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The impact of progestogens on RAAS – a systematic review

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Abstract

Background Progestogens, synthetic analogues of progesterone, are widely used in clinical practice for contraception, hormone replacement therapy, and the management of gynecological disorders. Understanding the specific impacts of different progestogens on the renin-angiotensin-aldosterone system (RAAS) is crucial due to their potential effects on cardiovascular and renal outcomes.

Objective This systematic review aims to synthesize existing research on the effects of various progestogens on the RAAS and associated clinical outcomes.

Methods We conducted a comprehensive search of databases up to the search date, including randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and qualitative studies. The NIH Study Quality Assessment Tool for Controlled Intervention Studies was used to evaluate the quality of the included studies. Data extraction and quality assessment were performed independently by two reviewers, with discrepancies resolved through discussion.

Results Forty-two studies on drospirenone (DRSP) were the most extensively investigated, showing either decreased or unchanged blood pressure (BP), mostly unchanged serum sodium, and an increased risk of hyperkalemia only in patients with mild renal impairment. Sixteen studies on norethindrone (NET/NETA) presented conflicting results on BP and a higher risk of hyperkalemia. Other progestogens, such as levonorgestrel (LNG) and medroxyprogesterone acetate (MPA), showed varied effects on RAAS parameters. Notably, changes in plasma renin activity (PRA), serum aldosterone, and angiotensin II levels were inconsistent across different progestogens and study designs.

Conclusion The effects of progestogens on the RAAS are complex and varied, influenced by the type of progestogen, dosage, and combination with estrogen. While some progestogens like DRSP may offer benefits in BP management with minimal electrolyte disturbances, others like NET/NETA might require more careful monitoring due to their associated risks. These findings highlight the importance of personalized medicine approaches in the use of progestogens, tailored to individual patient characteristics and specific hormonal profiles. Further research with standardized methodologies is needed to clarify these effects and guide clinical practice.

Trial registration This review was prospectively registered with PROSPERO.

Keywords Progestogens, Renin-angiotensin-aldosterone system, RAAS, Blood pressure, Aldosterone, Sodium, Potassium, Plasma renin activity, Angiotensin II, Systematic review

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Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in regulating blood pressure, fluid balance, and electrolyte homeostasis [1]. Its intricate hormonal cascade, initiated by renin release from the kidneys, leads to the formation of angiotensin II, a potent vasoconstrictor, and the secretion of aldosterone, which promotes sodium and water retention [1]. Given its centrality to cardiovascular function, understanding the interactions between various pharmacological agents and the RAAS is of paramount importance.

Progestogens, defined as the naturally occurring hormone progesterone as well as its synthetic analogues progestins, are widely used in clinical practice for various indications, including contraception, hormone replacement therapy, and the management of gynecological disorders [2, 3]. Despite their widespread use, the specific effects of different progestogens on the RAAS remain incompletely understood. This knowledge gap is particularly concerning given the known variability in the physiological effects of progestogens [4].

The rationale for undertaking this systematic review on the effect of different progestogens on the RAAS is rooted in several key considerations. Firstly, progestogens are recognized to exert varying influences on diverse physiological processes. A detailed understanding of the specific impacts of different progestogens on the RAAS pathway is integral to fully grasp their potential implications. However, despite the known variability in progestogen effects, there is a noticeable absence of a consolidated summary or synthesis of current knowledge concerning the influence of different progestogens on the RAAS. This gap limits healthcare practitioners' ability to make informed decisions when choosing progestogens, particularly with respect to their potential impacts on the RAAS.

Additionally, it is important to acknowledge that not all studies investigating progestogens include explicit information concerning the RAAS. Hence, to assess the available evidence on the specific influence of progestogens on the RAAS, a systematic review that can identify and collate relevant studies providing data on this topic is essential. The primary goal of this systematic review is to furnish valuable insights that will aid clinician decision-making. By conducting a thorough examination of the available evidence regarding the influence of different progestogens, this review aims to address the current knowledge gap and facilitate evidence-based clinical practice.

To achieve this goal, the review will systematically analyze data from studies examining various progestogens, including their modes of administration, dosages, and the resultant effects on key RAAS parameters such as blood pressure, plasma renin activity (PRA), serum aldosterone, and angiotensin II levels. The review will also consider the influence of progestogen-therapy in both monotherapy and combination therapy contexts, as well as the comparative effects observed with different control treatments.

Through this comprehensive synthesis, the review aims to provide a clear and detailed understanding of the interactions between progestogens and the RAAS, ultimately contributing to improved clinical outcomes and informed therapeutic decisions in the management of patients requiring progestogen therapy.

Materials and methods

Information sources and search strategy

To identify all potentially relevant documents on the topic, complex literature searches were designed and executed for the following information sources: (Fig. 1).

- MEDLINE (Ovid) (Ovid MEDLINE(R) ALL (1946–28/07/2023)).
- Embase (Ovid) (1974–28/07/2023).
- Cochrane Library (Wiley) (1996 -- Present).
- CINAHL (EBSCO) (CINAHL with Full Text (1981 -- Present).
- Web of Science Core Collection (Clarivate) (1900 -- Present).
- ClinicalTrials.gov (NLM).
- ICTRP (WHO)

An initial search strategy was developed in MEDLINE by a medical information specialist and tested against a list of core references. After refinement and consultation with the researchers, complex search strategies were set up by the information specialist for each information source based on database-specific index terms and free text terms. Synonyms, acronyms and similar terms were included in the free text search.

The following search concepts were applied: (1) "Progestogens", (2) "Renin-Angiotensin-Aldosterone-System". Studies concerning exclusively animals were excluded from the searches in MEDLINE, Embase and CINAHL by using double-negative search strategies based on the "Humans only" filters by Ovid and the CINAHL Plus RCT filter by Cochrane (https://training.cochrane.org/handbook/version-6/chapter-4-tech-suppl).

The searches in the Web of Science Core Collection and the trial registers were performed using free text search terms and acronyms only and without applying any filter strategies.

No database-provided limits have been applied in any of the sources considering study types, languages,

