent among users of acid-suppressing drugs. A second pooled 15 case-control and four cohort studies and reported estimates of 1.66 (95% CI 1.44–1.92) and 1.68 (95% CI 1.13–2.50) respectively, with combined SSRI and NSAID exposure at 4.25 (95% CI 2.82–6.42), and explicitly concluded that the risk was lower than had previously been estimated. A third, addressing bleeding of any site across 42 studies, reported 1.41 (95% CI 1.27–1.57). A fourth, restricted to individual agents, found a narrow range of 1.31 to 1.50 across molecules. The present review reproduces each of these findings within its respective domain while adding the lower gastrointestinal, temporal, renal-stratification, post-bleeding-outcome and absolute-risk dimensions that none of them addressed.^{13,14,16,28}

Clinical Implications

The evidence does not support routine avoidance of SSRIs on gastrointestinal safety grounds. Untreated depression carries substantial morbidity and mortality, and the randomised evidence in cardiovascular populations demonstrates that SSRI treatment is safe and, in at least one long-term trial, associated with a reduction in major adverse cardiac events. The appropriate clinical response is stratification rather than avoidance. Before initiating an SSRI, clinicians should ascertain the presence of the modifiable risk factors identified in this review: age above 65 years, prior peptic ulcer disease or gastrointestinal bleeding, chronic kidney disease, and concurrent NSAID, aspirin, antiplatelet, anticoagulant or systemic corticosteroid therapy. In patients with none of these, the absolute excess risk approaches a number needed to harm above 3000 and requires no specific action beyond routine counselling.^{18,30,32}

In patients with one or more risk factors, three interventions are supported by the evidence. First, proton pump inhibitor co-prescription, which reduces SSRI-associated upper gastrointestinal bleeding risk by approximately 60% and is of particular value in those on concurrent NSAIDs or antithrombotics. Second, preferential selection of an antidepressant with low serotonin transporter affinity, such as bupropion or mirtazapine, in patients at the highest bleeding risk; selection among SSRI molecules is a far weaker intervention given the narrow 1.31 to 1.50 range across agents.

123

Third, intensified clinical vigilance during the first four weeks of therapy and, where an anticoagulant is co-prescribed, during the first six months, given the demonstrated concentration of risk in that window. Where an NSAID is required in a patient established on an SSRI, the shortest effective course at the lowest effective dose with concomitant gastroprotection should be the default.^{7,11,14,21,26,28}

For patients admitted with peptic ulcer bleeding while taking an SSRI, the evidence argues against reflex discontinuation. SSRI exposure does not increase endoscopy-refractory bleeding, rebleeding or 30-day mortality, whereas abrupt cessation precipitates a discontinuation syndrome in approximately one third of patients and risks depressive relapse at a time of acute physiological stress. Where discontinuation is nonetheless judged necessary, gradual tapering with psychiatric liaison is preferable to abrupt withdrawal.¹⁸

Strengths of This Review

The strengths of this review include its adherence to PRISMA 2020 and SWiM reporting standards, its duplicate independent screening, extraction and quality appraisal with quantified inter-reviewer agreement, its use of design-appropriate risk-of-bias instrumentation, and its systematic verification of every cited reference through an independent academic search platform. The breadth of the outcome framework, spanning fourteen pre-specified domains, permits a genuinely stratified rather than an undifferentiated account of risk. The explicit foregrounding of self-controlled designs provides a direct empirical rebuttal to the principal alternative explanation for the observed association. The decision not to pool statistically, though it forgoes the appearance of precision, preserves and displays the clinically informative heterogeneity that a single pooled figure would conceal.

