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Evaluating the Limitations of Animal Models in Antihypertensive Drug Development

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Abstract

This report critically evaluates the principal animal models used in antihypertensive drug development and the systematic factors underlying the persistent gap between preclinical efficacy and clinical outcomes. Three model systems are examined, the spontaneously hypertensive rat (SHR), the Dahl salt-sensitive rat, and renovascular (two-kidney and one-kidney one-clip) models, assessing their experimental utility, translational limitations, and ethical implications against human essential hypertension.

Although each has yielded foundational mechanistic insight and supported major drug classes, their collective predictive validity is constrained by genetic homogeneity, the absence of common comorbidities (obesity, type 2 diabetes, chronic kidney disease), a pronounced bias toward male-only cohorts, short experimental timeframes, and interspecies divergence in key signalling pathways. Inconsistent experimental design, particularly blood-pressure measurement method and under-reporting of animal sex, further erodes reproducibility and cross-study synthesis.

The report situates these issues within the global research landscape, highlighting geographic and ancestry-related blind spots that limit relevance to under-represented populations, and within the Three Rs and current UK/EU regulatory and data-protection frameworks. Emerging bridging strategies, CRISPR-Cas9 models incorporating human-relevant blood-pressure QTLs, iPSC-derived vascular constructs and vessel-on-chip systems, and multi-omics integration with human cohort data are evaluated as routes to reducing translational attrition.

It concludes that closing the translational gap requires not only better models but mandatory sex-disaggregated design, rigorous transparent reporting, validated comorbid models, and reform of regulatory and ethical review, an institutional challenge as much as a scientific one.

Keywords: Hypertension, Animal models, The Spontaneously hypertensive rat, Antihypertensive drug development, Sex differences, Translational research, iPSC-derived vascular models.

1. Introduction

Hypertension, defined as sustained blood pressure exceeding 130/80 mmHg, constitutes a primary modifiable risk factor for cardiovascular disease, stroke and organ damage worldwide affecting over one billion individuals across healthcare systems of varying resource levels. Despite extensive research, the multifactoriall pathophysiology of essential hypertension remains incompletely elucidated, with pharmacological interventions demonstrating suboptimal efficacy in large patient cohorts. Animal models have provided essential mechanistic insights into haemodynamic, neurohumoral, and genetic contributors to hypertension, although no individual model comprehensively replicates human disease heterogeneity [1,2].

This report critically evaluates the principal animal models employed in hypertension research, the spontaneously hypertensive rat (SHR), Dahl salt-sensitive rat, and renovascular models, assessing their experimental utility, translational limitations, and associated ethical considerations.

The analysis situates these models within international research frameworks, identifies persistent evidence gaps, and proposes evidence-based strategies for methodological advancement. The central thesis holds that translational discrepancies between preclinical efficacy and clinical outcomes arise systematically from limitations in model selection, experimental design parameters, and interspecies physiological divergence.

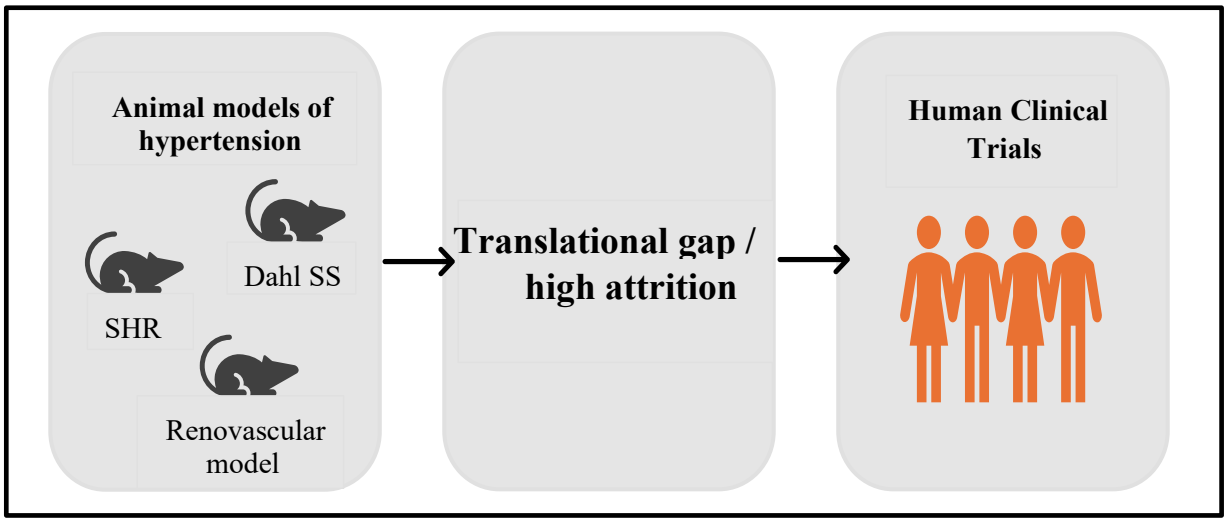

Figure 1: Schematic of translational gap between animal models of hypertension and human clinical outcomes in antihypertensive drug development.

