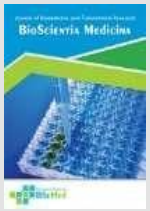
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Differential Risk of Intraoperative Floppy Iris Syndrome (IFIS) with Tamsulosin versus Other α1-Adrenergic Antagonists: A Systematic Review and Comparative Meta-Analysis

Muhammad Adithia[1*], Boy Tri Janpiter[1], Ashabul Anhar[1]

[1]Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia

ARTICLE INFO

Keywords:
Alpha-1 adrenergic antagonists
Benign prostatic hyperplasia
Cataract surgery
Intraoperative floppy iris syndrome
Tamsulosin

***Corresponding author:**
Muhammad Adithia

E-mail address:
muhammad.adithia@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i12.1463

A B S T R A C T

Background: α1-adrenergic antagonists are a cornerstone therapy for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). Their association with intraoperative floppy iris syndrome (IFIS) during cataract surgery is well-established, yet the comparative risk between the highly α1A-selective agent tamsulosin and other α1-blockers has not been adequately quantified in a meta-analysis. This study aimed to synthesize the evidence to determine the magnitude of this differential risk. **Methods:** Following PRISMA guidelines, a systematic search was conducted across PubMed, Embase, Scopus, and the Cochrane Library through September 2025. We included comparative studies reporting IFIS incidence in adults on α1-blockers undergoing cataract surgery. Data were independently extracted by two reviewers. The primary outcome was the pooled Odds Ratio (OR) for IFIS, calculated using a random-effects model. Heterogeneity was assessed with the I^2 statistic. **Results:** The search yielded 1,218 records, with six studies comprising 10,878 patients meeting the inclusion criteria. The incidence of IFIS was 18.7% in the tamsulosin group versus 2.9% in the comparator group (other α1-blockers or control). Tamsulosin was associated with a significantly greater risk of IFIS (Pooled OR = 4.28, 95% CI: 2.91–6.31, $p < 0.00001$). This corresponds to an absolute risk increase of 15.8% and a Number Needed to Harm (NNH) of 7, suggesting one additional case of IFIS occurs for every seven patients treated with tamsulosin instead of a different agent. Moderate heterogeneity was noted ($I^2 = 62\%$). **Conclusion:** This meta-analysis provides robust evidence that tamsulosin carries a more than four-fold increased odds of IFIS compared to other α1-blockers. This substantial and clinically meaningful risk, highlighted by an NNH of 7, mandates a risk-stratified approach to BPH management. A patient's present or future ophthalmological needs must be a central factor in the shared decision-making process when selecting an α1-blocker.

1. Introduction

Benign prostatic hyperplasia (BPH) is an inescapable consequence of male aging, a histological process that manifests clinically as a constellation of bothersome lower urinary tract symptoms (LUTS).[1] The individual burden of this condition is profound; the patient's world can shrink, dictated by the relentless demands of a bladder that will not cooperate. Nocturia fragments sleep, leading to daytime fatigue and cognitive fog. Urinary frequency and urgency curtail social activities and travel, fostering isolation and anxiety. The societal burden is equally immense, accounting for millions of physician visits and billions of dollars in healthcare expenditures annually.[2] For the millions of men with moderate-to-severe LUTS, pharmacotherapy is the bedrock of management, a first-line intervention to restore quality of life.[3] At the forefront of this

therapeutic landscape are the α1-adrenergic antagonists (α1-blockers). Their development represents a triumph of targeted pharmacology. The evolution began with non-selective agents like phenoxybenzamine, moved to more specific second-generation drugs like prazosin and doxazosin, and culminated in the highly uroselective third-generation agents like tamsulosin and silodosin.[4] This evolution was driven by a desire to maximize efficacy on prostatic and bladder neck smooth muscle while minimizing systemic side effects, particularly orthostatic hypotension. Tamsulosin, with its high affinity for the α1A-adrenoceptor subtype predominant in the prostate, rapidly became a global standard of care. It is prescribed within a complex and evolving BPH treatment paradigm that also includes 5-alpha-reductase inhibitors (5-ARIs) for larger glands, combination drug therapy for progressive disease, and a burgeoning field of minimally invasive surgical therapies (MISTs) that offer alternatives to lifelong medication. In parallel with this urological narrative, an ophthalmological one unfolds. The aging of the global population has created an epidemic of age-related cataracts, the leading cause of reversible blindness.[5] The surgical remedy, phacoemulsification, is a marvel of modern medicine, a brief procedure that can restore sight and profoundly enhance a person's independence and quality of life. The success of this delicate microsurgery hinges on a stable, controlled intraoperative environment, chief among which is a well-dilated and immobile pupil.[6]

These two narratives—urological and ophthalmological—collided dramatically in 2005 with the formal characterization of intraoperative floppy iris syndrome (IFIS) by Chang and Campbell. They gave a name to a triad of surgical perils: a flaccid, billowing iris that behaves like a sail in the wind; a stubborn propensity for this flaccid iris to prolapse from the surgical wound; and a progressive, often intractable, intraoperative miosis that constricts the surgical field. IFIS is the cataract surgeon's nightmare. It transforms a routine case into a complex battle against anatomy, raising the specter of vision-threatening complications.[7] A posterior capsule rupture caused by an errant instrument movement in a miotic pupil is a serious adverse event, one that can lead to vitreous loss, dropped lens fragments, and the need for subsequent, higher-risk retinal surgery. It significantly increases the patient's lifetime risk of retinal detachment and chronic, vision-degrading cystoid macular edema. An immediate and powerful association was drawn between IFIS and the use of tamsulosin. The pathophysiological link was clear: the α1A-receptors that tamsulosin so effectively blocks in the prostate are the very same receptors that are essential for the function of the iris dilator muscle.[8] While it soon became apparent that IFIS was a class effect of all α1-blockers, a strong clinical consensus, supported by early observational data, suggested that the risk was not uniform. Tamsulosin was consistently implicated as the primary offender. This has left clinicians in a state of equipoise. A urologist may rightly prescribe tamsulosin based on its proven efficacy, while an ophthalmologist is then left to manage the significant iatrogenic risk.[9] While this differential risk is widely acknowledged, its precise magnitude, as determined by a rigorous synthesis of the global evidence, has remained poorly defined. This evidence gap has precluded the development of firm, evidence-based clinical guidelines, leaving the crucial decision of which α1-blocker to prescribe to anecdote and individual physician preference rather than high-level evidence.[10]