Implications for Future Research

The most pressing evidence need is a pragmatic randomised trial in which patients requiring antidepressant therapy who are at elevated gastrointestinal risk are randomised either between a high-affinity SSRI and a low-affinity comparator, or to routine versus selective proton pump inhibitor co-prescription, with independently adjudicated gastrointestinal bleeding as a pre-specified primary safety endpoint. Such a trial would resolve the residual-confounding question definitively

and would directly test the gastroprotection hypothesis, which currently rests on a single case-control estimate with wide confidence limits. Second, further case-case-time-control and other bias-resistant self-controlled analyses are required to determine whether the apparent antithrombotic interaction survives adjustment for exposure time-trends. Third, prospective studies with endoscopic confirmation of bleeding source are needed to characterise the lower gastrointestinal signal, which currently rests on administrative coding. Fourth, pharmacogenomic studies examining CYP2C19 and CYP2C9 genotype and serotonin transporter polymorphisms may permit individualised risk prediction. Fifth, validation cohorts in South-East Asian populations, including Indonesia, are needed given the distinctive regional epidemiology of *Helicobacter pylori* infection and patterns of NSAID and traditional analgesic use.^{20,22,29}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of 23 controlled studies encompassing more than two million individuals demonstrates that exposure to selective serotonin reuptake inhibitors is associated with a statistically significant and reproducible increase in the risk of gastrointestinal bleeding. The relative increase for upper gastrointestinal bleeding in unselected populations lies most plausibly between 40% and 70%, with adjusted estimates across the literature ranging from 1.22 to 3.00 and ten of thirteen studies reaching statistical significance. The association extends to lower gastrointestinal bleeding, where it equals or exceeds the upper gastrointestinal signal, and to major bleeding at extra-gastrointestinal sites, indicating a systemic haemostatic mechanism arising from depletion of intraplatelet serotonin and consequent impairment of serotonin-amplified platelet aggregation. The primary hypothesis is therefore accepted and the null hypothesis rejected.^{1,8,12,15,16}

The magnitude of risk is powerfully modified by co-medication. Concurrent NSAID exposure raises risk approximately fourfold relative to non-use, and triple therapy with an NSAID and aspirin has been associated with an adjusted odds ratio of 28. Concomitant oral anticoagulation increases major bleeding by one third, concentrated within the first 30 days. Conversely, proton pump inhibitor co-therapy reduces the hazard by around 60% and in some analyses abolishes it within the upper gastrointestinal tract. A pharmacological gradient exists across agents ordered by

125

serotonin transporter affinity, risk emerges within 7 to 14 days of initiation and attenuates with prolonged exposure, and absolute excess risk rises steeply with age, prior bleeding and declining kidney function while relative risk remains constant.^{7,8,11,12,20,26}

Critically, once gastrointestinal bleeding has occurred, SSRI exposure does not increase endoscopy-refractory bleeding, rebleeding or 30-day mortality. SSRIs therefore raise the probability that an index bleed occurs without worsening its trajectory. Set against the substantial morbidity of untreated depression and against randomised evidence demonstrating cardiovascular safety and, in one long-term trial, cardiovascular benefit, these findings do not justify routine avoidance of SSRIs. They justify systematic risk stratification, targeted gastroprotection and time-limited vigilance. The absence of randomised evidence with adjudicated gastrointestinal endpoints remains the principal limitation of the field and the clearest priority for future investigation.^{18,30,32}

Recommendations

Recommendations for clinical practice

Table 24. Evidence-based risk stratification and management algorithm

Risk stratum	Defining characteristics	Recommended action	Supporting evidence
Low	Age <65 years; no prior peptic ulcer or GI bleeding; eGFR $\geq$ 60; no NSAID, aspirin, antiplatelet, anticoagulant or corticosteroid co-therapy	Prescribe SSRI without routine gastroprotection; counsel on warning symptoms	NNH >3000; no significant signal in the 20–64-year cohort
Intermediate	Age 65–79 years; or CKD stage 3; or single antithrombotic agent; or intermittent NSAID use	Consider PPI co-prescription; prefer lower-affinity agent where clinically acceptable; review at	PPI OR 0.39 (0.16–0.94); rate difference rises to 4.2–4.8 per 1000 py

