Turning a Clinical Question into a Research Project

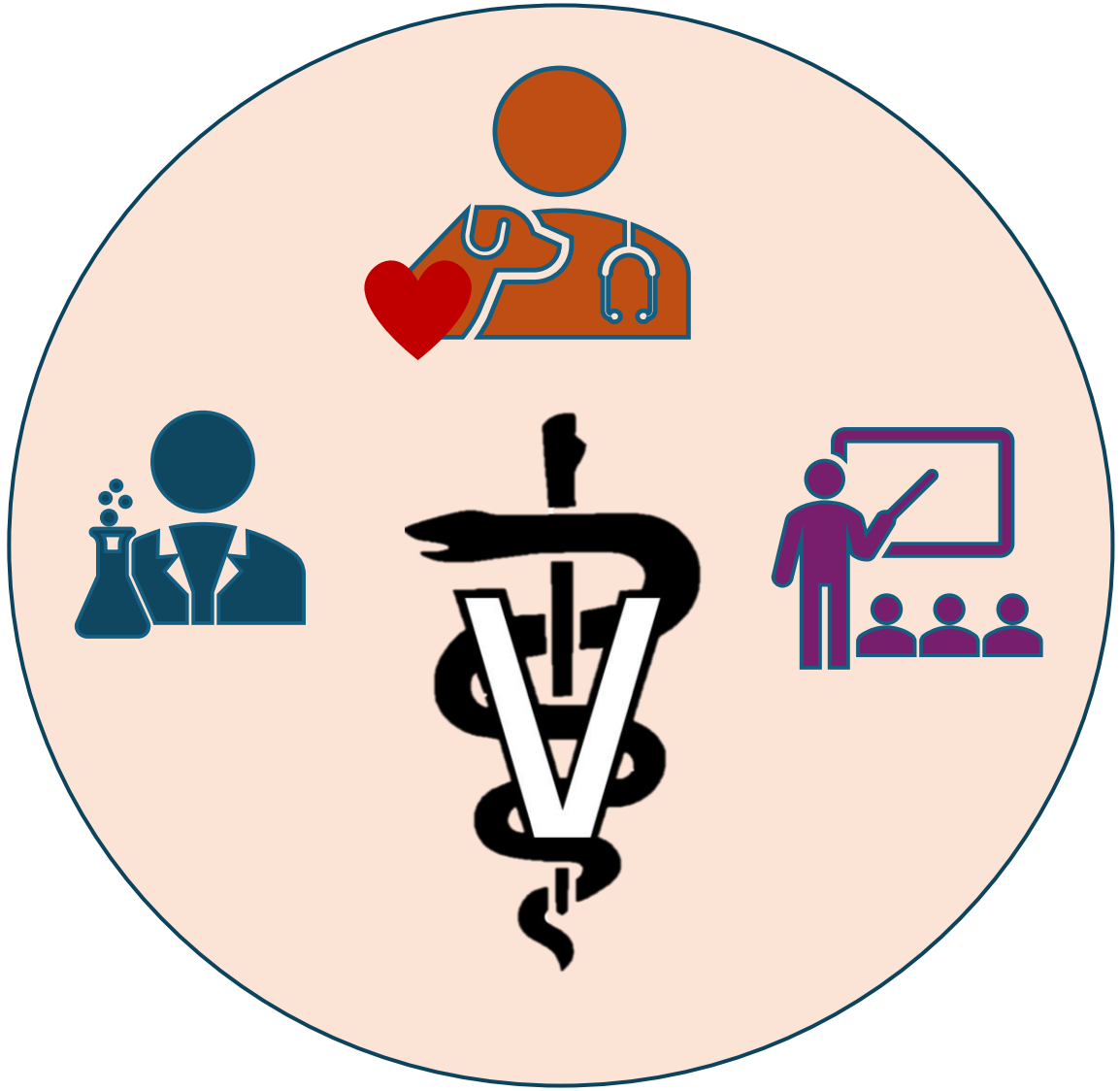
Darcy Adin, DVM, Diplomate ACVIM (Cardiology)
Associate Dean of Clinical Services – Small Animal
University of Florida

Aka “Designing Research with Purpose”

- Make it important – start with a clinical question
- The PICOT approach
- Collaboration and mentorship
- Developing research that builds upon itself

Why?

1. *So science, data, incentives, and culture align for constant improvement*
2. **New knowledge is seamlessly embedded into care delivery**
3. *New knowledge is captured from every patient experience to create a continuous feedback loop*
4. **Outcomes are personalized, with patients as active participants**



Clinician scientists integrate **real-world clinical insight** with **rigorous scientific methodology** to advance medicine and improve patient care

How do you “find” an area to study?

Exposure during residency (mentor’s research)

