RAAS inhibition in the treatment of Congestive Heart Failure

Prof Johan P Schoeman

BVSc, MMedVet, PhD, DSAM, Dipl. ECVIM-CA, FRCVS

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UNIVERSITEIT VAN PRETORIA
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Introduction

- **Chronic RAAS activation promotes**
  - Congestive heart failure
  - Systemic hypertension
  - Chronic kidney disease

- **Excessive Angiotensin II (Ang II) & Aldosterone**
  - Pro-fibrotic
  - Pro-inflammatory
  - Pro-hypertrophic milieu

Introduction (2)

- **Increased understanding of the role of the RAAS**
  - Led to numerous RAAS suppressive therapies
  - This helps us to modulate the system
  - Improve quality of life and survival

- **This presentation will focus on**
  - An update on new findings on the RAAS
  - Developments in RAAS suppressive therapy
  - Congestive heart failure

A brief overview of the RAAS

- **RAAS activation is compensatory in early stages**
  - Improves cardiac output
  - Increases blood pressure
  - Retains sodium and excretes potassium

- **Long-term activation is maladaptive**
  - Numerous adverse effects at multiple sites

TABLE 1 Aldosterone and angiotensin II: harmful cardiovascular and renal effects

Adverse effect	Direct effects of angiotensin II	Direct effects of aldosterone
Myocardial remodeling: fibrosis, hypertrophy, necrosis, apoptosis	Yes	Yes
Vascular remodeling: hypertrophy, fibrosis	Yes	Yes
Increase ROS	Yes	Yes
Pro-inflammatory (cytokines, ROS)	Yes	Yes
Arrhythmogenic	Yes	Yes
Vascular endothelial dysfunction (ET-1, vasopressin, acetylcholine-mediated vasodilatory dysfunctin)	Yes	Yes
Systemic hypertension	Yes	Yes
Glomerular damage	Yes	Yes
Glomerular dysfunction: proteinuria	Yes	Yes
Increased intraglomerular pressure	+++ (vasoconstriction)	+ (fluid retention & SNS)
Tubulointerstitial injury	Yes	Yes
Baroreceptor dysfunction→HR increase	Maybe	Yes
Increased SNS tone	Yes	Yes
Inotropy	Yes	No
Direct HR increase	Yes	No
Salt appetite	Yes	Yes
Increased thirst	Yes	No
Na^+ and H_2O retention, congestion	Yes	Yes
K^+ wasting	No	Yes

Abbreviations: ET-1, endothelin 1; HR, heart rate; SNS, sympathetic nervous system activation; ROS, reactive oxygen species.

RAAS suppressive strategies

- ACE – inhibitors (ACEi)
- Angiotensin II, type 1-receptor blockers (ARB)
- Mineralocorticoid receptor antagonists (MRA)

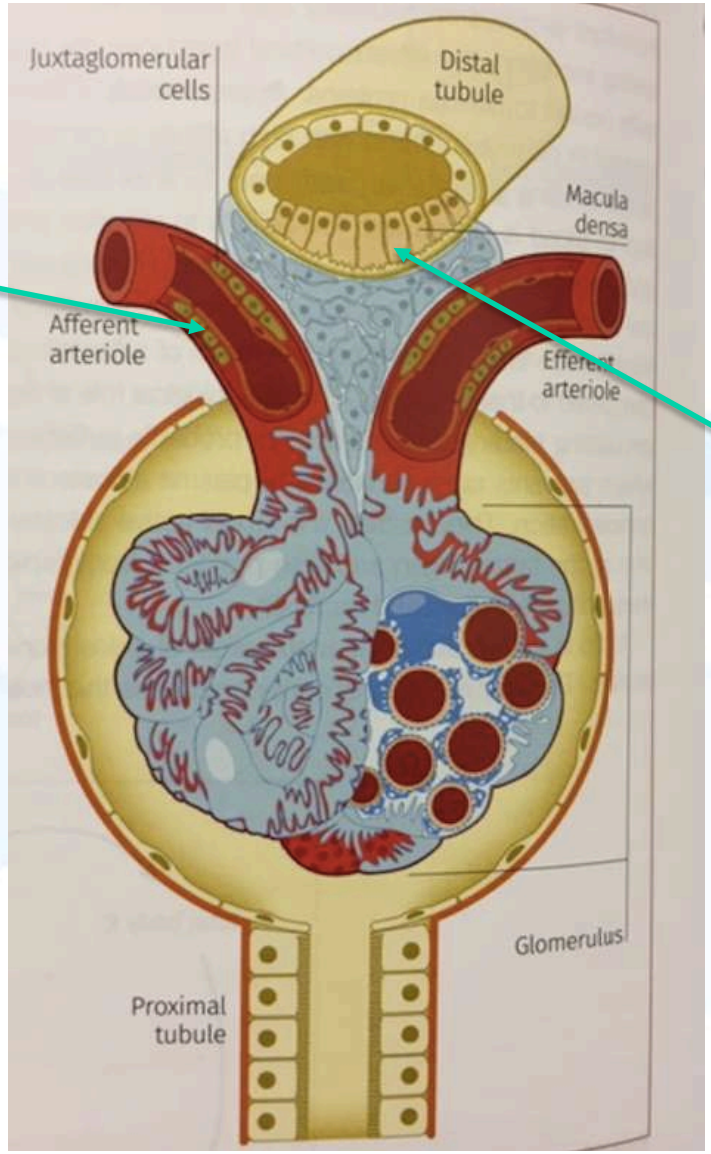
- Reduced efficacy of RAAS blockade
  - Redundancy that bypass the blockade (Aldosterone escape)
  - Suppression of beneficial components (Bradykinin)
  - Concomitant therapy that stimulate the RAAS
    - Furosemide, Amlodipine, Hydralazine, low salt diet….

Not all ACE-inhibitors are the same

- Benazepril (biliary and renal excretion)
- Enalapril (primarily excreted by the kidney)
- Ramipril (quite selective)
- Captopril, lisinopril, imidapril and elecapril
  - Differences in structure of active moieties
  - Lipophilicity
  - Bioavailability
  - Affinity for tissue – ACE
  - Elimination method

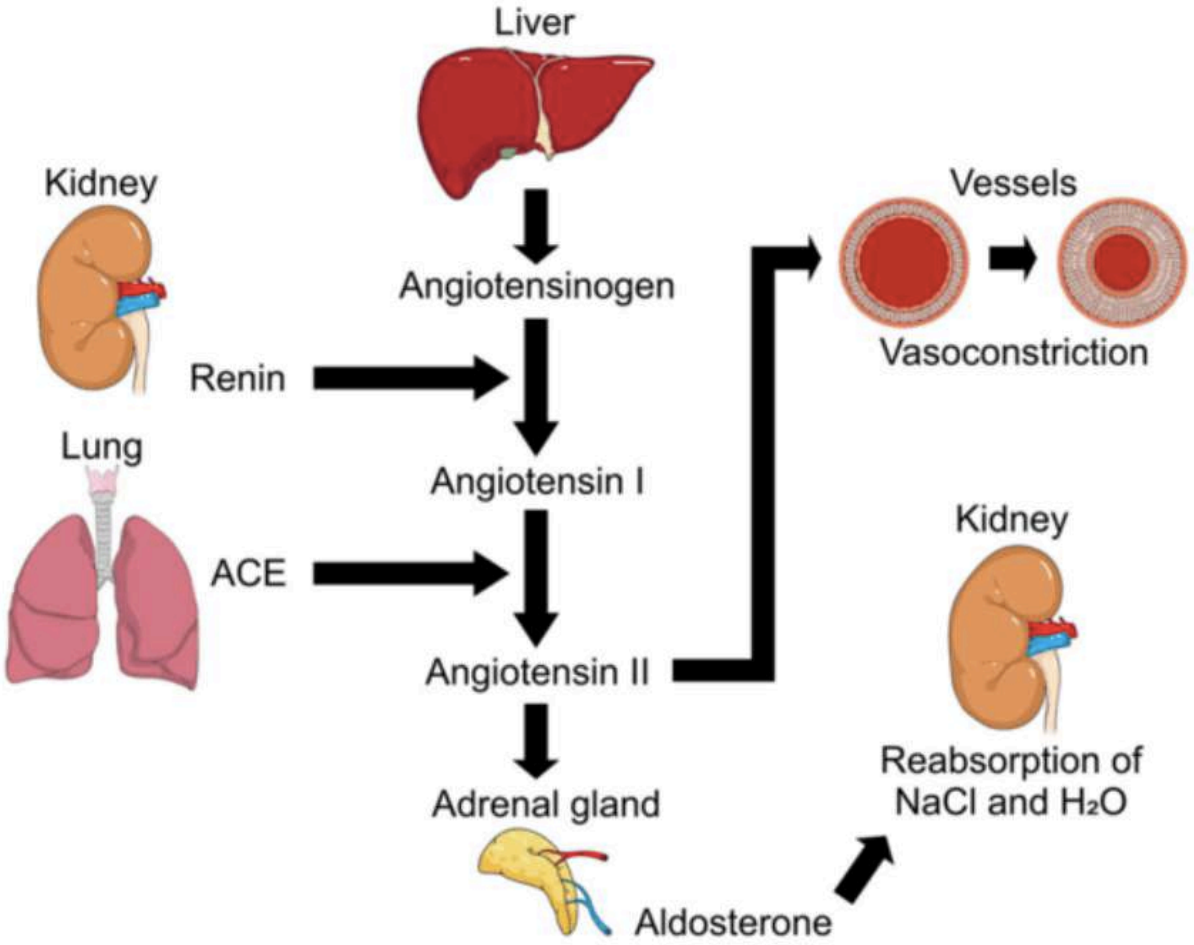
Pathophysiology…….(1)…JGA

Vascular baroreceptors in the afferent arteriole stimulate **renin** release in response to reduced **renal perfusion pressure**, such as following reduced **cardiac output**

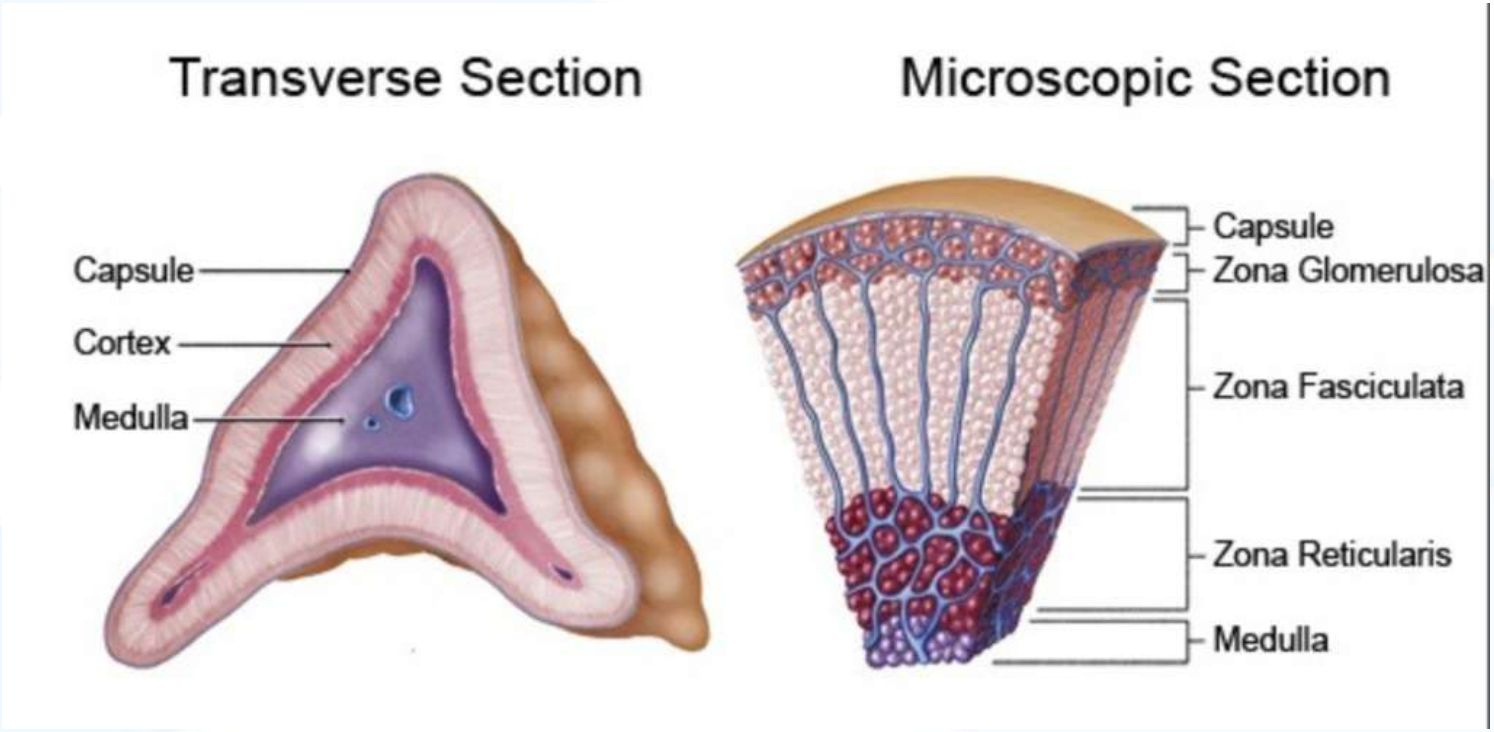


The macula densa in the distal tubule, adjacent to the afferent arteriole, senses **low distal tubular Na^+ & Cl^- delivery**, resulting in renin release

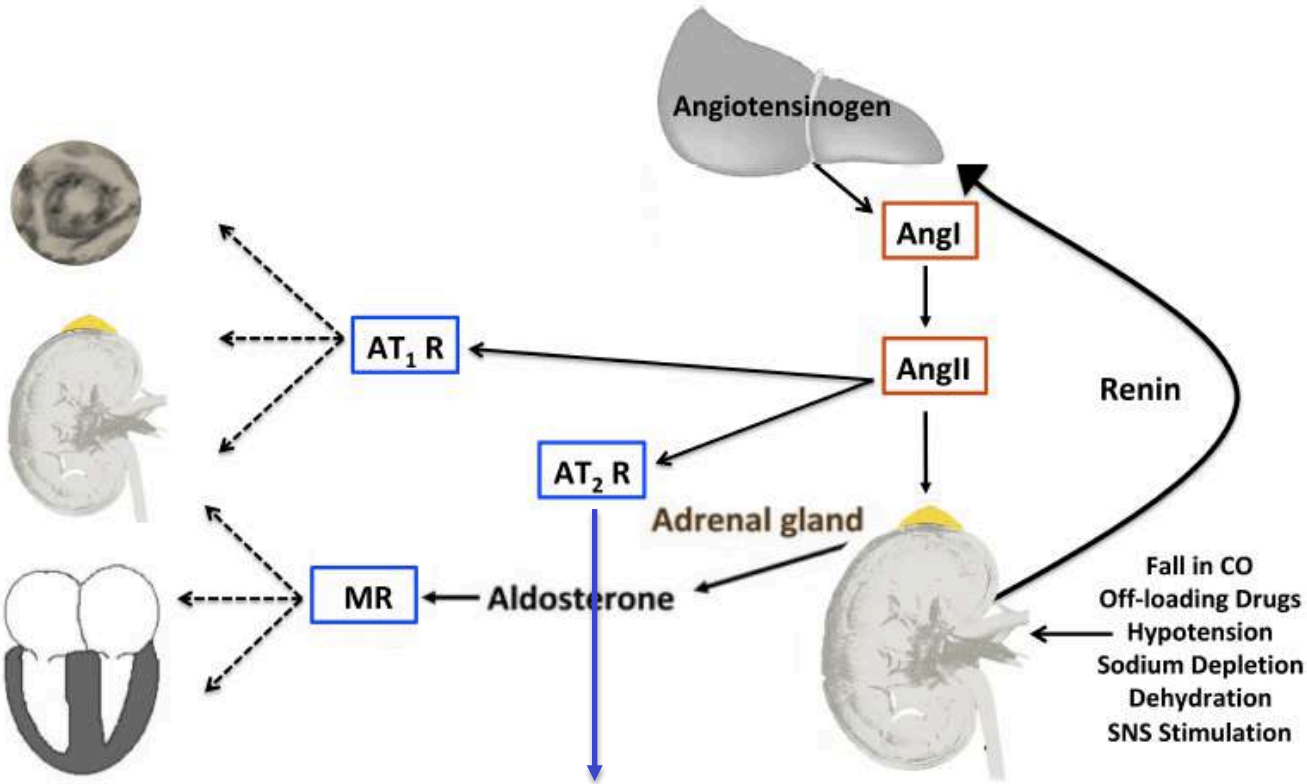
Pathophysiology (2)…RAAS components



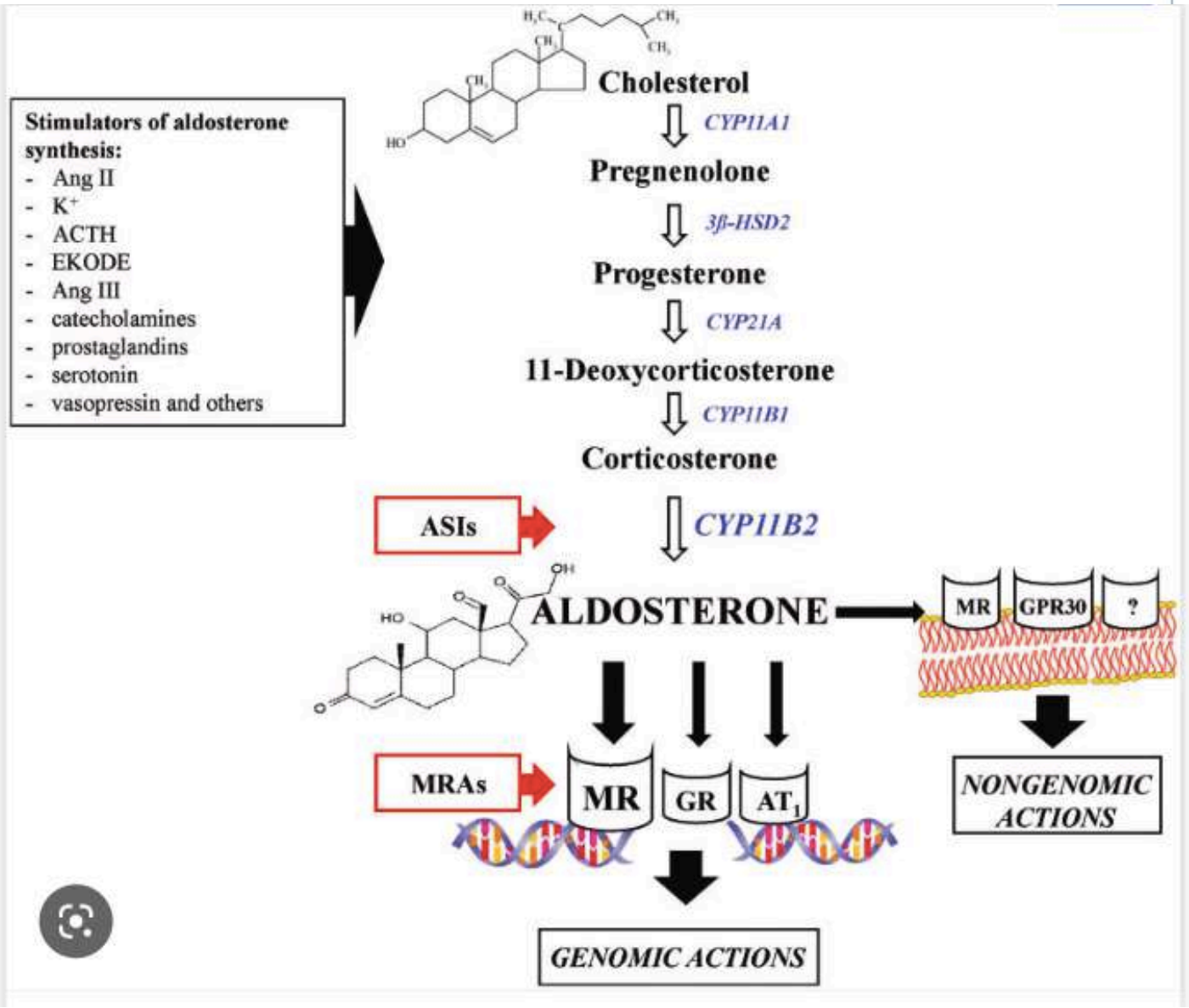
Adrenal gland



Pathophysiology (3)…..RAAS receptors



Anti-inflammatory
Anti-fibrotic
Vasodilatory


Stimulators of aldosterone synthesis:
- Ang II
- K+
- ACTH
- EKODE
- Ang III
- catecholamines
- prostaglandins
- serotonin
- vasopressin and others
Cholesterol
CYP11A1
Pregnenolone
3β-HSD2
Progesterone
CYP21A
11-Deoxycorticosterone
CYP11B1
Corticosterone
ASIs
CYP11B2
ALDOSTERONE
MR
GPR30
?
NONGENOMIC ACTIONS
MRAs
MR
GR
AT1
GENOMIC ACTIONS

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healthcare

Chronobiology of the renin-angiotensin-aldosterone system in dogs: relation to blood pressure and renal physiology†

Jonathan P. Mochel[1,2], Martin Fink[2], Mathieu Peyrou[3], Cyril Desevaux[4], Mark Deurinck[5], Jérôme M. Giraudel[6], and Meindert Danhof[1]

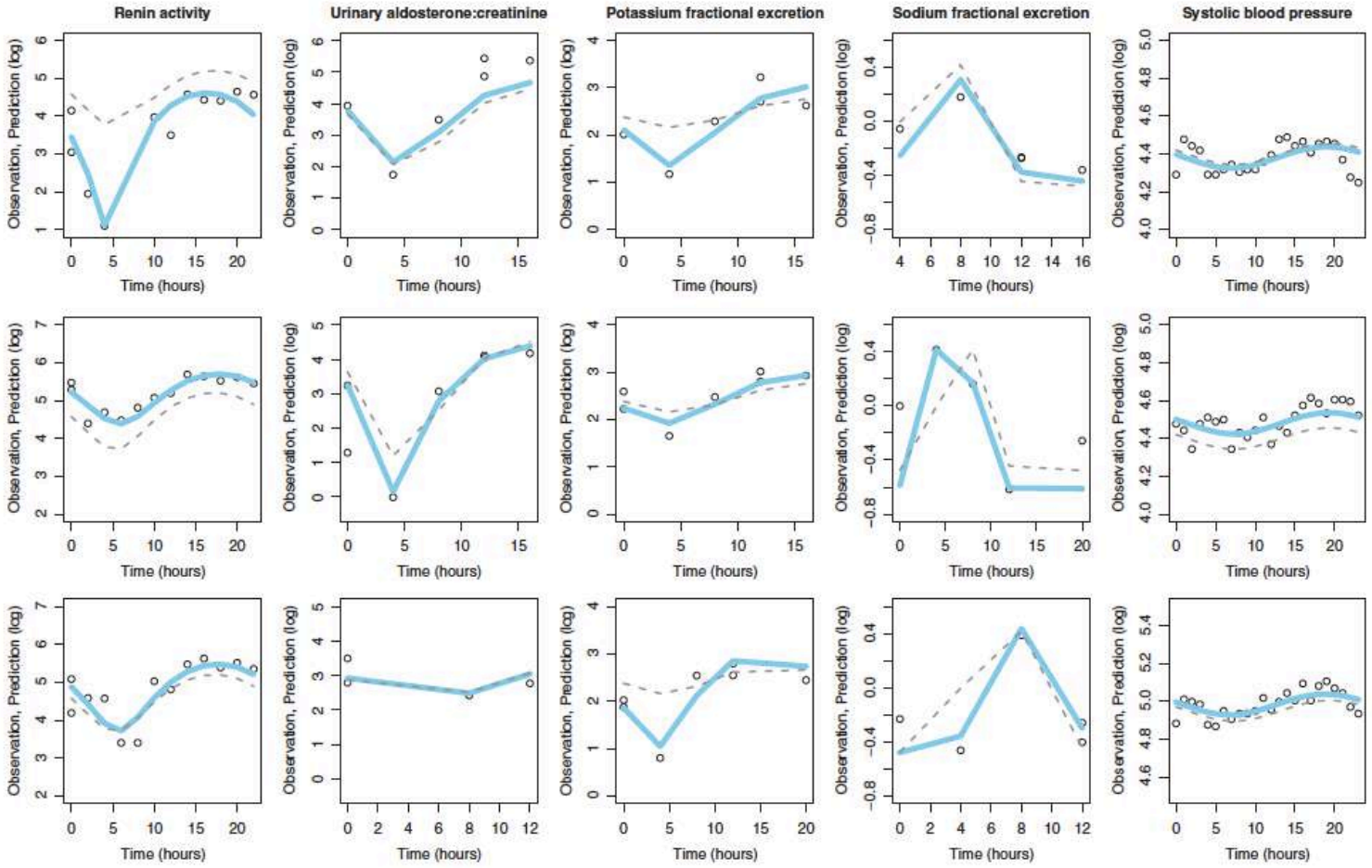
[1]Department of Pharmacology, Leiden-Academic Centre for Drug Research, Leiden, The Netherlands, [2]Department of Modeling and Simulation, Novartis Campus St. Johann, Basel, Switzerland, [3]Department of Therapeutics Research,

Might be important in determining the time-dependent efficacy of RAAS suppression

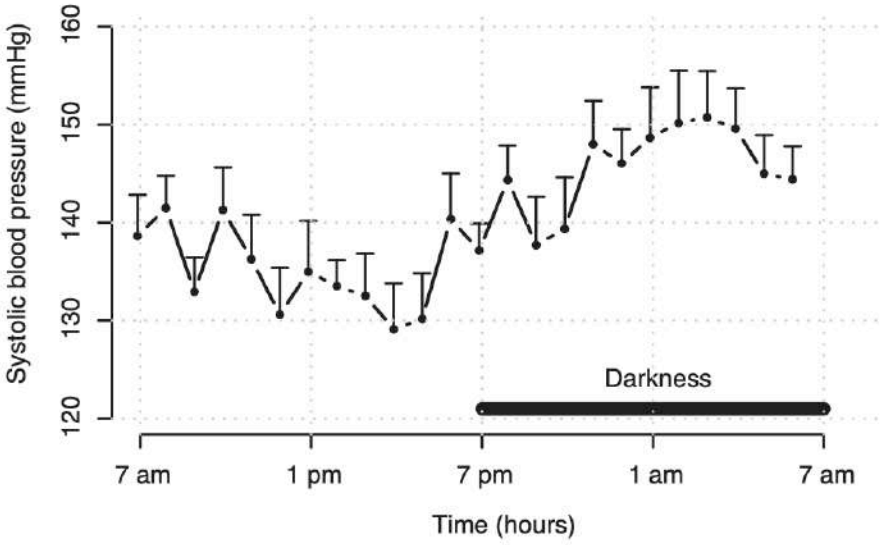
Chronobiology of the RAAS (1)