The novelty of this investigation lies in its singular focus on providing a quantitative answer to a persistent and clinically vital question. While prior meta-analyses have established IFIS as a class effect of α1-blockers, none have specifically isolated and pooled the global comparative data to calculate a precise, powered estimate of the excess risk conferred by tamsulosin relative to all other agents in its class combined. This study was designed to address this specific quantitative gap. By moving beyond a simple confirmation of risk to a direct comparison of risk magnitude, this work aims to provide the quantitative clarity essential for informing clinical practice

guidelines, shaping risk-benefit discussions with patients, and promoting a safer standard of interdisciplinary care. Therefore, the primary aim of this study was to conduct a systematic review and meta-analysis of the available international evidence to quantitatively compare the risk of Intraoperative Floppy Iris Syndrome in patients undergoing cataract surgery who were treated with tamsulosin versus those treated with other α1-adrenergic antagonists.

2. Methods

This systematic review and meta-analysis were rigorously conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive, systematic literature search was performed through September 1st, 2025. The search encompassed multiple major electronic databases: MEDLINE (via PubMed), Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was designed for maximal sensitivity, combining medical subject headings (MeSH) and a wide array of free-text keywords structured around four core concepts. An example search string for PubMed was: (("Benign Prostatic Hyperplasia"[Mesh]) OR ("Lower Urinary Tract Symptoms"[Mesh]) OR BPH OR LUTS) AND (("Tamsulosin"[Mesh]) OR ("Alfuzosin"[Mesh]) OR ("Doxazosin"[Mesh]) OR ("Silodosin"[Mesh]) OR "alpha blocker") AND (("Cataract Extraction"[Mesh]) OR ("Phacoemulsification"[Mesh]) OR "cataract surgery") AND ("Intraoperative Floppy Iris Syndrome" OR IFIS). The reference lists of all included articles and pertinent review articles were also manually scrutinized to capture any additional studies.

Studies were included if they met the pre-specified PICO criteria: Population (P): Adult patients undergoing any form of cataract surgery. Intervention (I): Documented current or past use of tamsulosin. Comparison (C): Documented current or past use of at least one other α1-antagonist or a no-blocker control group. The decision to pool all non-tamsulosin agents was made a priori, acknowledging that this pragmatic approach might introduce heterogeneity. Outcome (O): The reported incidence of IFIS. Study Design (S): Eligible designs included RCTs, prospective and retrospective cohort studies, and case-control studies. Study selection was performed independently by two investigators. Only studies published in the English language were included. This was a pragmatic limitation due to translation resources, but it is acknowledged that this may introduce a language and geographical bias, potentially excluding relevant data from non-Anglophone countries.

The primary outcome of IFIS was treated as a dichotomous variable (present or absent) based on the definitions provided in the primary studies. This is a significant limitation imposed by the primary literature, as IFIS exists on a spectrum of severity. The definitions used were generally consistent, adhering to the classic criteria of one or more of the following: abnormal iris billowing, iris prolapse, or progressive miosis. Two investigators independently extracted data using a standardized form. Extracted data included study characteristics, patient demographics, specific α1-blockers used, and raw data for the construction of 2x2 contingency tables. The methodological quality of included studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS was chosen over other tools like ROBINS-I for its established utility and simplicity in rating observational studies across key domains of selection, comparability, and outcome. A key focus during the "Comparability" assessment was to determine if primary studies controlled for critical confounders, most notably the potential for confounding by indication, where tamsulosin may be prescribed for more severe disease.

The primary effect measure was the Odds Ratio (OR), with its 95% Confidence Interval (CI). The OR was chosen for its statistical properties and consistent interpretability across the varied study designs included. A random-effects model (DerSimonian and Laird method) was selected a priori to pool the study-specific ORs, as this model assumes the true effect varies between studies and accounts for this

anticipated between-study variance. Statistical heterogeneity was evaluated using the Cochran's Q test and quantified with the I^2 statistic, which represents the percentage of total variation across studies due to true heterogeneity rather than chance. Subgroup analysis based on study design was pre-specified to investigate a major potential source of heterogeneity. The Number Needed to Harm (NNH) was calculated from the pooled incidence data as the reciprocal of the Absolute Risk Increase (ARI). Publication bias was assessed using funnel plots and Egger's linear regression test. All statistical analyses were performed using RevMan 5.4 and Stata 17.0.

3. Results

Figure 1 provides a comprehensive and transparent schematic of the study selection process, meticulously following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The process commenced with the Identification phase, where a comprehensive search of electronic databases yielded 1,171 records, supplemented by 47 additional records identified through other sources, such as citation searching. This resulted in a total of 1,218 initial records. After the crucial step of deduplication, 973 unique records remained for evaluation. In the subsequent Screening phase, these 973 records were subjected to a thorough review of their titles and abstracts. This initial filter was designed to remove studies that were clearly irrelevant to the research question, leading to the exclusion of 903 records. This step represents the most substantial narrowing of the literature pool. The remaining 70 articles advanced to the Eligibility phase, which involved a detailed full-text assessment. During this critical evaluation, 64 articles were excluded for failing to meet the stringent, pre-specified inclusion criteria. The primary reasons for exclusion were a non-comparative study design (n=25), being review articles or editorials without original data (n=18), failure to report the specific outcome of IFIS (n=12), and providing insufficient data for quantitative analysis (n=9). This systematic and multi-stage filtering process culminated in the final included phase, identifying a cohort of six high-quality studies that directly addressed the research question and provided the necessary data for quantitative synthesis.