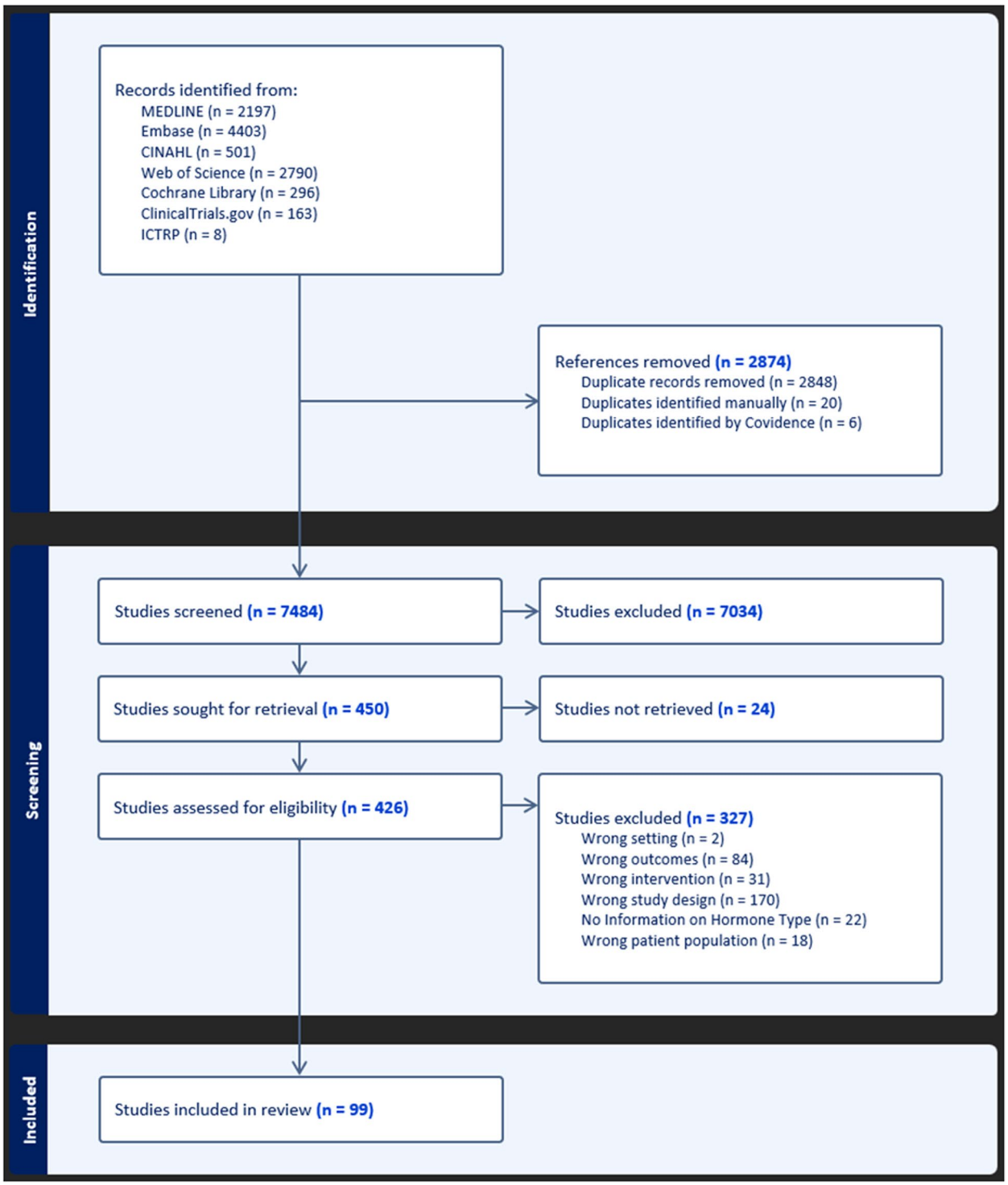

Fig. 1 PRISMA flow diagram

publication years or any other formal criteria. The final search was run on 31 July 2023. The full search strategies are available in the appendix and on searchRxiv.org.

Registration and protocol

This systematic review was registered in the PROSPERO database prior to the literature search. The

registration ID is CRD42023435202. No amendments were made to the protocol after registration.

Eligibility criteria

Study characteristics

- Participants: The study must involve women receiving progestogens.
- Interventions: Studies must investigate the administration of progestogens.
- Comparators: Studies may include a comparison group of women receiving no treatment or other hormonal treatments. Studies without comparators will also be included if they provide relevant data on outcomes.
- Outcomes: The primary outcomes must include changes in the renin-angiotensin-aldosterone system (RAAS) and associated clinical outcomes. Studies where changes in the RAAS are secondary outcomes will also be considered.
- Study Design: The review will include any study design that provides valid and relevant data to answer the review question. This includes randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, and qualitative studies.
- Setting: Studies conducted in any setting, such as hospitals, clinics, community settings, or other environments, will be included.
- Time Frame: Studies published at any time up to the search date will be considered.

Report characteristics

- Years Considered: There will be no restriction on the publication year. Studies published at any time up until the date of the search will be considered.
- Language: Only studies published in English or German will be included in the review.
- Publication Status: The review will include both published and unpublished studies (e.g., conference abstracts, theses) to minimize publication bias. However, unpublished studies must have sufficient data and methodological details available for quality assessment and data extraction.

Study selection process

All identified records were imported into EndNote, exported as RIS and deduplicated using the online tool Deduklick [5]. After deduplication, the records were imported into Covidence, an online systematic review management tool. Covidence was used for several key steps in the review process:

- Abstract Screening: Titles and abstracts of the imported records were screened independently by two reviewers to identify studies that potentially met the inclusion criteria. Discrepancies between reviewers were resolved through discussion or by a third reviewer.
- Full-Text Screening: Studies that passed the abstract screening were then subjected to a full-text review. The same independent screening process was followed, with two reviewers evaluating the full texts to confirm eligibility based on the predefined criteria. Any disagreements were again resolved through discussion or consultation with a third reviewer.
- Data Extraction: Covidence facilitated the standardized extraction of relevant data from each included study. Two reviewers independently extracted data on study characteristics, participant demographics, intervention details, comparator groups (if applicable), outcomes related to the RAAS, and other relevant clinical outcomes.
- Quality Assessment: The quality of each included study was assessed independently by two reviewers using appropriate tools and checklists suitable for the study designs (e.g., Cochrane risk of bias tool for RCTs, Newcastle-Ottawa Scale for cohort and case-control studies). Discrepancies in quality ratings were resolved through discussion or by a third reviewer.

This systematic approach ensured a thorough and unbiased selection of studies, allowing for a comprehensive analysis of the effects of progestogens on the renin-angiotensin-aldosterone system.

Synthesis methods

- Processes for Eligibility:
  Study eligibility was determined based on predefined criteria, including population, intervention, outcomes, and study design. Decisions were guided by inclusion tables and narrative synthesis protocols.
- Preparation for Presentation:
  Data were standardized, including the consistent use of units (e.g., serum aldosterone in ng/dL or pmol/L) and handling of missing data (e.g., studies without key RAAS outcomes excluded).

- Tabulation and Visualization:
  Study characteristics and key findings were summarized in tables, highlighting intervention details, participant demographics, and RAAS outcomes. Graphical summaries were created to compare changes in RAAS markers across studies.
- Results Synthesis and Rationale:
  Given the heterogeneity in study designs and outcomes, results were synthesized narratively rather than statistically. This approach was chosen due to the variability in progestogen types, dosages, and RAAS outcome measures.
- Exploration of Heterogeneity:
  Heterogeneity was qualitatively assessed by comparing RAAS responses across progestogen types and combinations with estrogen. Subgroup comparisons (e.g., premenopausal vs. postmenopausal women) were explored where data allowed.
- Sensitivity Analysis:
  Sensitivity analyses were not applicable due to the absence of pooled data or meta-analyses.

Data outcomes

The primary data outcomes of interest in this review are the changes in the renin-angiotensin-aldosterone system (RAAS) and associated clinical outcomes resulting from the administration of progestogens. Specifically, the following outcomes were assessed:

- Blood Pressure (BP): Changes in systolic and diastolic BP were measured to evaluate the cardiovascular impact of progestogens.
- Plasma Renin Activity (PRA): Levels of PRA were assessed to understand the activation of the RAAS.
- Serum Renin Concentration: The concentration of renin in the serum was measured to provide insights into the regulatory mechanisms of the RAAS.
- Serum Aldosterone: Levels of serum aldosterone were evaluated to determine the effects on aldosterone secretion and sodium retention.
- Aldosterone Excretion: Urinary excretion of aldosterone was measured to complement the serum aldosterone findings and provide a comprehensive view of aldosterone activity.
- Serum and Urine Sodium: Changes in serum and urine sodium levels were assessed to evaluate the effects on sodium balance and fluid regulation.
- Serum and Urine Potassium: Changes in serum and urine potassium levels were measured to assess the impact on potassium homeostasis.
- Angiotensin II: Levels of angiotensin II were measured to understand the downstream effects of RAAS activation.
- Angiotensinogen: Changes in angiotensinogen levels were assessed to evaluate the precursor availability for angiotensin II production.
- Angiotensin-Converting Enzyme (ACE) Activity: ACE activity was measured to understand the enzymatic regulation of angiotensin I to angiotensin II conversion.

Secondary outcomes included:

- Risk of Hyperkalemia: The incidence of hyperkalemia was assessed, particularly in studies comparing different progestogens or combination therapies.
- Clinical Symptoms and Adverse Events: Any reported clinical symptoms or adverse events related to progestogen therapy were documented and analyzed.
- Comparative Efficacy: The effectiveness of different progestogens in combination with estrogen or other treatments was compared, where applicable.