Cases

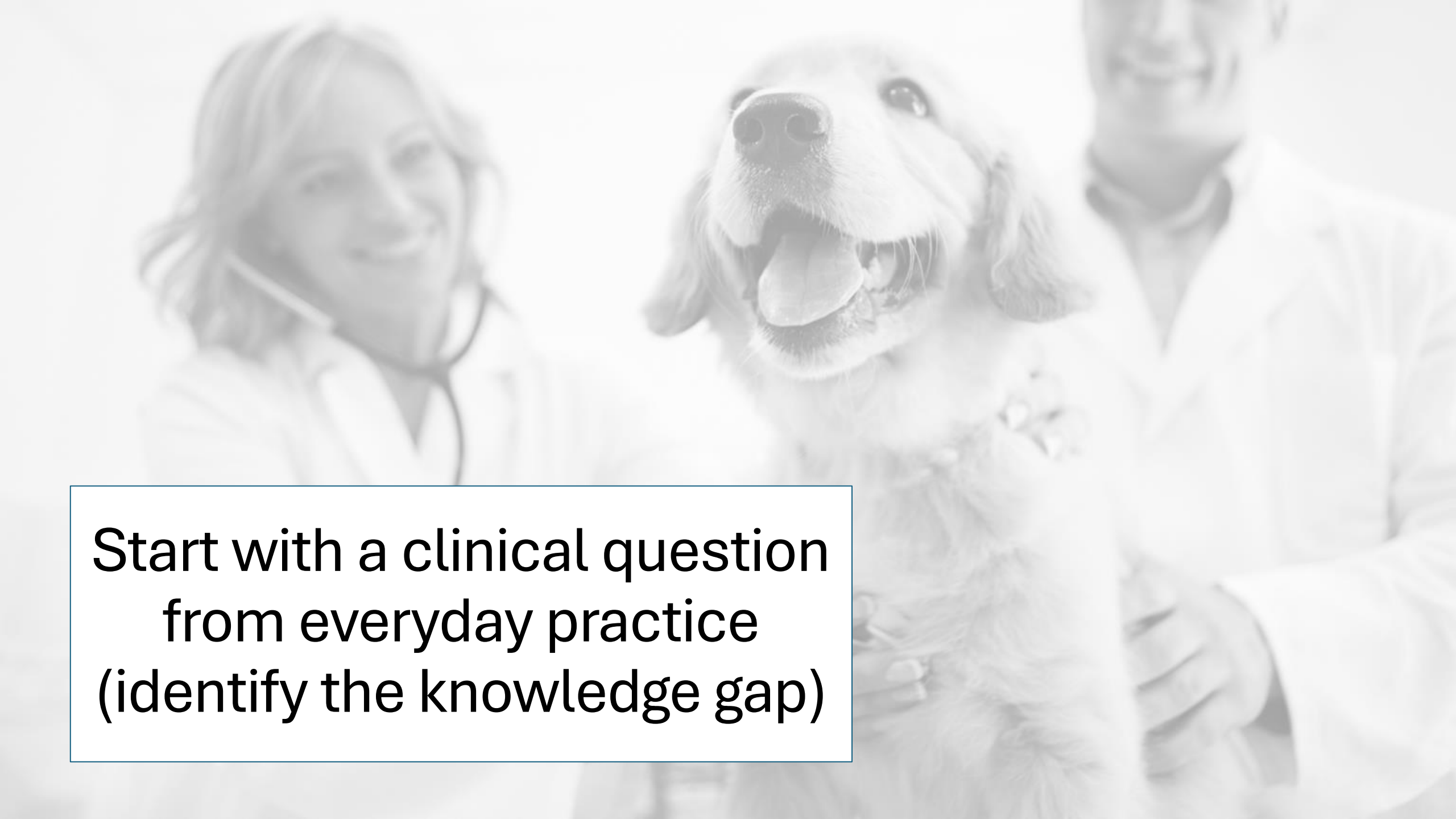
Interest

My career examples

Post-residency

Mid-career

Now

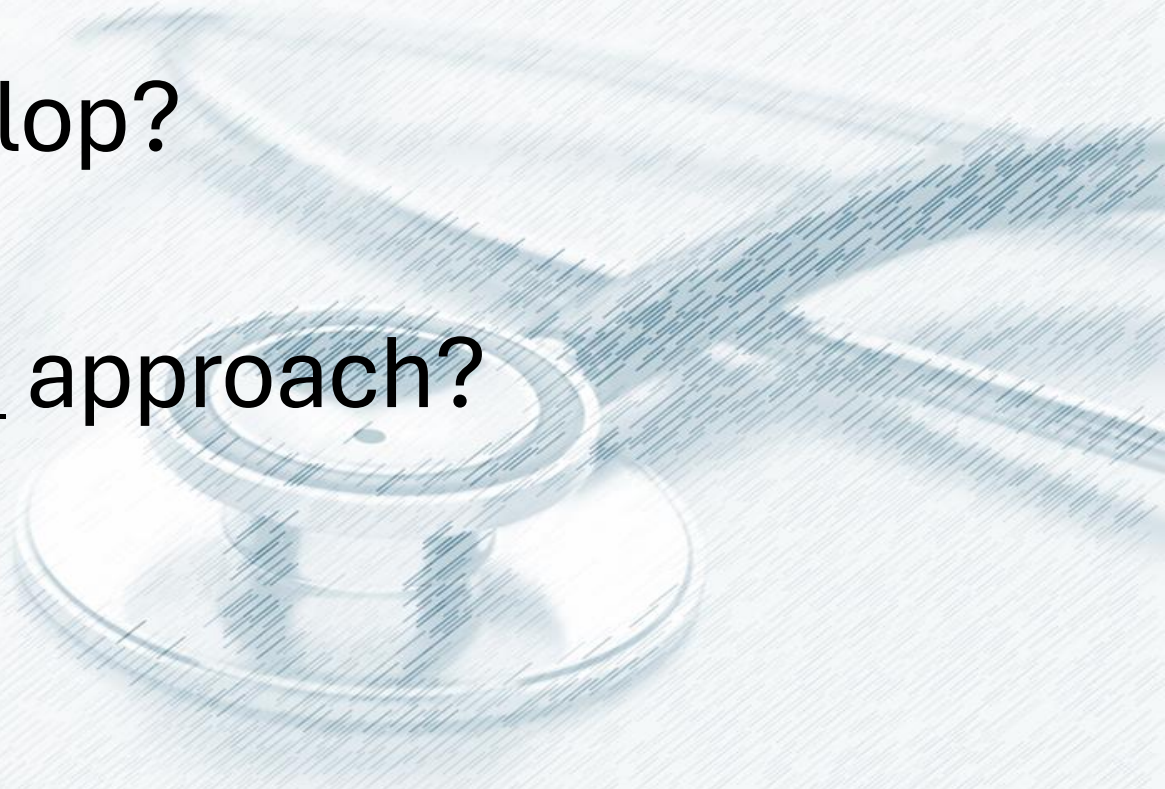


Start with a clinical question from everyday practice (identify the knowledge gap)

Why does this patient population get ____ disease?

How does this disease develop?

What if we treated with _____ approach?



Questions about the Clinical Question

Does it address a gap?

Is the problem common?

Can it be broken down into manageable projects?

Would a solution be impactful?

Am I passionate about this? (i.e. there are LOTS of knowledge gaps in vet med)

FACTS from my specialty:

- ❑ Millions of dogs in the US have heart disease
- ❑ 25% of these develop CHF
- ❑ CHF median survival time is 12 months

My questions: How do we give dogs with CHF better quality and quantity of life?

Where are the knowledge gaps?

We need more effective diuresis

Approaches to slowing disease progression

Ways to stratify risk

Better understanding of CHF pathophysiology

Personalized medicine

Maybe we can give furosemide as a CRI to get better diuresis?

25 years later

CHF associated hypochloremia is associated with poor outcomes – can we correct it?

You’ve got an idea – now what?

PICOT (S): the well-built clinical question

P **POPULATION / PATIENT / PROBLEM**

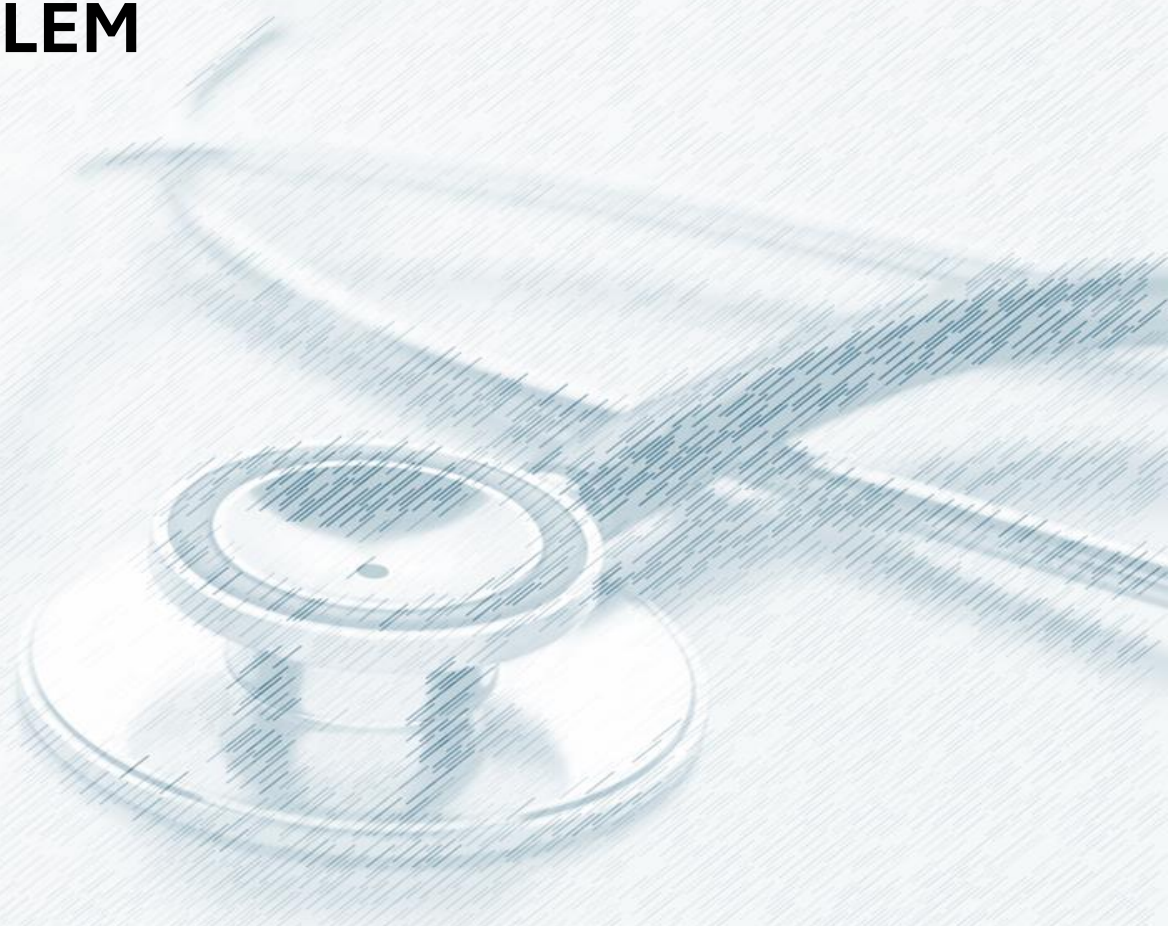
I **INTERVENTION**

C **COMPARISON / CONTROL**

O **OUTCOME**

T **TIME**

S **STUDY TYPE**



POPULATION / PATIENT / PROBLEM

- What is the patient population or primary problem?
- What are the relevant demographic factors or most important characteristics of the patient?
- What is the setting?

