Drug Interaction Between Sartans and Pyridostigmine With a Focus on Hypoglycaemia: A Critical Review

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***Abstract*- Sartans and pyridostigmine are frequently prescribed drugs, each with well-established therapeutic roles. Angiotensin II receptor blockers are widely used to manage hypertension, protect the cardiovascular system, and slow the progression of kidney disease, while pyridostigmine remains essential for conditions such as myasthenia gravis and autonomic dysfunction. Emerging evidence suggests that both classes of drugs can independently influence glucose metabolism. This review critically examines the global literature—including hospital case reports, pharmacovigilance signals, experimental studies, and mechanistic data—to evaluate their combined potential to precipitate . Although no large clinical series directly document such events, mechanistic plausibility and scattered clinical reports highlight the need for caution, particularly in high-risk patients. We also identify gaps in current knowledge and propose directions for future research.**

***Index terms*- Sartans, Angiotensin Receptor blockers, Pyridostigmine, Drug Interactions, , Diabetes Mellitus, Insulin Resistance, Myasthenia Gravis.**

I.INTRODUCTION

Drug–drug interactions that influence glucose homeostasis are clinically significant, especially in individuals with diabetes or those at risk of hypoglycaemia. Sartans, through renin–angiotensin system (RAS) blockade, demonstrate benefits beyond blood pressure control, including improvements in insulin sensitivity and endothelial function. Pyridostigmine, by inhibiting acetylcholinesterase, enhances cholinergic signalling, which can stimulate insulin release and improve metabolic control. This review synthesises case reports, observational studies, experimental work, and pharmacovigilance data to evaluate whether their co-prescription may increase the risk of hypoglycaemia.

II.SARTANS IN HYPERTENSION AND DIABETES: DUAL THERAPEUTIC ROLES

Sartans are a class of antihypertensive agents that selectively antagonize the angiotensin II type 1 (AT1) receptor. They produce vasodilation, reduce aldosterone secretion, and lower blood pressure while preserving AT2 receptor signaling; this pharmacologic profile underpins their broad use in hypertension, heart failure, and chronic kidney disease (CKD), including diabetic nephropathy.

ARBs competitively block angiotensin II binding at AT1 receptors, resulting in reduced vasoconstriction, sympathetic activation, sodium retention, and aldosterone-mediated potassium loss. By sparing AT2 receptors, ARBs may allow AT2-mediated vasodilatory and anti-proliferative effects. Differences among agents (affinity, half-life, tissue distribution, inverse agonism) explain some clinically observed heterogeneity.

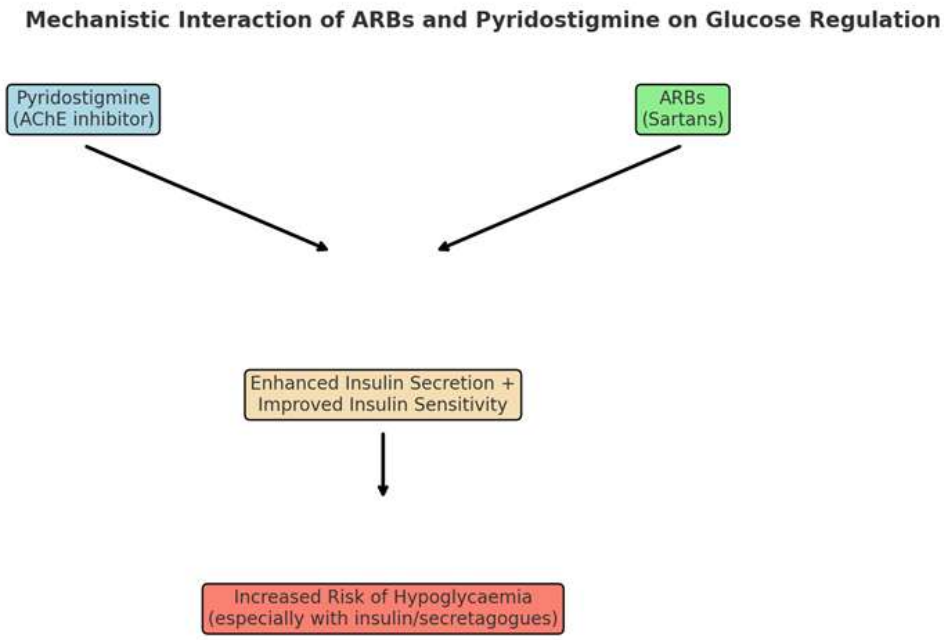
Several ARBs show beneficial metabolic effects beyond blood-pressure lowering. Telmisartan has been identified as a partial PPAR-γ agonist in preclinical and clinical studies, which may improve insulin sensitivity, glucose homeostasis, and some components of the metabolic syndrome. Meta-analyses and randomized trials suggest ARBs (and ACE inhibitors) are associated with a modest reduction in incidence of new-onset diabetes compared with placebo or other antihypertensives. These metabolic benefits vary between agents and may relate to PPAR activity, tissue penetration, and off-target effects.