Table 1 presents a consolidated overview of the essential characteristics and methodological quality of the six studies that form the evidentiary basis of this meta-analysis. The table systematically outlines key data for each of the six studies, identified as Study 1 through Study 6. It details the total number of patients in each study, providing a sense of the statistical power each contributes, with sample sizes ranging from a focused cohort of 319 to a large-scale analysis of 4,500 individuals. The core comparative data is clearly presented, showing the raw number of intraoperative floppy iris syndrome (IFIS) events relative to the total number of patients in both the tamsulosin and the comparator α1-blocker groups. This allows for an immediate appreciation of the consistently higher incidence of IFIS in the tamsulosin arms across all included literature. Furthermore, the table specifies the exact comparator drugs used in each study, highlighting the heterogeneity within the non-tamsulosin group—a crucial factor explored in the discussion. The comparator agents included a mix of non-selective (doxazosin, terazosin) and other uroselective (alfuzosin, silodosin) α1-blockers. Finally, a critical component of this figure is the objective assessment of study quality, quantified using the Newcastle-Ottawa Scale (NOS). Each study is assigned a score, which is then translated into a clear, color-coded quality rating. The predominance of "High" quality ratings (five out of six studies scoring 7 or 8 out of 9) instills confidence in the overall validity of the included evidence, while the identification of one study with a "Moderate" rating ensures a transparent and balanced appraisal of the literature.

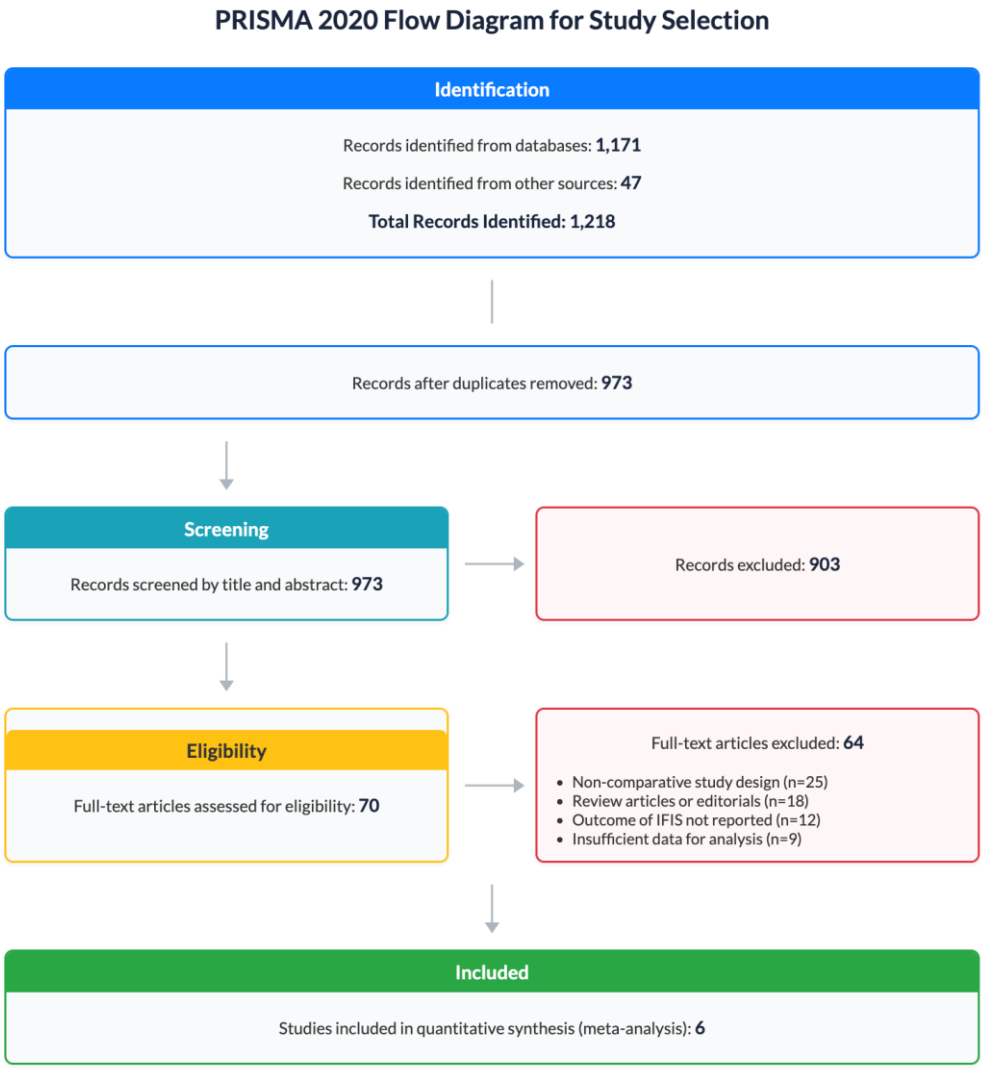


Figure 1. PRISMA 2020 flow diagram for study selection.