POPULATION / PATIENT / PROBLEM

Let's use one of my projects:

Does oral KCl supplementation raise serum Cl and suppress the RAAS in CHF?

What is the patient population or primary problem?

- Dogs with advanced CHF (poor outcomes)
- RAAS dysregulation contributes to disease progression

What are the relevant demographic factors or most important characteristics of the patient?

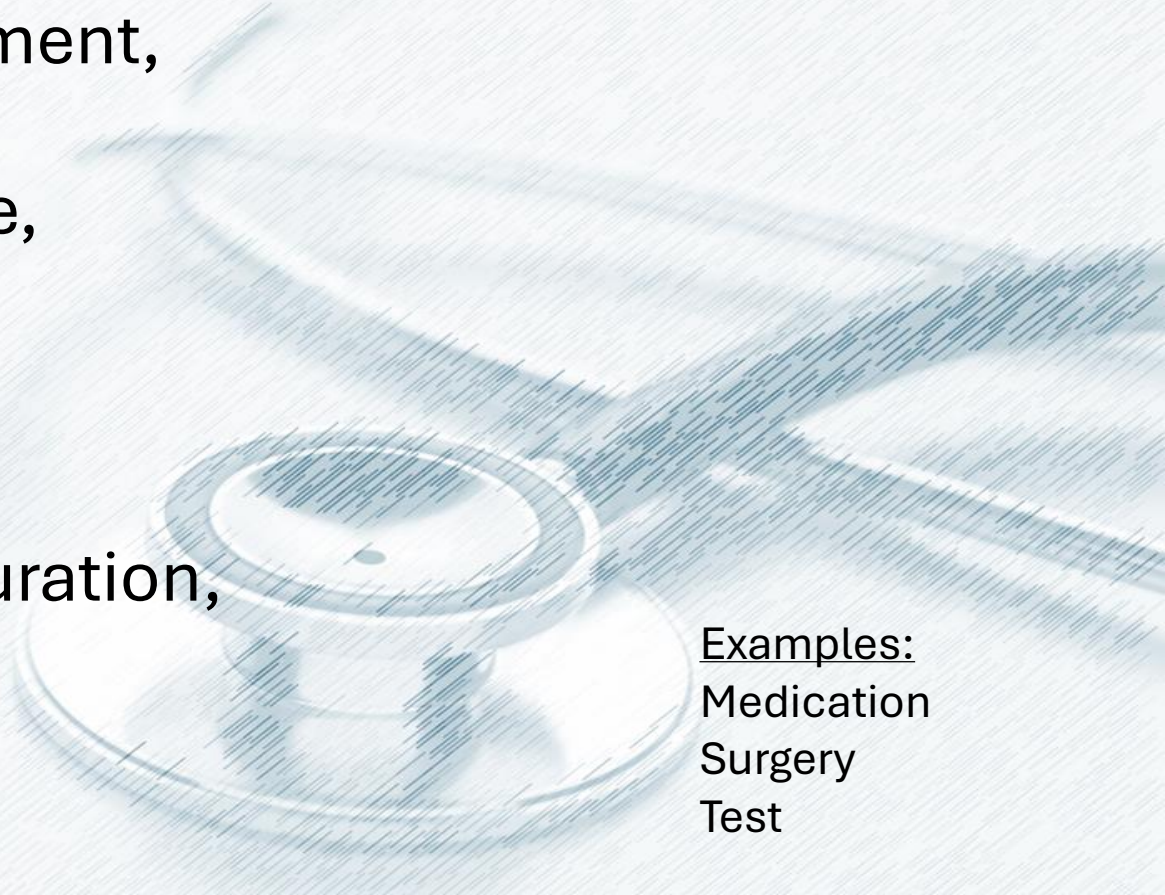
- Underlying irreversible heart disease
- Universal diuretic need
- Hypochloremia is found in 10-15%
- Survival is worse with hypochloremia
- Hypochloremia turns the RAAS on

What is the setting?

- Clinical referral cardiology practice

INTERVENTION

- What is the main intervention, treatment, diagnostic test, procedure, exposure, patient perception, or risk factor?
- What are the dosages, frequency, duration, and mode of delivery?



<u>Examples:</u>
Medication
Surgery
Test

INTERVENTION

Does oral KCl supplementation raise serum Cl and suppress the RAAS in CHF?

What is the main intervention, treatment, diagnostic test, procedure, exposure, patient perception, or risk factor?

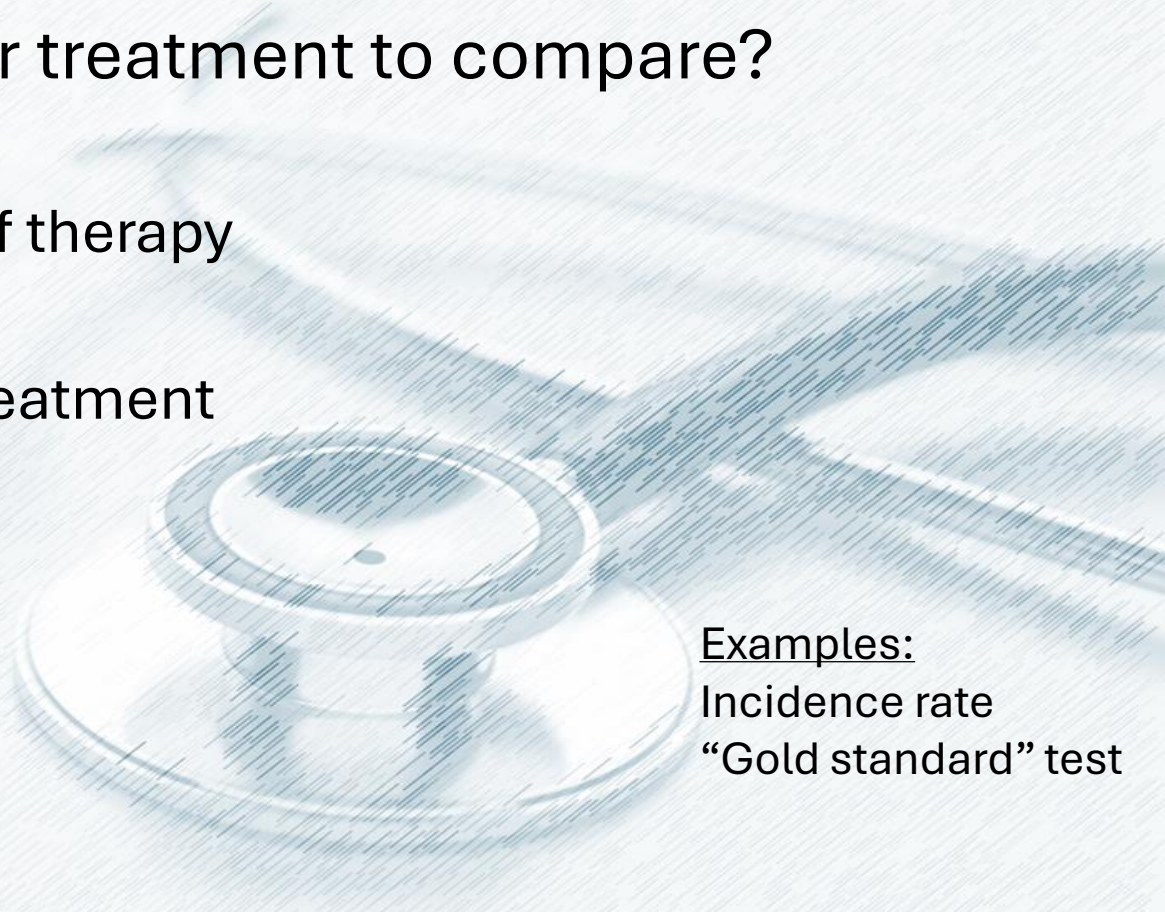
- Oral KCl administration for hypochloremia
- Serum biochemistry panel
- Comprehensive RAAS analysis

What are the dosage, frequency, duration, and mode of delivery?