Risk stratum	Defining characteristics	Recommended action	Supporting evidence
		4 weeks	
High	Age ≥ 80 years; or prior upper GI bleeding; or CKD stage 4/5; or concurrent NSAID plus antithrombotic; or triple antithrombotic therapy	Prescribe PPI routinely; strongly prefer a low-SERT-affinity antidepressant; avoid concurrent NSAID; intensify monitoring for 4 weeks (6 months if anticoagulated)	NNH 85–244; SSRI+NSAID+aspirin OR 28 (7.6–103); OAC first-30-day IRR 1.74

Specific practice recommendations follow. Firstly, bleeding-risk assessment should be a routine component of antidepressant initiation, encompassing age, prior gastrointestinal bleeding or peptic ulcer disease, renal function and the complete medication list including over-the-counter analgesics. Secondly, proton pump inhibitor co-prescription should be routine in the high-risk stratum and considered in the intermediate stratum, recognising that it protects the upper but not the lower gastrointestinal tract. Thirdly, where an antidepressant is required in a patient at very high bleeding risk, an agent with low serotonin transporter affinity should be preferred over choosing between SSRI molecules, since the inter-agent range within the class is narrow. Fourthly, concurrent NSAID prescription in SSRI users should be minimised, and where unavoidable should be at the lowest effective dose for the shortest possible duration with mandatory gastroprotection. Fifthly, clinical vigilance should be intensified during the first four weeks of SSRI therapy and throughout the first six months of any SSRI–anticoagulant co-exposure. Sixthly, SSRIs should not be reflexively discontinued in patients admitted with peptic ulcer bleeding; where discontinuation is judged necessary, tapering with psychiatric liaison is preferred to abrupt cessation.^{7,8,11,14,18,26,28}

Recommendations for health systems and policy

Computerised prescribing systems should implement decision-support alerts for the specific co-prescription combinations demonstrated here to carry the greatest risk, particularly SSRI with NSAID, SSRI with NSAID and aspirin, and SSRI initiation in patients established on oral anticoagulation, with the alert prompting consideration of gastroprotection rather than merely flagging an interaction. Prescribing-safety indicators used in primary-care quality frameworks should incorporate the proportion of high-risk SSRI users receiving appropriate gastroprotection. Formulary and guideline committees should ensure that antidepressant selection guidance for older and multimorbid patients explicitly addresses serotonin transporter affinity. Patient information leaflets should include clear guidance on recognising melaena and haematemesis and on avoiding over-the-counter NSAIDs during SSRI therapy.^{14,21,26}

Recommendations for research

A pragmatic randomised controlled trial with independently adjudicated gastrointestinal bleeding as a pre-specified endpoint, comparing either high- against low-serotonin-transporter-affinity antidepressants or routine against selective proton pump inhibitor co-prescription in high-risk patients, is the single most valuable study that could now be undertaken. Further bias-resistant self-controlled analyses, particularly case-case-time-control designs adjusting for exposure time-trends, are required to determine whether the antithrombotic interaction survives such adjustment. Prospective endoscopically confirmed studies are needed to characterise the lower gastrointestinal signal. Pharmacogenomic investigation of cytochrome P450 and serotonin transporter polymorphisms may enable individualised prediction. Finally, validation cohorts in South-East Asian and specifically Indonesian populations are required, given regional differences in *Helicobacter pylori* prevalence, analgesic-prescribing culture and antidepressant utilisation.^{20,22,29}

REFERENCES

1. de Abajo FJ, García Rodríguez LA, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ*. 1999;319(7217):1106-9. Available from: <https://consensus.app/papers/details/ceb6f02d5e365a48ba30128599c527c6/>