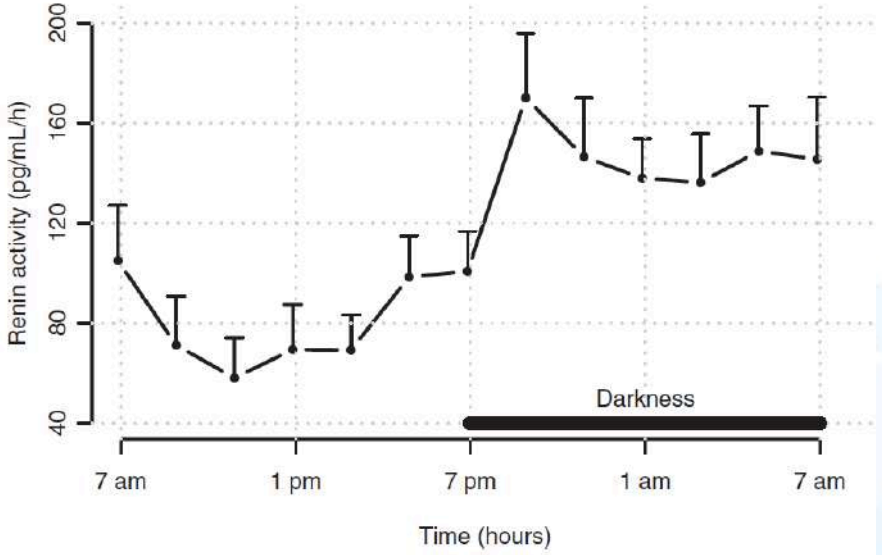
- RAAS peptides and ADH in a circadian periodicity
- Day-night-variation
  - Urine flow
  - Urinary electrolyte excretion
  - Blood pressure

- Timing of feeding affects these rhythms
- Dietary sodium is a key modulator
- Improved understanding will inform timing of the drugs

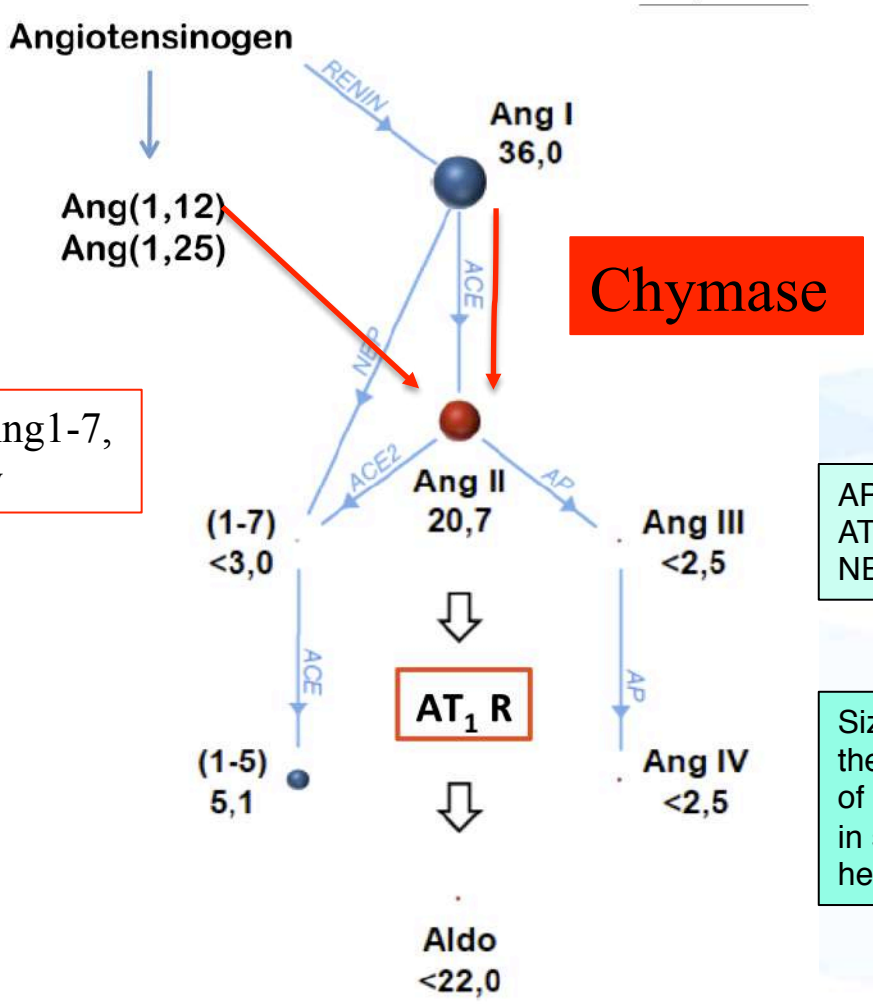

Renin activity
Urinary aldosterone:creatinine
Potassium fractional excretion
Sodium fractional excretion
Systolic blood pressure
Observation, Prediction (log)
Time (hours)

Chronobiology of the RAAS (2)





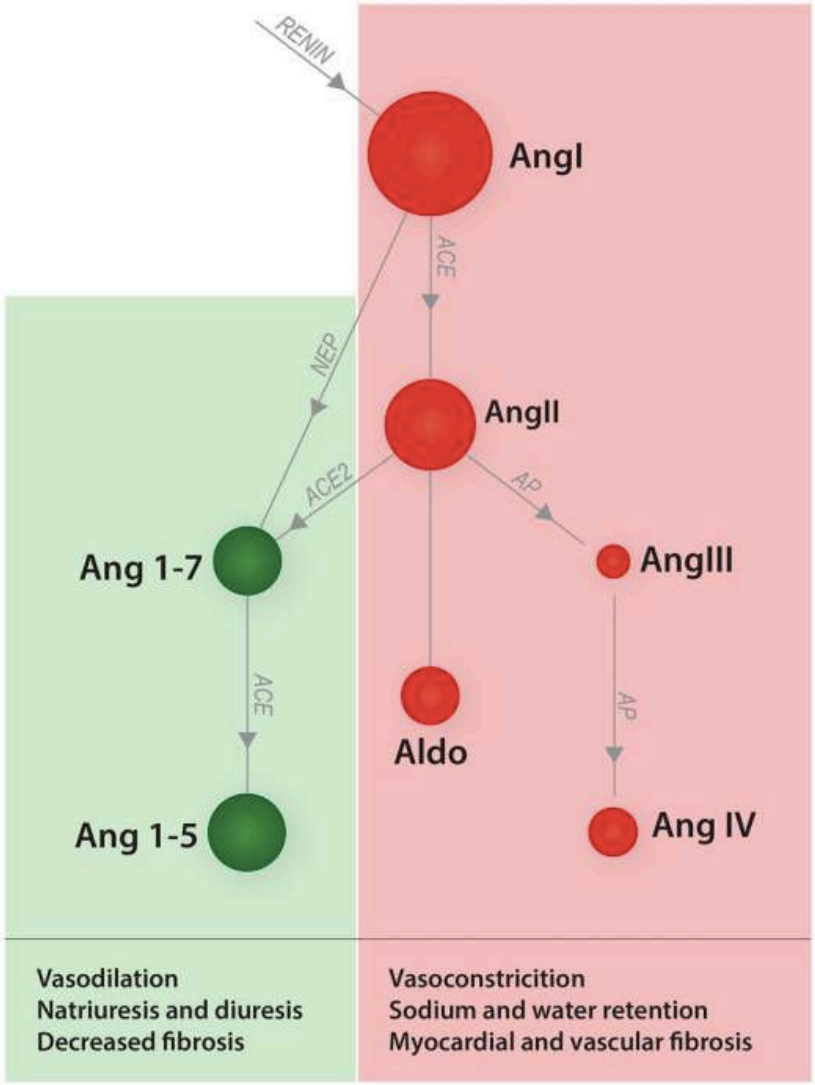
Assessment of RAAS activity – RAAS fingerprint



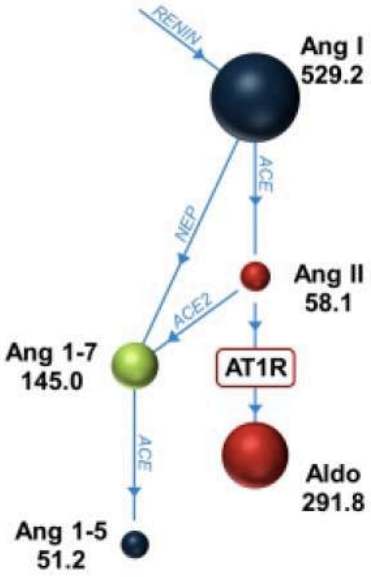
Counter-regulatory Ang1-7, vasodilatory pathway

AP = aminopeptidase
AT_1R = Angiotensin type-1 receptor
NEP = neutral endopeptidase

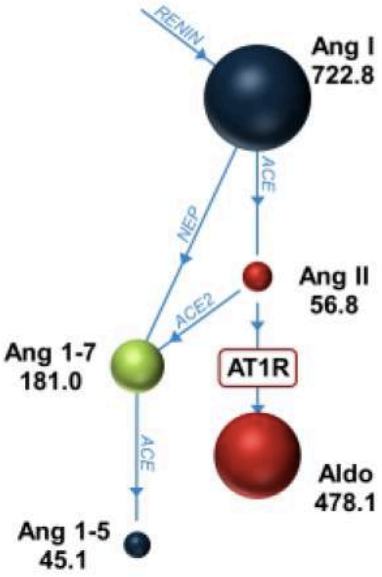
Size of spheres and numbers beside them represent absolute concentrations of angiotensins (pg/mL, median values) in serum samples from 6 middle-aged, healthy male Beagles


RENIN
AngI
ACE
NEP
AngII
ACE2
AP
Ang 1-7
AngIII
ACE
Aldo
AP
Ang 1-5
Ang IV
Vasodilation
Natriuresis and diuresis
Decreased fibrosis
Vasoconstricition
Sodium and water retention
Myocardial and vascular fibrosis

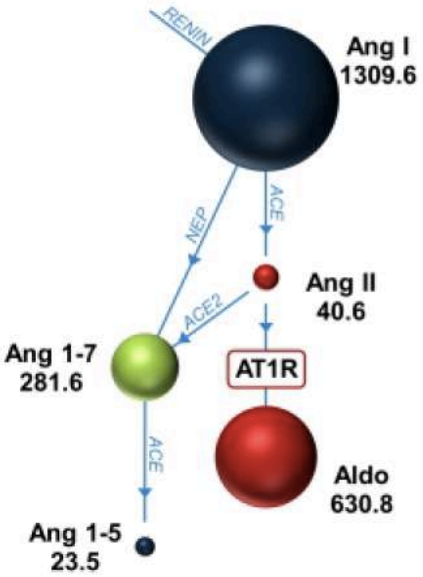
Label dose q24hr



Label dose q12hr



Double label dose q12hr



Assessment of RAAS activity

- Plasma renin activity
- Direct plasma renin levels
- Serum Aldosterone
- Serum Angiotensin II
- Plasma ACE activity
- Urine/Serum Na/K ratios
- Urinary fractional excretion (Na_{fe} and K_{fe})
- 24-hour urinary aldosterone excretion
- Urinary Aldosterone/Creatinine ratio

Genetic profiling of specific populations and individuals will also likely play a role in the development of future RAAS modulation strategies.

Ang II & aldosterone as cardiac & renal toxins (1)

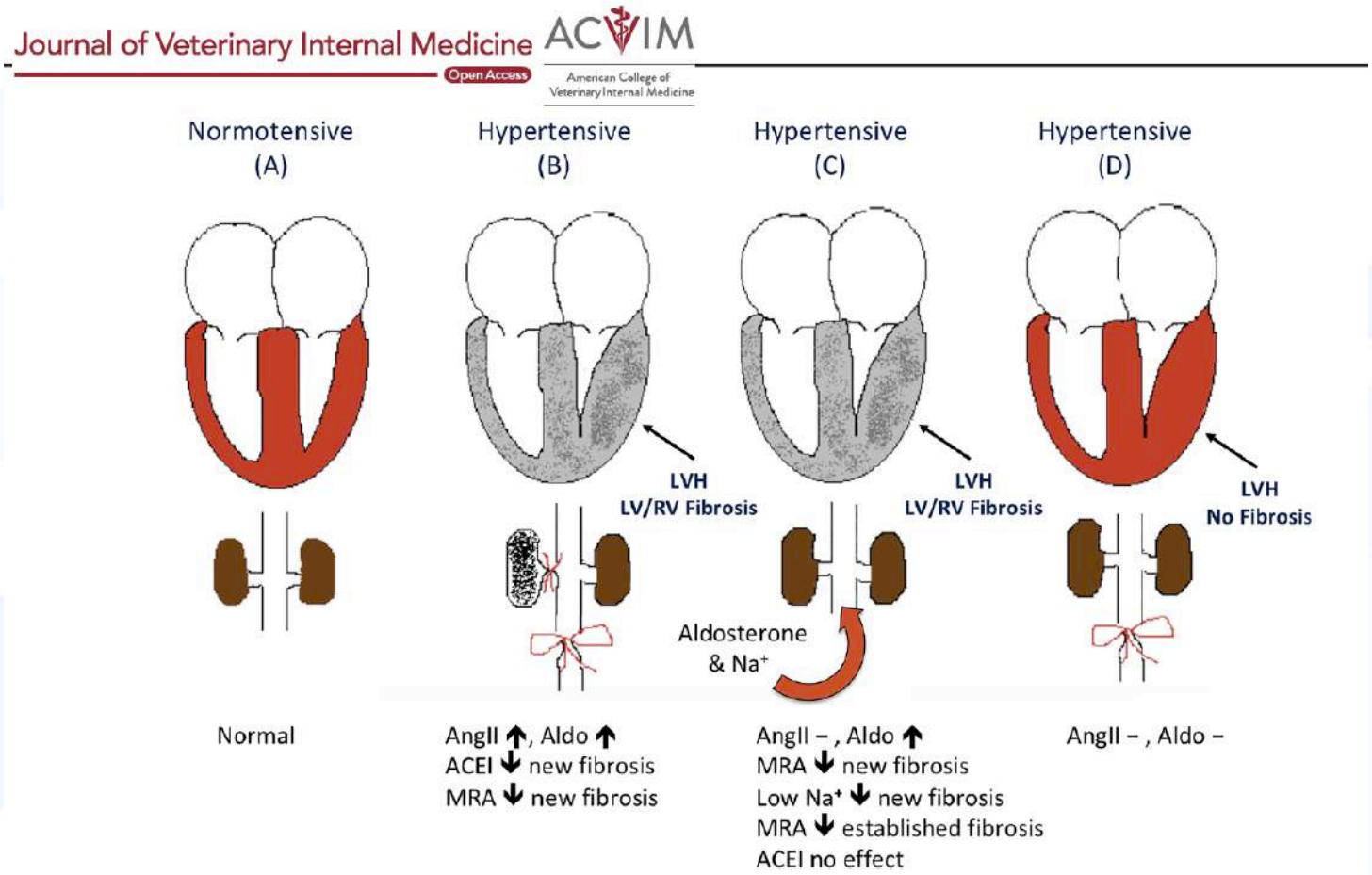
- Fibrosis that accompanies the remodeling
- Leads to myocardial, renal and vascular dysfunction
- Multifactorial mechanisms
  - Fibroblast stimulation
  - Generation of ROS
  - Inflammation via immune cell infiltration

- Aldosterone excess decreases baroreceptor sensitivity
  - Leads to undesirable tachycardia

Ang II & Aldosterone as cardiac & renal toxins (2)

- **More specifically the MR on macrophages gets stimulated**
  - Change from the anti-inflammatory M2-subtype
  - To the pro-inflammatory M1-subtype
  - Perpetuating inflammation & tissue remodeling

“Toxic” effects of Angiotensin II and Aldosterone



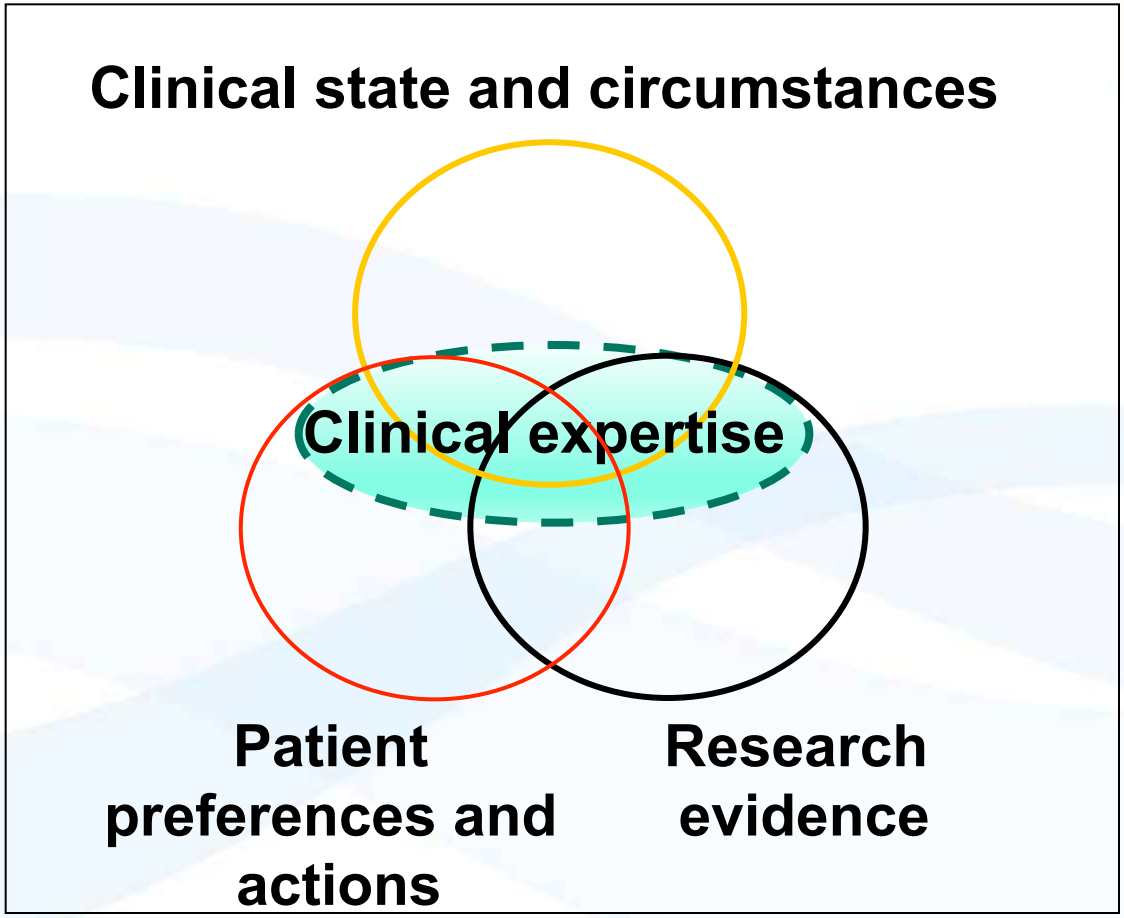
In sum…..(1)

- Chronic RAAS activation is maladaptive
- Direct “toxic effects of both Aldosterone and Ang II
- AT1R – vasoconstricting
- AT2R – vasodilatory
- Tissue RAAS generated by chymase pathway
- Various Ang peptides including the vasodilatory Ang1-7
- RAAS chronobiology unique to the dog

In sum…..(2)

- Individual RAAS fingerprinting likely in different dog breeds
- The MR is widely distributed throughout the body
- MR stimulation can change M2 to M1 phenotype
- Cortisol breakdown enzyme 11B-HSD2 scarce in the myocardium
- Role of ACE-I and MRA's in reducing fibrosis

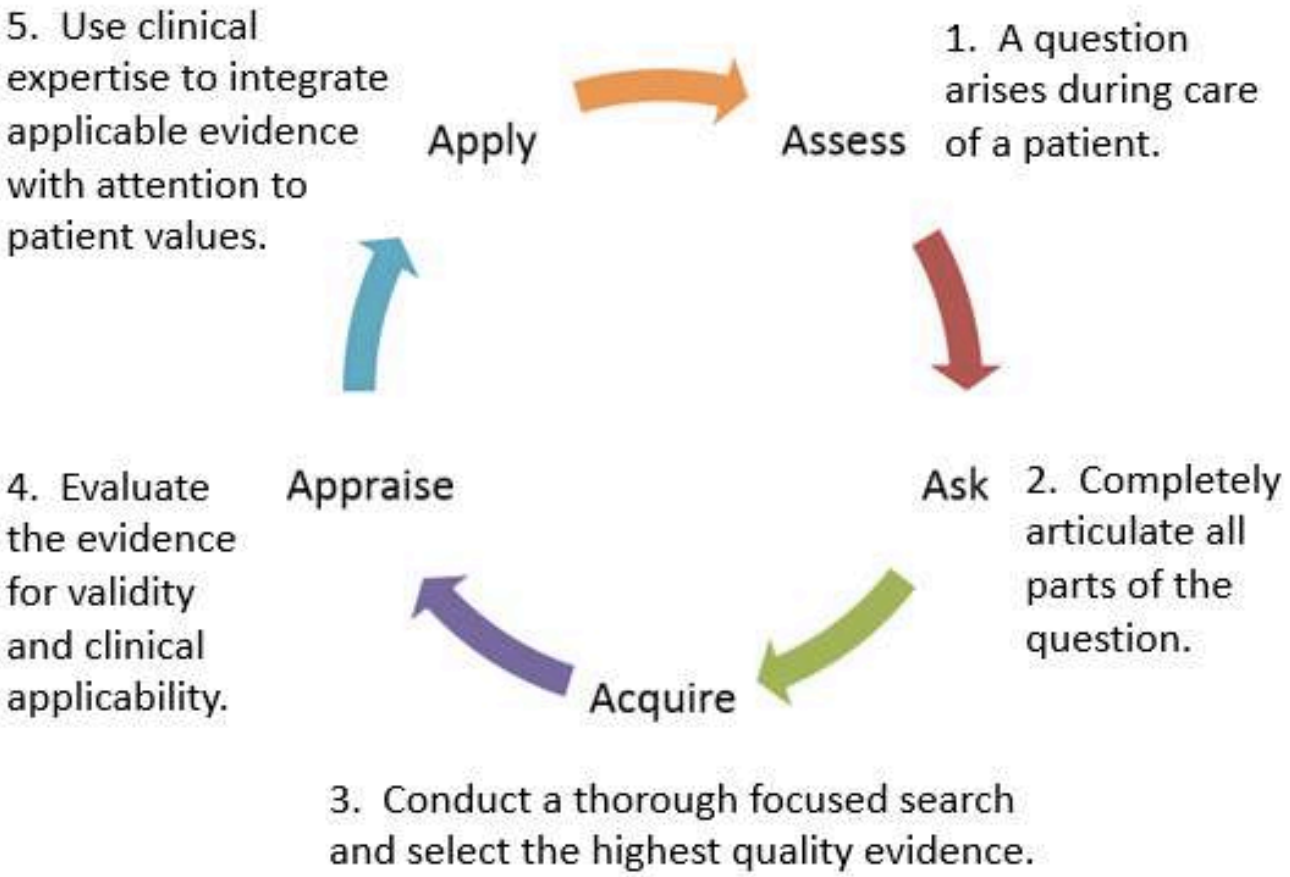
Evidence-based medicine (EBM)



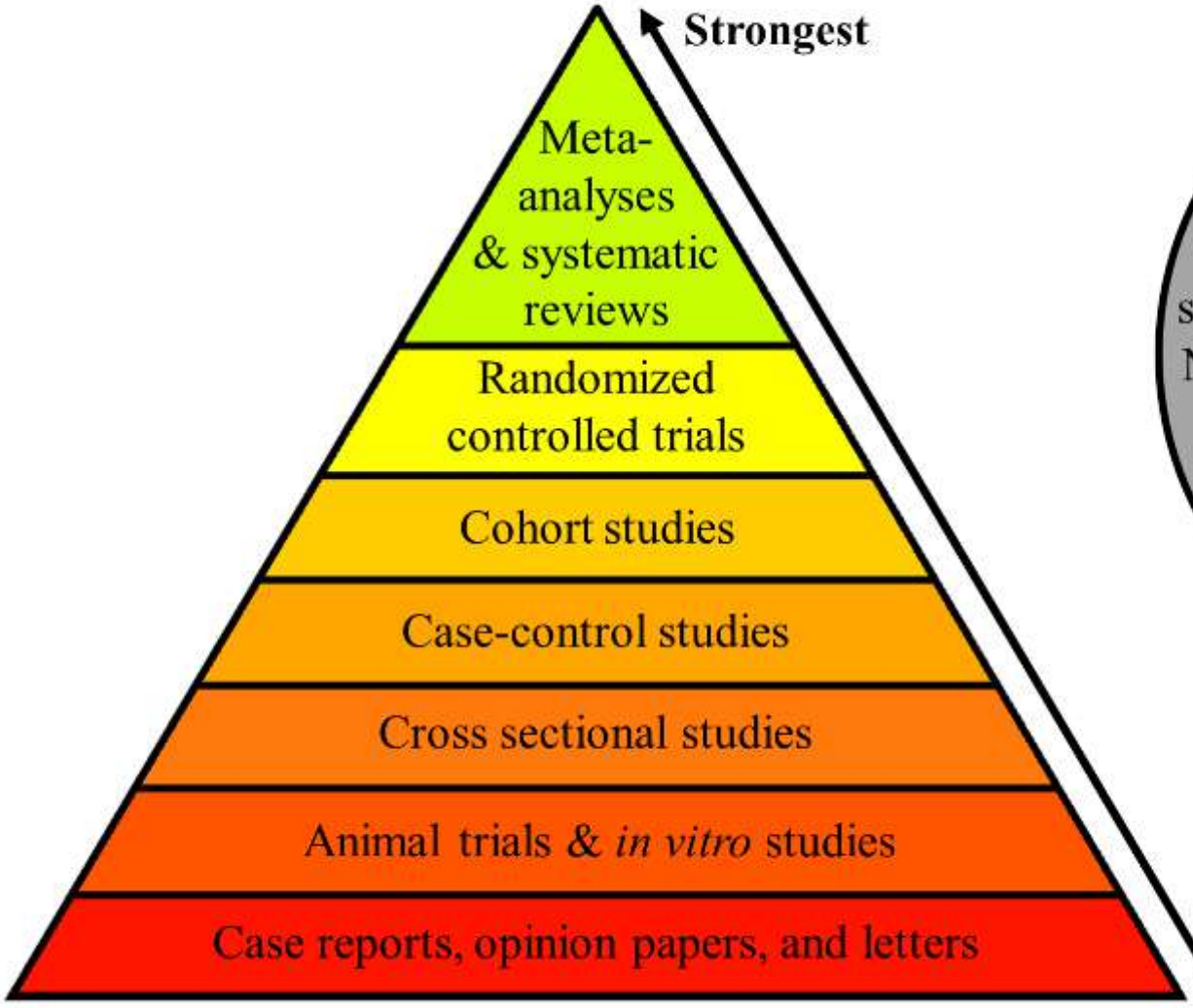
Clinical expertise refers to competence that is gained through education, training and experience

Sackett, D.L., Rosenberg, W.M.C., Gray, J.A.M., Haynes, R.B. & Richardson, W.S. 1996. Evidence based medicine: What it is and what it isn't: It's about integrating individual clinical expertise and the best external evidence. *British Medical Journal*, *312* (7023), 71-72.