- Placebo controlled, oral
- Blinded
- Short term (2 months) – first step study

COMPARISON / CONTROL

- Is there an alternative intervention or treatment to compare?
  - *Active:* a different drug, dose, or kind of therapy
  - *Inactive:* placebo, standard care, no treatment



<u>Examples:</u>
Incidence rate
“Gold standard” test

COMPARISON / CONTROL

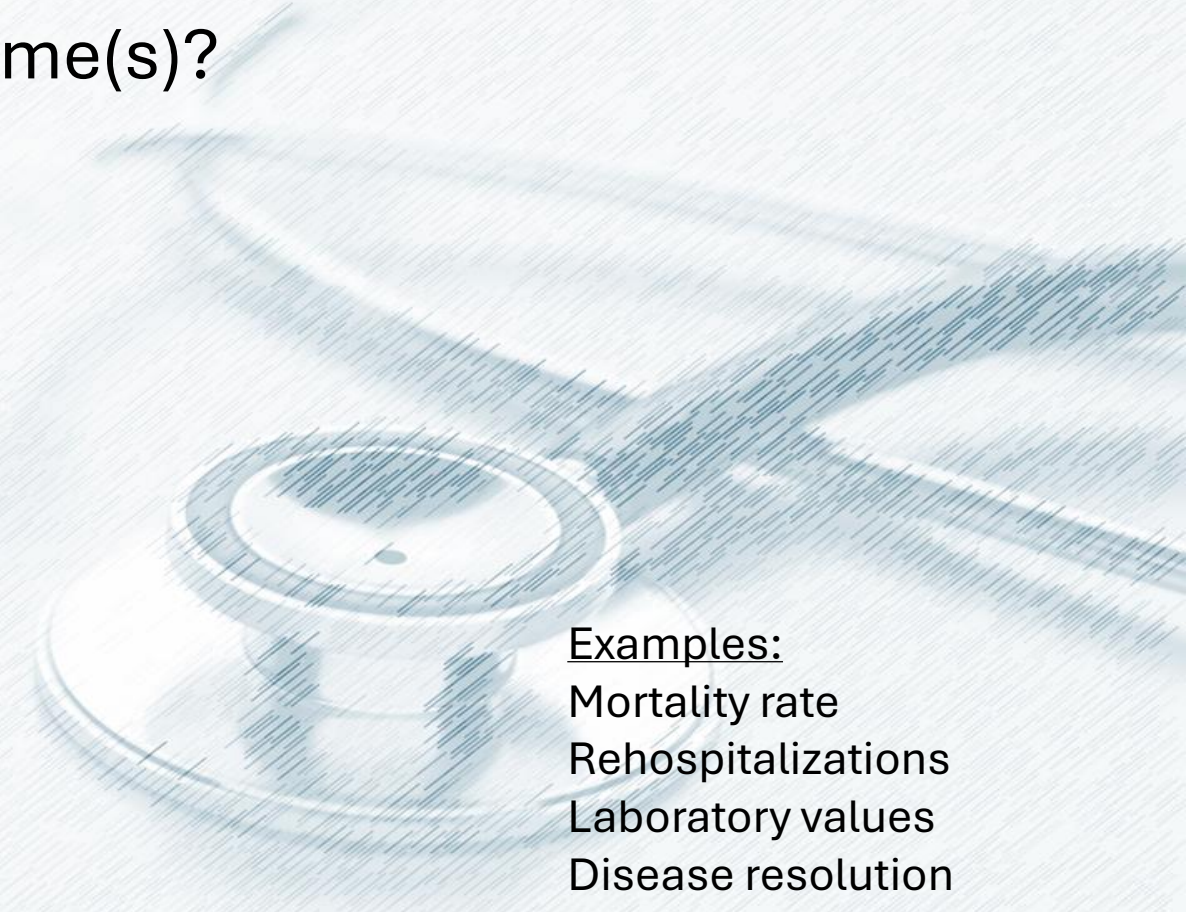
Does oral KCl supplementation raise serum Cl and suppress the RAAS in CHF?

Is there an alternative intervention or treatment to compare?

- Placebo plus standard CHF care for both treatment arms

OUTCOME

- What is(are) the ideal clinical outcome(s)?
  - Specific and measurable
  - Objective or subjective



<u>Examples:</u>
Mortality rate
Rehospitalizations
Laboratory values
Disease resolution
Test sensitivity/specificity

OUTCOME

Does oral KCl supplementation raise serum Cl and suppress the RAAS in CHF?

What is(are) the ideal clinical outcome(s)?

- Normalization of serum chloride concentrations
- RAAS damping
- Absence of adverse effects

TIME

- How much time does it take to demonstrate the clinical outcome(s)?
- Estimated time for study completion

TIME

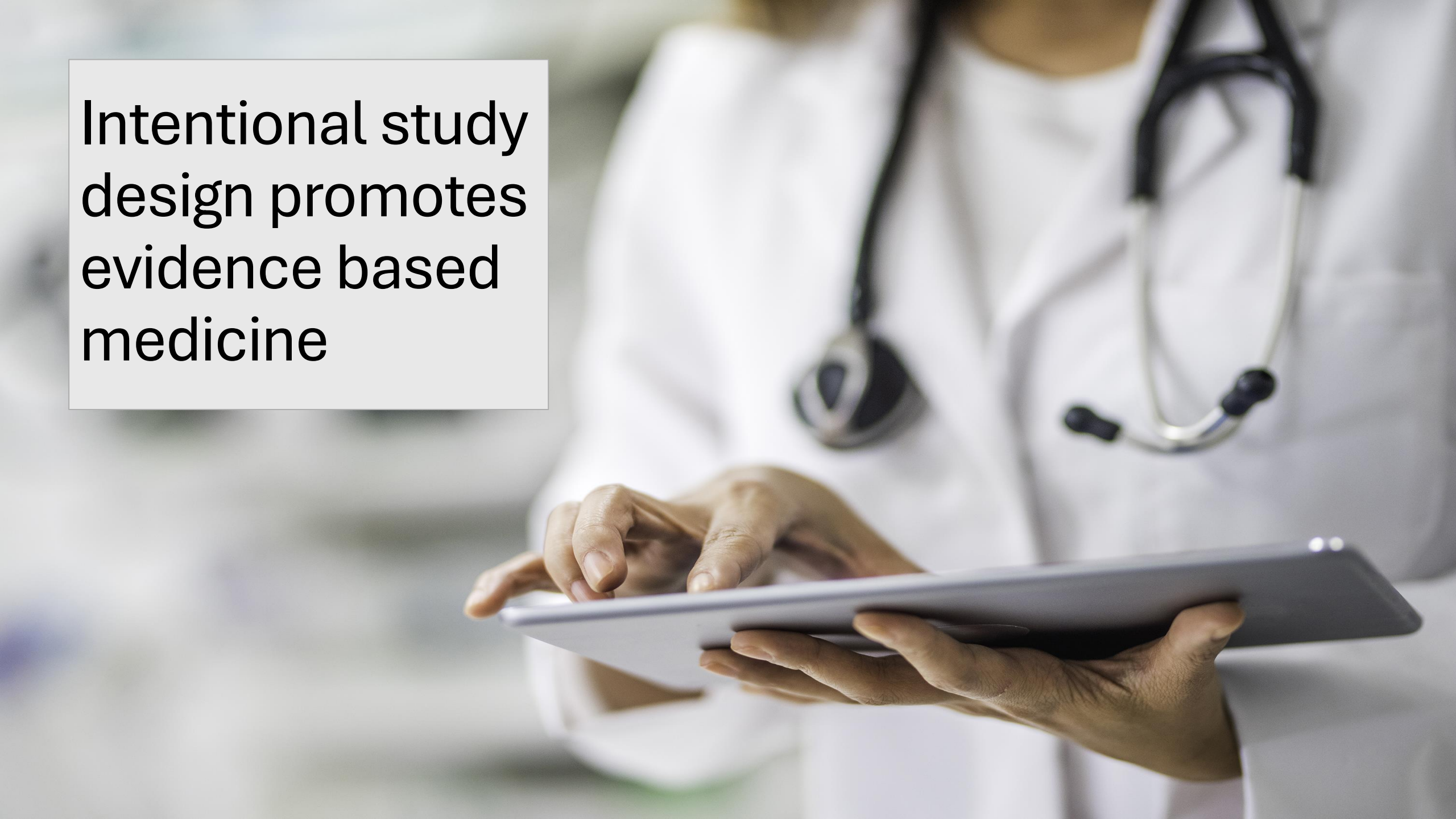
Does oral KCl supplementation raise serum Cl and suppress the RAAS in CHF?