III.PYRIDOSTIGMINE AT THE INTERFACE OF NEUROMUSCULAR AND GLYCEMIC CONTROL

Pyridostigmine is a reversible acetylcholinesterase inhibitor commonly used as first-line symptomatic therapy for myasthenia gravis (MG). By inhibiting cholinesterase it increases synaptic acetylcholine availability at the neuromuscular junction, improving neuromuscular transmission and muscle strength in patients with MG. It has also been studied for autonomic

disorders (orthostatic hypotension, postural orthostatic tachycardia syndrome — POTS) and investigated for metabolic effects on glucose and hormone responses**.**

Pyridostigmine is a quaternary ammonium carbamate that reversibly inhibits acetylcholinesterase, increasing acetylcholine concentrations at nicotinic and muscarinic receptors. Because it is charged, oral pyridostigmine has limited central nervous system penetration and primarily exerts peripheral cholinergic effects (skeletal muscle and autonomic synapses). Onset is relatively rapid with intermediate duration, which allows dose titration to balance efficacy and muscarinic side effects.



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IV.POTENTIAL INTERACTIONS BETWEEN ARBS AND PYRIDOSTIGMINE IN

Putting the above together, what might happen if a patient is taking **both** pyridostigmine and an ARB, especially when is present (either spontaneous or induced, e.g. by insulin or other glucose-lowering drugs)? There aren't many (if any) direct studies of this combination, so much is theoretical / extrapolated. Here's what plausible interactions might be, both beneficial and risk raising.

Preclinical and human studies suggest pyridostigmine influences metabolic and endocrine responses via enhanced cholinergic (vagal) activity. Small clinical and animal studies report increased insulin response to glucose loads in certain populations (e.g., obese subjects) and effects on glucose transport proteins, mitochondrial function, and oxidative stress in experimental models. These findings indicate potential for modulating post-prandial glycemia and peripheral glucose handling, but evidence is varied and largely exploratory. Recent animal and small human studies (and ongoing trials) have re-examined these metabolic effects.

Tabe-1: Impact of ARBs on Pyridostigmine's Hypoglycemic Effect:

Mechanism	How ARBs could modulate pyridostigmine's risk	Risk / Benefit	Notes / Conditions
Modulation of insulin secretion or sensitivity	ARBs may improve insulin sensitivity, reduce oxidative stress in pancreatic islets, reduce angiotensin II mediated insulin resistance. This may help buffer the hypoglycemic effect induced or facilitated by pyridostigmine (by increasing insulin).	**Protective**: ARB could attenuate exaggerated insulin-response induced by cholinergic overactivity.	More likely in persons with insulin resistance; less effect if insulin secretion is already very high with pyridostigmine.
Sympathetic/Parasympathetic balance	Pyridostigmine enhances parasympathetic (cholinergic) tone, which could lower blood glucose via increased insulin / decreased glucagon etc. ARBs might modulate sympathetic influence but likely less directly on parasympathetic.	Mixed: ARBs might blunt angiotensin II's inhibitory effects on insulin actions, or through vasodilation improve tissue glucose uptake. But could also worsen if they enhance insulin action too much.	In patients with autonomic dysfunction, or with impaired counter-regulation, risk is higher.
Renal function / glucose clearance	ARBs are kidney-protective; could affect renal glucose handling (e.g. gluconeogenesis, glucose reabsorption), possibly modifying recovery.	Probably beneficial: better renal perfusion, preserved kidney function supports more stable glucose homeostasis. But if kidney excretion / gluconeogenesis is altered, possibly slower recovery.	More relevant in chronic kidney disease; if ARB dose high, careful with renal compromise.