Five steps in Evidence-based medicine



Hierarchy of Scientific Evidence



Not Scientific Evidence

Youtube videos, personal anecdotes, gut feelings, parental instincts, some guy you know, websites like Natural News, Info Wars, Natural Health Warriors, Collective Evolution, Green Med Info, Mercola.com, Whale.to, etc.

thelogicofscience.com

Case
Babsie – 13-year-old Chihuahua

Haematology

				Range
WHITE CELL COUNT	15.01		x10^9/L	6 - 15
SEGMENTED NEUTROPHIL	10.51		x10^9/L	3 - 11.5
BAND NEUTROPHIL	0.00		x10^9/L	0 - .5
LYMPHOCYTE	3.30		x10^9/L	1 - 4.8
MONOCYTE	0.60		x10^9/L	.15 - 1.35
EOSINOPHIL	0.60		x10^9/L	.1 - 1.25
BASOPHIL	0.00		x10^9/L	0 - .1
OTHER	0.00		%	No Reference Range
PLATELET COUNT	509	H	x10^9/L	200 - 500
NRBC/100 WBC	1			0 - 9
MORPHOLOGY	1+ ANISOCYTOSIS, MILD MACROCYTOSIS			No Reference Range
PLATELET COMMENT	MILD PLATELET AGGREGATION, HIGH PLATELET COUNT ON SMEAR, FEW GIANT PLATELETS			No Reference Range

Serum biochemistry

. - CHEMISTRY

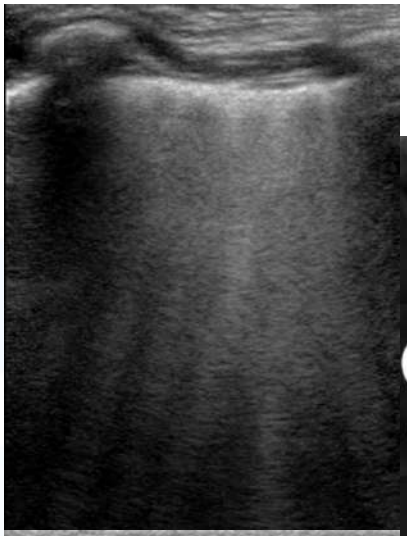
TEST	RESULT		UNITS	REF RANGE
TOTAL SERUM PROTEIN	45.1	L	g/L	56 - 73
ALBUMIN	30.5		g/L	28 - 41
GLOBULIN	14.6	L	g/L	20 - 41
A/G RATIO	2.1	H		.6 - 1.7
ALANINE AMINOTRANSFERASE	375.8	H	U/L	9 - 73
ALKALINE PHOSPHATASE	357	H	U/L	20 - 165
UREA NITROGEN	6.1		mmol/L	2.3 - 8.9
CREATININE	60		umol/L	59 - 109
PLASMA/ SERUM CONDITION	CLEAR			No Reference Range

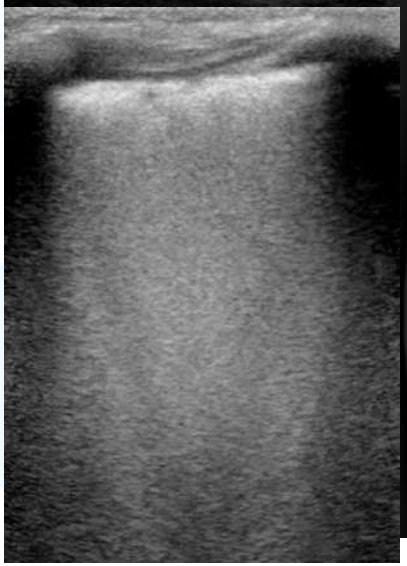
Further investigations

- The patient was found to be mildly tachypnoeic (Resp. rate 35 bpm)
- She was subjected to lateral and DV chest radiographs
- Subsequently she underwent a lung ultrasound (LUS) examination
- She also underwent abdominal ultrasonography
  - She should moderate hepatomegaly
  - The adrenal glands were moderately enlarged
  - There was no evidence of ascites

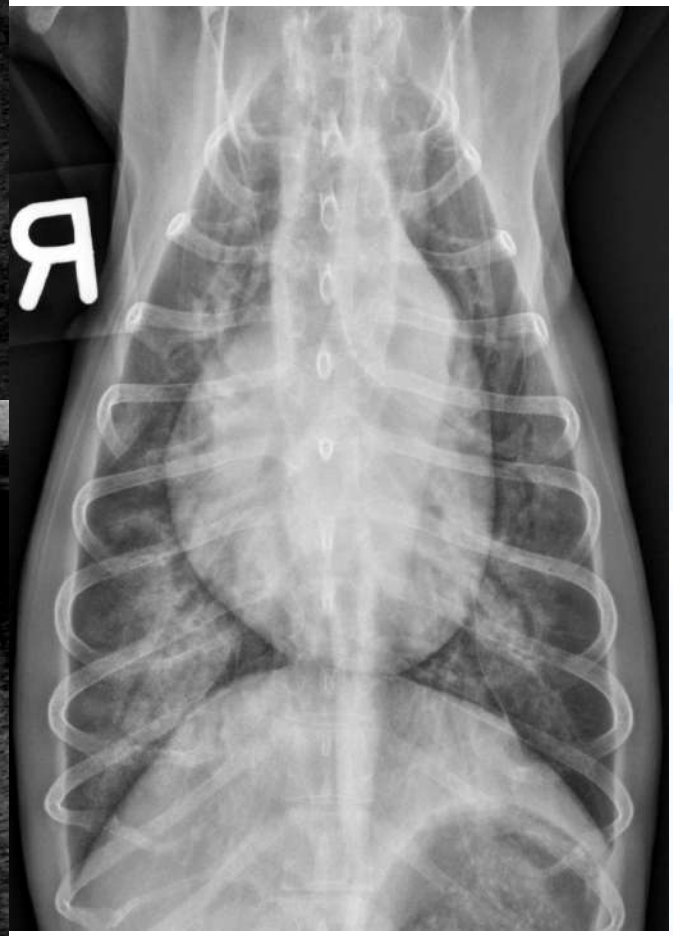
ACTH stimulation test results

- Basal cortisol 102 nmol/l (10 – 160)
- ACTH-stimulated cortisol **698** nmol/l (220 – 450)

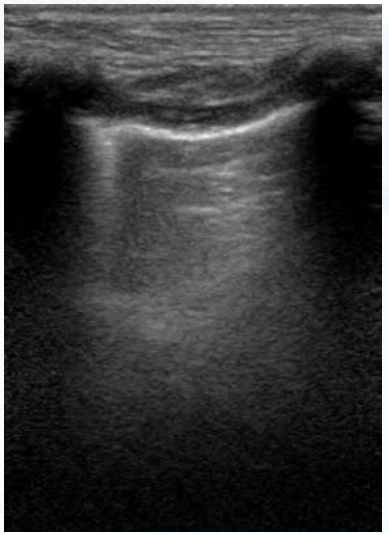




DV thoracic radiograph



3 x Lung ultrasound images



Vezzosi et al 2017

Journal of Veterinary Internal Medicine
Open Access
ACVIM

Standard Article

J Vet Intern Med 2017;31:700–704

Assessment of Lung Ultrasound B-Lines in Dogs with Different Stages of Chronic Valvular Heart Disease

T. Vezzosi, T. Mannucci, A. Pistoresi, F. Toma, R. Tognetti, E. Zini, O. Domenech, E. Auriemma, and S. Citi

Background: In dogs with chronic valvular heart disease (CVHD), early recognition of pulmonary edema (PE) is of paramount importance. Recent studies in dogs showed that lung ultrasound examination (LUS) is a useful technique to diagnose cardiogenic PE.

Objectives: To describe LUS features in dogs with different stages of CVHD, and to determine its diagnostic accuracy in detecting PE using thoracic radiography as the reference standard.

Animals: Sixty-three dogs with CVHD.

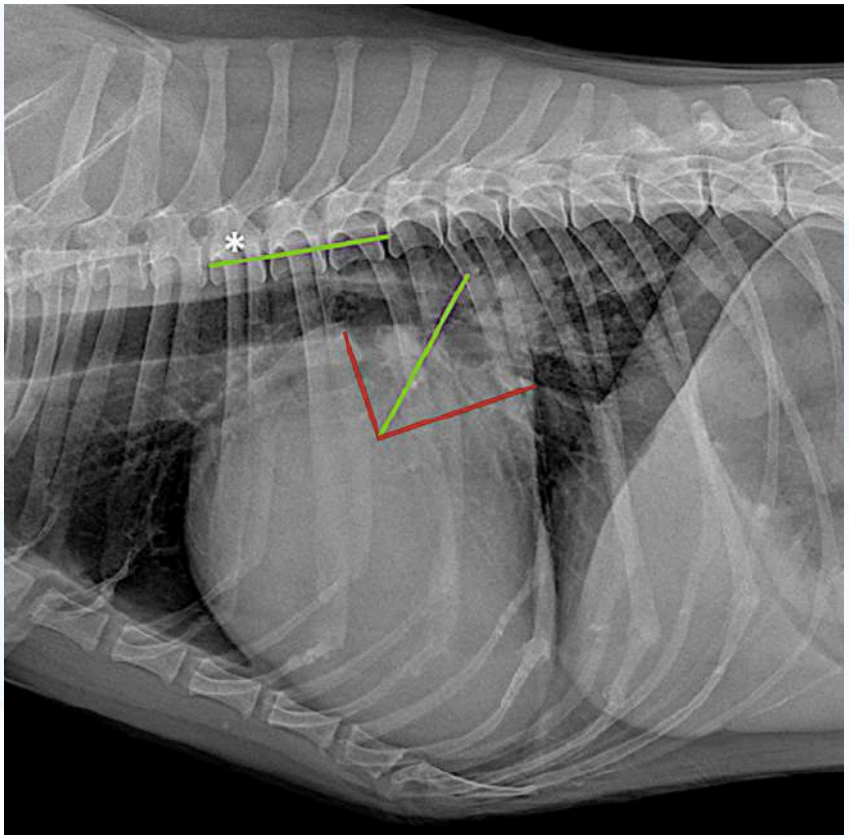
Methods: Prospective, multicenter, cross-sectional study. Each dog underwent physical examination, echocardiography, thoracic radiography, and LUS. The LUS findings were classified as absent, rare, numerous, or confluent B-lines. Sensitivity, specificity, and positive and negative predictive values of LUS B-lines to identify PE were calculated using thoracic radiography as the reference standard.

Results: Dogs in stage B1 had absent or rare B-lines in 14 of 15 cases (93.3%). Dogs in stage B2 had absent or rare B-lines in 16 of 18 cases (88.9%). All dogs in stage C, without radiographic signs of PE, had absent or rare B-lines. Dogs in stage C, with radiographic signs of PE, had numerous or confluent B-lines in 18 of 20 cases (90%). Lung ultrasound examination detected PE with a sensitivity of 90%, specificity of 93%, and with positive and negative predictive values of 85.7 and 95.2%, respectively.

Conclusions and Clinical Importance: Lung ultrasound examination showed good diagnostic accuracy to identify cardiogenic PE and might be helpful in staging dogs with CVHD. Lung ultrasound examination should be considered as a new, noninvasive diagnostic tool for clinicians managing CVHD in dogs.

Key words: Heart failure; Lung comets; Mitral valve; Pulmonary edema; Thoracic ultrasonography.

Lateral thoracic radiograph



Heart size?

- Heart size can be determined radiographically as well as ultrasonographically
- Radiographic measures are called the Vertebral heart score (VHS) and the Vertebral left atrial score (VLAS)
- There are many different ways to determine both of these measures – one of the VLAS methods is illustrated in the preceding radiograph

Puccinelli et al 2020

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ORIGINAL INVESTIGATION

WILEY

A radiographic study of breed-specific vertebral heart score and vertebral left atrial size in Chihuahuas

Caterina Puccinelli | Simonetta Citi | Tommaso Vezzosi | Silvia Garibaldi | Rosalba Tognetti

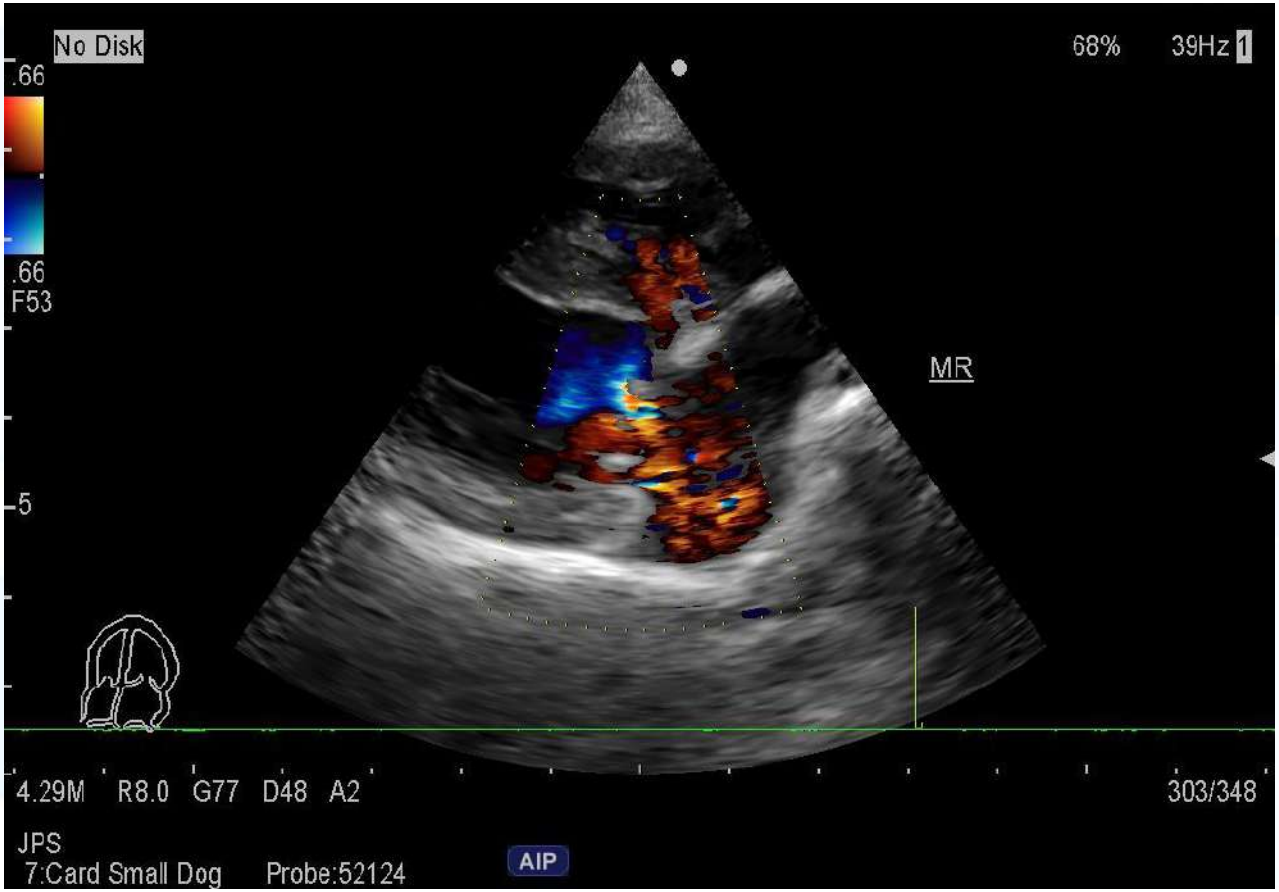
Department of Veterinary Sciences, University of Pisa, Pisa, Italy

Correspondence
Tommaso Vezzosi, Department of Veterinary Sciences, University of Pisa, Via Livornese, San Piero a Grado, 56010, Pisa, Italy.
Email: tommaso.vezzosi@vet.unipi.it

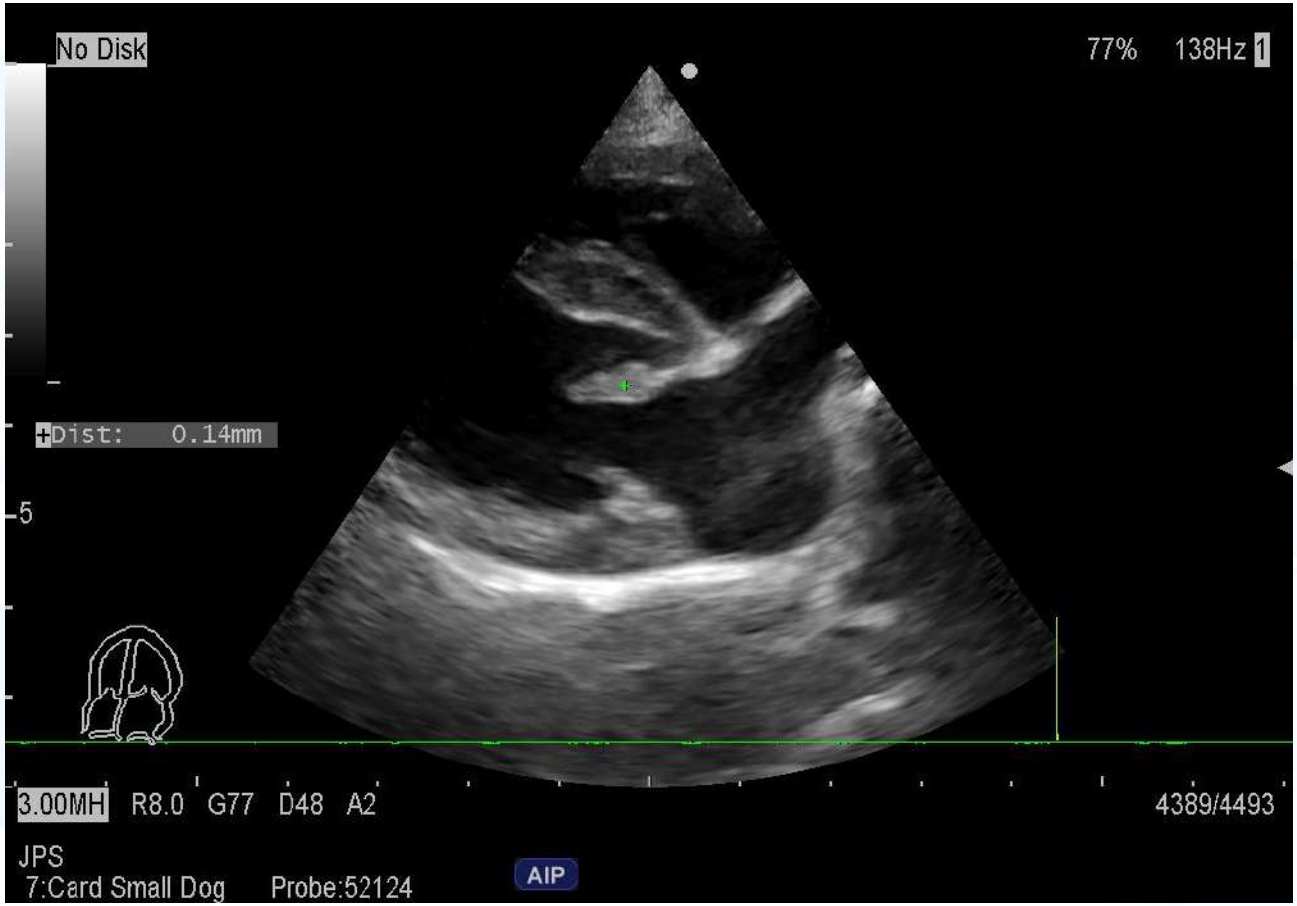
Abstract

Although echocardiography is the gold standard for the diagnosis of cardio-structural disease, thoracic radiography is a rapid, cost-effective, and widely accessible method for evaluating cardiac size in dogs. The vertebral heart score (VHS) and the vertebral left atrial size (VLAS) are established as objective measures of cardiomegaly on thoracic radiographs. However, several studies have shown significant variations in the VHS among different breeds. The Chihuahua is predisposed to both congenital and acquired cardiac diseases. The aim of this prospective, single-center, cross sectional study was thus to evaluate the VHS and the VLAS in healthy adult Chihuahua dogs. A total of 30 Chihuahuas were included. The VHS values in our sample population of Chihuahuas were 10.0 ± 0.6 (95% range, 8.9-11.0). This was significantly greater than the canine reference value of 9.7 ± 0.5 established by Buchanan and Bücheler ($P = .002$). The VLAS of Chihuahuas in our study was 1.8 ± 0.2 (95% range, 1.3-2.1). This was sig

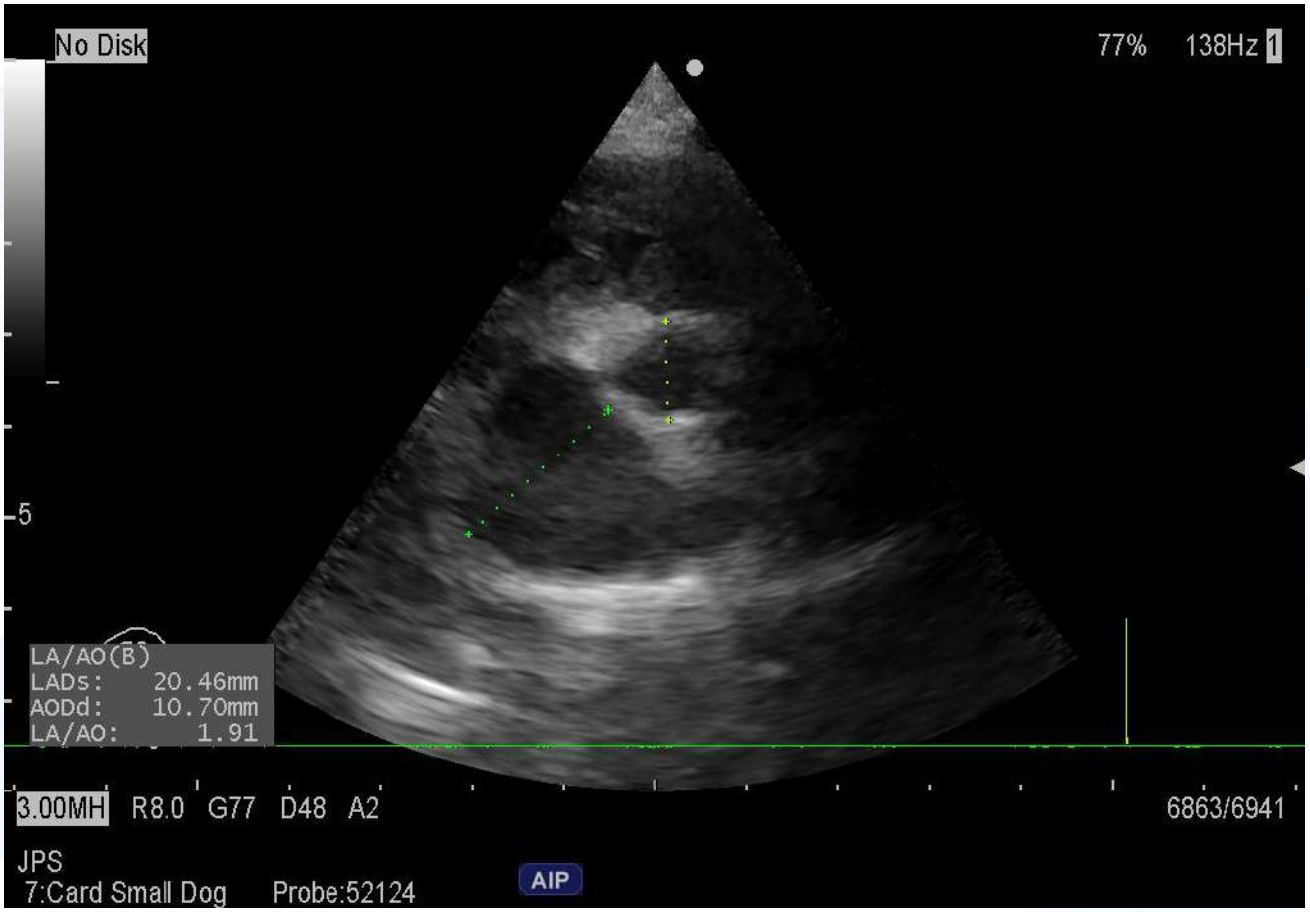
Right parasternal long axis echocardiogram Demonstrating severe mitral valve regurgitation



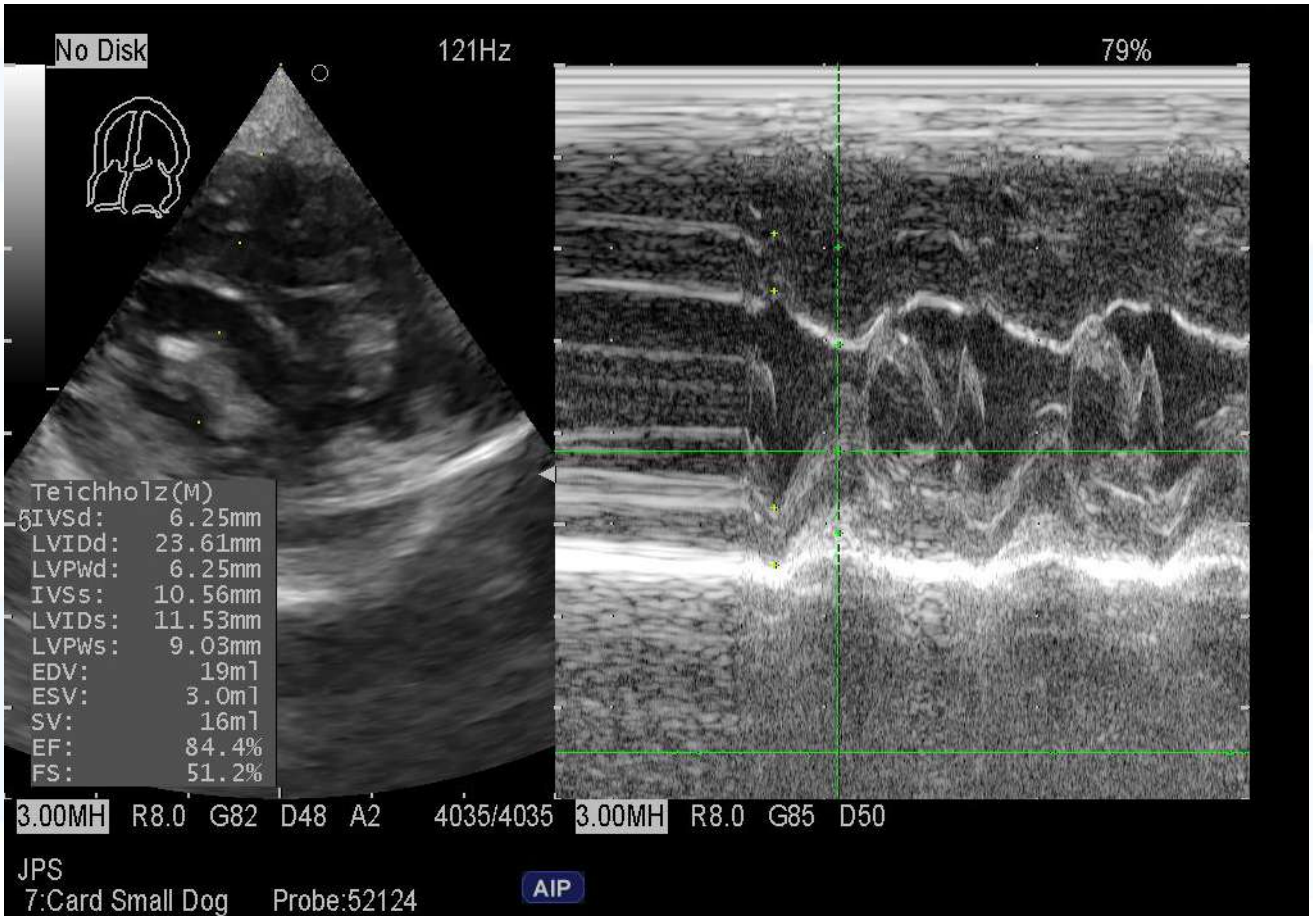
Mitral valve thickening, especially the septal leaflet