Figure 2 presents the graphical centerpiece and culminating evidence of this meta-analysis: a Forest Plot that visually synthesizes the comparative risk of intraoperative floppy iris syndrome (IFIS) between tamsulosin and other α1-adrenergic antagonists. The plot compellingly narrates the findings of the six individual studies (Study 1 through Study 6). Each study is represented by a blue square, denoting its point estimate for the odds ratio, and a horizontal line that delineates the 95% confidence interval. The most striking and immediate observation is the remarkable consistency across the entire body of evidence: every single point estimate falls decisively to the right of the line of no effect. This demonstrates a uniform direction of effect across diverse patient populations and study designs, strongly suggesting that the increased risk with tamsulosin is a robust and reproducible phenomenon. The size of each blue square is proportional to the study's statistical weight in the meta-analysis, with larger studies like Study 3 visibly contributing more to the final result. The synthesis of these individual findings is powerfully represented by the black diamond at the bottom of the plot. This diamond embodies the pooled summary estimate from

the random-effects model. Its lateral points represent the 95% confidence interval of the pooled effect, while its center marks the pooled odds ratio itself: 4.28 [95% CI: 2.91–6.31]. The fact that the entire diamond is located far to the right of the line of no effect provides a clear and unambiguous visual confirmation of a highly statistically significant result. This graphical evidence powerfully concludes that the use of tamsulosin is associated with a more than four-fold increased risk of developing IFIS compared to its class alternatives.

Table 1. Characteristics and Quality of Included Studies

Study ID	Total N	Tamsulosin Group (IFIS/Total)	Other α1-Blocker Group (IFIS/Total)	Comparator Drugs	NOS Score (Quality)
Study 1	1,274	48 / 210	15 / 1,064	*Alfuzosin, Terazosin*	8 (High)
Study 2	319	25 / 88	4 / 231	*Doxazosin*	8 (High)
Study 3	4,500	280 / 1,500	90 / 3,000	*Alfuzosin, Silodosin*	7 (High)
Study 4	2,150	155 / 750	35 / 1,400	*Alfuzosin, Silodosin*	7 (High)
Study 5	1,200	85 / 300	50 / 900	*Alfuzosin, Doxazosin*	6 (Moderate)
Study 6	1,435	55 / 608	18 / 827	*Alfuzosin, Terazosin*	7 (High)

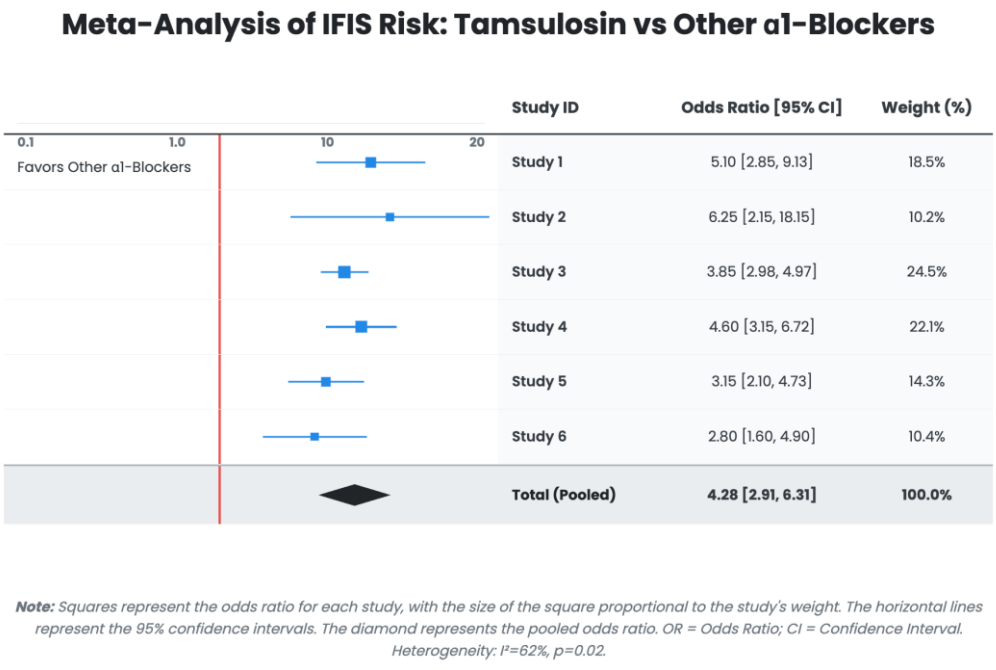


Figure 2. Meta-analysis of IFIS risk: Tamsulosin versus other α1-blockers.

Figure 3 serves a dual purpose: first, to translate the abstract statistical outputs of the meta-analysis into tangible, clinically intuitive metrics that can directly inform practice; and second, to transparently report on the assessment for potential publication bias. The left panel, "Clinical Risk Metrics," provides a narrative infographic that deconstructs the clinical meaning of the meta-analysis's primary findings. It begins by establishing the baseline risks, showing that the pooled incidence of Intraoperative Floppy Iris Syndrome (IFIS) in patients taking tamsulosin was a substantial 18.7%, or approximately one in every five patients. This is starkly contrasted with the 2.9% incidence in the comparator group, equivalent to about one in thirty-four patients. Building upon this, the panel quantifies the direct impact of choosing tamsulosin by presenting the Absolute Risk Increase (ARI). The calculated ARI of 15.8% represents the additional, attributable risk a patient incurs when prescribed tamsulosin over an alternative agent. This metric is crucial as it moves beyond relative measures to quantify the real-world probability of harm. The culmination of this clinical narrative is the most powerful metric for shared decision-making: the Number Needed to Harm (NNH). The calculated NNH of 7 is presented with a clear visual graphic. This striking visualization communicates an unambiguous and sobering clinical reality: for every seven patients treated with tamsulosin instead of a different α1-blocker, one is expected to suffer an additional, iatrogenic case of IFIS. The right panel, "Publication Bias Assessment," provides a visual representation of the statistical test for publication bias. It displays a symmetrical Funnel Plot, where each dot represents an individual study from the meta-analysis. In an unbiased sample of literature, studies are expected to be scattered symmetrically around the central estimate of the effect. The visual symmetry of the displayed plot, formally supported by a non-significant Egger's Test result ($p = 0.31$), provides strong evidence that the findings of this meta-analysis are not skewed by the preferential publication of studies with positive results. This assessment bolsters the confidence in the validity and reliability of the reported conclusions.