How much time does it take to demonstrate the clinical outcome(s)?

- Feasibility based on hypochloremic CHF caseload
- Short-term study (3 months)
- Future studies to look at outcomes

STUDY TYPE / DESIGN

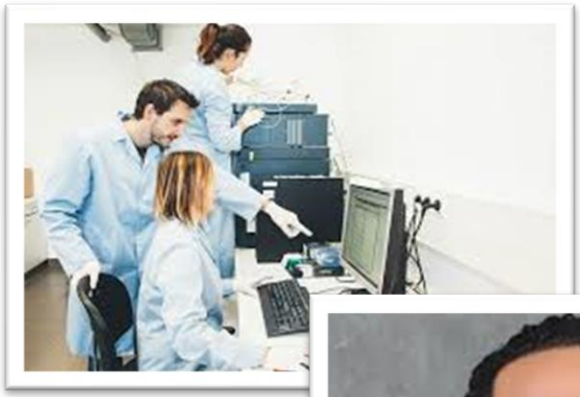
- Observational
  - Prospective, cohort
  - Case control
  - Cross-sectional
  - Retrospective
  - Descriptive
- Experimental
  - Prospective
  - Randomized controlled clinical trial


Intentional study design promotes evidence based medicine

Becoming a clinician scientist: how to complement the clinical training of a residency

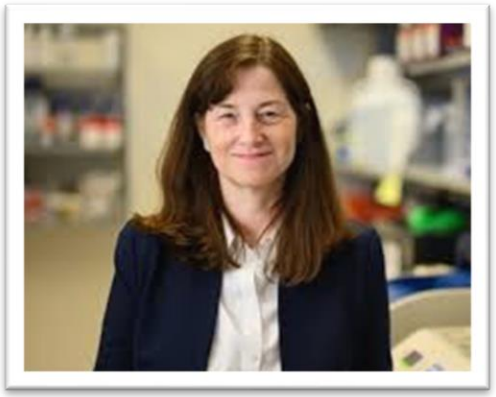
- Collaboration
- Mentorship
- In-residency training and support
- How can I do research when the clinic day is crazy?



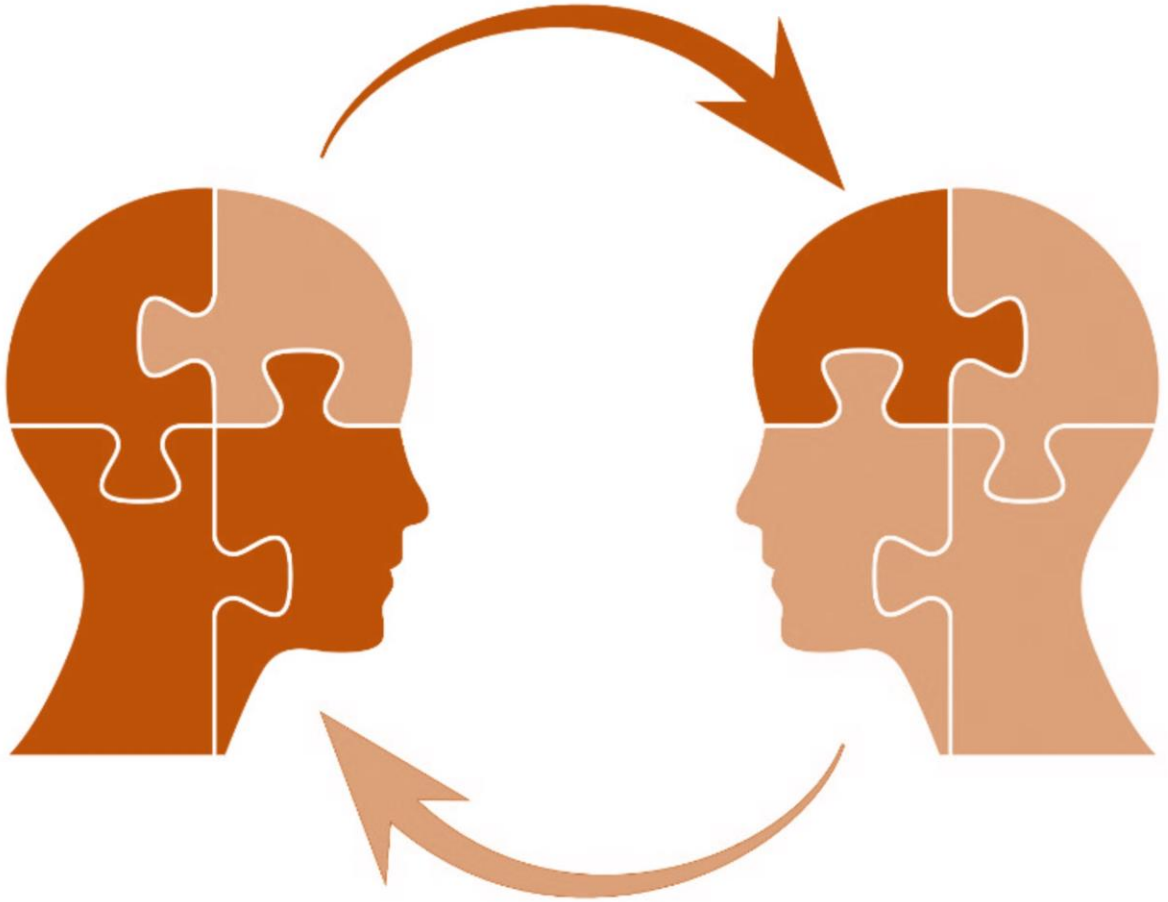



Pursue collaboration





Develop mentor / mentee relationships



https://scse.d.umn.edu/about/faculty-mentoring-program/benefits/mentee

My research journey: the importance of mentorship

J Vet Intern Med 2003;17:632–636

Intermittent Bolus Injection versus Continuous Infusion of Furosemide in Normal Adult Greyhound Dogs

Darcy B. Adin, Aaron W. Taylor, Richard C. Hill, Karen C. Scott, and Frank G. Martin