Data extraction was performed independently by two reviewers using Covidence, ensuring accuracy and consistency. Discrepancies were resolved through discussion or by involving a third reviewer. The extracted data were then synthesized to provide a comprehensive overview of the effects of progestogens on the RAAS and related clinical outcomes.

Quality assessment

The quality of the included studies was assessed using the NIH Study Quality Assessment Tool for Controlled Intervention Studies [6]. This tool provides a comprehensive framework to evaluate the internal validity of studies by addressing various aspects of study design, conduct, and reporting.

Each study was independently evaluated by two reviewers using these questions, ensuring a thorough and unbiased assessment of methodological quality. Discrepancies between reviewers were resolved through discussion or by consulting a third reviewer if necessary. The results of the quality assessments were used to inform the interpretation of the study findings and to assess the overall strength of the evidence.

Reporting bias assessment

To address the potential for reporting bias due to missing results, the following strategies were implemented:

- Grey Literature Searches: Unpublished studies, including conference abstracts and theses, were included to minimize publication bias.

- Comprehensive Search Scope: Searches were not restricted by publication status, date, or language (other than English and German). This approach aimed to include a wide range of studies and reduce selective reporting risks.
- Outcome Reporting Bias: Studies were reviewed for selective reporting by comparing their reported outcomes with stated objectives in the methodology sections. Discrepancies between planned and reported outcomes were documented during quality assessment.

Since a meta-analysis was not conducted, formal statistical heterogeneity metrics such as I^2 or p-values could not be calculated. Efforts to mitigate bias included thorough screening of all studies and an open approach to publication type and status. Heterogeneity was qualitatively assessed by comparing study characteristics, such as population demographics, progestogen types, dosages, and outcome measures. Variability in findings across studies was explored narratively, highlighting patterns and potential sources of heterogeneity to provide context for the synthesized results.

Results

The distribution of studies investigating the effects of various progestogens on the renin-angiotensin-aldosterone system (RAAS) is illustrated in Fig. 2. This graph shows the number of studies conducted for each progestogen. It highlights the breadth of research across different progestogens, with drospirenone (DRSP) being the most extensively studied and several other progestogens, such as promegestone and nomegestrol, having significantly fewer studies. (Table 1)

Overview

Progesterone

Eleven studies have investigated the effects of progesterone on the RAAS from 1961 to 2011 [7–17]. This body of research includes two RCTs and nine prospective trials, employing various administration methods such as oral, vaginal, intravenous, intramuscular, and subcutaneous. Monotherapy with progesterone was evaluated in six studies, while five studies examined progesterone in combination with estrogen. Daily dosages ranged from 75 to 400 mg. Controls varied from non-controlled to placebo-controlled, with two studies using NET as a control. Sample sizes ranged from 4 to 67 subjects, with study durations spanning from 3 days to 2 years.

The impact of progesterone on BP varied across studies; some reported no effect [7–9], while others indicated a reduction in BP during progesterone therapy [10–13]. Serum sodium levels showed no change in one study [13], while another reported a decrease [11].

Table 1 The effect of progestogens on parameters of the RAAS

		P4	DYD	MPA	CMA	CPA	PMG	NOM	NETA	LNG	NG	DNG	GSD	ENG	DSG	NGM	LYN	DRSP
BP		↓=		=↑↓	=	=↓	=	=	=↓	=↑	=	=	=↑		=		=	↓=
Sodium	Serum	=↓		=	↑	=				=		=						=↓
	Urine	↑=↓	=	=	=	=			=↓	=			↑					↑
Potassium	Serum	=		=	=	=			↑	=		=				↑		=
	Urine	=↑↓	=	=	=				=↓	=								=
Aldosterone	Serum	=↑	=	=↑		↓			↑	↓		=↑	↓=	=	=↑			↑
	Urine	↑		↓						↑	=							↑
Renin/Prorenin		↑		↓		↓			↓	↓			↓	=	↓			↑↓
Active Renin		=		=		=↓												
PRA		=↑	=	=↑↓	=	↓			↑	=↑	↑=	=	=↑	=	=↑		=	↑
Angiotensinogen				=↑		↑	=	↑	↑	↑=					↑			↑
Angiotensin I				=	=													
Angiotensin II		↑=↓		=	=					↓	↑	=↓					=	
ACE-Activity			↓	=↓					↓									

Legend

↓ reduced

= no change

↑ increased

If studies showed differing effects, all the effects are noted in the table

Abbreviations: BP Blood pressure, *PRA* Plasma renin activity, *ACE* Angiotensin-converting enzyme, *P4* Progesterone, *DYD* Dydrogesterone, *MPA* Medroxyprogesterone acetate, *CMA* Chlormadinone acetate, *CPA* Cyproterone acetate, *PMG* Promegestone, *NOM* Nomegestrol, *NETA* Norethisterone acetate, *LNG* Levonorgestrel, *NG* Norgestrel, *DNG* Dienogest, *GSD* Gestodene, *ENG* Etonogestrel, *DSG* Desogestrel, *NGM* Norgestimate, *LYN* Lynestrenol, *DRSP* Drospirenone

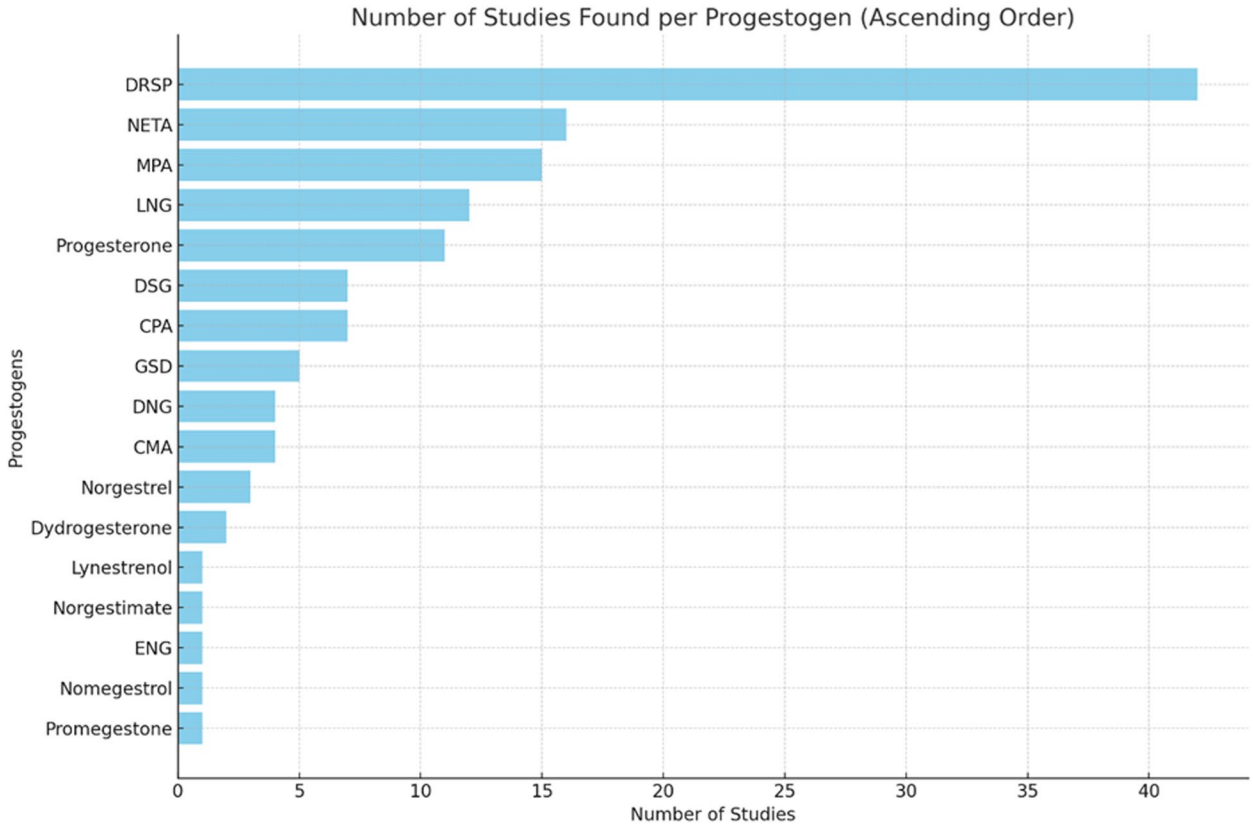

Fig. 2 Number of studies found per progestogen

Urinary sodium excretion was generally higher in many studies [8, 13–16], although some studies reported no change [14, 15], and one study noted lower sodium excretion [11].