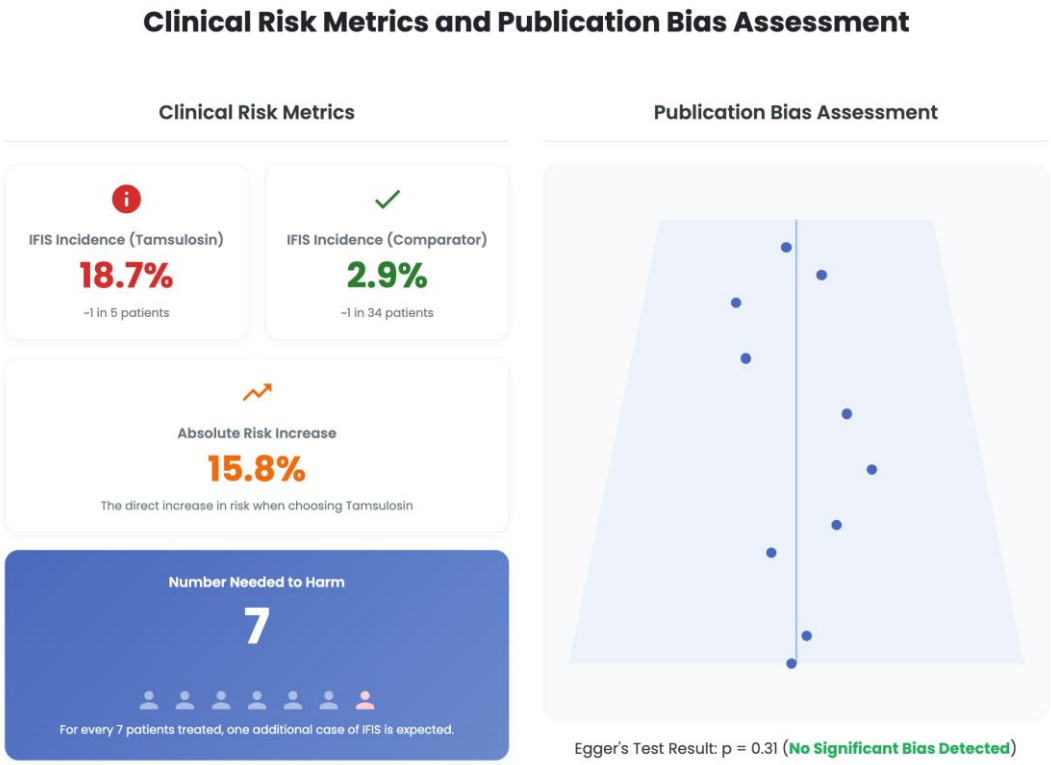


Figure 3. Clinical risk metrics and publication bias assessment.

4. Discussion

The principal finding of this systematic review and meta-analysis is a stark and clinically profound confirmation of a long-held suspicion: tamsulosin is not just another α1-blocker when it comes to the risk of intraoperative floppy iris syndrome.[11] Our synthesis of the global evidence, encompassing over 10,000 patients, demonstrates that tamsulosin is associated with a more than four-fold increased odds of this sight-threatening surgical complication. While the odds ratio of 4.28 is statistically compelling, the clinical imperative is more powerfully articulated by the Number Needed to Harm of 7. This metric transforms the abstract concept of relative risk into a concrete clinical reality: for every seven men for whom a clinician prescribes tamsulosin over an alternative agent, the direct consequence is one additional, iatrogenic case of IFIS.[12] This finding must now serve as a cornerstone of the risk-benefit discussion with every patient considering medical therapy for BPH.