Left atrium/Aorta ratio = 1.9



Right parasternal short axis measurements
FS = 51% (28 – 45)



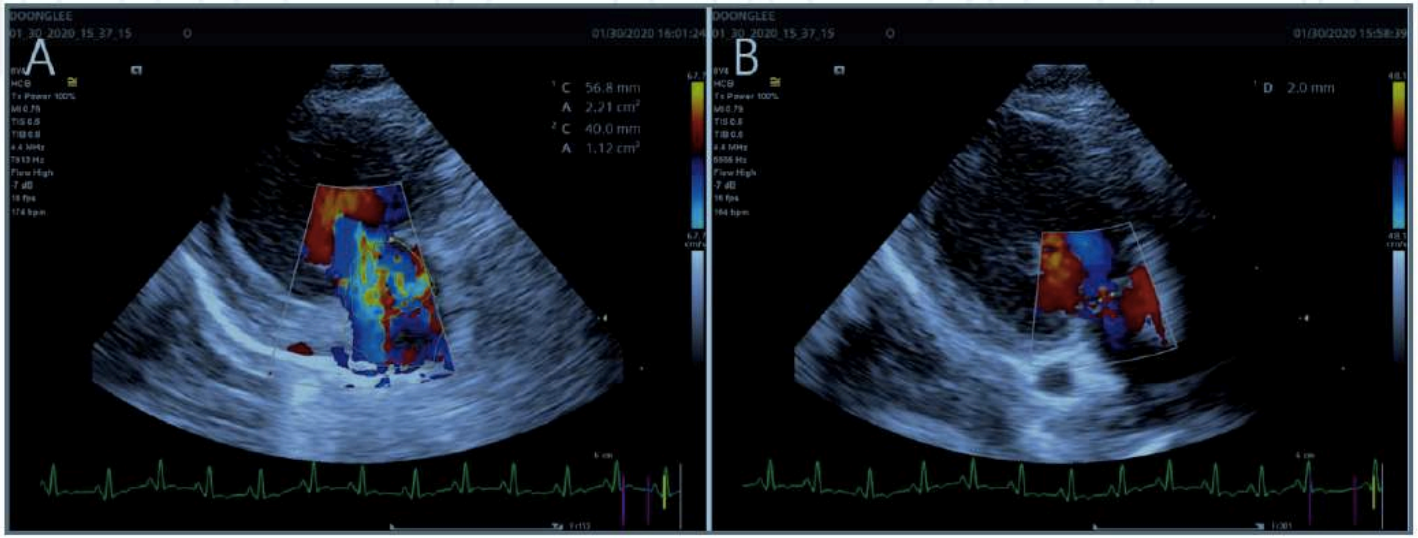
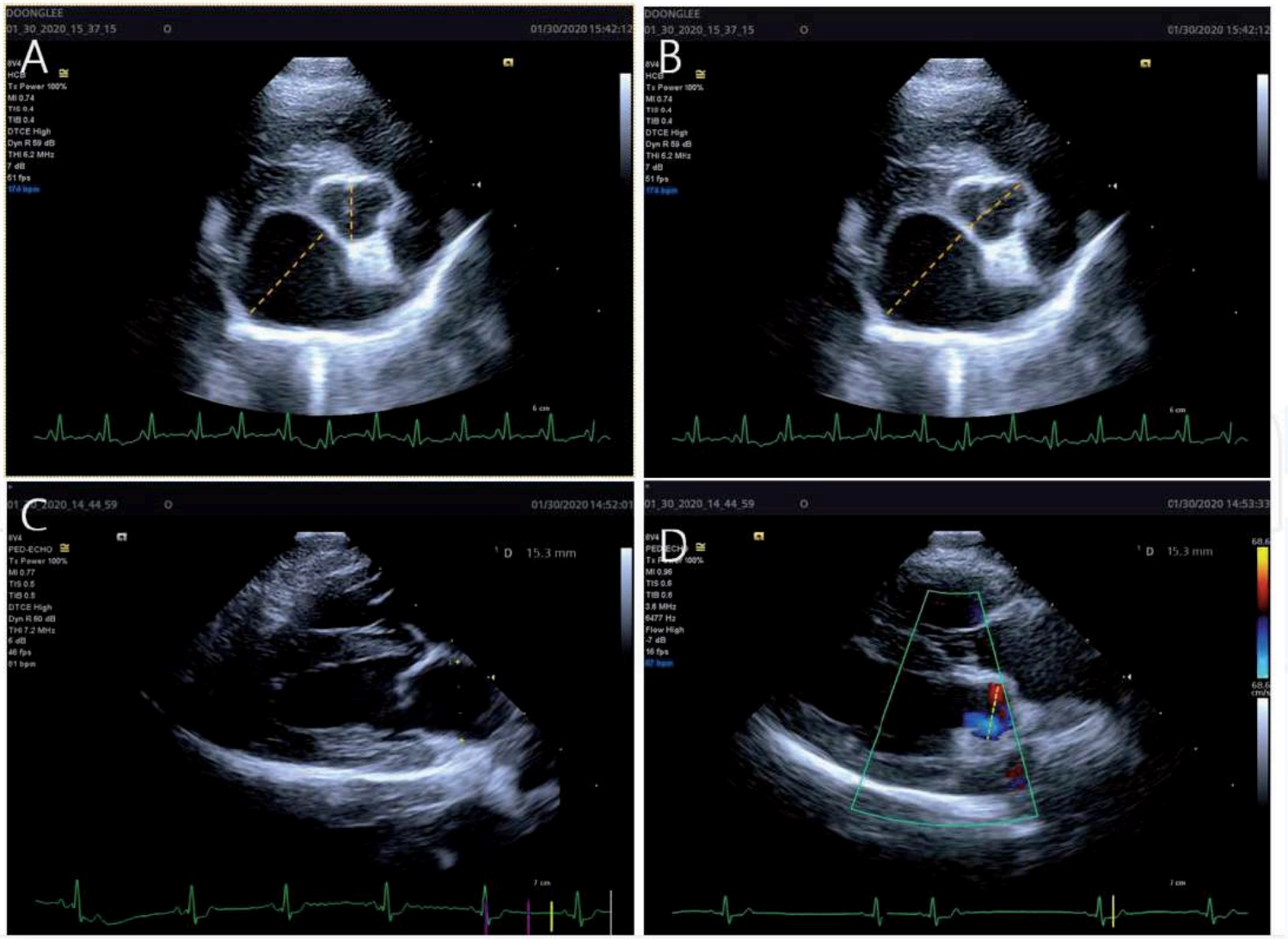


Figure 1.
(A) Semi-quantification of mitral regurgitation (MR). The maximal ratio of the regurgitant jet area signal to the left atrial area (ARJ/LAA ratio) was obtained from a left apical four-chamber view. The ARJ (1.12 cm²)/ LAA (2.12 cm²) of this case was 53%, indicating moderate MR. (B) the vena contracta diameter from a left apical four-chamber view (VC_L) was measured as the diameter of the narrowest point of the mitral regurgitation jet, downstream of the region of proximal flow convergence.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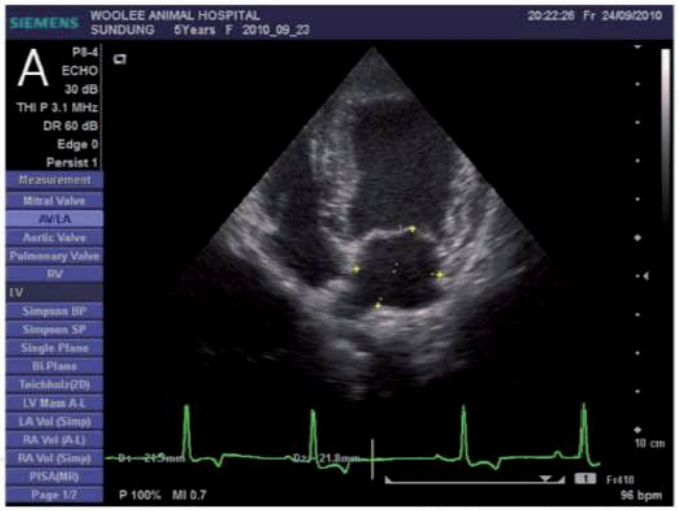
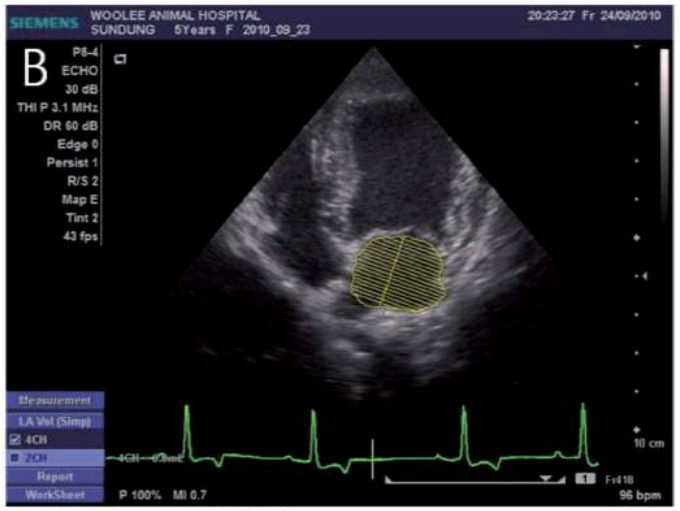
01/30/2020 15:42:12
01/30/2020 14:52:01
01/30/2020 14:53:33
15.3 mm


SIEMENS
WOOLEE ANIMAL HOSPITAL
SUNDUNG 5Years F 2010_09_23
20:22:26 Fr 24/09/2010
A
P8-4
ECHO
30 dB
THI P 3.1 MHz
DR 60 dB
Edge 0
Persist 1
Measurement
Mitral Valve
AV/LA
Aortic Valve
Pulmonary Valve
RV
LV
Simpson BP
Simpson SP
Single Plane
Bi Plane
Teichholz(2D)
LV Mass A-L
LA Vol (Simp)
RA Vol (A-L)
RA Vol (Simp)
PISA(MR)
Page 1/2
P 100% MI 0.7
10 cm
96 bpm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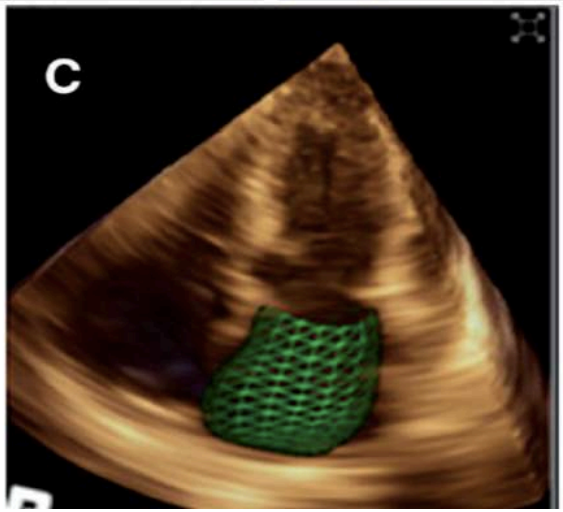
SUNDUNG 5Years F 2010_09_23
20:23:27 Fr 24/09/2010
B
P8-4
ECHO
30 dB
THI P 3.1 MHz
DR 60 dB
Edge 0
Persist 1
R/S 2
Map E
Tint 2
43 fps
Measurement
LA Vol (Simp)
4CH
2CH
Report
WorkSheet
P 100% MI 0.7
10 cm
96 bpm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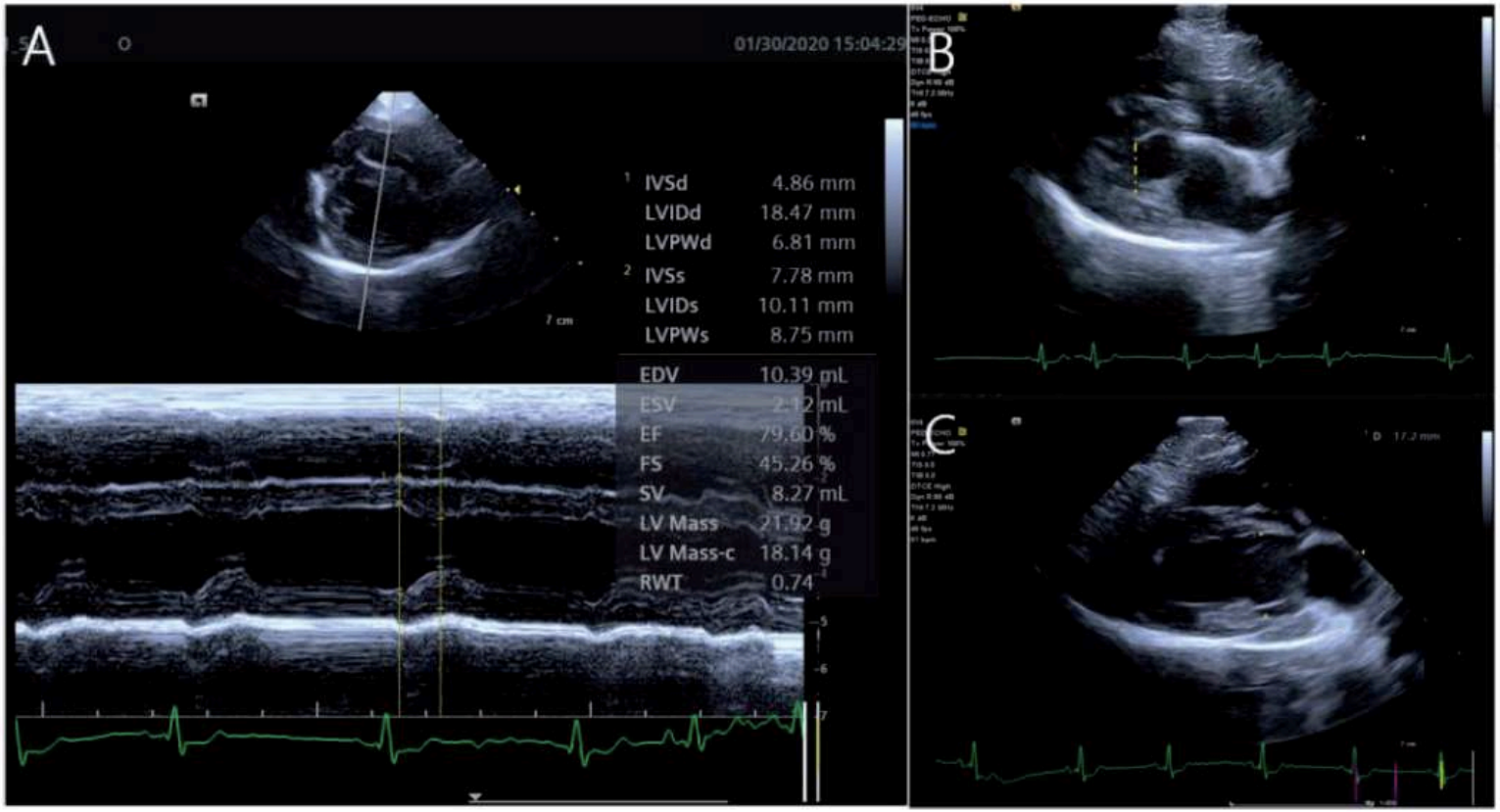


Figure 5.
Measurement of left ventricular internal dimension. (A) M-mode echocardiography obtained from a right parasternal short axis at the papillary muscle level and (B and C) 2D echocardiography obtained from a right parasternal long axis at systole (B) and diastole (C).

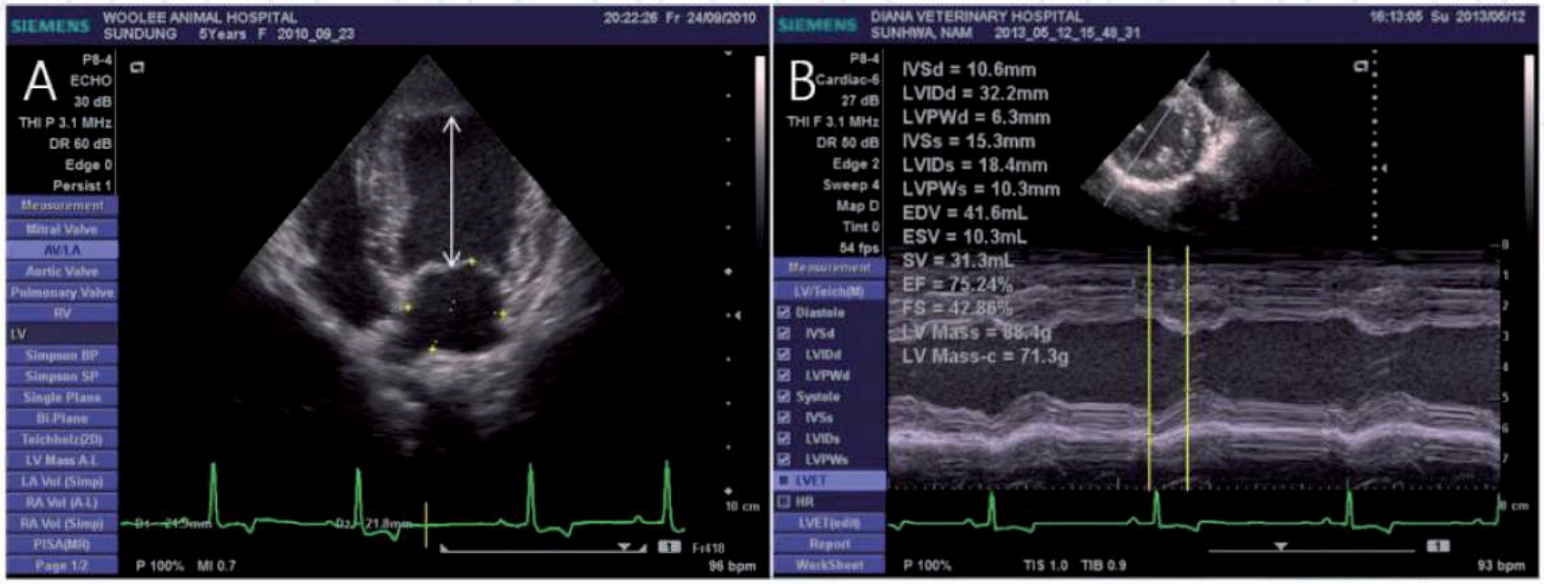
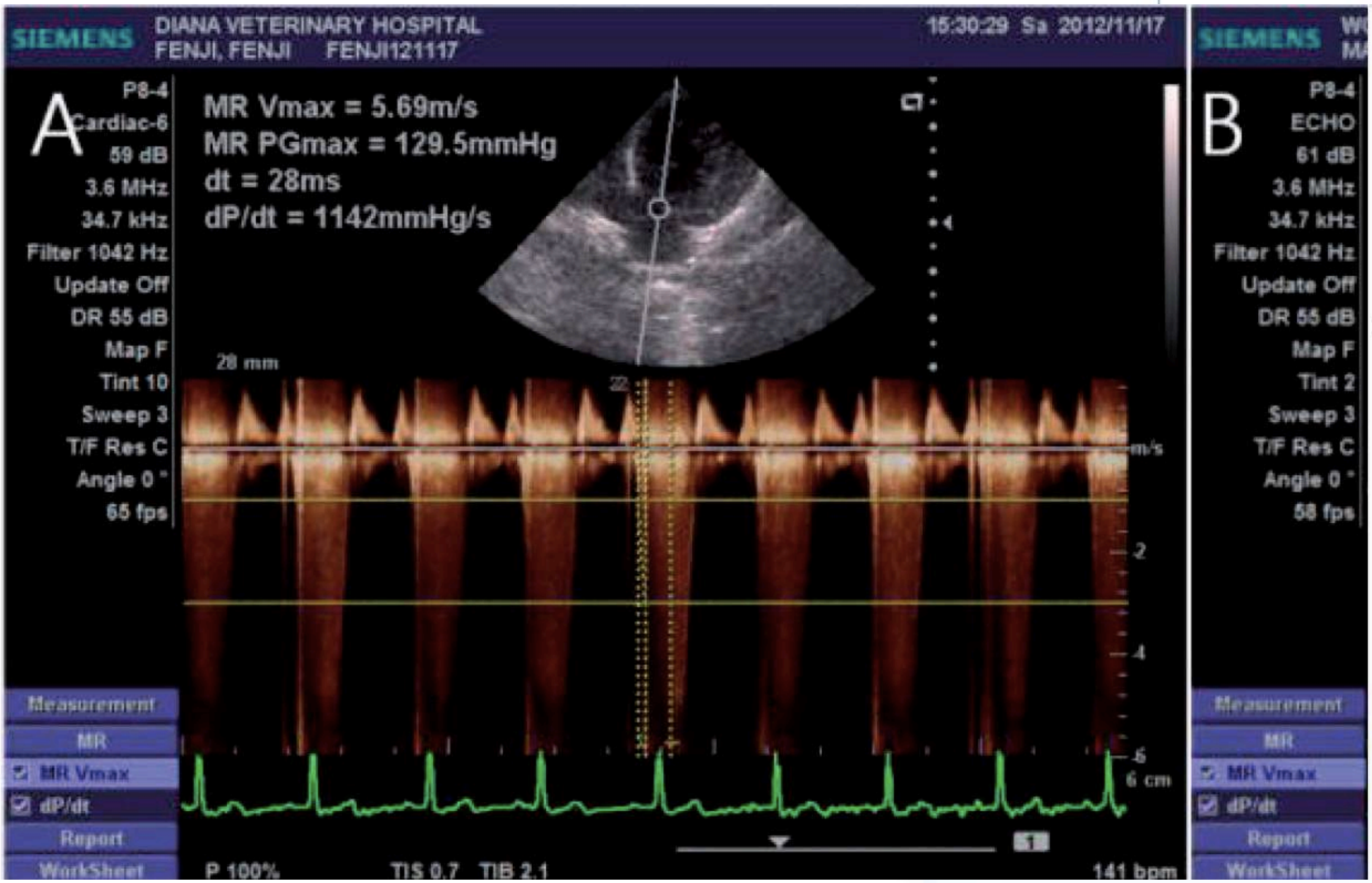
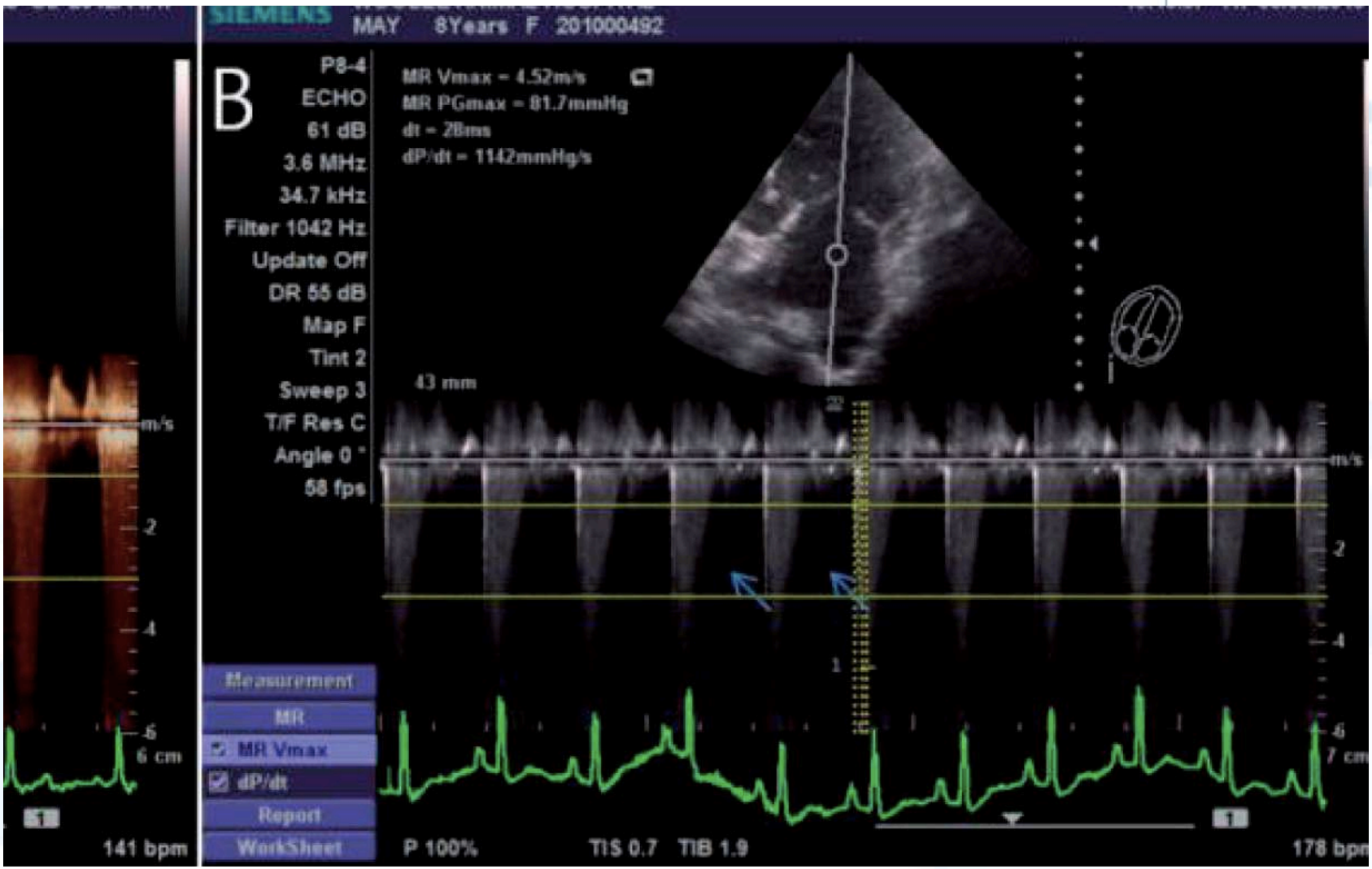
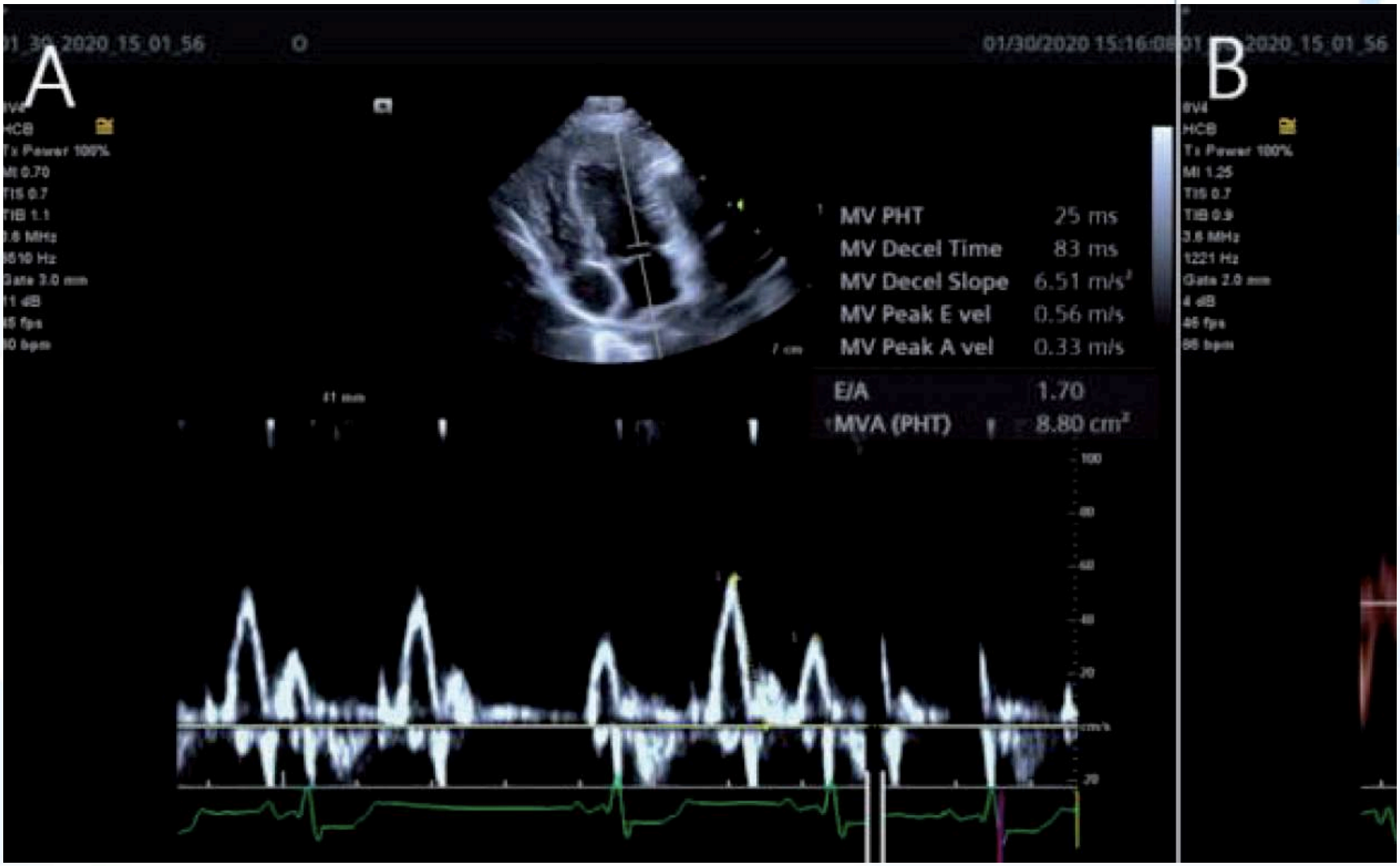
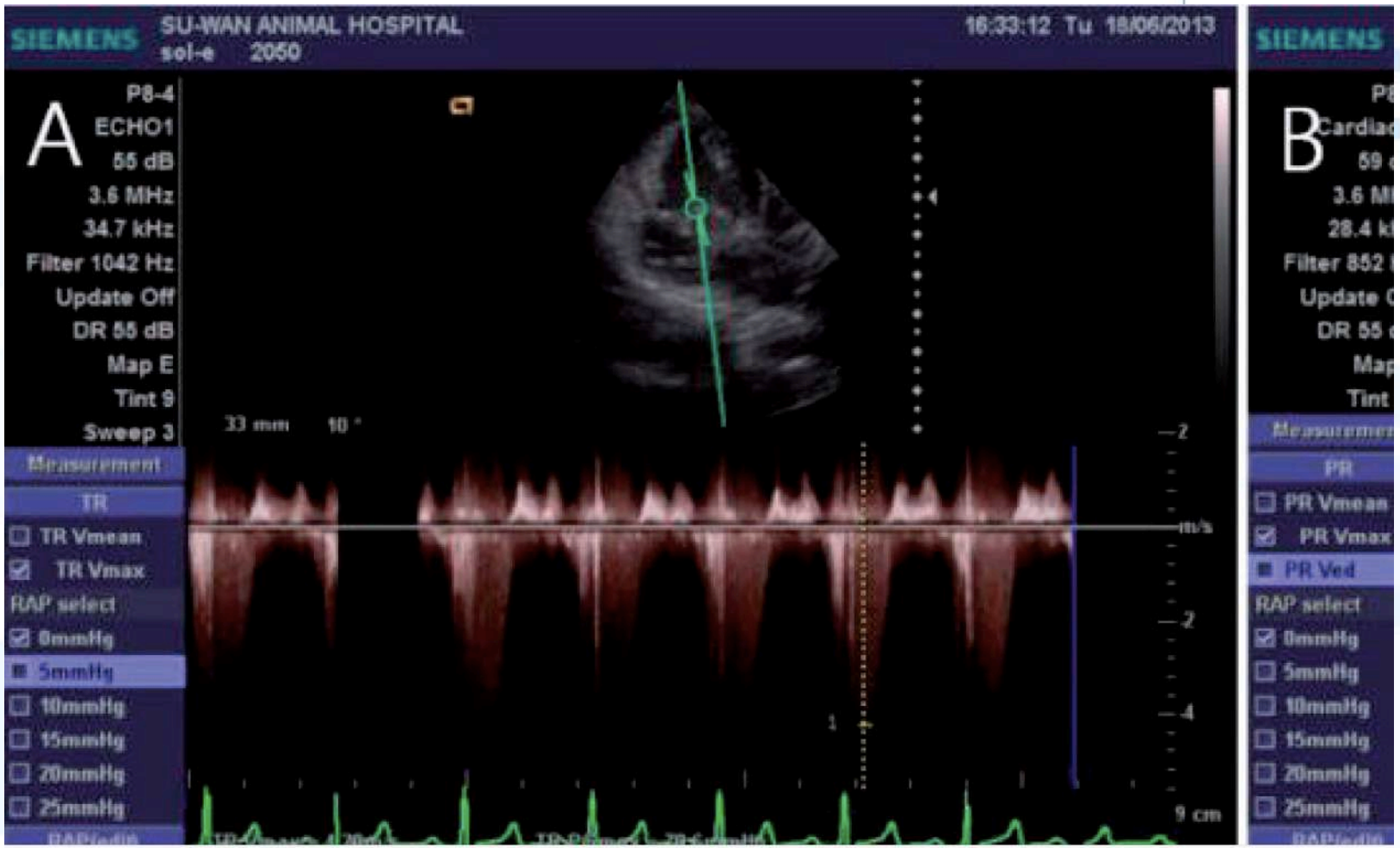