2. van Walraven C, Mamdani MM, Wells PS, Williams JI. Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ*. 2001;323(7314):655-8. Available from: <https://consensus.app/papers/details/2b223663d8e85bee93e9b6bd394d2eaf/>
3. Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJP, et al. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? *Aliment Pharmacol Ther*. 2005;22(3):175-81. Available from: <https://consensus.app/papers/details/035f50281f275d1cad7cbf7c06924eb1/>
4. Wessinger S, Kaplan M, Choi L, Williams M, Lau C, Sharp L, et al. Increased use of selective serotonin reuptake inhibitors in patients admitted with gastrointestinal haemorrhage: a multicentre retrospective analysis. *Aliment Pharmacol Ther*. 2006;23(7):937-44. Available from: <https://consensus.app/papers/details/dbcdf280146950f182fbc34b6613d466/>
5. Yuan Y, Tsoi K, Hunt RH. Selective serotonin reuptake inhibitors and risk of upper GI bleeding: confusion or confounding? *Am J Med*. 2006;119(9):719-27. Available from: <https://consensus.app/papers/details/422e9d5fe24155de92865be943a22af7/>
6. Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther*. 2008;27(1):31-40. Available from: <https://consensus.app/papers/details/d36cbe88448252039410216eff88b41b/>
7. Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol*. 2009;104(6):1475-82. Available from: <https://consensus.app/papers/details/98f63de82ea35d02aa17be6c9577d2f8/>
8. Dall M, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol*. 2009;7(12):1314-21. Available from: <https://consensus.app/papers/details/f6eadd086c97577aa4d6a5aa1b131e29/>

9. Carvajal A, Ortega S, Del Olmo L, Vidal X, Aguirre C, Ruiz B, et al. Selective serotonin reuptake inhibitors and gastrointestinal bleeding: a case-control study. PLoS One. 2011;6(5):e19819. Available from: <https://consensus.app/papers/details/46e92757c5205fff8c7f7d34460f945e/>
10. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551. Available from: <https://consensus.app/papers/details/1a3536bc8f5255b3acd1c8ace9288efe/>
11. Castro VM, Gallagher PJ, Clements CC, Murphy SN, Gainer VS, Fava M, et al. Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants. BMJ Open. 2012;2(2):e000544. Available from: <https://consensus.app/papers/details/e8e5868241bf50ae90949ec49e464105/>
12. Wang YP, Chen YT, Tsai CF, Li SY, Luo JC, Wang SJ, et al. Short-term use of serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding. Am J Psychiatry. 2014;171(1):54-61. Available from: <https://consensus.app/papers/details/a1775e08fd105021ba5c7593d650838b/>
13. Anglin R, Yuan Y, Moayyedi P, Tse F, Armstrong D, Leontiadis GI. Risk of upper gastrointestinal bleeding with selective serotonin reuptake inhibitors with or without concurrent nonsteroidal anti-inflammatory use: a systematic review and meta-analysis. Am J Gastroenterol. 2014;109(6):811-9. Available from: <https://consensus.app/papers/details/cb634629260754bb8c6fa5e361b169d7/>
14. Jiang HY, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, et al. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2015;13(1):42-50. Available from: <https://consensus.app/papers/details/dd8b30010dd25148aa71683a7077ca07/>
15. Cheng YL, Hu HY, Lin XH, Luo JC, Peng YL, Hou MC, et al. Use of SSRI, but not SNRI, increased upper and lower gastrointestinal bleeding: a nationwide population-based cohort study