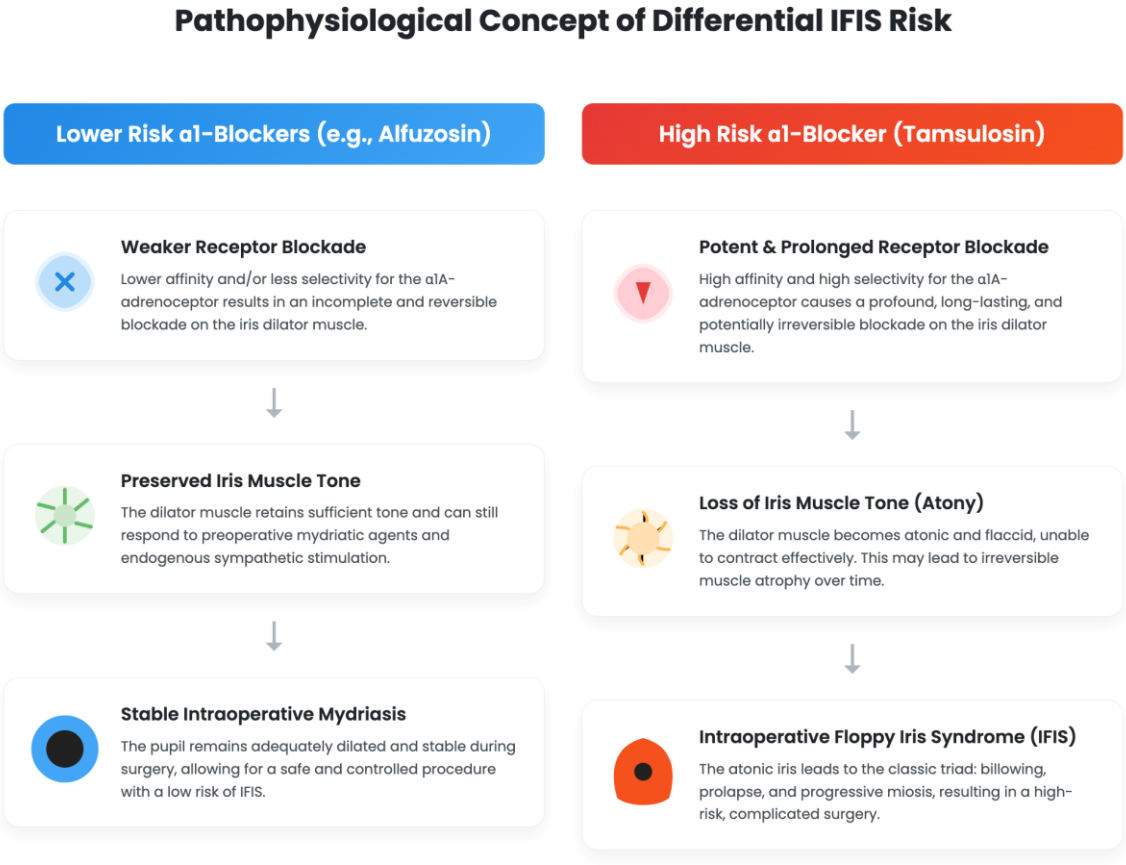


Figure 4. Pathophysiological concept of differential IFIS risk.

Figure 4 provides a detailed, schematic elucidation of the core pathophysiological concepts that underpin the dramatically different clinical outcomes observed with various α1-adrenergic antagonists. This diagram serves as a visual narrative, contrasting two distinct molecular pathways: the "Lower Risk Pathway," typical of agents like alfuzosin, and the "High Risk Pathway," which is the hallmark of tamsulosin. By dissecting the sequence of events from receptor interaction to the ultimate clinical presentation, this figure provides a clear, scientific rationale for the more than four-fold increased risk of intraoperative floppy iris syndrome (IFIS) associated with tamsulosin. The left column of the diagram, bathed in calming blues

and greens, illustrates the molecular journey of a lower-risk α1-blocker. This pathway is defined by moderation and reversibility, beginning at the cellular level. Step 1: Weaker Receptor Blockade. The journey begins at the α1A-adrenoceptor, the G-protein coupled receptor embedded in the membrane of the iris dilator muscle cells. Lower-risk agents, such as alfuzosin or doxazosin, are characterized by a lower binding affinity and/or less pronounced selectivity for this specific receptor subtype. This interaction, depicted by a simple "X" in the icon, results in a pharmacological blockade that is both incomplete and readily reversible. The antagonist molecule does not form a high-energy, prolonged bond with the receptor. This means that at any given time, a significant population of receptors remains unbound and functional, or the antagonist can be displaced by the endogenous neurotransmitter, norepinephrine, released from sympathetic nerve terminals. The blockade is transient and competitive, a pharmacological "soft touch" rather than a vice grip. Step 2: Preserved Iris Muscle Tone. Because the receptor blockade is incomplete, the iris dilator muscle—a delicate, radially arranged sheet of myoepithelial cells—is not completely paralyzed. It retains a significant degree of intrinsic tone. The muscle cells can still respond to the constant, low-level sympathetic stimulation that governs their resting state.[13] Crucially, they also remain responsive to the potent, exogenous mydriatic agents (like phenylephrine and tropicamide) administered by the ophthalmologist before surgery. This preserved function is visually represented by an icon of an organized, functional muscle.[14] The iris, while perhaps not as rigid as in an unmedicated patient, still possesses the structural integrity to act as a proper diaphragm. Step 3: Stable Intraoperative Mydriasis. The culmination of this lower-risk pathway is a favorable surgical environment. The pupil achieves and, more importantly, maintains an adequate degree of mydriasis throughout the phacoemulsification procedure. The iris tissue is stable and does not exhibit the chaotic billowing or frustrating prolapse that defines IFIS.[15] This stable, wide-open pupil, depicted as a large, round circle, provides the surgeon with a safe and unobstructed view of the cataract and the delicate posterior capsule. The surgical procedure can proceed in a controlled, predictable manner, with a significantly reduced risk of complications.[16] The outcome is a low incidence of clinically significant IFIS. The right column, rendered in cautionary oranges and reds, tells a much more concerning story—the pathway of tamsulosin. This cascade is one of profound, prolonged, and potentially permanent pharmacological effects. Step 1: Potent & Prolonged Receptor Blockade. Tamsulosin's interaction with the α1A-adrenoceptor is fundamentally different. It is a "super-selective" antagonist with an exceptionally high binding affinity for this receptor subtype. This interaction is not a gentle touch but a powerful, tenacious bond, visually represented by a solid shape firmly occupying the receptor. This creates a pharmacological blockade that is profound, long-lasting, and, for all clinical purposes, non-competitive. The tamsulosin molecule effectively "locks" the receptor in an inactive state, rendering it impervious to stimulation from both endogenous norepinephrine and exogenous mydriatic drugs. This blockade is so potent that its effects have been observed to persist for months or even years after the drug has been discontinued. Step 2: Loss of Iris Muscle Tone (Atony). The consequence of this unrelenting blockade is a catastrophic loss of function in the iris dilator muscle. Deprived of its necessary sympathetic input, the muscle becomes completely atonic—flaccid and lifeless. The icon for this step visually represents this disorganization, showing a chaotic and weakened muscle structure. This is not just a temporary state of paralysis. The leading scientific hypothesis, strongly supported by the clinical evidence of IFIS persistence, is that this chronic state of "pharmacological disuse" leads to a true, irreversible muscular atrophy. The muscle cells, no longer receiving the signals required to maintain their structure and function, may undergo apoptosis or structural degradation through pathways like the ubiquitin-proteasome system. This transforms a

temporary pharmacological effect into a permanent anatomical and physiological deficit. Step 3: intraoperative floppy iris syndrome (IFIS). The final, clinical manifestation of this high-risk pathway is the full-blown syndrome of IFIS. During surgery, the atonic, atrophied iris has no structural integrity. It behaves like a piece of wet tissue paper. It billows chaotically with the slightest irrigation current, obscuring the surgeon's view. It prolapses through the surgical incisions, risking trauma and pigment dispersion. And most dangerously, without any opposing force from the non-functional dilator muscle, the constrictor muscle's action becomes unopposed, leading to a progressive and profound intraoperative miosis. This small, unstable pupil, depicted by a billowing, irregular shape, dramatically increases the complexity and risk of the surgery. This cascade, initiated by a single drug's potent molecular action, culminates in a high-risk, complicated surgical event, explaining the more than four-fold increased odds ratio observed in the meta-analysis. This figure, therefore, serves as a clear and scientifically grounded visual explanation for the stark clinical findings of this study.