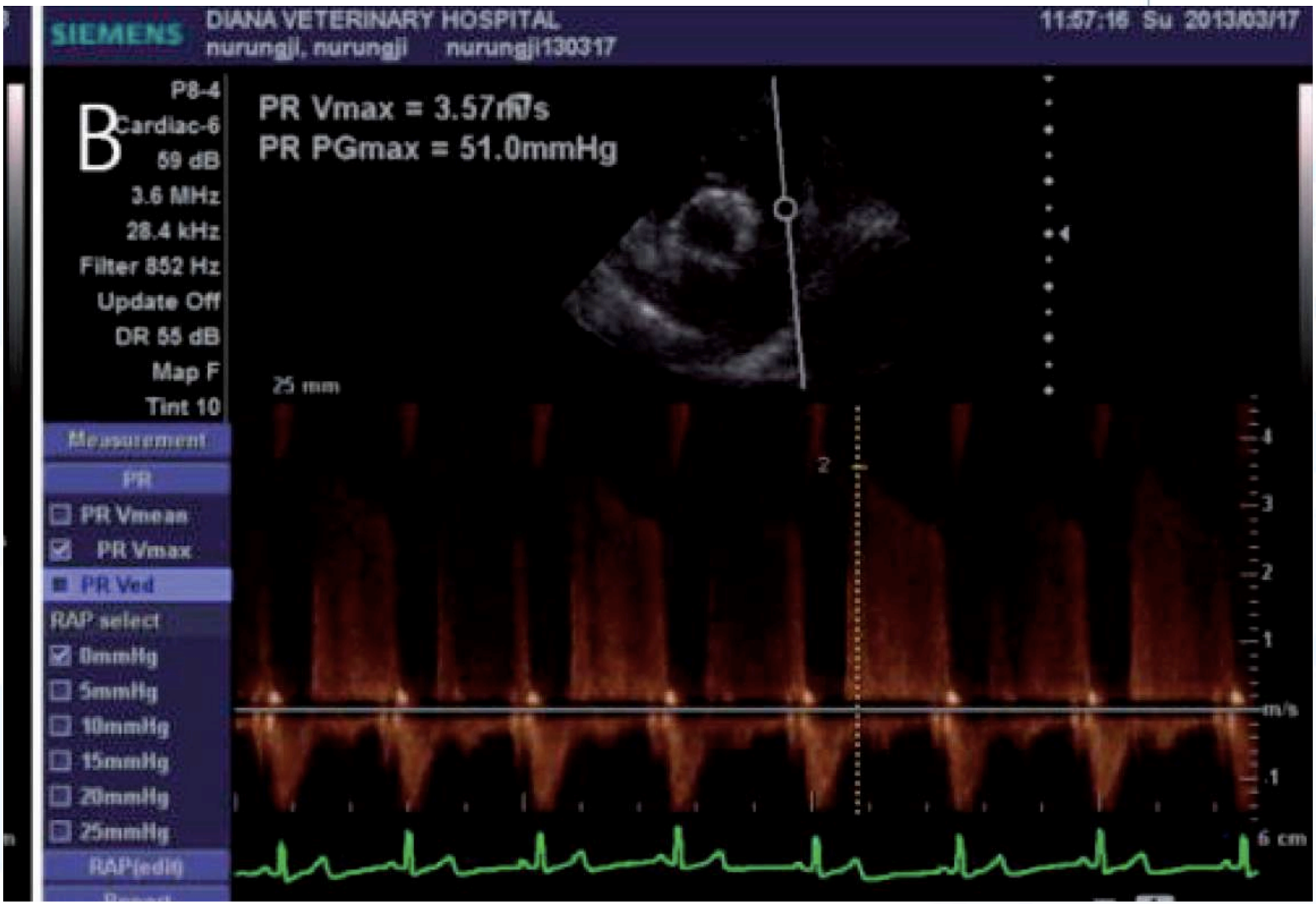
Figure 6.
The left ventricular (LV) sphericity index was calculated by the ratio of LV end-diastolic length (at left apical four-chamber plane; A) to the M-mode LV end-diastolic diameter (B).

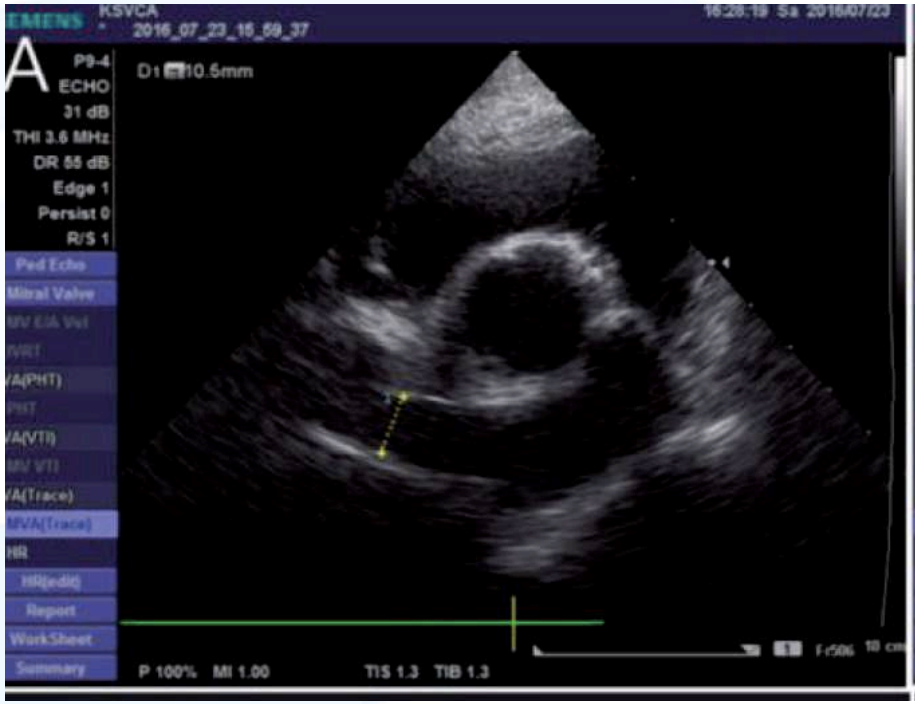

SIEMENS
DIANA VETERINARY HOSPITAL
FENJI, FENJI FENJI121117
15:30:29 Sa 2012/11/17
A
P8-4
Cardiac-6
59 dB
3.6 MHz
34.7 kHz
Filter 1042 Hz
Update Off
DR 55 dB
Map F
Tint 10
Sweep 3
T/F Res C
Angle 0 °
65 fps
MR Vmax = 5.69m/s
MR PGmax = 129.5mmHg
dt = 28ms
dP/dt = 1142mmHg/s
28 mm
m/s
2
4
6
6 cm
Measurement
MR
MR Vmax
dP/dt
Report
WorkSheet
P 100%
TIS 0.7 TIB 2.1
141 bpm
SIEMENS
B
P8-4
ECHO
61 dB
3.6 MHz
34.7 kHz
Filter 1042 Hz
Update Off
DR 55 dB
Map F
Tint 2
Sweep 3
T/F Res C
Angle 0 °
58 fps
Measurement
MR
MR Vmax
dP/dt
Report
WorkSheet

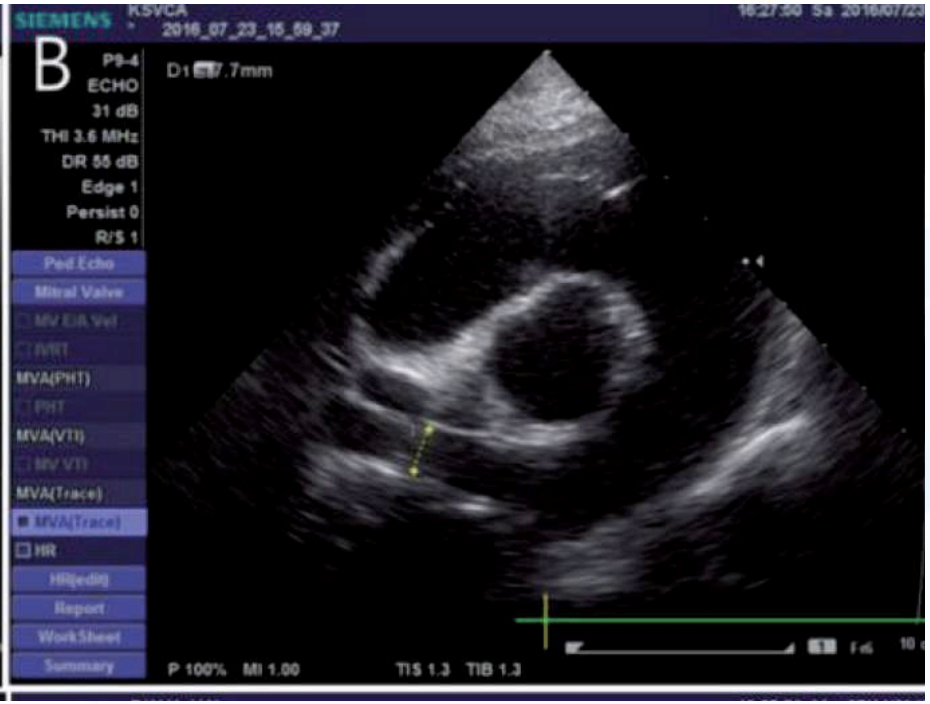

SIEMENS
MAY 8Years F 201000492
B
P8-4
ECHO
61 dB
3.6 MHz
34.7 kHz
Filter 1042 Hz
Update Off
DR 55 dB
Map F
Tint 2
Sweep 3
T/F Res C
Angle 0 °
58 fps
MR Vmax = 4.52m/s
MR PGmax = 81.7mmHg
dt = 28ms
dP/dt = 1142mmHg/s
43 mm
m/s
2
4
6
6 cm
7 cm
Measurement
MR
MR Vmax
dP/dt
Report
WorkSheet
P 100%
TIS 0.7
TIB 1.9
141 bpm
178 bpm

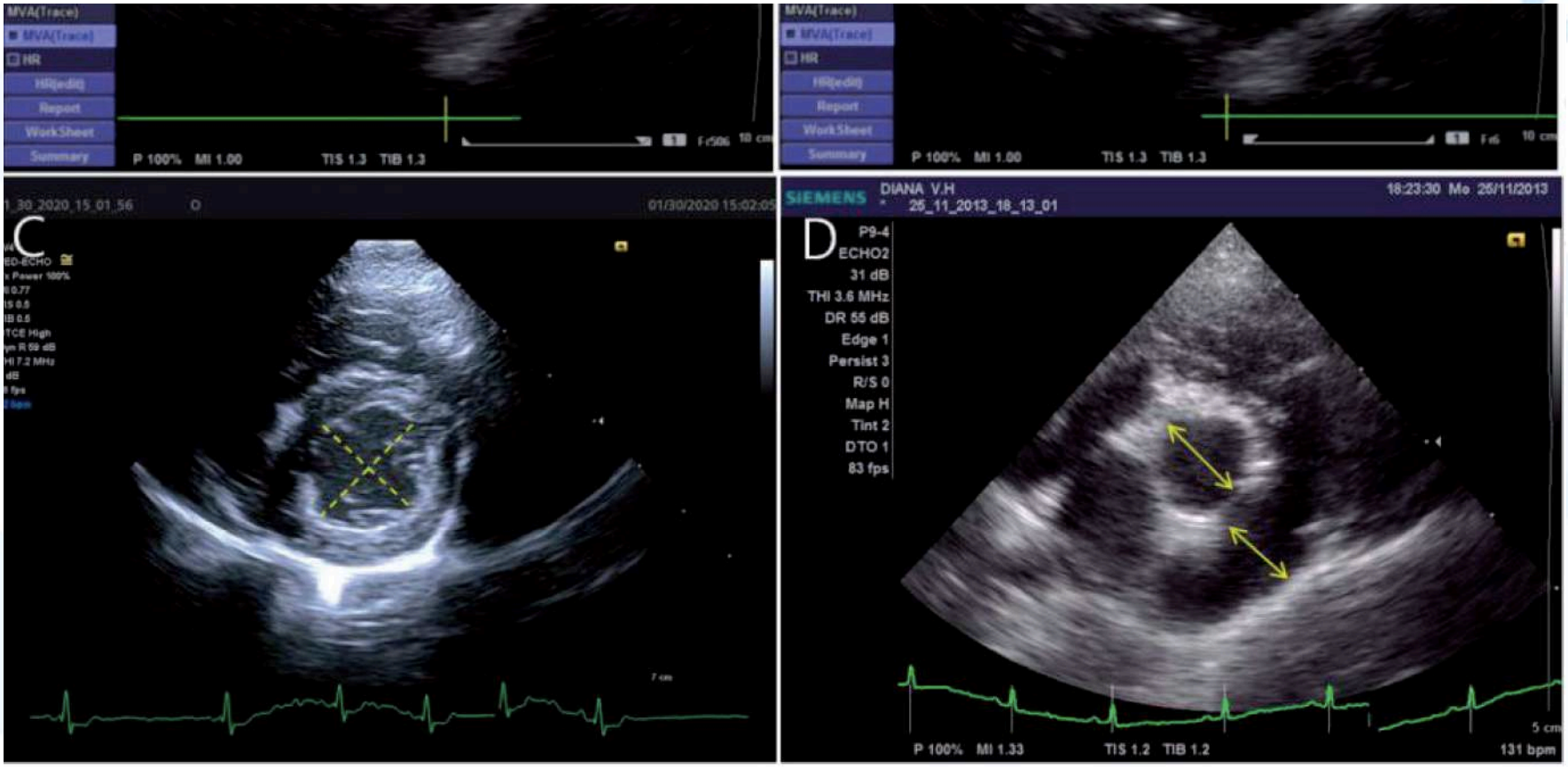

A
B
MV PHT 25 ms
MV Decel Time 83 ms
MV Decel Slope 6.51 m/s²
MV Peak E vel 0.56 m/s
MV Peak A vel 0.33 m/s
E/A 1.70
MVA (PHT) 8.80 cm²

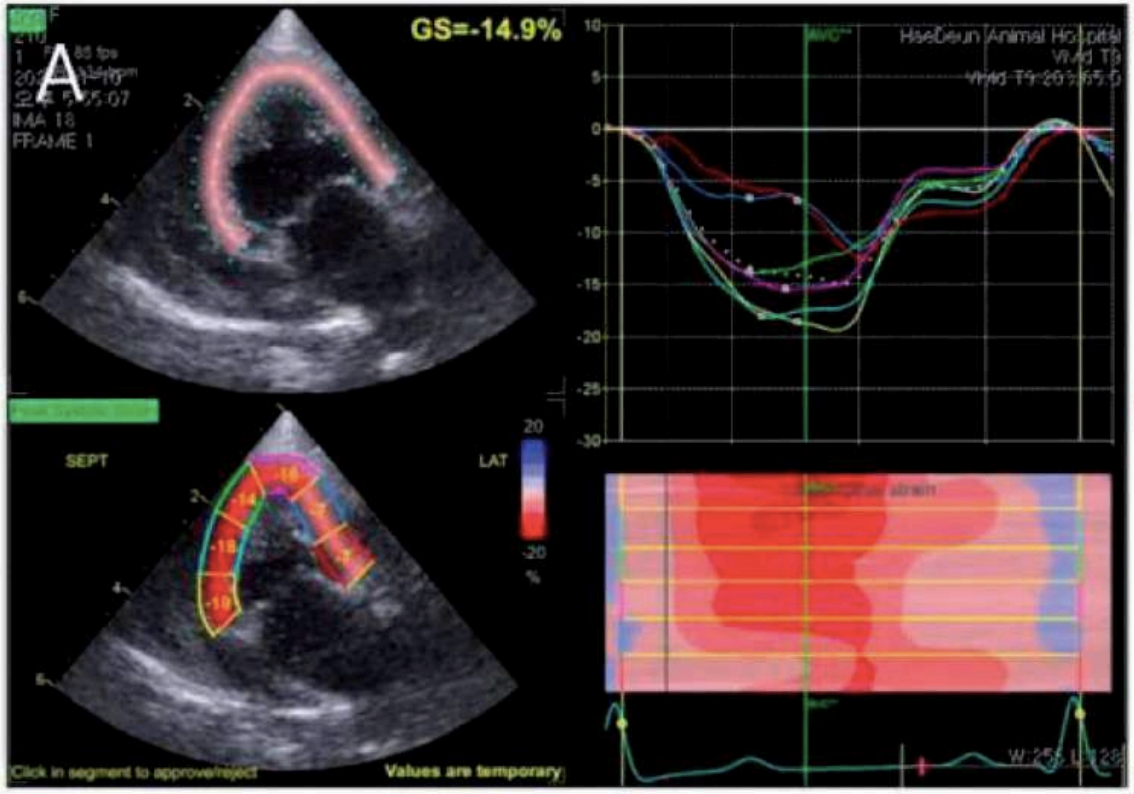

SIEMENS
SU-WAN ANIMAL HOSPITAL
sol-e 2050
16:33:12 Tu 18/06/2013
A
P8-4
ECHO1
55 dB
3.6 MHz
34.7 kHz
Filter 1042 Hz
Update Off
DR 55 dB
Map E
Tint 9
Sweep 3
33 mm
10 °
Measurement
TR
TR Vmean
TR Vmax
RAP select
0mmHg
5mmHg
10mmHg
15mmHg
20mmHg
25mmHg
m/s
9 cm
SIEMENS
B
PR
PR Vmean
PR Vmax
PR Ved
RAP select
0mmHg
5mmHg
10mmHg
15mmHg
20mmHg
25mmHg


SIEMENS
DIANA VETERINARY HOSPITAL
nurungji, nurungji nurungji130317
11:57:16 Su 2013/03/17
P8-4
Cardiac-6
59 dB
3.6 MHz
28.4 kHz
Filter 852 Hz
Update Off
DR 55 dB
Map F
Tint 10
PR Vmax = 3.57m/s
PR PGmax = 51.0mmHg
25 mm
Measurement
PR
PR Vmean
PR Vmax
PR Ved
RAP select
0mmHg
5mmHg
10mmHg
15mmHg
20mmHg
25mmHg
RAP(edit)
m/s
6 cm


A
SIEMENS
KSVCA
2016_07_23_15_59_37
P9-4
ECHO
31 dB
THI 3.6 MHz
DR 55 dB
Edge 1
Persist 0
R/S 1
Ped Echo
Mitral Valve
MV E/A Vel
IVRT
VA(PHT)
PHT
VA(VTI)
MV VTI
VA(Trace)
MVA(Trace)
HR
Hi[edit]
Report
WorkSheet
Summary
D1 10.5mm
P 100% MI 1.00
TIS 1.3 TIB 1.3


B
SIEMENS
KSVCA
2016_07_23_15_59_37
P9-4
ECHO
31 dB
THI 3.6 MHz
DR 55 dB
Edge 1
Persist 0
R/S 1
Ped Echo
Mitral Valve
MV E/A Vel
IVRT
MVA(PHT)
PHT
MVA(VTI)
MV VTI
MVA(Trace)
MVA(Trace)
HR
Hi[edit]
Report
WorkSheet
Summary
D1 7.7mm
P 100% MI 1.00
TIS 1.3 TIB 1.3