Serum potassium levels remained largely unchanged [13], whereas urinary potassium excretion showed no change in most studies [11, 14–16], with one study reporting an increase [8] and another a decrease in excretion [13]. Serum aldosterone levels appeared unchanged across most studies [8–10, 13], except for one study that observed an increase [7]. Aldosterone excretion was increased in two studies [14, 15].

Serum renin levels were increased [10], while active renin remained unchanged [10]. PRA was mostly unchanged [8–10], although one study found an increase in PRA [7], but only in combination with estrogen, not in monotherapy. Angiotensin II levels increased in combination therapy but not in monotherapy [7], with one study showing a decrease in angiotensin II levels [13].

Progesterone derivatives

Dydrogesterone

Two RCTs about DYD and RAAS were found from 1990 to 2003, studying oral DYD [17, 18]. One in monotherapy and one in combination with E2. Dosages ranged from 10 to 20 mg/d. One was placebo-controlled and the other used both placebo and estrogen-monotherapy as controls. Sample sizes ranged from 22 to 62 subjects, with study durations from 28 days to 36 weeks.

Sodium and potassium excretion seemed unchanged [18]. No changes in PRA or serum aldosterone [18]. ACE activity was lower in combination therapy, even lower than estrogen monotherapy [17].

Medroxyprogesterone acetate

Fifteen studies have investigated the effects of MPA on RAAS, ranging from 1969 to 2023. This includes 7 RCTs and 8 prospective trials. Application methods include oral and intramuscular injections. Two studies examined MPA monotherapy while the majority include MPA in combination therapy. Daily dosages ranged from 1.5 mg to 10 mg, while the intramuscular injections included dosages of up to 1000 mg in one injection. Controls included placebo, estrogen monotherapy, no controls, and comparisons with CPA, DRSP, and NG. Sample sizes ranged from 4 to 69 subjects, with study durations from 3 weeks to 24 months. Additionally, a secondary analysis of the WHI study included 9332 patients over 9 years.

The studies report conflicting results on BP: some studies show no effect [19–22], some show a decrease [23–26], and one study shows an increase over placebo [27]. Serum and urinary sodium and potassium seem unchanged [22, 28, 29].

Serum aldosterone remains mostly unchanged [21–23, 25, 26], with one study showing an increase [28]. Urinary aldosterone was decreased in one study [30]. Renin concentration was decreased in one study [28], while active renin was unchanged [29]. PRA was unchanged in many studies [23, 25, 26, 30, 31], increased in some [28] and had a tendency to decrease in on study [32].

Angiotensinogen was unchanged [23] in one study and increased in another [32]. Angiotensin I/II showed no change in one studiy [25]. In one study, Angiotensin I/II and PRA rose only in hypertensive women, whereas in normotensive women, no significant difference was found [21]. A similar rise in PRA, Angiotensin I/II was seen only in oral application, with no change in transdermal application [24]. ACE activity was unchanged in some studies [25] and decreased in others [19–21].

Chlormadinone acetate

Four studies, spanning from 1979 to 2020, have investigated the effects of CMA on the RAAS [33–36]. These include one RCT and three prospective trials, two of which are controlled. All studies examined oral CMA exclusively in combination with estrogen, with no monotherapy investigated. Dosages varied from 2 to 10 mg/day. The trials, both controlled and non-controlled, used other combination therapies containing NET, DRSP and LNG as comparators. Sample sizes ranged from 16 to 102 subjects, with study durations spanning 3 to 24 months.

The collective findings from these studies indicate minimal activation of the RAAS. There were no significant changes in blood pressure [33, 35], PRA [34], or serum angiotensin levels [34]. Additionally, serum and urine potassium levels remained unchanged [33, 36]. A slight increase in serum sodium was observed [33], though levels remained within the normal range, and there was no change in urine sodium levels [36].

Cyproterone acetate

Seven studies, spanning from 1991 to 2012, have investigated the effects of CPA on the RAAS [32, 37–42]. These include 4 RCT's and 3 proscpective trials. Application method was always oral. 5 of them investigated CPA in combination with estrogen, two trials investigated CPA monotherapy. Dosages ranged from 1 to 2 mg/d up 50 or even 170 mg/m^2/d. Controls ranged from non-controlled to estrogen monotherapy to other progestins like MPA, DSG and DRSP. Sample sizes ranged form 6 to 171 subjects, while study durations ranged from 3 to 24 months.

The findings are the following: Blood pressure seems mostly unchanged [32, 37, 39–42]; however one study found a slight reduction in blood pressure. Sodium was studied in the serum [38] and in the urine [39] and was unchanged. Potassium was only studied in the serum and was too unchanged [38]. Serum aldosterone [38] and Renin showed a decrease in one study. Active Renin was unchanged in one study [39] and decreased in another [38]. PRA decreased [32, 38]. Angiotensinogen increased [32, 37].

Promegestone

Only one RCT from 1995 investigated the effect of Promegestone on the RAAS [43]. It was a 2-year, placebo-controlled, randomized trial with 23 participants. Participants received 500 mcg of Promegestone per day in a 21/7 cycle. The study demonstrated no change in BP or angiotensinogen levels.

Nomegestrol

Only one trial from 1995 investigated the effect of NOMAC on the RAAS [44]. It was a placebo-controlled, randomized, double-blinded trial with an estrogen and NOMAC therapy. Dosages ranged from 2.5 to 3.75 mg of NOMAC per day. The study included 57 subjects over 3 cycles. It showed an increase in angiotensinogen and no change in BP after the 3 cycles. (Table 2)

Progesterone derivatives - summary

In summary, blood pressure was predominantly unaffected across the studies. Both CPA and MPA demonstrated reductions in blood pressure in some studies, while one study on MPA reported an increase in blood pressure compared to placebo.

Serum sodium levels were examined in studies involving MPA (no change), CPA (no change), and CMA (increase). Urinary sodium levels remained unchanged across all studies.

Serum and urinary potassium levels were consistently unchanged in the studies reviewed.

Serum aldosterone levels were unchanged in studies on Dydrogesterone, decreased in CPA, and either unchanged or increased in MPA. Urinary aldosterone levels were only assessed in MPA, showing a decrease.

Serum renin levels were examined in studies on MPA and CPA, with both showing a decrease. Active renin levels were unchanged in MPA, while CPA studies reported conflicting results, showing both no change and a decrease.