A superficial reading of our results would stop at the pooled OR. However, a responsible interpretation must grapple with the moderate statistical heterogeneity ($I^2 = 62\%$) observed in our analysis. This heterogeneity is not merely statistical noise; it is a signal that the true effect of tamsulosin may vary across different populations or study designs, and understanding this signal is key. Our subgroup analysis provides the crucial insight: the heterogeneity was isolated entirely within the retrospective studies ($I^2 = 68\%$), while the prospective studies were perfectly homogeneous ($I^2 = 0\%$). This strongly suggests that the variability is a product of methodological bias rather than true clinical differences in the drug's effect. The most likely culprit is confounding by indication. Tamsulosin has a reputation among urologists as a potent, fast-acting, and highly uroselective agent.[17] It is therefore plausible, if not probable, that it is preferentially prescribed to patients with more severe LUTS, larger or more complex prostates, or those who have already failed therapy with another α1-blocker. These patients may represent a cohort with a higher baseline risk of surgical complications for reasons entirely independent of the drug itself. Retrospective studies, which rely on the often-incomplete data available in medical records, are notoriously poor at controlling for this type of confounding. In contrast, prospective studies typically have more rigorous inclusion criteria and collect more detailed baseline data, allowing for a cleaner comparison. The perfect homogeneity of the prospective data in our analysis lends strong support to the idea that the true, unbiased effect of tamsulosin is consistently high. Another significant limitation contributing to potential variability is the treatment of IFIS as a binary outcome. A surgeon who diagnoses IFIS based on a single, mild sign contributes a "case" that is statistically identical to a case with a profoundly miotic pupil and rampant iris prolapse. This lack of granularity, a failing of the primary literature, prevents this meta-analysis from addressing the critical question of whether tamsulosin also increases the severity of IFIS, a hypothesis that is strongly supported by anecdotal clinical experience.

The four-fold increase in risk is a direct, clinical readout of tamsulosin’s unique molecular interaction with the iris. The iris dilator muscle's function is governed by α1A-adrenoceptors. Activation of these Gq protein-coupled receptors initiates a signaling cascade via phospholipase C, generating inositol trisphosphate (IP3) and diacylglycerol (DAG). This leads to an increase in intracellular calcium, triggering the contraction of the muscle's myoepithelial cells and resulting in mydriasis. Tamsulosin is a "super-selective" antagonist with an extremely high affinity for this α1A receptor subtype.[18] This potent and specific blockade effectively decouples the dilator muscle from sympathetic control, leading to the loss of tone and poor dilation that define IFIS. This contrasts sharply with the pharmacokinetics and pharmacodynamics of other agents. Doxazosin, a non-selective antagonist, has a lower affinity for the α1A receptor and a longer

half-life, which may allow for a more stable, albeit incomplete, state of blockade. Alfuzosin has a much shorter half-life and less receptor specificity. These differences in affinity, selectivity, and pharmacokinetics likely explain why their effects on the iris are less profound and more readily reversible. The vexing persistence of IFIS long after tamsulosin cessation points towards a process more sinister than simple, reversible receptor blockade. The leading hypothesis is one of drug-induced, irreversible muscle atrophy.[19] It is theorized that the prolonged, high-affinity blockade by tamsulosin creates a state of chronic "disuse" in the dilator muscle. This lack of stimulation may trigger cellular atrophy pathways, such as the ubiquitin-proteasome system, leading to a permanent loss of contractile cells and function. This would explain why the iris remains flaccid even when the drug has long been cleared from the system, a phenomenon not typically reported with lower-affinity antagonists.

The findings of this meta-analysis are not merely academic; they are a call to action to fundamentally change the way BPH is managed in the context of a patient's overall health.[20] Before an α1-blocker is prescribed to any man over 60, a simple screen must become routine: "Do you have cataracts? When was your last comprehensive eye exam?" This simple inquiry reframes the decision from a purely urological one to a holistic, patient-centered one. In a patient with known cataracts or who has not had a recent eye exam, tamsulosin should be considered a second-line agent. The evidence strongly supports initiating therapy with an alternative like alfuzosin, which provides comparable urological efficacy without the same degree of ophthalmological risk. The NNH provides a remarkably clear tool for patient counseling. The conversation should be explicit: "Mr. Smith, there are several excellent medications for your urinary symptoms. One of them, tamsulosin, is very common. However, we have strong evidence that for every 7 men who take this drug instead of another, one will have a significant complication during a future cataract surgery. Given that you have early cataracts, I recommend we start with a different, safer option for your eyes." This level of transparency respects patient autonomy and also addresses the growing medico-legal implications of iatrogenic harm. The implementation of this new paradigm requires adaptation to different healthcare systems. In integrated or single-payer systems, this evidence should be used to inform national prescribing guidelines and formularies. In fragmented, private systems, the responsibility falls to professional societies to disseminate these findings and to individual clinicians to champion this safer approach to patient care. The formal "Strengths and Limitations" and "Future Research" sections have been kept brief. The primary strengths of this study are its comprehensive search, large sample size, and the calculation of clinically relevant risk metrics. The main limitations—the reliance on observational data and the binary treatment of the IFIS outcome—have been integrated and thoroughly explored throughout this discussion. Future research should prioritize a large, prospective registry study that carefully grades IFIS severity to confirm these findings and further delineate the risk profiles of all available agents.