MVA(Trace)
HR
Report
WorkSheet
Summary
P 100% MI 1.00 TIS 1.3 TIB 1.3
C
01/30/2020 15:02:05
D
SIEMENS
DIANA V.H
25_11_2013_18_13_01
18:23:30 Mo 25/11/2013
P9-4
ECHO2
31 dB
THI 3.6 MHz
DR 55 dB
Edge 1
Persist 3
R/S 0
Map H
Tint 2
DTO 1
83 fps
P 100% MI 1.33 TIS 1.2 TIB 1.2
131 bpm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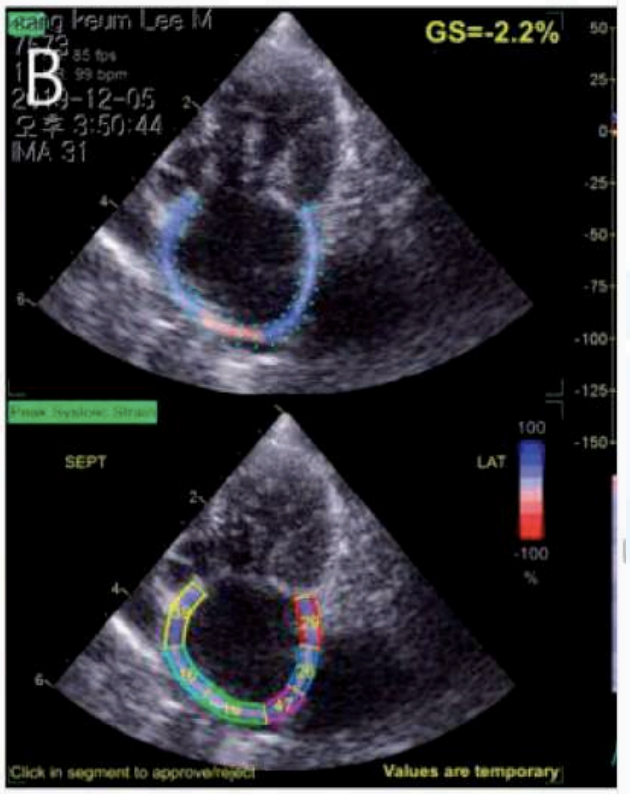
GS=-14.9%
SEPT
LAT
20
-20
%
Click in segment to approve/reject
Values are temporary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LAT
100
-100
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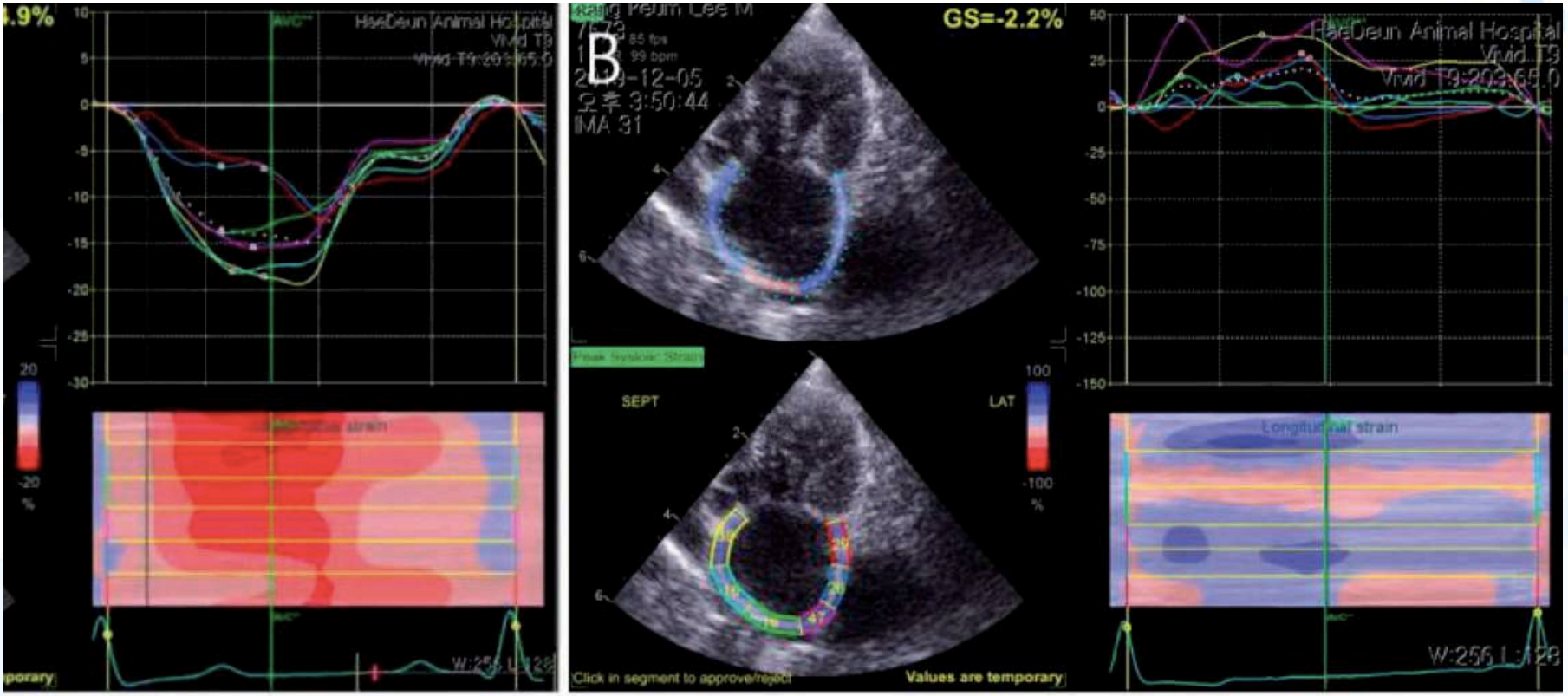
Values are temporary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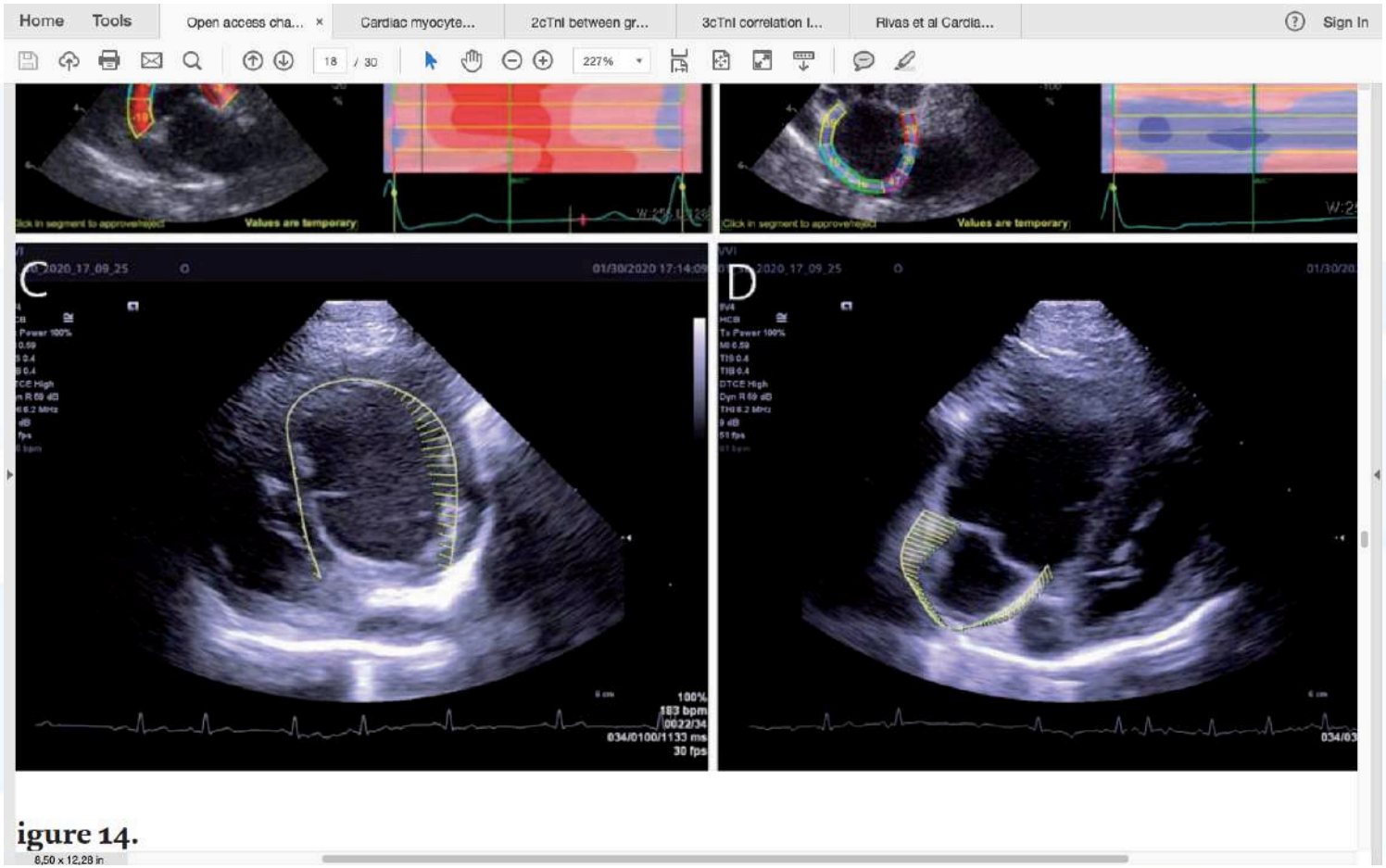
LAT
Values are temporary



igure 14.

8,50 x 12,28 in

Diagnosis

- Babsie was diagnosed with stage C, myxomatous mitral valve disease
- She has evidence of left heart failure with pulmonary oedema
- The clinician needs to formulate a treatment plan
- This plan has to be formulated according to current best evidence

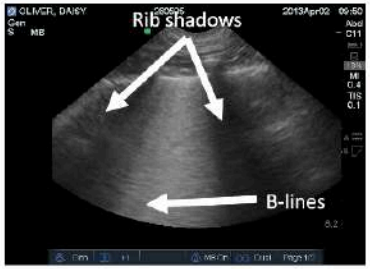
Dr Jessica Ward
DVM, DACVIM(Cardiology)
Associate Professor
Assistant Dean for Extramural Student Programs
Veterinary Clinical Sciences
jward@iastate.edu

Acknowledged for slides from here

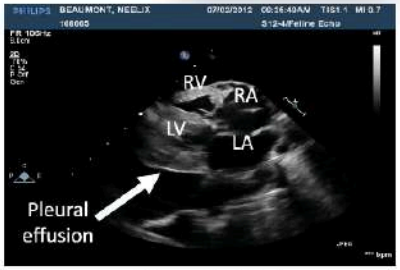
Translational RAAS Interest Group

Diagnosis of CHF: point-of-care ultrasound

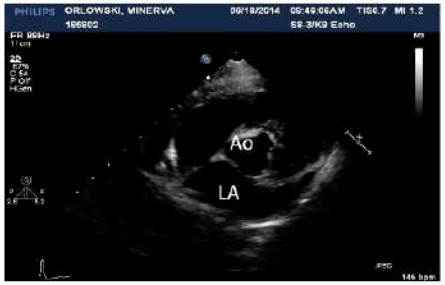
- Evidence of fluid accumulation
  - B-lines (suggest pulmonary edema)
  - Pleural effusion *(cats)*
  - Pericardial effusion *(cats)*

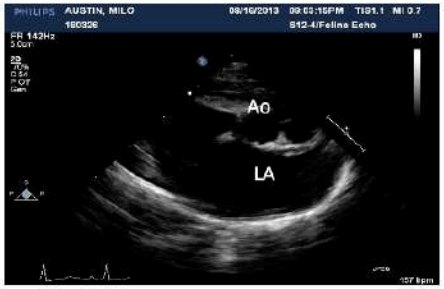


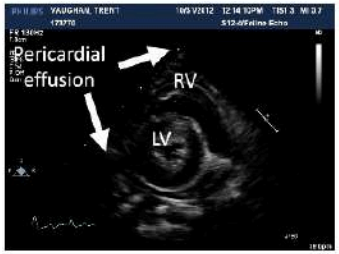
B-lines



Pleural effusion



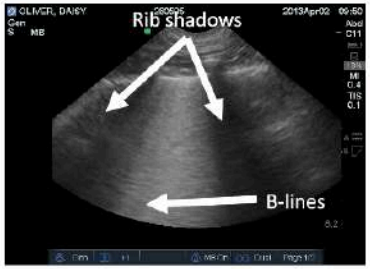




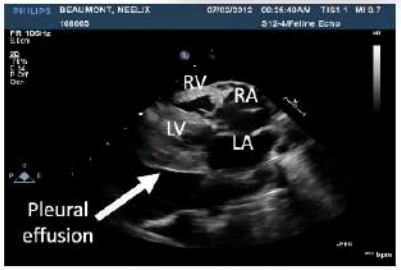
Pericardial effusion

Diagnosis of CHF: point-of-care ultrasound

- Evidence of fluid accumulation
  - B-lines (suggest pulmonary edema)
  - Pleural effusion *(cats)*
  - Pericardial effusion *(cats)*
- Evidence of severe LA dilation
  - LA:Ao > 2.0

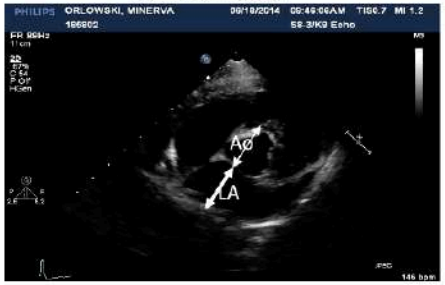


B-lines

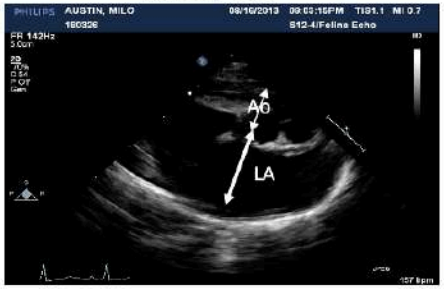


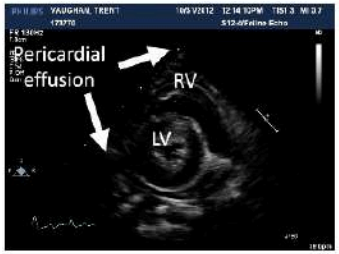
Pleural effusion

Normal LA:Ao



LA:Ao > 2.0





Pericardial effusion

What is the definition of stage B2 MMVD?

"Moderate to severe" left heart enlargement:

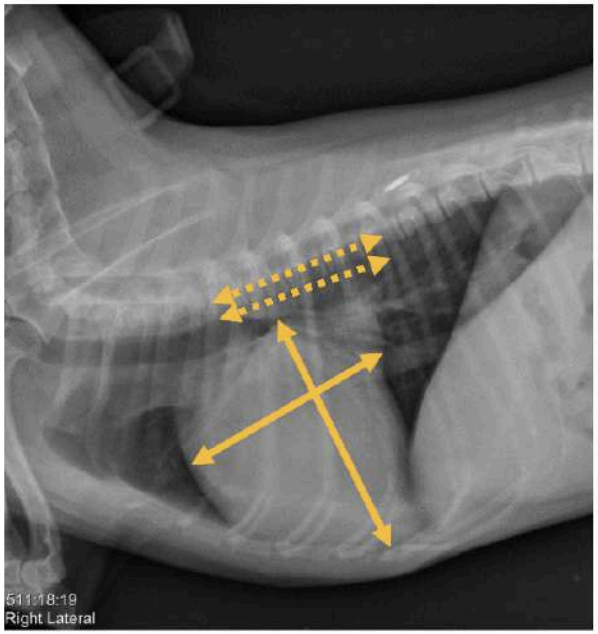
1. VHS > 10.5
2. LA:Ao > 1.6
3. LVIDDn > 1.7

Effect of Pimobendan in Dogs with Preclinical Myxomatous Mitral Valve Disease and Cardiomegaly: The EPIC Study—A Randomized Clinical Trial

ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs Updated 2019

What is the definition of stage B2 MMVD?

1. **VHS > 10.5**
2. LA:Ao > 1.6
3. LVIDDn > 1.7



What is the definition of stage B2 MMVD?

1. VHS > 10.5
2. LA:Ao > 1.6
3. LVIDDn > 1.7

Easiest to evaluate (TXR)
LEAST specific (too "inclusive")

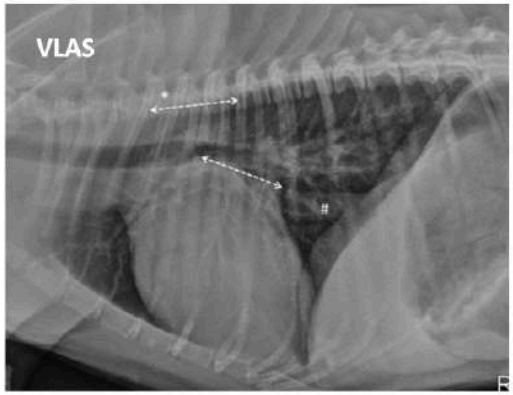
Hardest to evaluate (echo)
MOST specific (most "exclusive")

Defining stage B2 MMVD *without* echo

1.VHS > 11.5 (or at least >11.0)
- ~75% accurate for B2 EPIC

2.Vertebral LA size (VLAS) > 2.5
- ~75% accurate for LA:Ao > 1.6

3.Consider systemic blood pressure!
- Systemic hypertension WORSENS mitral regurgitation
- Borderline hypertension "lowers" my threshold for treatment



Malcolm JVIM 2018

	Likely B2	Grey zone	Likely B1
VHS	>11.5	10.5-11.5	<10.5
VLAS	>3.0	2.5-3.0	<2.5

Formulating a treatment plan

- Treatment of MMVD
  - Including echocardiographic criteria for diagnosis and treatment
  - Formulate your treatment plan for a dog in stage C MMVD

ACVIM consensus statement

DOI: 10.1111/jvim.15488

CONSENSUS STATEMENT

Journal of Veterinary Internal Medicine Open Access ACVIM American College of Veterinary Internal Medicine

Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ACVIM Board of Regents oversees selection of relevant topics, identification of panel members with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership which may be incorporated into the statement. It is then submitted to the *Journal of Veterinary Internal Medicine*, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs

Bruce W. Keene[1] | Clarke E. Atkins[1] | John D. Bonagura[1,2] | Philip R. Fox[3] | Jens Häggström[4] | Virginia Luis Fuentes[5] | Mark A. Oyama[6] | John E. Rush[7] | Rebecca Stepien[8] | Masami Uechi[9]

[1]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina

[2]Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, Ohio

Abstract

This report, issued by the ACVIM Specialty of Cardiology consensus panel, revises guidelines for the diagnosis and treatment of myxomatous mitral valve disease

ACVIM cardiac disease classification

Journal of Veterinary Internal Medicine Open Access
ACVIM American College of Veterinary Internal Medicine

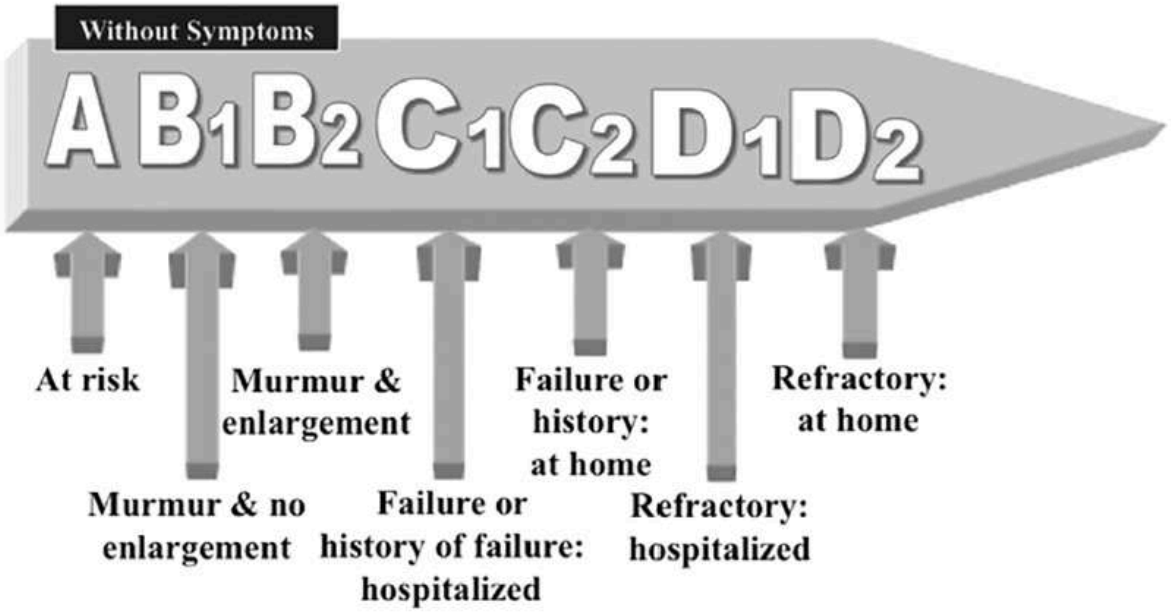


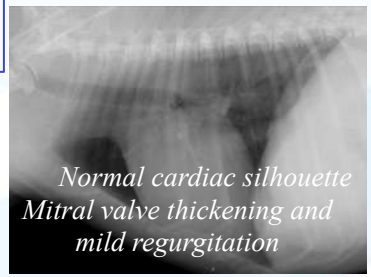
FIGURE 4 The American College of Veterinary Internal Medicine (ACVIM) classification of cardiac disease. From at risk of heart failure to refractory heart failure[173]

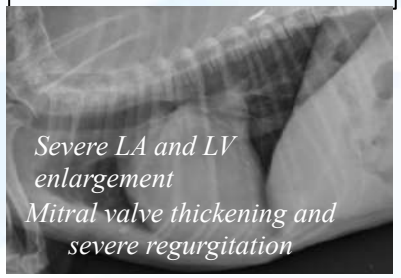
Staging of heart disease

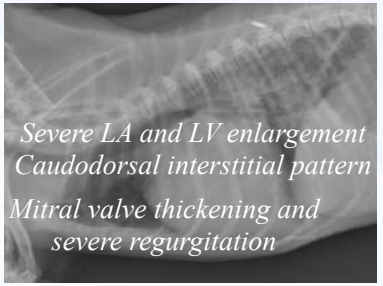
Dr J. Ward Iowa State University

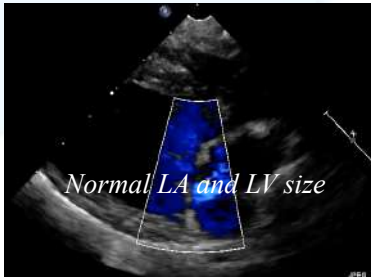
This classification system was designed for MMVD but has been adapted for HCM and DCM. Learn more about MMVD staging and treatment by reading the ACVIM Consensus Statement!

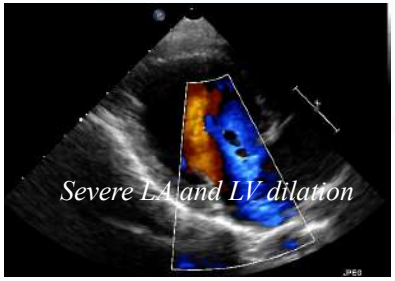
Stage A	Stage B1	Stage B2	Stage C	Stage D
Breeds at risk No current heart disease	Heart disease No to mild heart enlargement	Heart disease Moderate to severe heart enlargement	Current or previous CHF (decompensated vs. compensated)	Refractory CHF (decompensated vs. compensated)

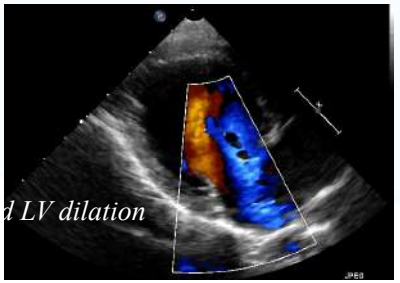




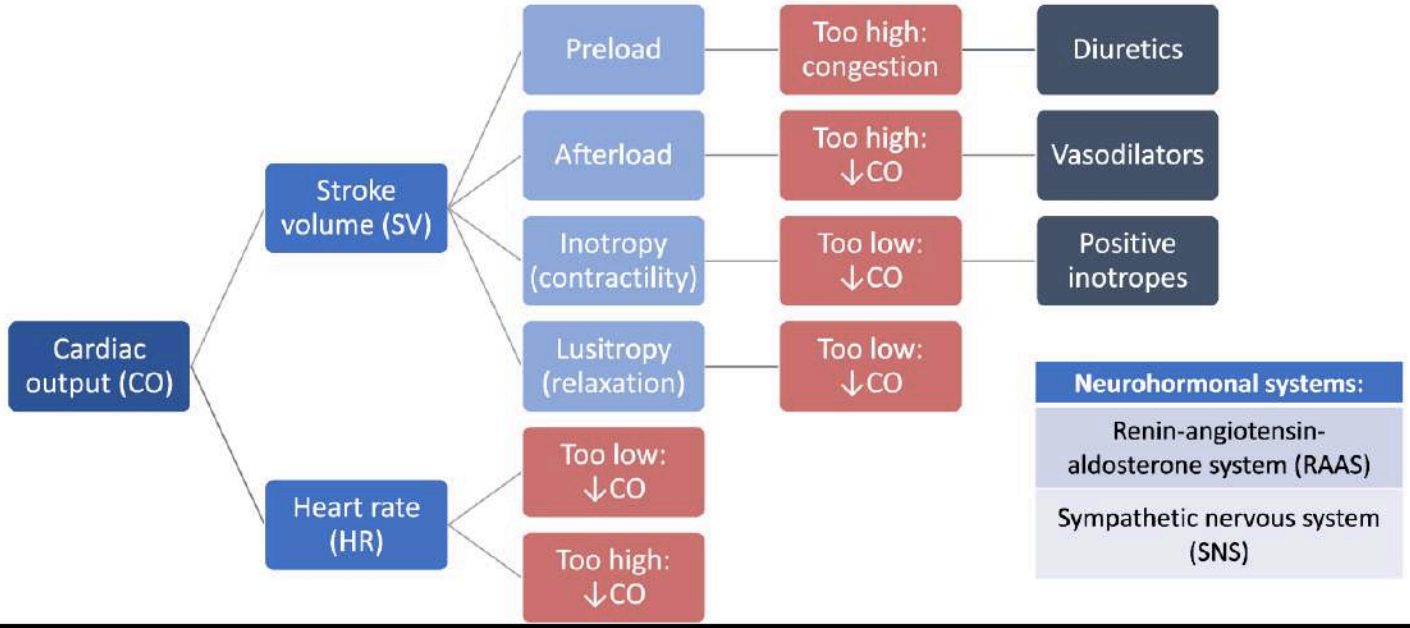








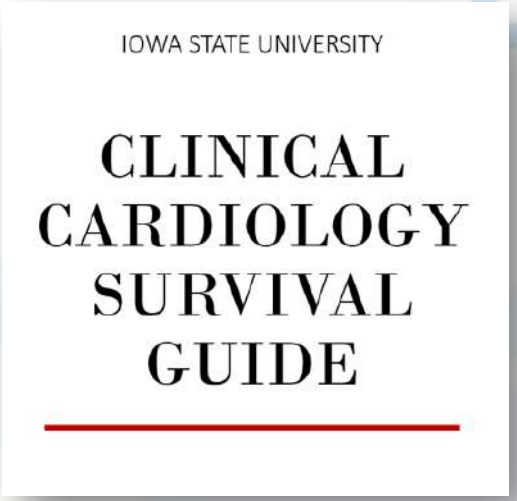
Drug therapy for heart failure addresses the pathophysiologic derangements



Categories of drug therapy for heart disease reflect the pathophysiologic basis of CHF

Dr J. Ward Iowa State University

Pathophysiologic target	Drug categories	Examples
Decrease preload	Diuretics	Furosemide, spironolactone
	Venodilators	ACE inhibitors, nitroprusside
Increase inotropy	Positive inotropes	Pimobendan
Decrease afterload	Arteriodilators	ACE inhibitors, amlodipine
Optimize heart rate	Anti-arrhythmics	Diltiazem, sotalol
Neurohormonal modulation	RAAS inhibitors	ACE inhibitors, spironolactone



For detailed information regarding individual drugs used in the treatment of heart disease (including mechanism of action, indications, side effects, and dosages), please see the Cardiology Drug Formulary available in the ISU Clinical Cardiology Survival Guide.