Table 2 Progesterone Derivatives – Summary

		DYD	MPA	CMA	CPA	PMG	NOM
BP			=↑↓	=	=↓	=	=
Sodium	Serum		=	↑	=		
	Urine	=	=	=	=		
Potassium	Serum		=	=	=		
	Urine	=	=	=			
Aldosterone	Serum	=	=↑		↓		
	Urine		↓				
Renin/Prorenin			↓		↓		
Active Renin			=		=↓		
PRA		=	=↑↓	=	↓		
Angiotensinogen			=↑		↑	=	↑
Angiotensin I			=	=			
Angiotensin II			=	=			
ACE-Activity		↓	=↓				

Legend

↓ reduced

= no change

↑ increased

If studies showed differing effects, all the effects are noted in the table

Abbreviations: BP Blood pressure, *PRA* Plasma renin activity, *ACE* Angiotensin-converting enzyme, *P4* Progesterone, *DYD* Dydrogesterone, *MPA* Medroxyprogesterone acetate, *CMA* Chlormadinone acetate, *CPA* Cyproterone acetate, *PMG* Promegestone, *NOM* Nomegestrol

PRA was unchanged in studies on Dydrogesterone and CMA, decreased in CPA, and demonstrated conflicting results in MPA, showing an increase, a decrease, and no change.

Angiotensinogen levels were unchanged in studies on Promegestone and MPA, while increases were observed in studies on MPA, CPA, and Nomegestrol.

Angiotensin I and II levels were unchanged in studies on MPA and CMA.

ACE activity was decreased in studies on Dydrogesterone and MPA, although MPA also had studies reporting no effect on ACE activity.

Testosterone derivatives

Norethisterone acetate

Sixteen studies from 1961 to 2015 investigated the effect of NET/NETA on the RAAS [13, 34, 36, 45–57]. This includes 7 RCTs, 8 prospective trials, and one retrospective cohort study. All studies used oral application, with monotherapy in 2 studies and combination therapy with estrogen in the rest. Dosages ranged from 0.125 to 10 mg/day. Controls included non-controlled, placebo, and other progestins such as DRSP, LNG, EDA, progesterone, dydrogesterone, and CMA. Sample sizes ranged from 4 to 106 subjects, with the retrospective cohort study including 1.15 million patients. In the prospective trials, study durations ranged from 3 days to 24 months.

BP was mostly unchanged [46, 52, 54], with two studies reporting a decrease [53, 55]. Sodium was only studied in urine, with two studies finding no change [36, 45] and one study reporting a decrease [52]. The only trial studying serum potassium was the retrospective cohort study that reported a significantly higher risk of hyperkalemia with NET/NETA compared to LNG [57]. Urine potassium was investigated in three studies; two found no change [36, 52], while one reported a decrease [45]. Serum aldosterone increased in two studies [47, 51]. Renin levels appeared to decrease [46, 47, 50], while PRA increased [34, 46, 47, 50, 51]. Angiotensinogen levels increased [46, 47, 50, 54], and ACE activity decreased [48, 49].

Levonorgestrel

Twelve studies have investigated the effect of LNG on the RAAS, dating from 1979 to 2021 [37, 54, 56–65]. This includes 7 RCTs, 4 prospective trials, and 1 retrospective cohort study. Application methods were oral and via a vaginal ring. All studies examined LNG in combination with estrogen. Dosages ranged from 100 to 150 mcg/day orally to 217–293 mcg/day for the LNG vaginal ring. Controls varied from non-controlled to other combination therapies with DNG, DRSP, DSG, Norelgestromin, NET, CMA, and Norgestimate. Sample sizes ranged from 12 to 115 subjects, with the retrospective cohort study including 1.15

million participants. Study durations ranged from 1 to 24 months.

BP seemed mostly unchanged [54, 58, 59], although one study found an increase [60]. Urine and serum sodium and potassium levels were unchanged [36, 61]. One study found a lower risk of hyperkalemia compared to NET and Norgestimate [57]. Serum aldosterone decreased [62], while aldosterone excretion increased [60]. Serum renin decreased [56], while PRA was either unchanged [59] or increased [56]. Three studies found an increase [56, 61, 62] in angiotensinogen, another found no change [58]. Angiotensin II levels decreased [63].

Norgestrel/Norelgestromin

Three studies investigated the effects of NG and Norelgestromin on the RAAS [31, 64, 65], from 1977 to 2015. These were 3 prospective trials studying transdermal and oral applications. One study involved monotherapy, and two involved combination therapy with estrogen. Dosages ranged from 150 to 250 mcg/day. Controls included estrogen monotherapy, no hormonal treatment, and progestin treatment with MPA, lynestrenol, or LNG, either as monotherapy or in combination with estrogen. Sample sizes ranged from 8 to 35 participants, with study durations from 3 weeks to 4 months.

One study found that contraceptive patch users had significantly lower PRA, Ang II, and angiotensinogen [64] levels compared to oral estrogen + LNG treatment. In oral applications, there was an increase in PRA in one study [65] but no change in another [31]. Ang II levels increased [65]. BP, ADH, and aldosterone excretion were unchanged [31, 65].

Dienogest

Four studies investigated the effects of DNG on the RAAS from 1999 to 2010 [60, 67, 68]. These included 2 RCTs and 2 prospective trials. Only oral application was investigated, with one study examining monotherapy and three in combination with estrogen. Dosages ranged from 2 to 30 mg/day. Controls included non-controlled, placebo-controlled, and LNG in combination with estrogen. Sample sizes ranged from 21 to 2290 participants, with study durations ranging from 6 to 22 months.

BP remained unchanged [66]. Serum sodium and potassium levels were unchanged [67]. Serum aldosterone was unchanged in one study [66] but significantly increased in another [63]. PRA was unchanged [66]. Ang II levels were unchanged in one study [66] and decreased in another [63].

Gestodene

Five studies investigated the effects of GSD on the RAAS from 1988 to 2012 [69–73]. These included 1 RCT and 4 prospective trials. All studies examined oral combination treatment with estrogen. Dosages ranged from 60 to 75 mcg/day. Controls included non-controlled, no hormonal treatment, and treatment with other progestins like DSG and DRSP. Sample sizes ranged from 18 to 656 participants, with study durations ranging from 3 to 24 months.

BP was unchanged [68–70] in two studies and slightly increased in another [71], but no manifest hypertension was observed. Sodium levels were only studied in urine and were found to be increased [71]. Serum aldosterone was unchanged [72] in one study and decreased in others [69, 71]. Renin levels were shown to decrease [71, 72], while PRA was either unchanged [72] or increased [69].

Etonogestrel

One prospective trial from 2011 studied subdermal etonogestrel monotherapy [73]. Dosages ranged from 60 to 70 mcg/day. The trial was controlled with DRSP in combination with estrogen. Thirty-two participants were studied over 3 to 6 weeks. There were no significant changes in serum aldosterone, renin, and PRA.

Desogestrel

Six studies investigated the effects of DSG on the RAAS from 1979 to 2012 [41, 64, 72, 75–77]. These included 2 RCTs and 4 prospective trials. All studies investigated oral combination therapy with dosages ranging from 125 to 150 mcg/day. Controls included no hormonal treatment and other estrogen + progestin combinations with CPA, DRSP, GSD, and LNG. Sample sizes ranged from 7 to 86 subjects, with study durations ranging from 1 to 24 months.

BP was unchanged [40, 59, 74, 75]. Serum aldosterone was either unchanged [72] or increased [75]. Renin levels decreased [72], while PRA was either unchanged [59, 72] or increased [75, 76]. Angiotensinogen levels increased [75].

Norgestimate

One study investigated the effects of NGM on the RAAS [57]. It was a retrospective cohort study from 2011 studying oral combination therapy with estrogen. The dosage was not specified. The study examined the risk of hyperkalemia in 1.15 million participants compared to LNG combination therapy. It found an increased risk of hyperkalemia with NGM (HR 1.27) compared to LNG.

Lynestrenol

One study in 1977 investigated the effects of lynestrenol on the RAAS [65]. It was a comparative trial studying oral lynestrenol monotherapy, controlled with oral lynestrenol or norgestrel in combination with estrogen. The dosage was 0.5 mg/day, with a sample size of 32 participants and a study duration of 4 months.