Several studies in human subjects have demonstrated greater diuresis with constant rate infusion (CRI) furosemide than intermittent bolus (IB) furosemide. This study was conducted to compare the diuretic efficacy of the same total dose of IB furosemide and CRI furosemide in 6 healthy, adult Greyhound dogs in a randomized crossover design with a 2-week washout period between treatments. For IB administration, dogs received 3 mg/kg at 0 and 4 hours. For CRI administration, dogs received a 0.66 mg/kg loading dose followed by 0.66 mg/kg/h over 8 hours. The same volume of fluid was administered for both methods. Urine output was quantified hourly. Urine electrolyte concentrations, urine specific gravity (USG), packed cell volume (PCV), total protein (TP), serum electrolyte concentrations, total carbon dioxide (TCO_2), serum creatinine (sCr), and blood urea nitrogen (BUN) were determined every 2 hours. Urine production and water intake were greater ($P \leq 0.05$) for CRI than IB. Urine sodium and calcium losses were greater ($P < 0.05$) and urine potassium loss was less ($P = 0.03$) for CRI than IB, but there was no evidence of a difference between methods for urine magnesium and chloride losses. Serum chloride concentration was less ($P < 0.001$), sCr concentration greater ($P = 0.04$), TP greater ($P = 0.01$), and PCV greater ($P = 0.003$) for CRI than IB. No differences in USG, TCO_2, BUN, or serum potassium, sodium, and magnesium concentrations were detected between methods. The same total dose of CRI furosemide resulted in more diuresis, natriuresis, and calciuresis and less kaliuresis than IB furosemide in these normal Greyhound dogs over 8 hours, suggesting that furosemide is a more effective diuretic when administered by CRI than by IB.

Key words: Diuretic; Dog; Heart failure; Lasix; Salix.

s are considered the most effective medication he symptomatic treatment of congestive heart HF) in both human and veterinary medicine.[1–3] tics inhibit the renal Na^+-K^+-$2Cl^-$ cotransporter ascending limb of Henle's loop and are consid- st potent class of diuretics.[2,3] These drugs cause s of water, hydrogen ions, and electrolytes, in- lium, potassium, chloride, calcium, and magne- the loop diuretics, furosemide is the most com- scribed in human and veterinary cardiology.[1–3] route, and frequency of furosemide administra- able, depending on the severity of CHF, but it administered IV as an intermittent bolus (IB) 6 hours for the initial treatment of pulmonary ogs.[1] The diuretic effect of IV furosemide lasts hours after each bolus, and rebound sodium and tion because of neurohumoral activation can oc- n doses.[2–4] Continuous rate infusion (CRI) of fu- humans has been shown to result in more di- less intravascular volume shifts than an equiv- ur cumulative dose of furosemide administered sumably resulting in less neurohumoral activa- gh-dose IV bolus injection of furosemide also in toxic blood concentrations, with the specific ototoxicity in people. The administration of CRI overcomes this concern by delivering furose-

epartment of Small Animal Clinical Sciences (Adin, Tay- lt), College of Veterinary Medicine, and the Department Martin), University of Florida, Gainesville, FL.

available. Address correspondence to: Darcy B. Adin, sity of Florida, College of Veterinary Medicine, Depart- ment of Clinical Sciences, P.O. Box 100126, Gainesville, FL 32610; e-mail: adind@mail.vetmed.ufl.edu.

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mide molecules continuously to the nephron with less variation in serum and renal tubular drug concentrations.[8,10]

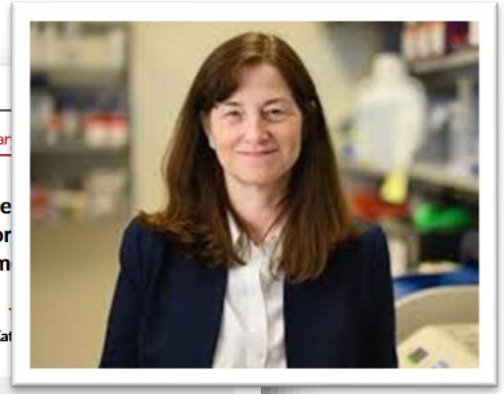
CRI furosemide also has been shown to produce more diuresis than IB in normal horses[11] and in normal dogs given IV fluid replacement[12]; however, it has not been examined in normal dogs in the absence of IV fluid replacement, a situation that would simulate clinical use of the drug in the treatment of CHF. The purpose of this study was to compare the diuretic efficacy of furosemide administered by IB and CRI to normal Greyhound dogs in the absence of IV fluid replacement.

Materials and Methods

The Institutional Animal Care and Use Committee at the University of Florida approved this study. Six healthy, adult Greyhound dogs that were 2 to 4 years of age and weighed 23 to 33 kg (5 males, 1 female) were used. Before the study, dogs received physical examinations, and CBC, serum biochemistry, and urinalysis were performed to verify that the dogs were normal. The study was performed in a randomized, crossover design, whereby dogs received furosemide by CRI or by IB over 8 hours with a 2-week washout period between treatments.

Treatment Protocol

Dogs were weighed before and after each treatment. The general demeanor of the dogs was subjectively observed during each treatment, but the investigators were not blinded to the treatment method administered. Dogs were kept in kennels and monitored continuously without access to food for 2 hours before and during each treatment. An 18-gauge IV catheter was placed in the left cephalic vein for furosemide administration, and another 18-gauge IV catheter was placed in the right cephalic vein for blood sampling. Intravenous catheters were kept patent with saline containing lithium heparin. An 8F red rubber urinary catheter was inserted into the bladder through the urethra and connected to a closed collection system.[9] The urinary bladder was emptied before the start of each baseline period. Urine specific gravity (USG) was determined with a refractometer before each treatment. For both methods of administration, 50 mg/mL furosemide[9] was diluted with 5% dextrose in water to a final concentration of 10 mg/mL on each study day.[10] This procedure allowed the CRI to flow at a rate that maintained catheter patency. A 2-hour baseline period (−2 to 0 hours) preceded drug administration (time 0), and dogs were mon-



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STANDARD ARTICLE

Journal of Veterinar

Renin-angiotensin aldosterone profile be angiotensin-converting enzyme-inhibitor dogs with angiotensin-converting enzym

Darcy Adin[1] | Clarke Atkins[2] | Oliver Domenig[3] | Bruce Keene[2] | Sandra Tou[2] | Joshua A. Stern[4] | Kat

[1]College of Veterinary Medicine, University of Florida, Gainesville, Florida

[2]College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina

[3]Attoquant Diagnostics, Vienna, Austria

[4]Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California

Correspondence
Darcy Adin, College of Veterinary Medicine, University of Florida, 2015 SW 16th Avenue, Gainesville, FL 32608.
Email: adind@ufl.edu

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Abstract

Background: An angiotensin-converting enzyme (ACE) gene polymorphism occurs in dogs; however, functional importance is not well studied.

Hypothesis: We hypothesized that dogs with the polymorphism would show alternative renin-angiotensin aldosterone system (RAAS) pathway activation and classical RAAS pathway suppression before and after ACE-inhibitor administration, as compared to dogs without the polymorphism that would show this pattern only after ACE-inhibitor administration.

Animals: Twenty-one dogs with mitral valve disease that were genotyped for the ACE gene polymorphism.