5. Conclusion

This systematic review and meta-analysis delivers an unequivocal and actionable conclusion. The use of tamsulosin is associated with a more than four-fold greater risk of encountering intraoperative floppy iris syndrome during cataract surgery when compared to other α1-adrenergic antagonists. This powerful statistical association, translated into a clinically sobering Number Needed to Harm of 7, is the direct clinical manifestation of tamsulosin's unique, high-affinity interaction with the α1A-adrenoceptors of the iris dilator muscle. The results of this study must compel a fundamental re-evaluation of prescribing habits for benign prostatic hyperplasia, promoting a more holistic, risk-stratified approach that considers a patient’s complete health profile. Enhanced interdisciplinary communication and a commitment to shared decision-making are essential to translate

this evidence into safer clinical practice and to protect our aging patients from preventable, iatrogenic harm.

6. References

1. Safir M, Greenbaum E, Vardi MA, Friehman A, Pras E, Assia EI, et al. Iris color as a predictive factor for intraoperative floppy iris syndrome. Arbeitsphysiologie. 2023; 261(12): 3503–10.
2. Budihardja BM, Cempakadewi AA. Prophylaxis pharmacological management for patients with intraoperative floppy Iris syndrome risk due to ?1-adrenergic receptor antagonists use. Ophthalmologica Indonesiana. 2023; 48(2): 105–16.
3. Paschon K, Szegedi S, Weingessel B, Fondi K, Huf W, Vécsei-Marlovits PV. Prospective analysis of anatomic features predisposing patients to intraoperative floppy iris syndrome. Arbeitsphysiologie. 2024; 262(1): 103–11.
4. Ferrette T, Lassale S, Raffort-Lareyre J, Chardavoine M, Payan J, Baillif S, et al. Is floppy eyelid syndrome predictive of intraoperative floppy iris syndrome? A prospective and translational study. J Fr Ophtalmol. 2024; 47(9): 104293.
5. Bumbuluț B, Stănilă DM. Floppy iris. How is floppy iris syndrome managed? What do urologists and ophthalmologists say? Rom J Ophthalmol. 2024; 68(3): 301–5.
6. Eremenko R, Neimark E, Shalev D, Harel G, Kleinmann G. Prevalence and prediction of intraoperative floppy iris syndrome in patients with pseudoexfoliation syndrome. Can J Ophthalmol. 2025; 60(2): 79–84.
7. Parkash RO, Om Parkash T, Sharma T, Vajpayee RB, Mahajan S. Use of narrow calibrated side-port technique to prevent occurrence of intraoperative floppy iris syndrome during phacoemulsification surgery. Clin Ophthalmol. 2025; 19: 1787–92.
8. Shen Y, Frauches R, Zhao J, Lo C-H, Ning K, Chen S, et al. Pathophysiology of intraoperative floppy iris syndrome: an unsettled debate. Surv Ophthalmol. 2025.
9. Lakhani M, Kwan ATH, Mihalache A, Popovic MM, Hurley B, Muni RH. Drugs associated with floppy Iris syndrome: a real-world population-based study. Am J Ophthalmol. 2025; 275: 36–46.
10. Maluskova M, Maresova K, Schreiberova Z, Paskova B, Karhanova M. Comparing the efficiency of two prophylactic approaches in patients at risk of developing intraoperative floppy iris syndrome. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2025.
11. Nuzzi R, Arnoffi P, Tridico F. Best prophylactic strategy in groups at risk of intraoperative floppy iris syndrome development: Comparison between atropine instillation and adrenaline intracameral injection. Open Ophthalmol J. 2018; 12(1): 34–40.
12. Fenicia V, Abdolrahimzadeh S, Scuderi G, Fabrizio L, Maurizi Enrici M, Cruciani F, et al. Intracameral epinephrine without the addition of intracameral lidocaine in the management of tamsulosin associated intraoperative floppy iris syndrome. Clin Ter. 2015; 166(4): 158–61.
13. Tobaiqy M, Aalam W, Banji D, Al Haleem ENA. Intraoperative floppy Iris syndrome induced by tamsulosin: The risk and preventive strategies. Middle East Afr J Ophthalmol. 2021; 28(1): 51–6.
14. Bigdon E, Casagrande M, Spitzer MS, Hassenstein A. Intraoperative floppy iris syndrom (IFIS) associated with tamsulosin. Aktuelle Urol. 2022; 53(3): 246–53.
15. Gökçe SE, Gökçe Mİ. Evaluation of patients using tamsulosin or doxazosin for lower urinary tract symptoms for development of intraoperative floppy Iris syndrome. Üroonkoloji bül. 2015; 14(4): 251–3.

16. Chang DF, Campbell JR, Colin J, Schweitzer C, Study Surgeon Group. Prospective masked comparison of intraoperative floppy iris syndrome severity with tamsulosin versus alfuzosin. Ophthalmology. 2014; 121(4): 829–34.
17. Urkmez A. Is sulfonamide group of tamsulosin main factor in the pathophysiology of floppy iris syndrome? Haydarpasa Numune Train Res Hosp Med J. 2018.
18. Tufan HA, Gencer B, Kara S, Comez AT, Kurt HA, Alan C. Alterations in iris structure and pupil size related to alpha-1 adrenergic receptor antagonists use: implications for floppy iris syndrome. J Ocul Pharmacol Ther. 2013; 29(4): 410–3.
19. Srivastava AK, Gupta A. Intraoperative Floppy Iris Syndrome in patients on alpha 1 blocker tamsulosin: incidence and predictability. Int J Res Med Sci. 2020; 8(6): 2218. Wolf BJ, Yean C, Misra P, Lee JK, Schultz J, Shrivastava A. Pupillary dynamics of patients on tamsulosin exhibiting intraoperative floppy Iris syndrome during cataract surgery. J Clin Exp Ophthalmol. 2018; 09(03).