Trajectory method

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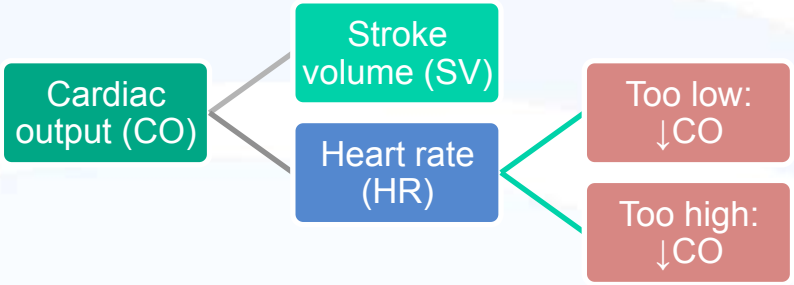
CHRONIC TREATMENT

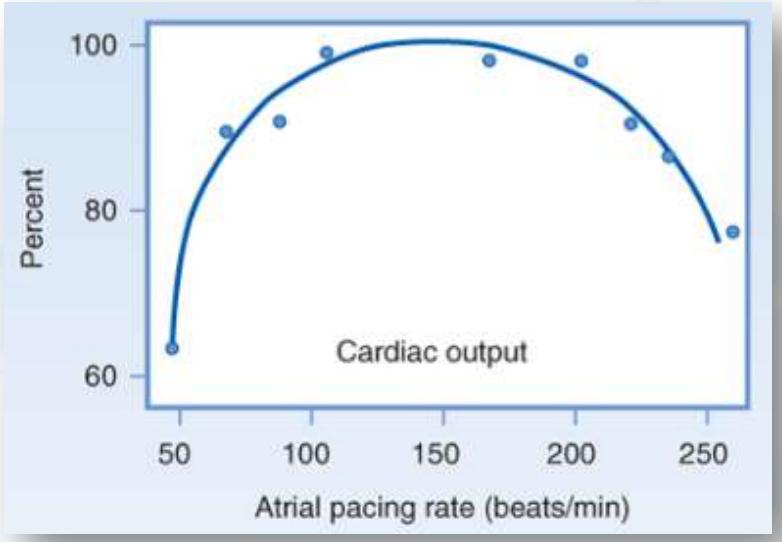
ACUTE TREATMENT

Stage A	Stage B1	Stage B2	Stage C	Stage D
		Pimobendan ACE inhibitor	Dietary Na+ restriction Spironolactone Furosemide Pimobendan ACE inhibitor	Dietary Na+ restriction Spironolactone Furosemide → torsemide Pimobendan ACE inhibitor +/- Sildenafil (if PHT) +/- Amlodipine +/- Hydrochlorothiazide
Oxygen and sedation (with a cardiovascularly-sparing sedative like butorphanol) are nonspecific treatments indicated for **any patient with respiratory distress**.			Oxygen supplementation Sedation (butorphanol) Furosemide Pimobendan	Oxygen supplementation Sedation (butorphanol) Furosemide Pimobendan +/- Dobutamine +/- Nitroprusside

For patients with arrhythmias, heart rate optimization is required for adequate CHF control
Dr J. Ward Iowa State University



- Treat tachyarrhythmias or bradyarrhythmias that compromise cardiac output
- The most common pathologic arrhythmias in dogs and cats are atrial fibrillation and ventricular ectopy (VPCs/VT)



This chart shows the relationship between HR (X-axis) and CO (Y-axis, as percent of maximal CO) in dogs. Note that maximal CO occurs at a heart rate of ~150bpm. This is the expected heart rate of a dog with sympathetic nervous system stimulation – which **explains why dogs with CHF typically have sinus tachycardia at hearts rates of ~150bpm**!

Monitoring cardiac therapy involves assessing for resolution of CHF and screening for drug side effects

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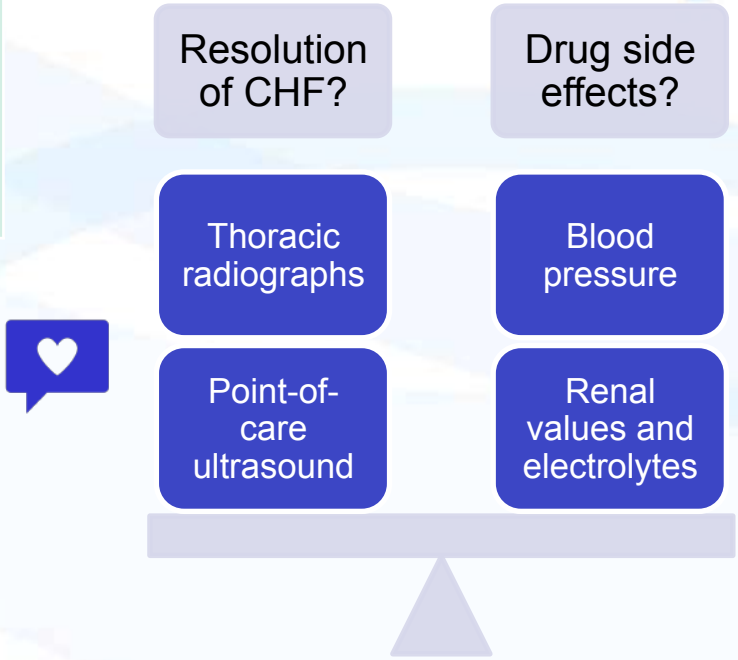
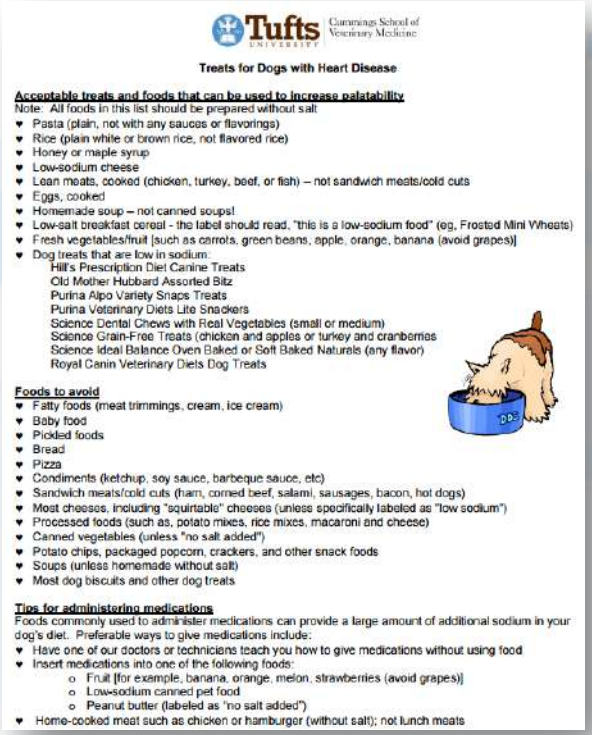
Side effects of diuretics:	Side effects of vasodilators:
Polyuria/polydipsia Dehydration Azotemia Electrolyte imbalances	Hypotension

"Gastrointestinal upset" is a relatively uncommon side effect for cardiac drugs; most cardiac drugs only cause hyporexia or vomiting if they cause azotemia or electrolyte disturbances. However, a few cardiac drugs are **more commonly associated with GI upset**, including **diltiazem**, **mexiletine**, **clopidogrel** (the pill itself is bitter-tasting and can cause hypersalivation).



Moderate dietary sodium restriction is indicated for heart disease stages C and D
Dr J. Ward Iowa State University

- Moderate Na+ restriction
  - 50-80mg Na+ per 100kcal
  - ~0.2% Na+ on dry matter basis
  - Consider food AND treats
- Ensure adequate protein/calories to avoid cachexia
- Refer owners to Tufts Veterinary Nutrition website:
  - http://vet.tufts.edu/heartsmart/diet



Tufts University Cummings School of Veterinary Medicine

Treats for Dogs with Heart Disease

Acceptable treats and foods that can be used to increase palatability

Note: All foods in this list should be prepared without salt

- Pasta (plain, not with any sauces or flavorings)
- Rice (plain white or brown rice, not flavored rice)
- Honey or maple syrup
- Low-sodium cheese
- Lean meats, cooked (chicken, turkey, beef, or fish) – not sandwich meats/cold cuts
- Eggs, cooked
- Homemade soup – not canned soups!
- Low-salt breakfast cereal - the label should read, "this is a low-sodium food" (eg, Frosted Mini Wheats)
- Fresh vegetables/fruit [such as carrots, green beans, apple, orange, banana (avoid grapes)]
- Dog treats that are low in sodium:
  - Hill's Prescription Diet Canine Treats
  - Old Mother Hubbard Assorted Bitz
  - Purina Alpo Variety Snaps Treats
  - Purina Veterinary Diets Lite Snackers
  - Science Dental Chews with Real Vegetables (small or medium)
  - Science Grain-Free Treats (chicken and apples or turkey and cranberries
  - Science Ideal Balance Oven Baked or Soft Baked Naturals (any flavor)
  - Royal Canin Veterinary Diets Dog Treats

Foods to avoid

- Fatty foods (meat trimmings, cream, ice cream)
- Baby food
- Pickled foods
- Bread
- Pizza
- Condiments (ketchup, soy sauce, barbeque sauce, etc)
- Sandwich meats/cold cuts (ham, corned beef, salami, sausages, bacon, hot dogs)
- Most cheeses, including "squirtable" cheeses (unless specifically labeled as "low sodium")
- Processed foods (such as, potato mixes, rice mixes, macaroni and cheese)
- Canned vegetables (unless "no salt added")
- Potato chips, packaged popcorn, crackers, and other snack foods
- Soups (unless homemade without salt)
- Most dog biscuits and other dog treats

Tips for administering medications

Foods commonly used to administer medications can provide a large amount of additional sodium in your dog's diet. Preferable ways to give medications include:

- Have one of our doctors or technicians teach you how to give medications without using food
- Insert medications into one of the following foods:
  - Fruit [for example, banana, orange, melon, strawberries (avoid grapes)]
  - Low-sodium canned pet food
  - Peanut butter (labeled as "no salt added")
- Home-cooked meat such as chicken or hamburger (without salt); not lunch meats

Patients with CHF will require lifestyle changes
Dr J. Ward Iowa State University

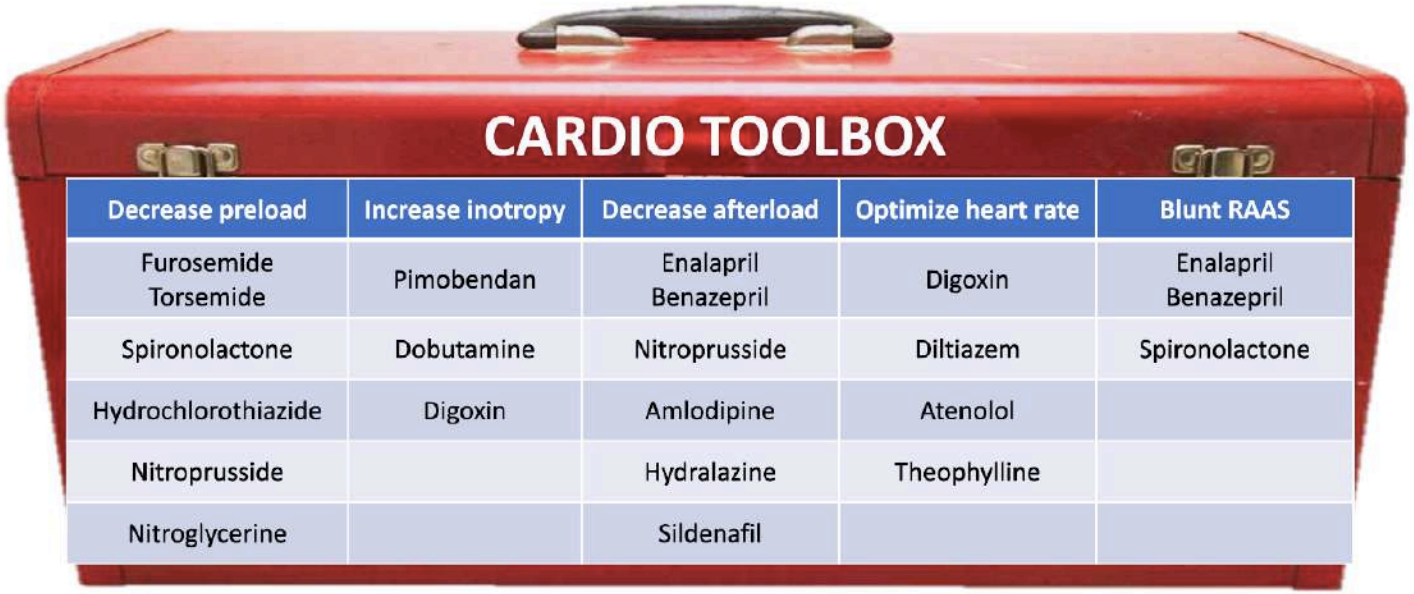
- Medications
  - Frequency: every 8-12 hours
  - Administration: food, treats, “pill popper” guns, capsules

- Exercise/activity
  - Allow pets to self-regulate
  - Avoid strenuous or repetitive activity
  - Keep cats indoors

Preserving quality of life is the goal of CHF treatment
Dr J. Ward Iowa State University

- Maintain “compensation” (no fluid)
- Minimize hospitalizations
- Maintain acceptable activity tolerance
- Maintain acceptable appetite/weight

Cardiac drug "toolbox"



Decrease preload	Increase inotropy	Decrease afterload	Optimize heart rate	Blunt RAAS
Furosemide Torsemide	Pimobendan	Enalapril Benazepril	Digoxin	Enalapril Benazepril
Spironolactone	Dobutamine	Nitroprusside	Diltiazem	Spironolactone
Hydrochlorothiazide	Digoxin	Amlodipine	Atenolol	
Nitroprusside		Hydralazine	Theophylline	
Nitroglycerine		Sildenafil		

Cardiac treatment: MMVD

CHRONIC TREATMENT

Stage A	Stage B1	Stage B2	Stage C	Stage D
		Pimobendan	Dietary Na+ restriction	+/- Amlodipine
		ACE inhibitor	Furosemide	+/- Hydrochlorothiazide
			Spironolactone	+/- Sildenafil (if PHT)
			Pimobendan	Dietary Na+ restriction
			ACE inhibitor	↑ Furosemide → torsemide
				Spironolactone
				↑ Pimobendan
				ACE inhibitor

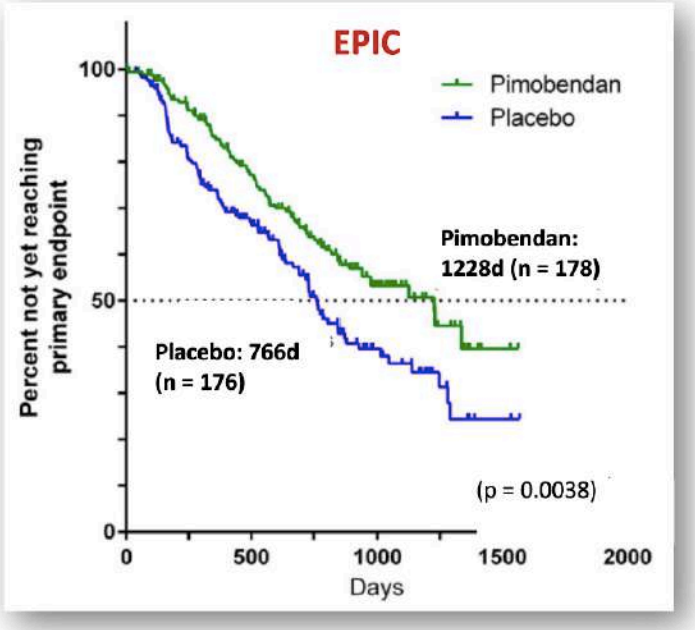
ACUTE TREATMENT

Stage C	Stage D
Oxygen supplementation	Oxygen supplementation
Sedation (butorphanol)	Sedation (butorphanol)
Furosemide	Furosemide
Pimobendan	Pimobendan
	+/- Dobutamine
	+/- Nitroprusside

How I treat stage B2 MMVD (and why):

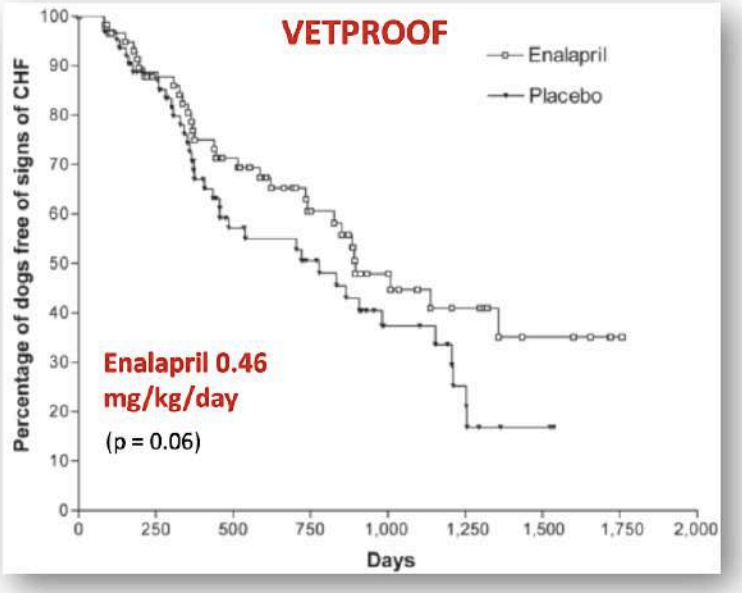
- Why pimobendan?
- Why ACEi? What dose of ACEi?
- Why not spironolactone?

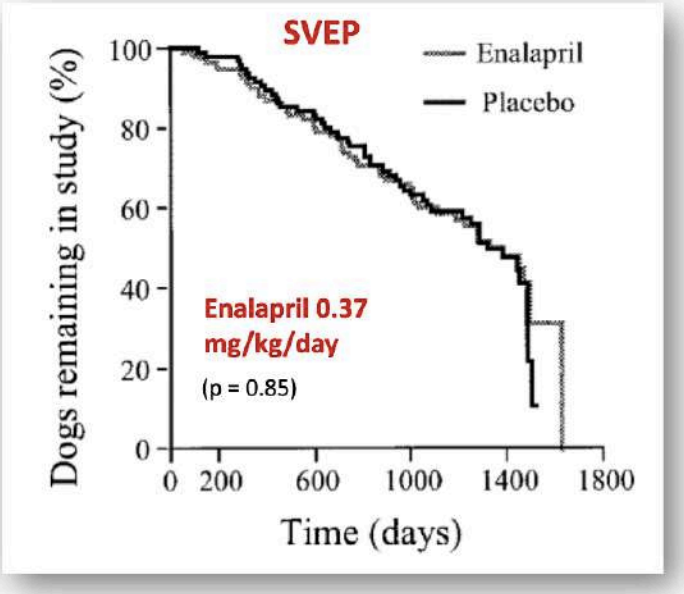
Why pimobendan in MMVD B2?



Boswood et al. JVIM 2016

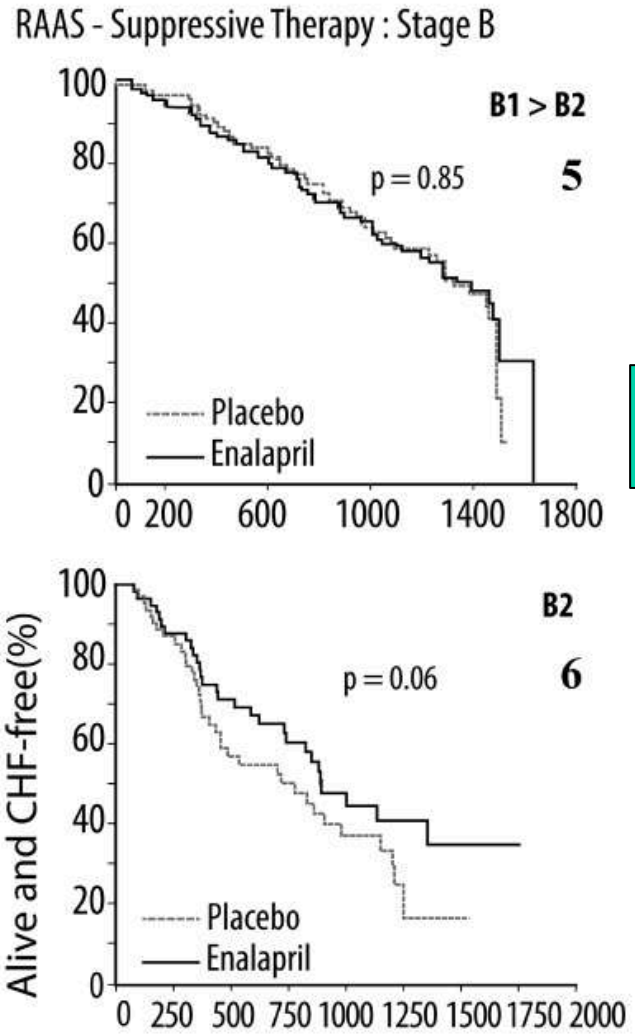
Why ACEi in MMVD B2?





Kvart et al. JVIM 2002; Atkins et al. JAVMA 2007

Suppressive therapy: Stage B



5. Kvart et al JVIM 2002, 16: 80-88
6. Atkins et al JAVMA 2007, 231: 1061-1069

First MMVD meta-analysis in veterinary cardiology

BSAVA

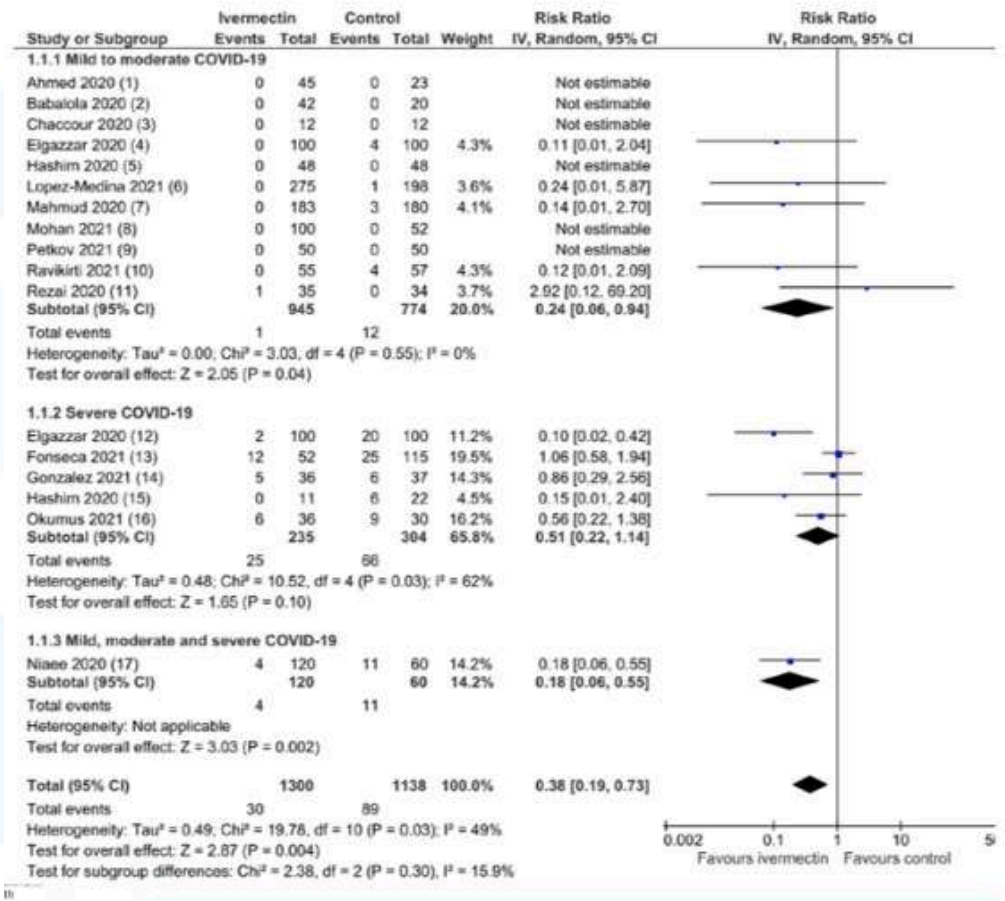
ORIGINAL ARTICLE

Angiotensin-converting enzyme inhibitors in preclinical myxomatous mitral valve disease in dogs: systematic review and meta-analysis

P. Donati [1,*], A. Tarducci[†], R. Zanatta[†], N. Verdier[*,‡], G. Belerenian[§], I. Cordero[¶], C. Villalta[¶], J. Franco [‖] and L. Tarragona[*]

[*]Universidad de Buenos Aires, Facultad de Ciencias Veterinarias, Cátedra de Anestesiología y Algiología, Av. Chorroarín 280, CP 1427, Ciudad Autónoma de Buenos Aires, Argentina
[†]Department of Veterinary Sciences, University of Turin, Largo Paolo Braccini 2-5, 10095, Grugliasco Turin, Italy
[‡]Department of Anesthesiology and Perioperative Intensive Care, University of Veterinary Medicine, Veterinärplatz 1, 1220 Vienna, Austria
[§]Luis Pasteur Zoonosis Institute, Av. Díaz Vélez 482, CP 1405, Ciudad Autónoma de Buenos Aires, Argentina
[¶]Clinica Veterinaria VET'S, Suecia 3580, Providencia, Ñuñoa, Región Metropolitana, Chile
[‖]Instituto Universitario Hospital Italiano, Argentine Cochrane Centre, Potosi 4234, CP 1199, Ciudad Autónoma de Buenos Aires, Argentina

Another meta-analysis…..