BP was unchanged. There was no change in PRA and Ang II with lynestrenol monotherapy; however, in combination with estrogen, both PRA and Ang II increased. (Table 3)

Testosterone derivatives - summary

Blood pressure remained largely unchanged, with some studies reporting a decrease in NETA and an increase in LNG and GSD.

Serum sodium levels were stable in LNG and DNG, while urinary sodium levels were unchanged in LNG, either unchanged or decreased in NETA, and increased in GSD.

Serum potassium remained unchanged in LNG and DNG but showed an increase in NETA and NGM. Urinary potassium was unchanged in LNG, while NETA studies reported both no change and a decrease.

Serum aldosterone levels were unchanged in DNG, GSD, ENG, and DSG, but increases were observed in NETA, DNG, and DSG, while decreases were reported in LNG and GSD. Urinary aldosterone levels were unchanged in NG but increased in LNG.

Renin levels were predominantly decreased in studies on NETA, LNG, GSD, and DSG, with no change observed in ENG. Active renin was not studied in testosterone derivatives. PRA results varied, with no change reported for LNG, NG, DNG, GSD, ENG, DSG, and LYN, while increases were observed in NETA, LNG, NG, GSD, and DSG.

Angiotensinogen levels were mostly increased in studies on NETA and DSG, while LNG showed both an increase and no change. Angiotensin I was not studied in testosterone derivatives. Angiotensin II levels were stable in LYN and DNG, though some studies on DNG reported a decrease, which was also observed in LNG, while NG studies showed an increase.

ACE activity was only studied in NETA and showed a decrease.

Spironolactone derivatives

Drospirenone

The largest body of evidence is found on DRSP and its effect on the RAAS [35, 40–42, 53, 55, 57, 61, 62, 70, 72, 73, 75, 77–104].

There are 42 studies from 1991 to 2022, including 23 RCTs, 17 prospective trials, and 2 retrospective cohort studies. All studies involved oral application, with 5 examining monotherapy and the rest in combination

Table 3 Testosterone Derivatives – Summary

		NETA	LNG	NG	DNG	GSD	ENG	DSG	NGM	LYN
BP		=↓	=↑	=	=	=↑		=		=
Sodium	Serum		=		=					
	Urine	=↓	=			↑				
Potassium	Serum	↑	=		=				↑	
	Urine	=↓	=							
Aldosterone	Serum	↑	↓		=↑	↓=	=	=↑		
	Urine		↑	=						
Renin/Prorenin		↓	↓			↓	=	↓		
Active Renin										
PRA		↑	=↑	↑=	=	=↑	=	=↑		=
Angiotensinogen		↑	↑=					↑		
Angiotensin I										
Angiotensin II			↓	↑	=↓					=
ACE-Activity		↓								

Legend

↓ reduced

= no change

↑ increased

If studies showed differing effects, all the effects are noted in the table

Abbreviations: BP Blood pressure, *PRA* Plasma renin activity, *ACE* Angiotensin-converting enzyme, *NETA* Norethisterone acetate, *LNG* Levonorgestrel, *NG* Norgestrel, *DNG* Dienogest, *GSD* Gestodene, *ENG* Etonogestrel, *DSG* Desogestrel, *NGM* Norgestimate, *LYN* Lynestrenol

with estrogen. Dosages ranged from 0.5 to 4 mg/day. Controls included non-controlled, non-hormonal treatment, placebo-controlled, and other progestin treatments such as CPA, CMA, NETA, GSD, MPA, LNG, and ENG. Sample sizes ranged from 24 to 3417 participants in the prospective trials, with one retrospective cohort study including 1.15 million participants. Study durations ranged from 14 days to 24 months.

BP was mostly decreased [53, 55, 61, 70, 77, 79, 80, 84–86, 89, 90, 93, 95, 100, 101] or unchanged [35, 40–42, 75, 78, 81, 87, 88, 91, 92, 94, 96–98, 102, 103]. Serum sodium was mostly unchanged [61, 73, 81, 94, 97], with one study finding a decrease [83], while urine sodium was increased [41]. Most studies found serum potassium unchanged [61, 73, 79–83, 94, 97, 100, 102] and no increased risk of hyperkalemia [57, 78, 79, 82, 84, 104]. Only one study found an increase in serum potassium in patients with mild renal impairment [89]. Urine potassium was unchanged [41]. One study investigated potassium change during antihypertensive treatment with hydrochlorothiazide and found the potassium decrease to be less in combination treatment with DRSP [85].

Serum aldosterone was increased [41, 61, 62, 72, 73, 75, 80, 89, 92, 97, 100], with one study also finding increased aldosterone excretion [41]. Renin was increased in two studies [72, 100] and decreased in one [73]. Most studies found PRA to be increased [41, 61, 72, 75, 89, 92], with one study finding no change [86]. Angiotensinogen was increased [61, 62, 75, 86].

Quality assessment

All studies included in this review were evaluated using the NIH Quality Assessment Tool for Controlled Intervention Trials [6] and the respective answers have been shown in the table below.

Overall, the quality of the included studies was assessed as mostly fair, with a significant proportion rated as poor, particularly regarding RAAS parameters as outcomes. This is likely due to the fact that RAAS-related measures were often secondary outcomes, leaving many studies insufficiently powered to detect meaningful changes. Few high-quality RCTs with adequate sample sizes were identified, which further limits the generalizability of findings. An exception is the robust data available for DRSP where outcomes such as blood pressure and serum potassium have been evaluated in large, adequately powered studies. (Table 4)

Discussion

The findings from this systematic review provide a comprehensive overview of the effects of various progestogens on the renin-angiotensin-aldosterone system (RAAS) and associated clinical outcomes. The included studies highlight significant variability in the impact of different progestogens on RAAS parameters, reflecting the complexity and heterogeneity of these hormonal agents.

Progestogens such as drospirenone (DRSP), norethindrone (NET/NETA), and levonorgestrel (LNG) have been extensively studied, with varying effects on blood pressure (BP), plasma renin activity (PRA), and serum aldosterone levels. DRSP, for instance, was frequently associated with either decreased [53, 55, 61, 70, 77, 79, 80, 84–86, 89, 90, 93, 95, 100, 101] or unchanged BP [35, 40–42, 75, 78, 81, 87, 88, 91, 92, 94, 96–98, 102, 103], aligning with its known antimineralocorticoid activity [105]. In contrast, NET/NETA showed conflicting results on BP [46, 52–55], likely reflecting differences in study design, dosages, and population characteristics. The hyperkalemia risk associated with NET/NETA, as reported in one large retrospective cohort study [57], underscores the need for careful monitoring of electrolyte levels in patients at risk receiving these progestogens.

The variability in RAAS responses to progestogens can be attributed to several factors, including the specific molecular structures of the progestogens, their dosages, and the presence of estrogen in combination therapies. Estrogen alone has been demonstrated to increase angiotensin II, but not aldosterone, and to lower BP [106]. For example, studies on nomegestrol acetate (NOMAC) and promegestone demonstrated differential effects on PRA and angiotensin II when used in combination with estrogen, highlighting the influence of estrogen on RAAS modulation [43, 44].

Notably, the majority of studies reported unchanged serum and urine sodium and potassium levels, suggesting that progestogens do not significantly alter electrolyte balance in most cases. However, the increased serum aldosterone and aldosterone excretion observed in some studies, particularly with DRSP [41, 61, 62, 72, 73, 75, 80, 89, 92, 97, 100], indicates a potential for increased mineralocorticoid activity, which could have clinical implications for fluid retention and hypertension.

The evidence also highlights the differential impact of progestogens on angiotensinogen and angiotensin II levels. Increased angiotensinogen levels were observed with both DRSP [61, 62, 75, 86] and LNG [56, 61, 62], whereas conflicting results were noted for angiotensin II [7, 13], reflecting the complexity of RAAS regulation by these agents. The observed decrease in ACE activity in some studies [19–21] further complicates the understanding of how progestogens interact with the RAAS.