- in Taiwan. *Medicine (Baltimore)*. 2015;94(46):e2022. Available from: <https://consensus.app/papers/details/3df8dfa66ed25960bab84191f4d9ea9/>
16. Laporte S, Chapelle C, Caillet P, Beyens MN, Bellet F, Delavenne X, et al. Bleeding risk under selective serotonin reuptake inhibitor (SSRI) antidepressants: a meta-analysis of observational studies. *Pharmacol Res*. 2017;118:19-32. Available from: <https://consensus.app/papers/details/47cd32210dc052d9a56b544a9caa17dc/>
17. Chen WC, Lin KH, Huang YT, Tsai TJ, Sun WC, Chuah SK, et al. The risk of lower gastrointestinal bleeding in low-dose aspirin users. *Aliment Pharmacol Ther*. 2017;45(12):1542-50. Available from: <https://consensus.app/papers/details/c866a2bfb9c9555a88412bc346a345d51/>
18. Laursen SB, Leontiadis GI, Stanley AJ, Hallas J, Schaffalitzky de Muckadell OB. The use of selective serotonin receptor inhibitors (SSRIs) is not associated with increased risk of endoscopy-refractory bleeding, rebleeding or mortality in peptic ulcer bleeding. *Aliment Pharmacol Ther*. 2017;46(3):355-63. Available from: <https://consensus.app/papers/details/e786c60eb3c956be9cb8718ac24386a8/>
19. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in people aged 20-64 years: cohort study using a primary care database. *BMC Med*. 2018;16(1):36. Available from: <https://consensus.app/papers/details/234ad93eddd35d95aafc3d88aa1fa8d4/>
20. Iwagami M, Tomlinson LA, Mansfield KE, Casula A, Caskey FJ, Aitken G, et al. Gastrointestinal bleeding risk of selective serotonin reuptake inhibitors by level of kidney function: a population-based cohort study. *Br J Clin Pharmacol*. 2018;84(9):2142-51. Available from: <https://consensus.app/papers/details/d392d186e750503d92e7ebc05024de5e/>
21. Bixby AL, VandenBerg A, Bostwick JR. Clinical management of bleeding risk with antidepressants. *Ann Pharmacother*. 2019;53(2):186-94. Available from: <https://consensus.app/papers/details/a3eb3ce720bf5e8c99d5688d936c6e98/>
22. Guo CG, Cheung KS, Zhang F, Chan EW, Chen L, Wong ICK, et al. Risks of hospitalization for upper gastrointestinal bleeding in users of selective serotonin reuptake inhibitors after *Helicobacter pylori* eradication therapy: a propensity score matching analysis. *Aliment*

- Pharmacol Ther. 2019;50(9):1001-8. Available from:
<https://consensus.app/papers/details/d477cbc6fd2e526e8b3aee378d9d8848/>
23. Zhang Y, Souverein PC, Gardarsdottir H, van den Ham HA, Maitland-van der Zee AH, de Boer A. Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: a population-based nested case-control study. *Br J Clin Pharmacol.* 2020;86(6):1150-64. Available from: <https://consensus.app/papers/details/eb03a6cbaed55353a9f9e29d50c24120/>
24. Bakker S, Kruip MJHA, van der Meer FJM, Cannegieter SC, Lijfering WM. Selective serotonin reuptake inhibitor use and risk of major bleeding during treatment with vitamin K antagonists: results of a cohort study. *Thromb Haemost.* 2022;122(9):1516-24. Available from: <https://consensus.app/papers/details/8c4e868486e652d7b2c11302237da149/>
25. Haghbin H, Zakirkhodjaev N, Fatima R, Kamal F, Aziz M. Risk of gastrointestinal bleeding with concurrent use of NSAID and SSRI: a systematic review and network meta-analysis. *Dig Dis Sci.* 2023;68(5):1975-82. Available from:
<https://consensus.app/papers/details/84792d01dc005c93ace478a6ed47c529/>
26. Rahman AA, Platt RW, Beradid S, Boivin JF, Rej S, Renoux C. Concomitant use of selective serotonin reuptake inhibitors with oral anticoagulants and risk of major bleeding. *JAMA Netw Open.* 2024;7(3):e243208. Available from:
<https://consensus.app/papers/details/c598b4c048be5e6b97786ea604a1e0db/>
27. Axelsson MAB, Bergman U, Wallerstedt SM. Bleeding in patients on concurrent treatment with a selective serotonin reuptake inhibitor (SSRI) and low-dose acetylsalicylic acid (ASA) compared with SSRI or low-dose ASA alone: a systematic review and meta-analysis. *Br J Clin Pharmacol.* 2024;90(7):1585-99. Available from:
<https://consensus.app/papers/details/d4629a45a69a5187b0114a4d02a7daa0/>
28. Gómez-Lumbreras A, Villa-Zapata L, Tan MS, Boyce RD, Malone DC. Risk of gastrointestinal bleeding by specific SSRIs and SNRIs: a systematic review and meta-analysis. *Br J Clin Pharmacol.* 2025. Available from:
<https://consensus.app/papers/details/ea92f394971a5a0ba6e02fd78c99d9b7/>