2. Model Systems

2.1 The Spontaneously Hypertensive Rat (SHR)

The SHR represents the predominant genetic model of hypertension in contemporary research. This strain manifests progressive hypertension from 8-12 weeks of age, accompanied by left ventricular hypertrophy, renal arteriolar thickening, and polygenic inheritance patterns analogous to human essential hypertension [3]. Well-characterised sympathetic hyperactivity and renal tubular sodium retention further support the SHR as a

foundational platform for cardiovascular pharmacology and pathogenesis studies [4].

However, the translational applicability of SHR findings warrants substantial qualification. The model's genetic homogeneity fails to capture the environmental-genetic interactions characteristic of human essential hypertension. Notably absent are salt sensitivity, dietary influences, and metabolic comorbidities - obesity, insulin resistance, dyslipidaemia, prevalent among clinical populations [1,4]. Additionally, the literature documents limited replication of SHR-derived blood pressure quantitative trait loci in human genome-wide association studies, compromising genetic face validity [1,2].

Pharmacodynamic disparities constitute a further constraint. SHR demonstrates heightened responsiveness to renin-angiotensin system blockade relative to human cohorts, potentially overestimating clinical relevance of RAS-targeted therapies [2,4]. Divergent vascular smooth muscle calcium signalling and oxidative stress responses between SHR and human resistance arteries undermine direct mechanistic extrapolation. The normotensive control strain exhibits anomalous cardiovascular reactivity, introducing more interpretive challenges [1].

2.2 The Dahl Salt-Sensitive (SS) Rat

The Dahl SS rat models environmentally induced salt-sensitive hypertension, exhibiting marked blood pressure elevation under high-sodium dietary conditions. This phenotype demonstrates clinical relevance, a substantial proportion of hypertensive patients manifest salt responsiveness, particularly among Black populations and older adults. Compared to SHR, the model possesses superior utility for investigating dietary-renal interactions and aldosterone dysregulation, functioning as a complementary experimental system [1].

Mathematical modelling of salt-induced blood pressure dynamics in the Dahl SS rat has further characterised the temporal relationship between sodium intake and pressure elevation, providing a quantitative framework for interpreting dose-response relationships in this model [5]. However, translational limitations remain pronounced. Supra-physiological sodium requirements (4-8% NaCl diets) exceed typical human consumption patterns, potentially activating non-physiological pathways [5]. Substantial divergence exists between Dahl renal transcriptomic profiles and those of salt-sensitive human subjects [1]. The accelerated severity of renal pathology under salt challenge further limits applicability to early-stage human salt-sensitive hypertension.

2.3 Renovascular Models

Renovascular models, principally the two-kidney one-clip (2KIC) and one-kidney one-clip (1KIC) stimulate secondary hypertension from renal artery stenosis, a condition affecting a small minority of hypertensive patients [5,6]. They reliably reproduce RASdriven hypertension and were instrumental in establishing the physiological rationale for ACE inhibitor therapy [7].

However, it must be noted that surgical clip placement introduces acute inflammatory and haemodynamic perturbations absent in the gradual onset of human renovascular disease, and the models are poorly suited to modelling essential hypertension where the RAS is only one of several pathological drivers.

2.4 Comparative Overview of Model Systems

The table below synthesises the principal strengths, limitations, and translational fit of each model system. No single model captures the full complexity of human essential hypertension; model selection should be hypothesis-driven and explicitly justified against the specific research question [1].

Model	Aetiology	Key Strength	Key Limitation	Translational Fit
SHR	Genetic / polygenic	Stable progressive hypertension; endorgan damage	No salt-sensitivity or metabolic comorbidities; sex bias	Moderate neurogenic & renal mechanisms
Dahl SS	Dietary salt / renal	Models salt-sensitive phenotype; aldosterone dysregulation	Requires supra - physiological NaCl; divergent renal transcriptome, sex bias	Moderate specific salt-sensitive sub populations
2KIC /1KIC	Surgical/ renovascular	High construct validity for RAS-driven hypertension	Acute surgical perturbations absent in human disease, sex bias	Low for essential; high for renovascular subtype
CRISPR / Transgenic	Human QTL / genetic	Improved face validity; human-relevant loci	Early-stage; limited phenotype characterisation	Emerging high potential

Table 1: *Comparative summary of principal animal models of hypertension. Translation fit assessed relative to human essential hypertension.*

CRISPR-Cas9 models are particularly valuable because they allow direct mechanistic testing of human-relevant blood pressure QTLs identified through GWAS in the whole-organism context, offering a level of genetic face validity unachievable with current inbred strains [2].