V.EVIDENCE FROM CLINICAL REPORTS AND HOSPITAL STUDIES

Clinical evidence remains limited and heterogeneous:

1. **India (2024, Kalinga Institute of Medical Sciences):** Telmisartan was temporally linked to recurrent hypoglycaemia, though later attributed to autoimmune insulin syndrome.
2. **French Pharmacovigilance Database (2008):** Signalled possible association between ARB use and hypoglycaemia, though reporting bias is likely.
3. **USA (ACE inhibitor reports):**Severe recurrent hypoglycaemia described in non-diabetic patients, suggesting class effects relevant to ARBs.

Experimental observations: Losartan blunted hormonal responses to insulin-induced hypoglycaemia.
Hospital cohort studies: Some analyses show reduced in-hospital hypoglycaemia in ARB users, highlighting variability.
Animal data: Losartan potentiated the glucose-lowering effects of glimepiride.
Pyridostigmine evidence: Italian and Chinese studies demonstrated enhanced insulin responses and improved glucose metabolism in both obese humans and diabetic mice, findings supported by recent rat studies.

Table 2: Selected Case Reports and Observational Evidence

Year / Country	Setting	Findings	Implications
2024, India	Hospital (Cureus report)	Telmisartan linked to recurrent , later autoimmune insulin syndrome	Highlights potential unmasking of latent risk
2008, France	Pharmacovigilance database	Signal of ARBs associated with reports	Suggests class-level plausibility
2001, USA	Clinical pharmacology	Losartan reduced hormonal responses to insulin-induced	Supports impaired counter-regulation

VI.HETEROGENEITY ACROSS ARBS

There are several ARBs (losartan, valsartan, candesartan, telmisartan, irbesartan, olmesartan, etc.). Differences between them (lipophilicity, half-life, metabolism, PPAR-γ partial activation in some) might lead to different magnitudes of effect on glucose/ risk:

- **Telmisartan** is known for more PPAR-γ activity and some favorable metabolic effects. In a study comparing Azilsartan and Telmisartan, Telmisartan had a somewhat greater effect on HbA1c-reduction in T2DM + hypertension patient[9]
- Others may have less of these pleiotropic metabolic effects.

Thus, if there is a situation of potential risk (due to pyridostigmine + insulin or sulfonylureas, etc.), using an ARB with better metabolic profile (e.g. telmisartan) may be somewhat safer / more protective — though again, data on the specific interaction is lacking.

VII.IDENTIFIED RESEARCH GAPS

1.No direct hospital-based case series documenting pyridostigmine–ARB combination-induced hypoglycaemia.

2.There are inconsistencies between pharmacovigilance reports, which suggest a signal for interaction, and hospital database studies, which often fail to confirm the same risk.

3.So far, no controlled human studies using oral glucose tolerance tests (OGTT) or continuous glucose monitoring (CGM) have been carried out to directly explore this interaction.

4.It is still unclear whether all ARBs behave the same way, since differences

5. Under-reporting of co-prescription events in pharmacovigilance systems.

6. Lack of real-world studies quantifying counter-regulatory hormone responses under RAAS blockade.

7.Many studies of ARBs and risk are in diabetic populations, under usual therapies; these do not typically include cholinesterase inhibitors like pyridostigmine.

8.Mechanisms of cholinesterase inhibitor–induced changes in glucose metabolism are not fully delineated; in particular, how they affect counterregulatory hormone release (glucagon, epinephrine) during is less well studied.