Progestogens influence the renin-angiotensin-aldosterone system (RAAS) through several molecular mechanisms, primarily mediated by their interactions with progesterone and mineralocorticoid receptors [107].

Table 4 Quality assessment - table

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Zacharieva 2004 [29]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Zacharieva 2002 [39]	No	N/A	N/A	No	No	N/A	Yes	Yes	N/A	Yes	Yes	No	Yes	N/A
Yu 1988 [34]	No	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	N/A	Yes	No	Yes	N/A
Yildizhan 2009 [70]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Wiegratz 2003 [63]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
White 2005 [79]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
White 2006 [80]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Vexiau 1995 [37]	Yes	Yes	N/A	No	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Umeda 2001 [21]	No	N/A	N/A	No	No	N/A	N/A	N/A	N/A	Yes	Yes	No	Yes	Yes
Tremollieres 1995 [43]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	N/A	Yes	Yes	No	Yes	Yes
Taneepanichskul 2007 [81]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	N/A	Yes	N/A
Suthipongse 2004 [77]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Sumino 1999 [19]	No	N/A	N/A	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Stevenson 2004 [49]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Stark 1963 [15]	No	N/A	N/A	No	No	N/A	Yes	N/A	Yes	N/A	Yes	N/A	Yes	N/A
Stark 1962 [14]	No	N/A	N/A	No	No	N/A	Yes	N/A	Yes	N/A	Yes	No	Yes	N/A
Stachenfeld 2005 [7]	No	N/A	N/A	No	No	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	N/A
Spritzer 2003 [19]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	N/A
Soveri 1977 [65]	No	N/A	No	No	No	N/A	Yes	Yes	N/A	N/A	Yes	No	Yes	N/A
Seely 1999 [10]	Yes	Yes	N/A	Yes	Yes	N/A	Yes	N/A	N/A	Yes	Yes	No	Yes	N/A
Schutt 2007 [82]	Yes	Yes	N/A	No	No	N/A	Yes	N/A	N/A	Yes	Yes	No	Yes	N/A
Schurmann 2006 [83]	No	N/A	No	No	No	N/A	Yes	N/A	N/A	Yes	Yes	No	Yes	N/A
Schindler 2010 [67]	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	No	Yes	N/A
Roy 1980 [54]	Yes	Yes	N/A	No	No	Yes	No	No	N/A	Yes	Yes	No	Yes	N/A
Punnonen 1981 [31]	No	No	No	No	No	N/A	Yes	N/A	Yes	N/A	Yes	No	Yes	N/A
Proudler 2003 [17]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Proudler 1995 [48]	No	No	No	No	No	Yes	Yes	N/A	N/A	Yes	Yes	No	Yes	N/A
Preston 2005 [84]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	N/A	N/A	Yes	Yes	Yes	Yes	N/A
Preston 2007 [85]	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Preston 2002 [86]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	N/A
Plaza De Los Reyes 1962 [16]	No	N/A	No	No	No	N/A	Yes	N/A	Yes	N/A	Yes	No	Yes	N/A
Pizzolo 2010 [71]	No	N/A	No	No	No	N/A	Yes	N/A	N/A	Yes	Yes	No	Yes	N/A
Picolet 1990 [18]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Manwaring 2000 [26]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A	Yes	Yes	Yes	No	Yes	Yes
Parsey 2000 [87]	No	N/A	N/A	N/A	N/A	N/A	No	N/A	Yes	Yes	Yes	N/A	Yes	N/A
Paoletti 2015 [55]	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	N/A
Pang 1993 [23]	Yes	Yes	No	No	No	Yes	N/A	N/A	N/A	Yes	Yes	No	Yes	Yes
Ohyama 1991 [38]	No	N/A	N/A	No	No	N/A	Yes	N/A	N/A	N/A	Yes	No	Yes	N/A
Oelkers 2000 [75]	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Yes	No	Yes	N/A
Oelkers 1995 [61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Oelkers 1991 [41]	No	N/A	N/A	No	No	N/A	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Odutayo 2015 [64]	No	N/A	N/A	No	No	Yes	N/A	N/A	N/A	Yes	Yes	No	Yes	N/A
Nogawa 2001 [20]	No	N/A	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	N/A
Nisenbaum 2014 [88]	No	N/A	N/A	N/A	N/A	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Moore 1999 [66]	Yes	N/A	N/A	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	No	Yes	N/A
Loughlin 2008 [104]	No	N/A	N/A	N/A	Yes	Yes	N/A	N/A	N/A	N/A	Yes	Yes	Yes	N/A
Locsei 2012 [72]	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	No	N/A	N/A
Liukko 1979 [76]	No	N/A	N/A	No	No	No	Yes	N/A	N/A	Yes	Yes	No	Yes	N/A
Liukko 1987 [59]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes

Table 4 (continued)

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Lelli 1984 [22]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A	Yes	N/A	Yes	N/A
Lee 2011 [12]	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Yes	Yes	No	Yes	N/A
Langrish 2009 [13]	Yes	Yes	N/A	No	Yes	N/A	No	No	N/A	Yes	Yes	No	Yes	Yes
Klipping 2021 [62]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Klinger 1979 [36]	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	Yes	No	N/A	N/A
Kimble 2020 [101]	No	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	Yes	Yes	N/A	Yes	Yes
Karara 2007 [89]	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Junge 2009 [53]	Yes	Yes	N/A	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	N/A
Jiang 2023 [27]	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	No	Yes	N/A
Jenkins 1961 [45]	No	No	No	No	No	N/A	Yes	N/A	Yes	N/A	Yes	No	N/A	N/A
Ichikawa 2006 [24]	Yes	Yes	N/A	No	No	Yes	N/A	N/A	Yes	Yes	Yes	No	Yes	N/A
Ichikawa 2008 [25]	No	N/A	No	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Huber 2000 [90]	Yes	Yes	No	No	No	Yes	No	No	N/A	Yes	Yes	No	Yes	Yes
Hoppe 1988 [68]	No	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	Yes	No	Yes	N/A
Heintz 1996 [60]	No	N/A	N/A	No	No	N/A	Yes	Yes	N/A	Yes	Yes	No	Yes	N/A
Goretzlehner 1996 [33]	No	N/A	N/A	No	No	N/A	Yes	N/A	N/A	N/A	Yes	No	Yes	N/A
Giribela 2012 [91]	No	No	No	No	Yes	Yes	N/A	N/A	N/A	Yes	Yes	Yes	Yes	No
Giribela 2015 [92]	No	N/A	No	No	No	N/A	Yes	N/A	N/A	Yes	Yes	No	Yes	No
Gambacciani 2011 [93]	Yes	Yes	No	No	No	Yes	Yes	Yes	N/A	Yes	Yes	No	Yes	Yes
Fruzzetti 2010 [42]	Yes	Yes	No	No	No	Yes	Yes	Yes	N/A	N/A	Yes	No	Yes	N/A
Fruzzetti 2007 [94]	No	N/A	No	No	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A
Elkik 1986 [58]	No	N/A	No	No	No	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	N/A
Dogo 2021 [95]	No	N/A	No	No	No	No	N/A	N/A	N/A	N/A	Yes	Yes	Yes	N/A
DeSoldati 1966	No	N/A	No	No	No	No	Yes	N/A	Yes	Yes	Yes	No	Yes	Yes
de Nadai 2015 [96]	Yes	Yes	N/A	No	Yes	Yes	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes
de Morais 2014 [97]	No	N/A	No	No	No	No	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes
De Leo 2001 [69]	No	N/A	No	No	No	Yes	Yes	Yes	N/A	N/A	Yes	No	Yes	Yes
Crane 1969 [30]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A	Yes	N/A	Yes	N/A
Conard 1995 [40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	Yes	N/A	Yes	Yes
Chen 2022 [102]	No	N/A	N/A	N/A	No	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	Yes
Brons 1981 [50]	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	Yes
Briggs 1982 [56]	Yes	Yes	No	No	No	Yes	N/A	N/A	N/A	N/A	Yes	N/A	Yes	Yes
Branczeisz 1983 [51]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Yes	No	Yes	N/A
Bradford 1963 [52]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A	Yes	N/A	Yes	N/A
Borges 2006 [98]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	N/A
Bissonnette 1997 [32]	Yes	Yes	No	No	No	Yes	Yes	Yes	N/A	N/A	Yes	No	Yes	Yes
Bird 2011 [57]	No	N/A	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A
Bhattacharya 2012 [40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Beckerhoff 1973 [46]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	Yes
Beckerhoff 1973 [47]	No	N/A	N/A	N/A	N/A	N/A	Yes	Yes	N/A	N/A	Yes	N/A	Yes	N/A
Bayer 2007 [103]	Yes	N/A	Yes	Yes	Yes	N/A	Yes	Yes	N/A	N/A	Yes	N/A	Yes	Yes
Bayer 2004 [100]	Yes	N/A	N/A	Yes	Yes	Yes	N/A	N/A	N/A	N/A	Yes	N/A	Yes	Yes
Bayer 2002 [99]	No	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Yes	N/A	Yes	N/A
Atallah 1988 [8]	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	Yes	N/A
Archer 2015 [78]	No	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	Yes	Yes	N/A	Yes	N/A
Arangino 1998 [74]	No	N/A	N/A	N/A	N/A	Yes	N/A	N/A	N/A	Yes	Yes	N/A	Yes	N/A
Ahmed 2017 [28]	No	N/A	No	No	No	Yes	No	N/A	Yes	Yes	Yes	N/A	Yes	Yes
Ahmed 2011 [73]	No	N/A	No	No	No	N/A	No	N/A	N/A	Yes	Yes	No	Yes	N/A