3. Experimental Design

A recurring criticism of hypertension model research is the inconsistency of experimental design across laboratories, which limits reproducibility and cross-study synthesis. Key sources of inter-study variability include blood pressure measurement methodology and, critically, the sex of animals used. These factors interact in complex ways that are rarely reported comprehensively in published studies [1].

Blood pressure measurement method is a foundational design choice. Radiotelemetry providing continuous, undisturbed recordings from conscious, freely moving animals is broadly regarded as the gold standard, capturing circadian variation and acute stress responses more accurately than alternatives [9]. Yet tail-cuff plethysmography remains prevalent due to its substantially lower cost and technical accessibility. The latter introduces

restraint-related stress artefacts that can artificially inflate readings and systematically bias group comparisons, particularly in models with heightened sympathetic reactivity such as the SHR. Without transparent reporting of measurement method, between-study comparisons are compromised.

Sex is a critical and historically neglected experimental variable. The vast majority of SHR studies have used exclusively male animals, despite well-established sex differences in blood pressure regulation, hormonal modulation of vascular tone, and antihypertensive drug response. Female SHRs develop a milder, later-onset hypertensive phenotype, likely reflecting oestrogen-mediated vasodilation, and differential RAS activity [1,4]. Extrapolating findings from male-only cohorts to female patients, represents a significant portion of the hypertensive individuals globally, is therefore methodologically unjustifiable. This omission directly contributes to the underperformance of antihypertensive agents in female clinical trial populations, a pattern increasingly recognised in translational cardiovascular research [10,11].

Temporal design represents a further limitation. Most experimental studies examine short-term haemodynamic responses over days to weeks, while hypertension in humans develops over decades. The consequent absence of longitudinal study designs limits the capacity to model progressive endorgan sequelae, left ventricular hypertrophy, renal fibrosis, retinal arteriole remodelling that define clinical disease burden. Where longitudinal designs are employed, standardisation of time points, outcome measures and sacrifice protocols across studies remains inconsistent, hampering metaanalytic synthesis. Collectively, these design deficiencies compound the translational limitations inherent in the models themselves and represent a modifiable source of evidence quality loss that rigorous reporting standards could address [12].

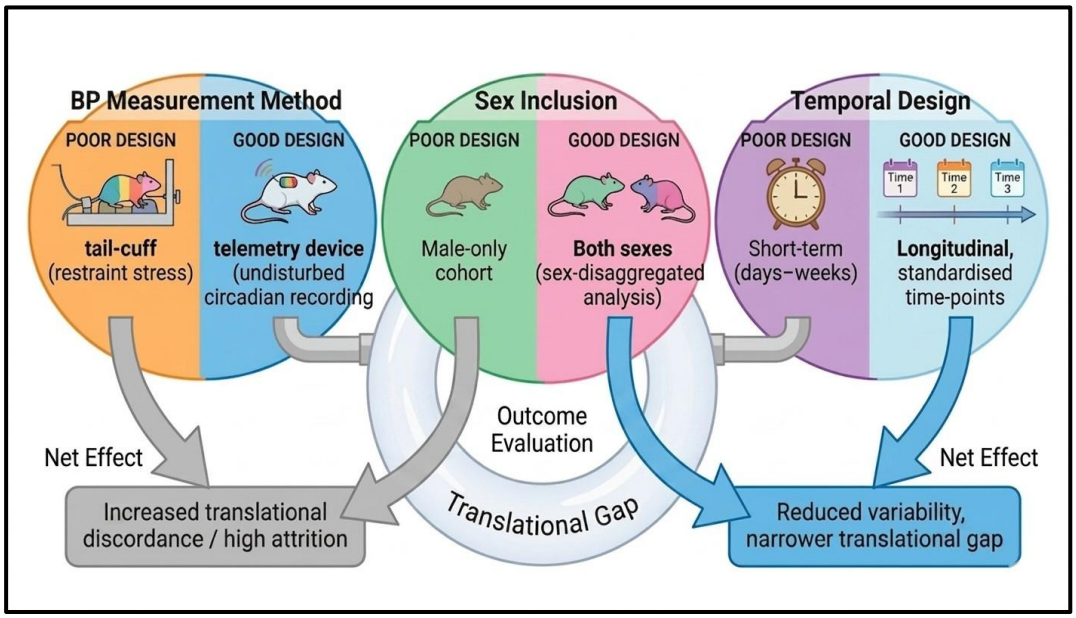

Figure 2: *Schematic showing how key experimental choices (blood pressure measurement method, sex inclusion, and temporal design) caneither widen or narrow the translational gap in animal models of hypertension.*