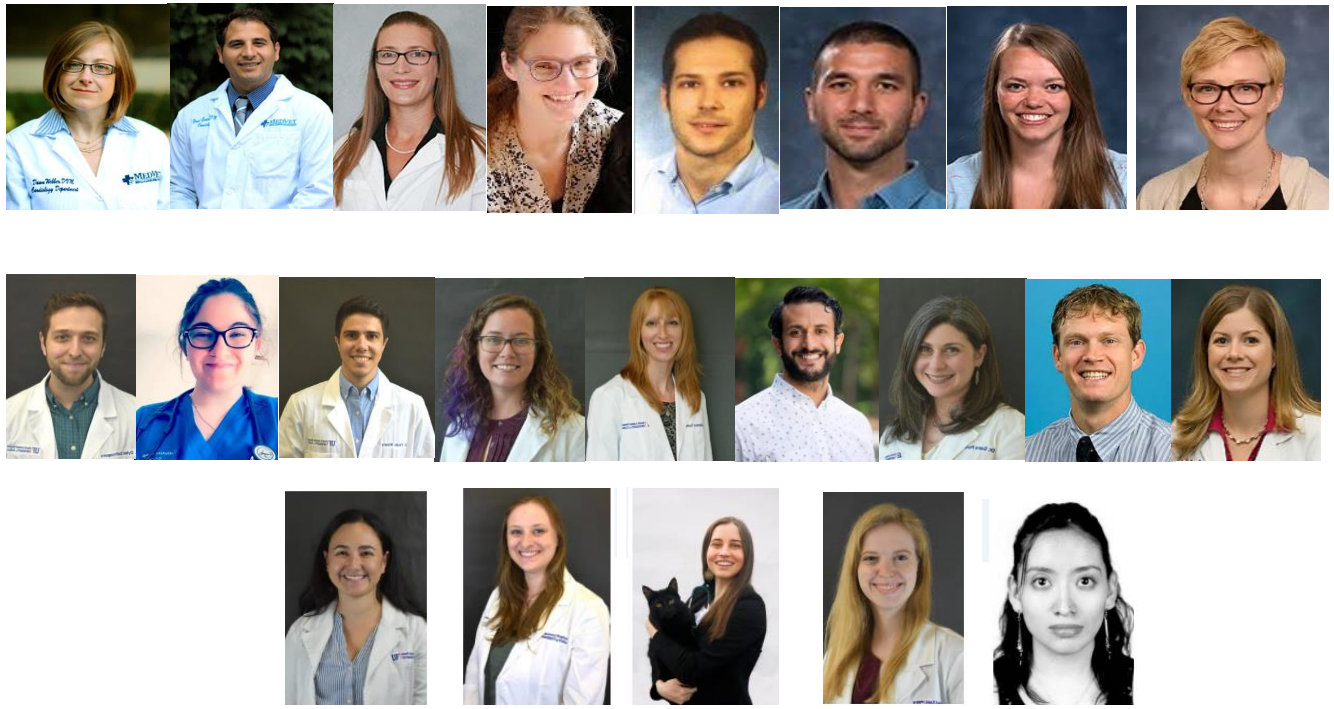
Methods: This retrospective study utilized stored samples from 8 ACE gene polymorphism-negative (PN) dogs and 13 ACE gene polymorphism-positive (PP) dogs before and after enalapril administration. Equilibrium analysis was performed to evaluate serum RAAS metabolites and enzyme activities. Results were compared before and after enalapril, and between groups.

Results: The classical RAAS pathway was suppressed and the alternative RAAS pathway was enhanced for both genotypes after administration of enalapril, with no differences before enalapril administration. Aldosterone breakthrough occurred in both PN (38%) and PP (54%) dogs despite angiotensin II suppression. Aldosterone was significantly higher ($P = .02$) in ACE gene PP dogs (median, 92.17 pM; IQR, 21.85-184.70) compared to ACE gene PN dogs (median, 15.91 pM; IQR, <15.00-33.92) after enalapril.

Conclusions and Clinical Importance: The ACE gene polymorphism did not alter baseline RAAS activity. Aldosterone breakthrough in some dogs suggests non-angiotensin mediated aldosterone production that might be negatively influenced by genotype. These results support the use of aldosterone receptor antagonists with

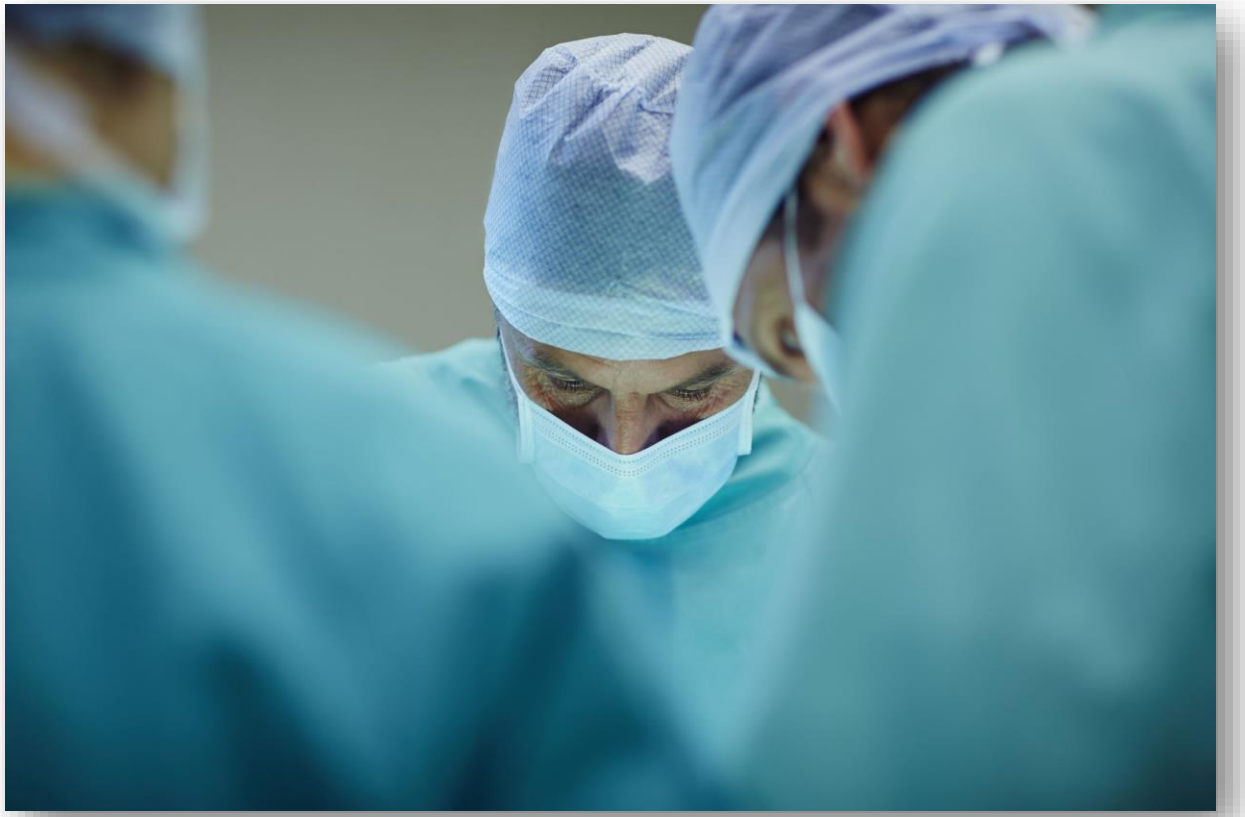
Abbreviations: AA2, aldosterone to angiotensin II ratio; ABT, aldosterone breakthrough; ACE, angiotensin-converting enzyme; ACE-S, angiotensin-converting enzyme activity marker; PCR, polymerase chain reaction; PN, polymorphism negative; PP, polymorphism positive; PRA-S, plasma renin activity marker; RAAS, renin-angiotensin aldosterone system.