9.Interindividual variability (e.g. kidney function, autonomic function, concurrent medications) likely matters a lot, but data is sparse.

VIII.PRACTICAL IMPLICATIONS

Based on what is known, here are recommendations / cautions if someone is or will be using pyridostigmine and an ARB and has risk of :

1. **Monitor blood glucose more closely** when starting pyridostigmine in a patient already on hypoglycaemic agents + ARB, or when starting ARB in someone on pyridostigmine + insulin/sulfonylurea.
2. Be alert for signs of **exaggerated** (e.g. tremor, sweating, confusion) particularly if the patient has other risk factors (kidney disease, autonomic neuropathy, poor nutrition, hepatic impairment).
3. Adjust doses of insulin / sulfonylureas etc. as needed when starting or increasing pyridostigmine.

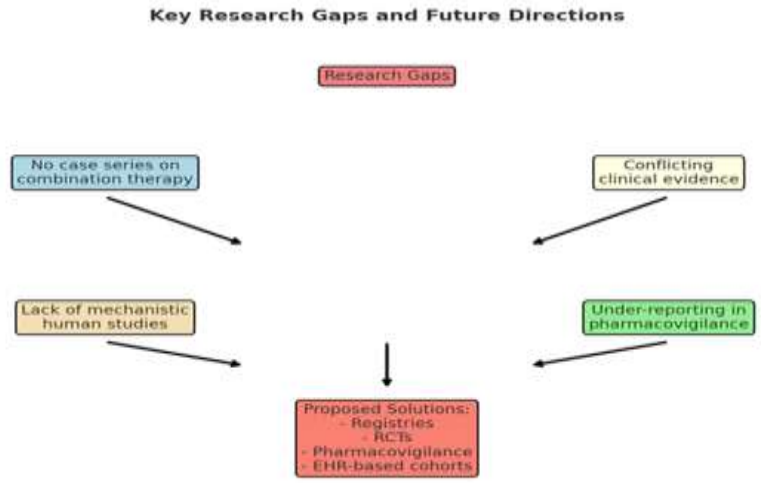
4. Consider choice of ARB: those with more metabolic benefits (e.g. telmisartan) might offer some buffering, but this is not proven.
5. Consider timing of medications, meals, and pyridostigmine dosing — since enhanced parasympathetic activity (from pyridostigmine) could increase insulin response especially if food intake is delayed or inconsistent.
6. Watch renal function; if ARB causes changes (e.g. impact on renal perfusion / GFR), recovery from may be altered.
7. Evaluate overall autonomic function: in patients with impaired counterregulation (e.g. diabetic autonomic neuropathy), any agent that increases insulin release or suppresses glucagon / epinephrine could be risky in .

IX.PROPOSED FUTURE RESEARCH DIRECTIONS

- Establish multicentre registries to capture real-world cases of hypoglycaemia during combined therapy.
- Conduct propensity-matched cohort analyses using EHR data.
- Perform randomised crossover mechanistic studies comparing pyridostigmine, ARBs, and their combination.
- Undertake drug-specific evaluations, especially for telmisartan versus other ARBs.
- Strengthen pharmacovigilance reporting for co-prescription scenarios.

Table-3:Proposed Solutions to avoid research gaps

Gap	Proposed Solution
No case series on pyridostigmine + ARB	Multicenter prospective registry
Conflicting evidence from different data sources	Large EHR-based cohort with propensity matching
No mechanistic human studies	Randomized crossover OGTT/CGM studies



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X.CONCLUSION

Likely net effect: ARBs are more likely to *reduce* risk (or at least make glycemic control more stable) in many settings, in part by improving insulin sensitivity, protecting pancreatic β-cells, and modulating renin-angiotensin system's deleterious effects. **Pyridostigmine** may increase risk of under certain conditions (especially with hypoglycemic drugs, or in patients with certain vulnerabilities). When used together, there is no strong evidence of a harmful drug-drug interaction, but there is a plausible risk of additive or synergistic effects leading to in susceptible individuals. clinicians should be cautious, adjust doses of hypoglycemic therapy if needed, and monitor.

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