4. Clinical and Translational Relevance

The fundamental challenge in translating animal model findings to human hypertension is the biological complexity and heterogeneity of the human condition. Essential hypertension is not a single disease entity but a syndrome encompassing multiple aetiological subsets: neurogenic, renal, metabolic, endocrine, that current animal models capture only in part. This explains, at least partly, the high attrition rate of antihypertensive candidates that demonstrate robust preclinical efficacy but later fail in phase II-III clinical trials [1].

There are three domains in which the translational gap is most pronounced. First, rodent models lack co-morbid disease representation: obesity, type 2 diabetes and chronic kidney disease are prevalent in the human hypertensive population but absent from standard preclinical models. These co-morbidities alter vascular biology, renal sodium handling and pharmacokinetics in ways that significantly modify drug response and their omission risks generating preclinical efficacy data that does not hold in realworld patient populations.

Second, animal studies rarely model polypharmacy effects, most hypertensive patients receive two or more antihypertensive agents simultaneously yet preclinical studies overwhelmingly examine single-drug interventions. The absence of combination therapy testing may contribute to the underestimation of drug interactions and adverse effects profiles. Third, the duration of preclinical studies, typically weeks to months, is incommensurate with the lifelong nature of antihypertensive therapy, limiting assessment of long-term tolerability and efficacy maintenance [12].

Pharmacogenomic heterogeneity represents an additional barrier. Pharmacogenetic determinants of antihypertensive response found in the SHR do not consistently replicate in human GWAS data, reflecting the genetic diversity of human populations that inbred rodent strains cannot represent. ESC/ESH 2018 guidelines emphasise patient stratification based on cardiovascular risk profile as a cornerstone of clinical management, a concept that current animal models cannot operationalise, as they represent single-risk-profile phenotypes rather than the spectrum of patient presentations encountered in clinical practice [13].

Regulatory agencies are increasingly moving towards multi-model evidence requirements and mandatory sex-stratified analysis, reflecting growing recognition that single model preclinical packages are insufficient to predict human outcomes [12].

Emerging bridging strategies include the integration of human induced pluripotent stem cell (iPSC)derived vascular constructs, endothelial cells, smooth muscle cells, and three-dimensional vessel-onchip system alongside traditional animal studies. These platforms retain human genetic context, can be derived from patient-specific backgrounds, including those with specific comorbidities, and can be used for high-throughput drug screening prior to in vivo validation. Critically, iPSC models do not replace the whole-organism physiological integration that animal models provide, but they can significantly de-risk translational decisions at the mechanistic level. The systems biology integration of rodent multi-omics data with human patient cohort datasets can prospectively identify mechanistic pathways with poor translational conservation, a powerful strategy for reducing preclinical attrition before costly clinical investment [2].

5. Global Research Context

The global landscape of hypertension research reflects significant regional variation in model preferences and translational priorities. North American and European groups have historically dominated SHR-based mechanistic research, while East Asian institutions, particularly in Japan and China have contributed to studies of salt sensitivity and genetic predisposition, reflecting the higher prevalence of salt-sensitive hypertension in these populations. This geographic clustering of research creates systematic blind spots: the models most commonly employed may not be optimal for understanding hypertension in sub-Saharan African or South Asian populations, where prevalence is rapidly increasing but research investment remains disproportionately low compared to disease burden [1].

A substantive theoretical conflict persists about the renal versus neurogenic primacy in hypertension pathogenesis. A framework positioning chronic renal sodium retention and pressure-natriuresis as the ultimate long-term blood pressure determinant has been challenged by robust evidence of primary sympathetic nervous system dysregulation from SHR studies. This mechanistic disagreement has practical consequences for drug development prioritisation, influencing whether central sympathetic agents or natriuretic strategies receive investment. Consequently, the preclinical evidence base reflects the model preferences of the research groups that generated it rather than an unbiased assessment of therapeutic relevance across patient populations, a structural bias that perpetuates the translational gap.