Becoming faculty means giving back through mentorship at the same time as being mentored



Success is not counted by how high you have climbed
but by how many people you brought with you
Dr. Wil Rose

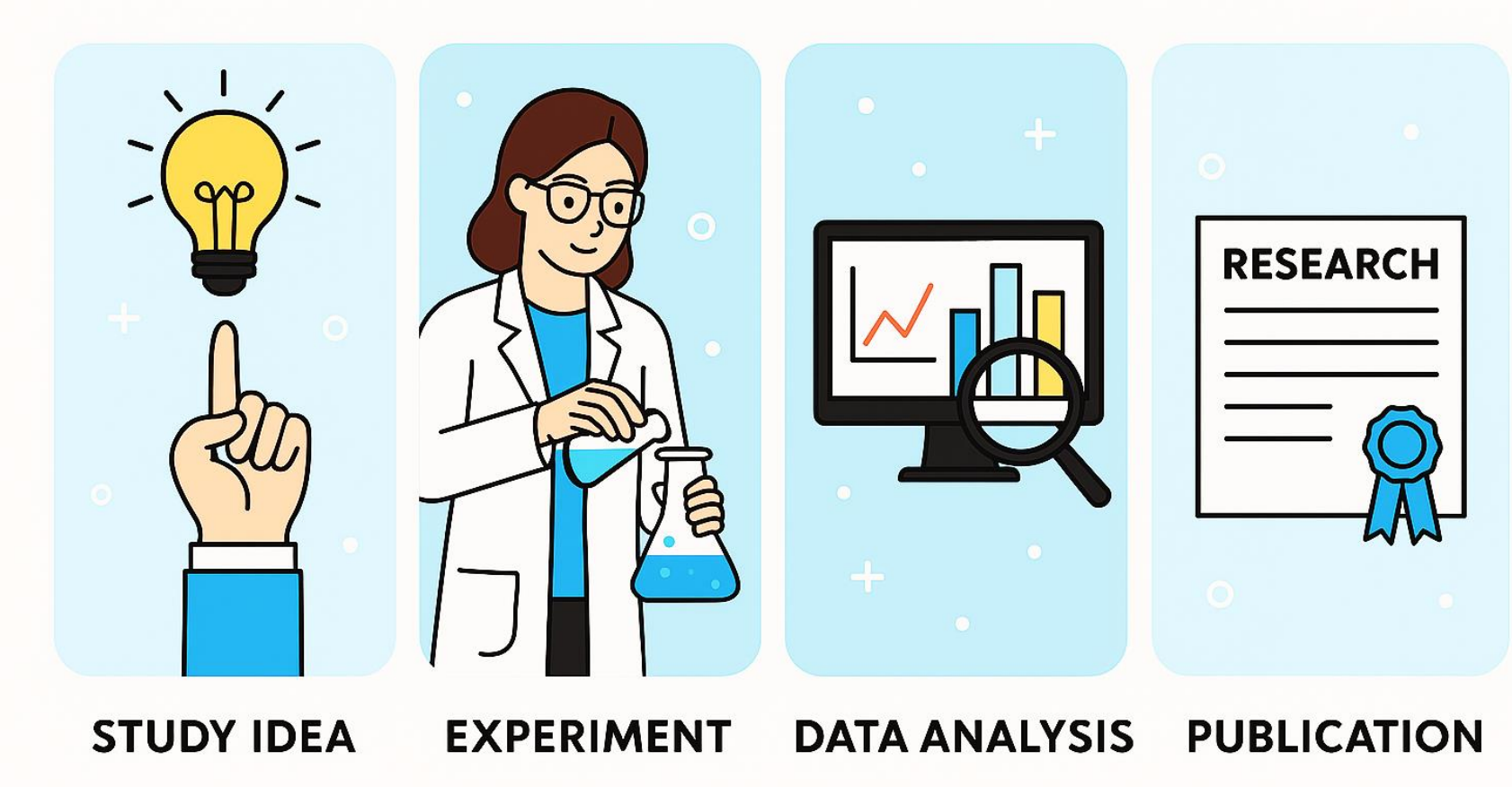
How can I do research when the clinic day is crazy? Dovetailing research with clinics



Congrats!

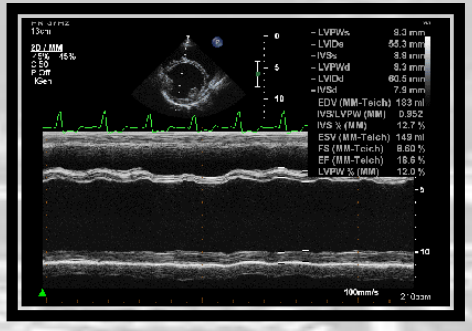
You designed a great study, got funding, carried out the study, presented at a meeting, wrote a manuscript, and got it published!

What's next?

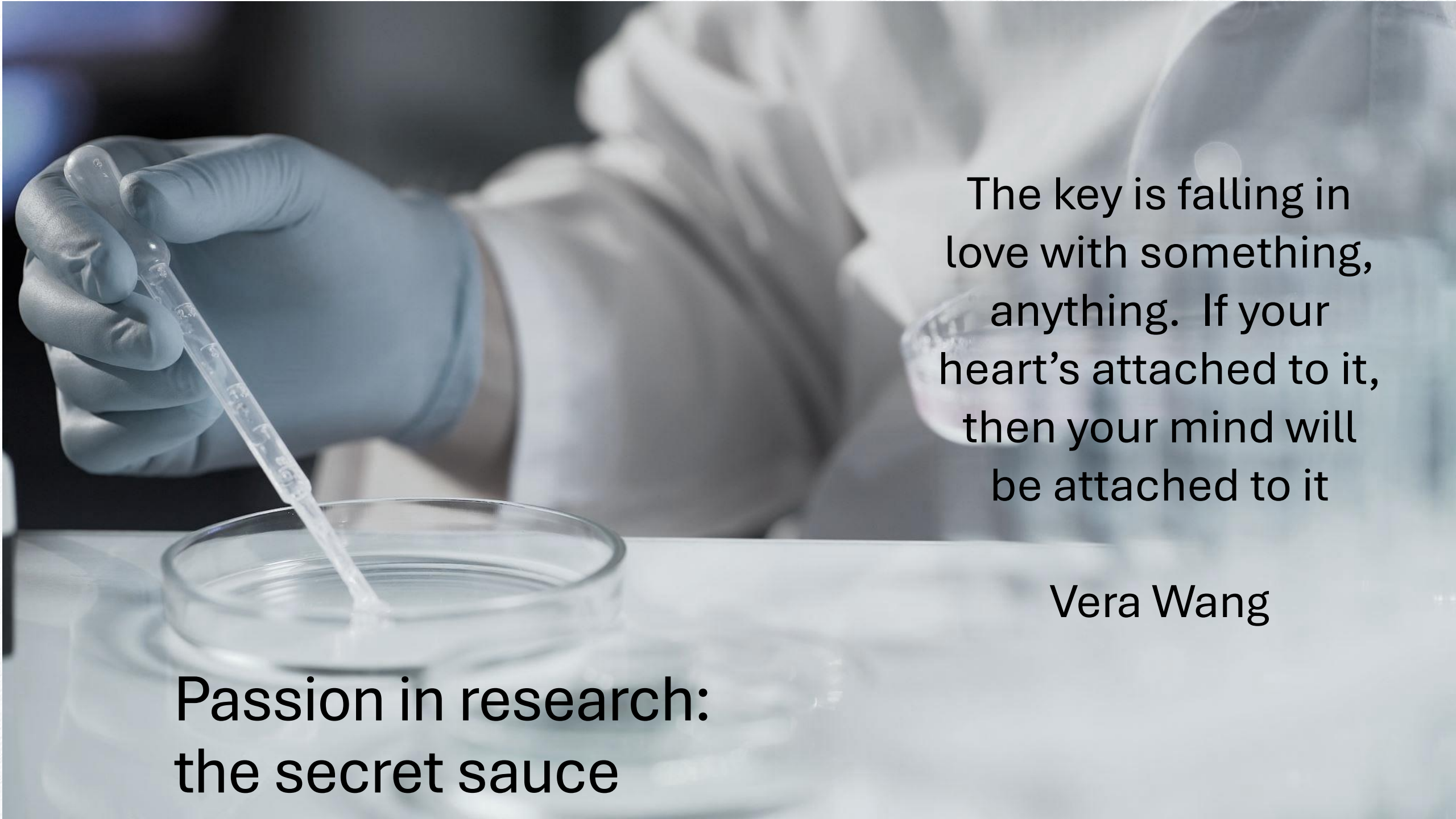


Challenges: What if the study is a dead end?

- “This is why we call it re-search”……
- Interests and opportunities change
- Side bars are ok



And what if my interests change?



The key is falling in love with something, anything. If your heart's attached to it, then your mind will be attached to it

Vera Wang

Passion in research: the secret sauce