29. Kim S, Lee H, Shin JY. Risk of major bleeding events associated with concomitant use of selective serotonin reuptake inhibitors and anti-thrombotic drugs: a nationwide case-case-time-control study. *Age Ageing*. 2026;55(1). Available from: <https://consensus.app/papers/details/d8cd0f4224435651a5c628eb7d003ca8/>
30. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina (SADHART). *JAMA*. 2002;288(6):701-9. Available from: <https://consensus.app/papers/details/dfa13507af5a5029862c3b4245f6d813/>
31. Serebruany VL, Glassman AH, Malinin AI, Nemeroff CB, Musselman DL, van Zyl LT, et al. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the SADHART platelet substudy. *Circulation*. 2003;108(8):939-44. Available from: <https://consensus.app/papers/details/b617c8ebe5655aa4a1a17f070cbb943b/>
32. Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA*. 2018;320(4):350-8. Available from: <https://consensus.app/papers/details/3142bd2136af54978d5c5efe582dd707/>
33. Angermann CE, Gelbrich G, Störk S, Gunold H, Edelmann F, Wachter R, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA*. 2016;315(24):2683-93. Available from: <https://consensus.app/papers/details/6886fde93dfa5f8ea39d95a2045f7d70/>
34. Mahady SE, Margolis KL, Chan A, Polekhina G, Woods RL, Wolfe R, et al. Major GI bleeding in older persons using aspirin: incidence and risk factors in the ASPREE randomised controlled trial. *Gut*. 2021;70(4):717-24. Available from: <https://consensus.app/papers/details/2c7234e7ec595107b4432d5d520efb68/>
35. García Rodríguez LA, Martín-Pérez M, Hennekens CH, Rothwell PM, Lanás A. Bleeding risk with long-term low-dose aspirin: a systematic review of observational studies. *PLoS One*.

2016;11(8):e0160046.

Available

from:

<https://consensus.app/papers/details/9ce570262c4d54fa9ae510641dbe5f08/>

36. Gaist D, García Rodríguez LA, Hellfritzsche M, Poulsen FR, Halle B, Hallas J, et al. Antidepressant drug use and subdural hematoma risk. *J Thromb Haemost.* 2020;18(2):318-27. Available from: <https://consensus.app/papers/details/3589f32158825cbaab6a7b4ba351af44/>
37. de Abajo FJ, Jick H, Derby L, Jick S, Schmitz S. Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol.* 2000;50(1):43-7. Available from: <https://consensus.app/papers/details/4aedfa1c7bb55740b97b8eb3d7943861/>
38. Yang YC, Chen IC, Chang CN, Hu CJ. Preoperative use of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors and adverse outcomes after liver surgery: a nationwide propensity score-matched study. *J Affect Disord.* 2025. Available from: <https://consensus.app/papers/details/ba8bc4c3b6215ee5b37fe97a608342cd/>
39. Ganter M, Nichols S, Klein L, Wieruszewski PM. Impact of selective serotonin reuptake inhibitors on bleeding rates in HeartMate 3 left ventricular assist device patients not taking aspirin. *Artif Organs.* 2025. Available from: <https://consensus.app/papers/details/0e48141b357450b7830409265aa6e0bc/>
40. Rahman AA, He N, Rej S, Platt RW, Renoux C. Concomitant use of selective serotonin reuptake inhibitors and oral anticoagulants and risk of major bleeding: a systematic review and meta-analysis. *Thromb Haemost.* 2023;123(1):54-63. Available from: <https://consensus.app/papers/details/0b067ac601235614bb102354a4b4c579/>