Encouragingly, multi-model validation strategies are gaining traction in leading research groups. A recent systems biology analysis across multiple rodent datasets, identifying transcriptomic signatures predictive of poor translational outcomes, findings that are beginning to influence how preclinical regulatory packages are assembled. Standardisation of this approach internationally would represent a significant improvement in the evidence base underpinning antihypertensive drug development.

6. Ethical and Regulatory Considerations

The use of animal models in hypertension research raises substantive ethical questions within the Three Rs framework Replacement, Reduction and Refinement. The SHR is an animal bred to suffer chronic, progressive cardiovascular disease, requiring explicit harm-benefit justification under the UK Animals (Scientific Procedures) Act 1986. Surgical renovascular models are classified as moderateto-severe severity procedures under EU Directive 2010/63/EU necessitating refinement strategies including peri-operative analgesia, optimised clip placement technique, and telemetric monitoring to minimise handling stress. These practices are expected but inconsistently reported in primary literature, limiting reproducibility assessment. Given the demonstrated low predictive validity of SHR for human clinical outcomes, the harm-benefit calculus underpinning ethical approval of these models warrant re-examination, particularly where alternative platforms such as iPSC-derived vascular constructs can address equivalent mechanistic questions.

The integration of human biobank and electronic health record data into translational hypertension research introduces a distinct ethical domain. Secondary use of patient-level cardiovascular data, including genomic data linked to blood pressure phenotypes from UK Biobank, must follow the UK Data Protection Act 2018 and UK GDPR with particular attention to re-identification risk in small genomic subgroups.

Critically, the well-documented representation of European ancestry individuals within major biobanks including UK Biobank directly undermines the multi-omics bridging strategies described in section 4, as transcriptomic signatures derived from non-representative cohorts cannot reliably validate findings from rodent models intended to inform therapy for globally diverse patient populations.

7. Future Directions

Several evidence-based improvements to the preclinical hypertension research paradigm are warranted. The most immediately actionable is mandatory sex-disaggregated study design and reporting, aligned with growing institutional mandates and the expanding body of evidence documenting sex differences in hypertensive pathophysiology [10,11]. The default use of male-only animal cohorts is scientifically unjustifiable and perpetuates clinical evidence gaps. Alongside this, the development and systematic validation of comorbid models more faithfully representing the hypertensive patient population, including the spontaneously hypertensive obese (SHROB) rat and fructose-fed SHR variants, should be prioritised.

These models are promising but require rigorous, standardised phenotype and pharmacological characterisation before they can reliably inform drug development decisions. Formalising multiplatform validation frameworks, primary rodent data, iPSC-derived vascular constructs, and human biobank cohort analysis, as a required preclinical pathway before Phase I trial authorisation would significantly reduce translational attrition without requiring reduction of animal use below scientifically necessary thresholds. In the longer term, the application of CRISPR-Cas9-edited rodent models incorporating humanrelevant blood pressure QTLs shown through GWAS represents the most methodologically rigorous route to improving the genetic face validity of hypertension models [2]. These models would allow direct mechanistic testing of human-relevant genetic variants in a whole-organism context currently unachievable with iPSC platforms alone [2].

8. Conclusion

Animal models of hypertension have generated foundational mechanistic insights and supported the development of major antihypertensive drug classes, with the SHR remaining useful for studying neurogenic and renal mechanisms, the Dahl salt-sensitive rat for salt-responsive phenotypes and renovascular models for RAS-dependent secondary hypertension. However, their collective translational value is limited by genetic homogeneity, absence of co-morbid disease, sex bias, and physiological differences between species in key signalling pathways, all of which contribute to the persistent gap between preclinical efficacy and clinical outcomes.

Closing this gap will require not only improved models, but also rigorous model selection, stronger experimental design, and more transparent reporting of translational limitations. Emerging approaches such as CRISPR-edited models, iPSC-derived vascular systems, and multi-omics integration offer a realistic route toward more predictive preclinical research. However, technical improvement alone is insufficient, without corresponding reform of experimental design, standard regulatory requirements and ethical review frameworks, more sophisticated models risk being deployed with the same methodological weaknesses that have limited their predecessors. Addressing the translation gap in antihypertensive drug development is as much an institutional and regulatory challenge as a scientific one, and this remains a priority for the more than 1 billion people living with hypertension globally.

Conflict of Interest Statement

Disha Jain declares no conflicts of interest. The work was conducted independently, ensuring objectivity and scientific integrity.

Data Availability Statement

All data discussed in this review are available from the cited sources. No new data were generated for this review.

9. References

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