Progestogens can antagonize the mineralocorticoid receptor (MR), reducing aldosterone's sodium-retaining effects, thereby promoting natriuresis and influencing fluid and electrolyte balance.

This MR antagonism is particularly notable for DRSP, which mimics the effects of spironolactone [105].

The variability in progestogen impact on RAAS may also be explained by differences in receptor binding affinity and their potential to induce conformational changes in the receptor-ligand complex, altering gene transcription [107].

Furthermore, progestogens have also been found to be linked to angiogenesis in mouse models [108] and have been found to influence vascular remodeling in vitro [109]. DRSP as hormonal replacement therapy significantly improves vascular parameters and the composition relevant for vascular protection in early post-menopausal normotensive women [110].

These mechanisms highlight the intricate interplay between progestogens and the RAAS, with implications for blood pressure regulation, fluid homeostasis, and cardiovascular risk.

Despite the extensive data, several gaps and inconsistencies remain. The heterogeneity in study designs, population characteristics, and methodologies makes it challenging to draw definitive conclusions in our study. Furthermore, many studies focused on secondary outcomes related to RAAS, which may limit the robustness of the findings.

To address the variability observed in the reviewed studies and improve comparability, we recommend that future research focus on high-quality randomized controlled trials (RCTs) comparing progestogen monotherapy with combination therapy involving estrogen. These studies should include both pre- and postmenopausal women to account for hormonal differences across life stages.

Standardized dosages should be consistently applied, with clearly defined routes of administration. Key parameters to monitor include blood pressure, serum and urine sodium and potassium levels, serum and urine aldosterone, serum renin, plasma renin activity, and angiotensinogen, as well as angiotensin I and II.

Additionally, clinical outcomes such as bloating and weight gain should be systematically assessed to capture the broader clinical implications of RAAS modulation. Measurements should follow a standardized timeline, including baseline, midpoint, and endpoint assessments, to evaluate short- and long-term effects. These recommendations aim to enhance the methodological rigor and clinical relevance of future research.

Furthermore, given the critical role of the RAAS in blood pressure regulation and vascular homeostasis, as well as its status as a primary target for antihypertensive therapies, incorporating sex- and gender-specific considerations into research and clinical guidelines is essential. Notably, these factors are insufficiently addressed in current ESC and other major guidelines [111], underscoring an urgent need for their integration to improve personalized care and treatment outcomes.

Given the diverse effects of progestogens on the RAAS and their varying side-effect profiles, we propose a clinical pathway to guide clinicians in progestogen selection based on patient-specific needs. The decision-making will invariably be complex and needs to take all the different factors into account.

Initial assessment should include a comprehensive evaluation of cardiovascular risk factors, such as baseline blood pressure, testing of renal function when indicated, co-medication and CVD/VTE history and risk, as well as patient-reported concerns like bloating and weight gain and need for an antiandrogenic progestogen.

For patients at higher cardiovascular risk, progestogens such as DRSP could be recommended due to their antihypertensive and MR-antagonistic properties, which reduce fluid retention and blood pressure. Progesterone is also favorable due to its potentially beneficial effect on the RAAS and its lower VTE risk [112, 113]. Conversely, we have found NETA and LNG may be less suitable for these patients. In contraceptive users, the increased VTE risk of DRSP in combination with EE [114] as compared to LNG needs to be discussed with the patient.

Monitoring should include regular assessments of blood pressure and patient satisfaction to ensure optimal outcomes and minimal adverse effects.

Conclusion

This systematic review underscores the complex and varied effects of progestogens on the RAAS. Key findings indicate that progestogens like DRSP may offer benefits in terms of BP reduction and minimal electrolyte disturbances, whereas others like NET/NETA might require more careful monitoring due to their associated risks, including hyperkalemia. The variability in RAAS responses highlights the necessity of personalized medicine approaches when using progestogens, considering individual patient characteristics and specific hormonal profiles.

Standardizing study designs and methodologies in future research will be essential to clarify these effects further. Comprehensive and detailed studies are needed to provide more definitive conclusions and to guide clinical practice effectively. The insights gained from this review can inform clinical decisions, improve patient outcomes, and direct future research efforts in the field of hormonal therapies and RAAS interactions.

Abbreviations

ACE	Angiotensin-converting enzyme
BP	Blood pressure
CEE	Conjugated equine estrogens
CMA	Chlormadinone acetate
CPA	Cyproterone acetate
DNG	Dienogest
DRSP	Drospirenone
DSG	Desogestrel
DYD	Dydrogesterone
E2	17-beta Estradiol
E2V	Estradiol valerate
EE	Ethinyl estradiol
ENG	Etonogestrel
EPT	Estrogen-progestogen-therapy
ET	Estrogen (only) therapy
GSD	Gestodene
IUD	Intrauterine device
LNG	Levonorgestrel
LYN	Lynestrenol
MGA	Megestrol acetate
MHT	Menopausal hormone therapy
MP	Micronized progesterone
MPA	Medroxyprogesterone acetate
NET(A)	Norethisterone (acetate)
NG	Norgestrel
NGM	Norgestimate
NOM	Nomegestrol
NOMAC	Nomegestrol acetate
P4	Progesterone
PMG	Promegestone
PRA	Plasma renine activity
PRS	Plasma renine substrate (Angiotensinogen)
RAAS	Renin-angiotensin-aldosterone-system
RCT	Randomized controlled trial

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Authors' contributions
AS served as the corresponding author, reviewed all data, and drafted the manuscript. KS acted as the second reviewer and critically checked the manuscript. MvG contributed as the data specialist and developed the search strategy. CD also reviewed and checked the manuscript for accuracy. PS guided and consulted throughout the project, providing critical feedback and making amendments to the manuscript. All authors approved the final version of the manuscript.

Data availability
The data supporting this review are derived from publicly available sources, as referenced throughout the manuscript. No new datasets were generated or analyzed during the course of this study. The Data Extraction Table has been included in a supplementary file.

Declarations

Competing interests
The authors declare no competing interests.

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