Bryant et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines Am J Therapeutics 2021

Forest plot following a meta-analysis

Study or Subgroup	ACE inhibitor Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atkins 2007	2	59	2	58	10.4%	0.98 [0.14, 6.75]
Borgarelli 2020	15	68	13	60	89.6%	1.02 [0.53, 1.96]
Total (95% CI)		**127**		**118**	**100.0%**	**1.01 [0.54, 1.89]**
Total events	17		15			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

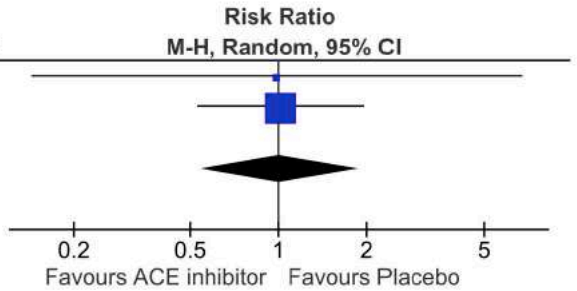


FIG 3. Forest plot of the outcome "cardiovascular-related mortality" showing the number of dogs with myxomatous mitral valve disease with cardiomegaly treated with angiotensin-converting enzyme inhibitors *versus* placebo. A Mantel–Haenszel (M–H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown. ACE Angiotensin-converting enzyme

Study or Subgroup	ACE inhibitor Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atkins 2007	36	59	37	58	38.4%	0.96 [0.72, 1.27]
Borgarelli 2020	27	68	20	60	14.2%	1.19 [0.75, 1.89]
Kvart 2002	32	41	26	35	47.3%	1.05 [0.82, 1.35]
Total (95% CI)		**168**		**153**	**100.0%**	**1.03 [0.87, 1.23]**
Total events	95		83			

Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

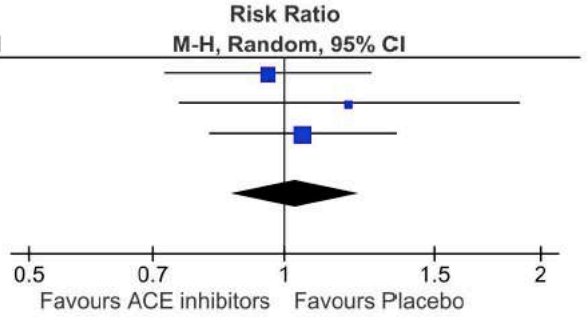


FIG 4. Forest plot of the outcome "congestive heart failure" showing the number of dogs with myxomatous mitral valve disease with cardiomegaly treated with angiotensin-converting enzyme inhibitors *versus* placebo. A Mantel–Haenszel (M–H) random effects model was used for this meta-analysis. The results of the relative risk with a 95% confidence interval (95% CI) are shown. ACE Angiotensin-converting enzyme

Why the discordant results?

- Dog demographics and disease stage?

- ACE polymorphism prevalence in CKCS?

- ACEi dose?

Where did the original (label) dose of ACEi come from?

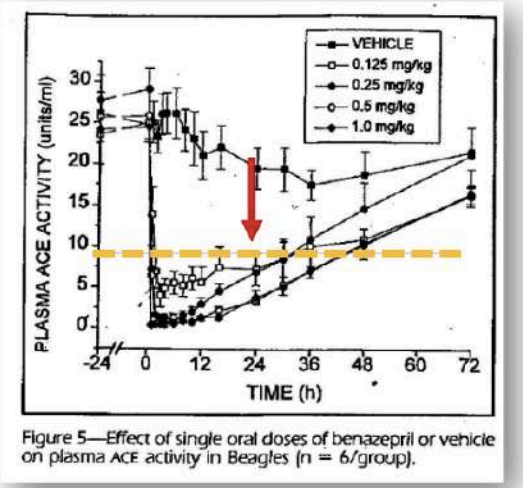
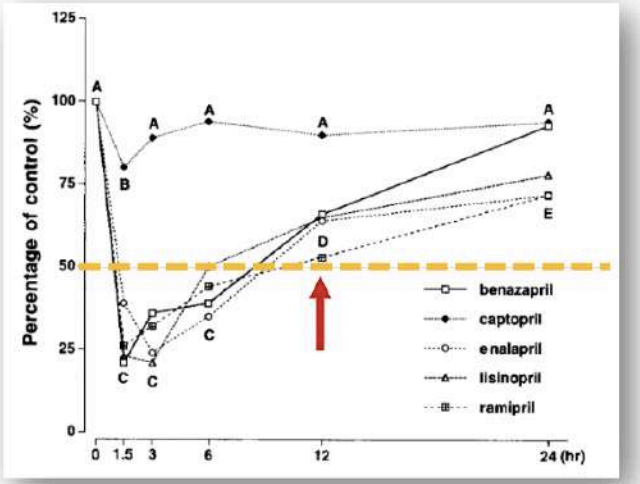


Figure 5—Effect of single oral doses of benazepril or vehicle on plasma ACE activity in Beagles (n = 6/group).

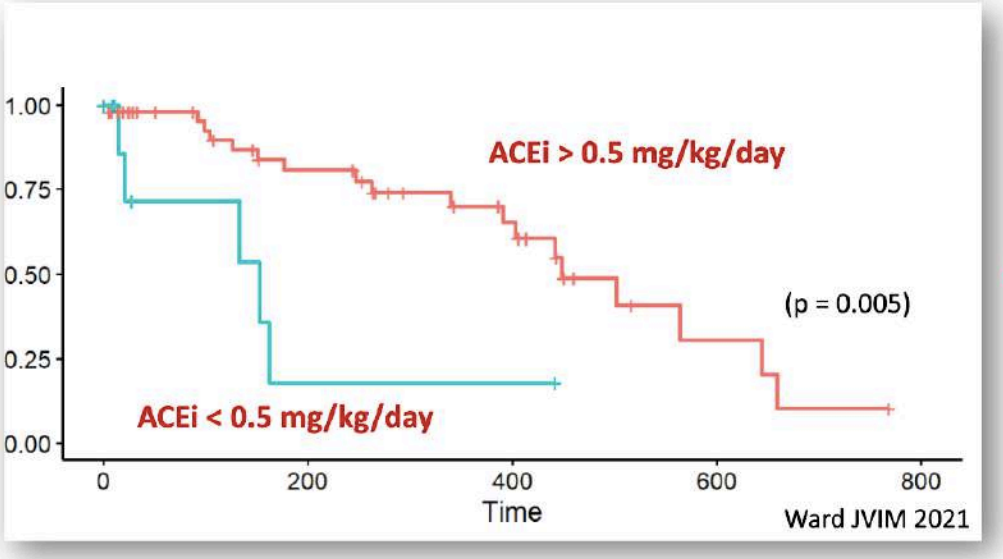


Benazepril's effect on ACE activity lasts >24 hours and is independent of doses > 0.25 mg/kg

Duration of effect on ACE activity is only ~12 hours for enalapril or benazepril at 0.5 mg/kg

King et al. AJVR 1995; Toutain J Pharm Exp Ther 2000; Hamlin & Nakayama J Vet Intern Med 1998

Higher ACEi dose (>0.5 mg/kg/day) associated with longer survival from time of first-onset CHF (retrospective)



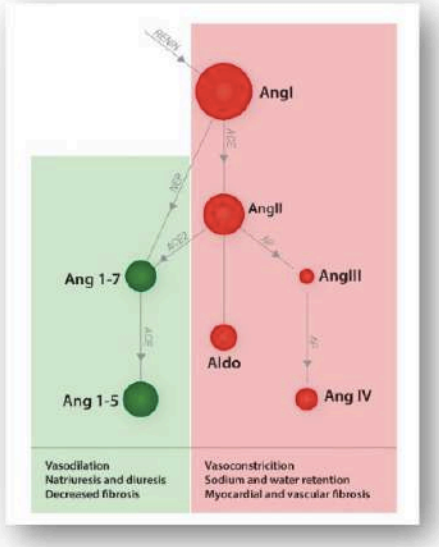
Higher doses of benazepril (>0.5 mg/kg/day or q12hr dosing) were associated with longer survival in dogs with CHF

ACEi were safe and well-tolerated, even at high(er) doses

- Side effects related to ACEi: 8 dogs (5.6%)
  - Azotemia, lethargy/hypotension
- ACEi discontinued due to side effects: 3 dogs (2.1%)
- ACEi dose increased in 27 dogs (19%)
  - Increased or high normal BP, clinician preference

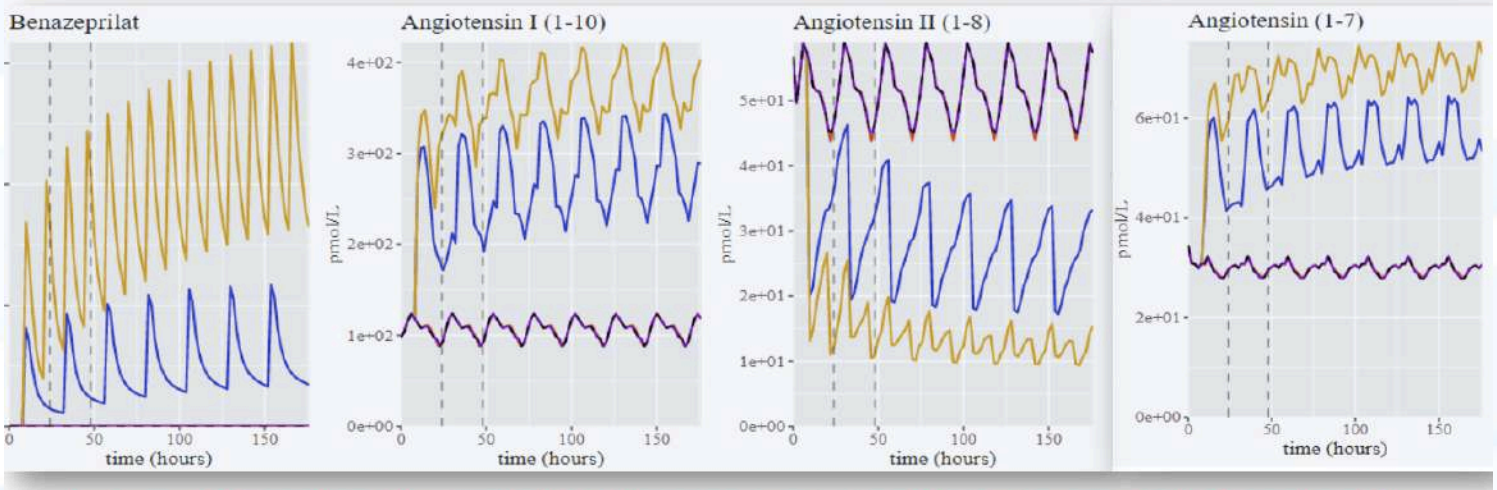
Prospective dose-response of benazepril on comprehensive RAAS biomarkers in healthy dogs

- 9 healthy beagle dogs
- RAAS activation via low-sodium diet (h/d)
- 3-way crossover study (benazepril 0.125 mg/kg q12hr, 0.25 mg/kg q12hr, 0.5 mg/kg q24hr)
- 24-hour blood sampling for PK and RAAS fingerprinting

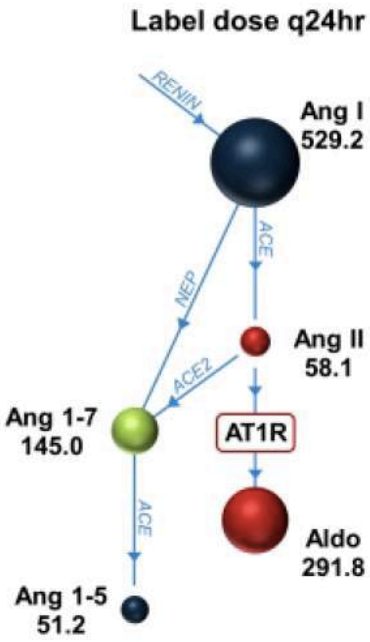


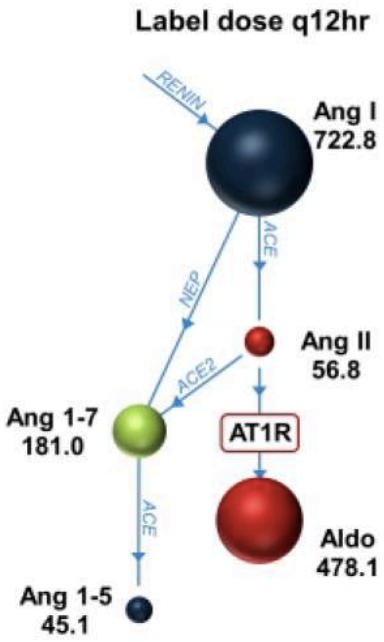
Sotillo et al. 2023

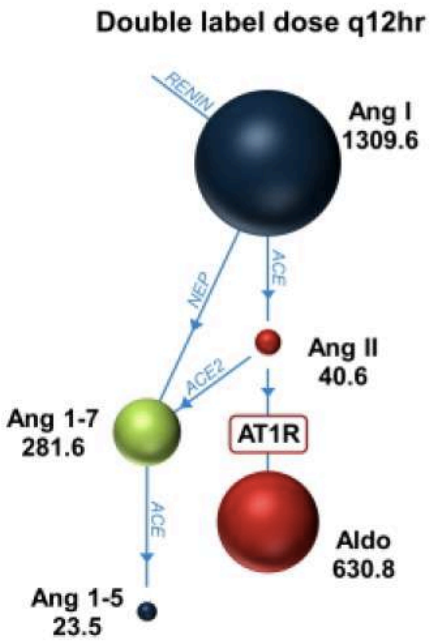
Higher dose and frequency of ACEi lead to decreased AngII and increased Ang1-7

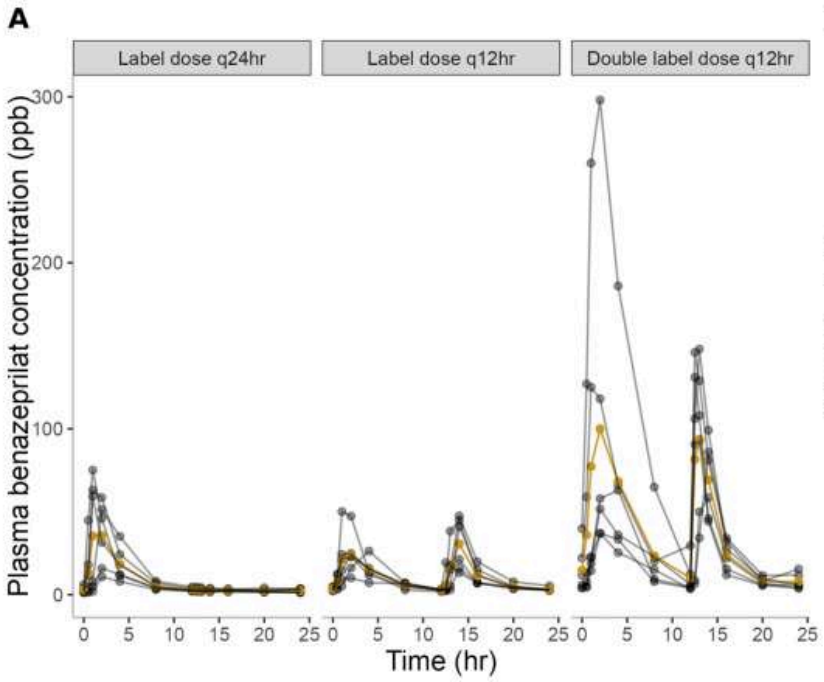


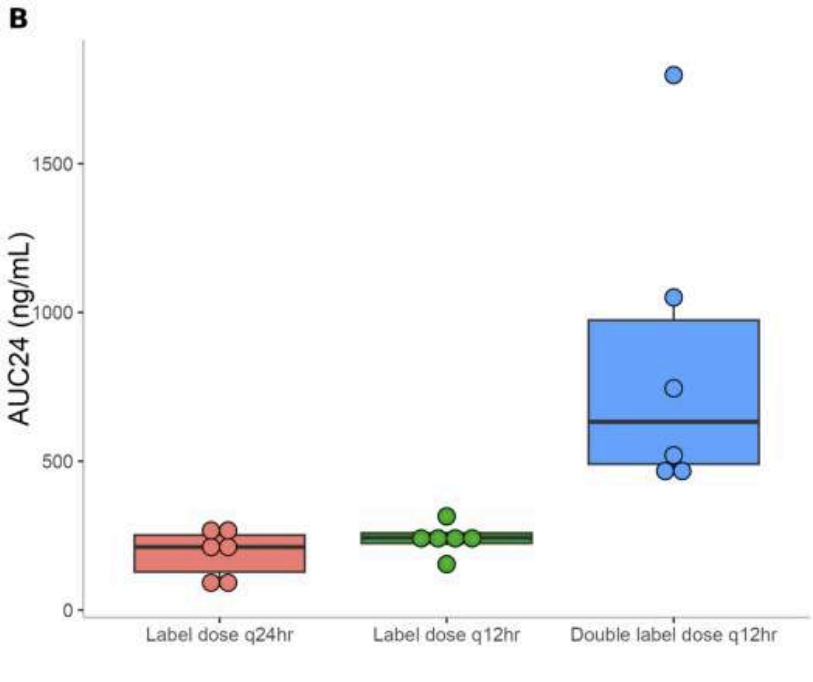
Benazepril 0.5 mg/kg q12hr resulted in ~2x more suppression of AngII compared to 0.25 mg/kg q24hr

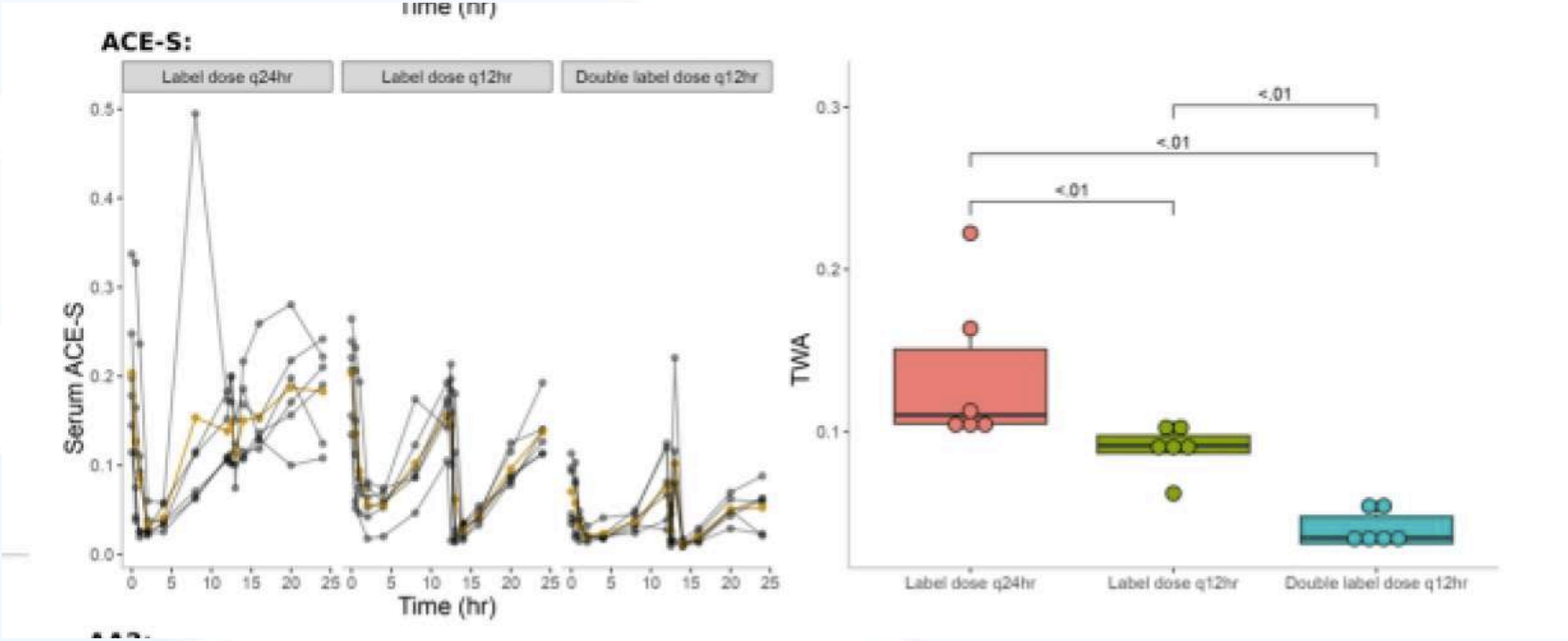

Label dose q24hr
RENIN
Ang I
529.2
ACE
NEP
Ang II
58.1
ACE2
Ang 1-7
145.0
AT1R
Aldo
291.8
ACE
Ang 1-5
51.2


Label dose q12hr
RENIN
Ang I
722.8
ACE
NEP
Ang II
56.8
ACE2
Ang 1-7
181.0
AT1R
Aldo
478.1
ACE
Ang 1-5
45.1

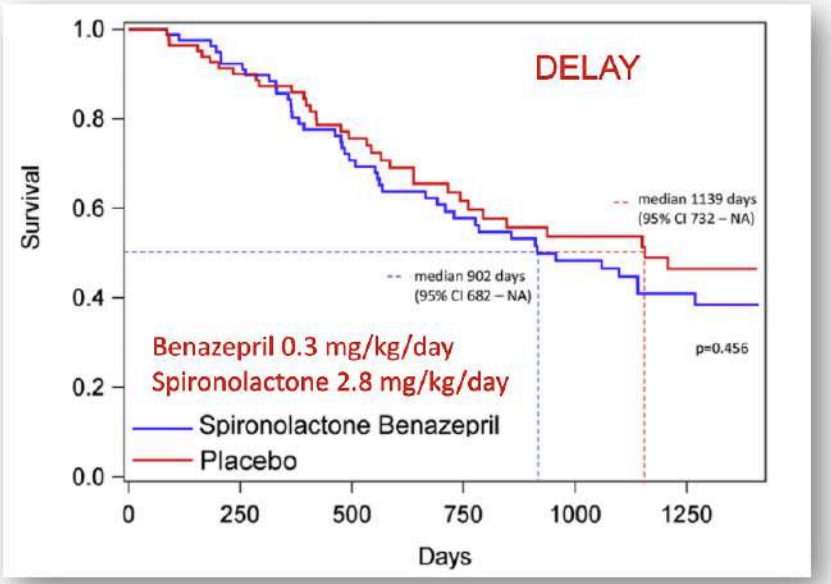

Double label dose q12hr
RENIN
Ang I
1309.6
ACE
NEP
Ang II
40.6
ACE2
Ang 1-7
281.6
AT1R
Aldo
630.8
ACE
Ang 1-5
23.5


A
Label dose q24hr
Label dose q12hr
Double label dose q12hr
Plasma benazeprilat concentration (ppb)
300
200
100
0
0 5 10 15 20 25
Time (hr)


B
AUC24 (ng/mL)
1500
1000
500
0
Label dose q24hr
Label dose q12hr
Double label dose q12hr

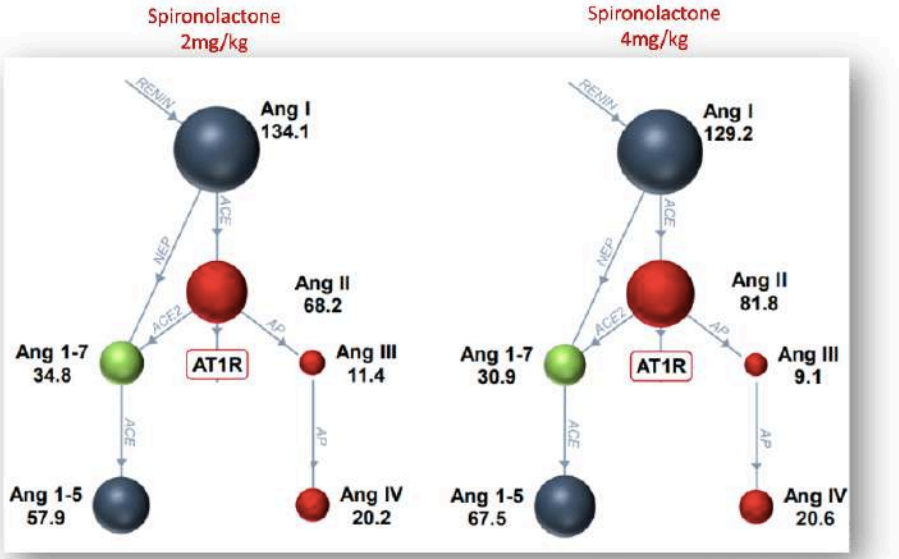

Time (hr)
ACE-S:
Label dose q24hr
Label dose q12hr
Double label dose q12hr
Serum ACE-S
0.0
0.1
0.2
0.3
0.4
0.5
0 5 10 15 20 25
Time (hr)
TWA
<.01
<.01
<.01
Label dose q24hr
Label dose q12hr
Double label dose q12hr

Why not spironolactone in MMVD B2?



Borgarelli et al. JVC 2020

Spironolactone's effect on RAAS is independent of doses >2mg/kg q24hr



Masters ACVIM 2022

Do I ever use spironolactone in B2 MMVD?

- Severity or progression of echocardiographic changes ("advanced" stage B2)?

- ACE polymorphism?

- Owner preference?

IOWA STATE UNIVERSITY

Cardiac treatment: MMVD

CHRONIC TREATMENT

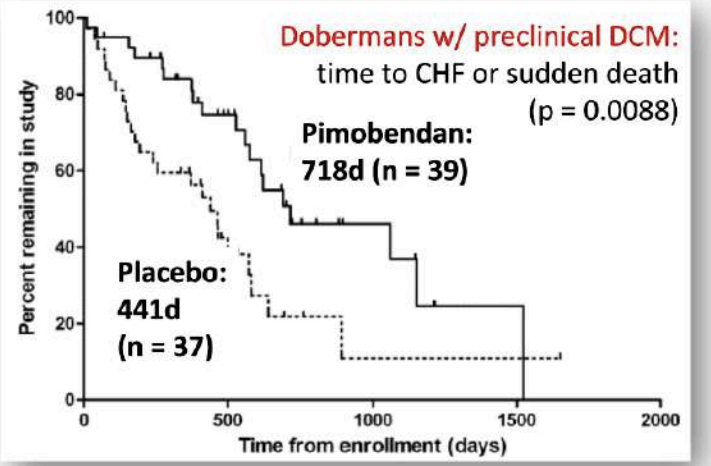
Stage A	Stage B1	Stage B2	Stage C	Stage D
		Pimobendan	Dietary Na+ restriction	+/- Amlodipine
		ACE inhibitor	Furosemide	+/- Hydrochlorothiazide
			Spironolactone	+/- Sildenafil (if PHT)
			Pimobendan	Dietary Na+ restriction
			ACE inhibitor	↑ Furosemide → torsemide
				Spironolactone
				↑ Pimobendan
				ACE inhibitor

ACUTE TREATMENT

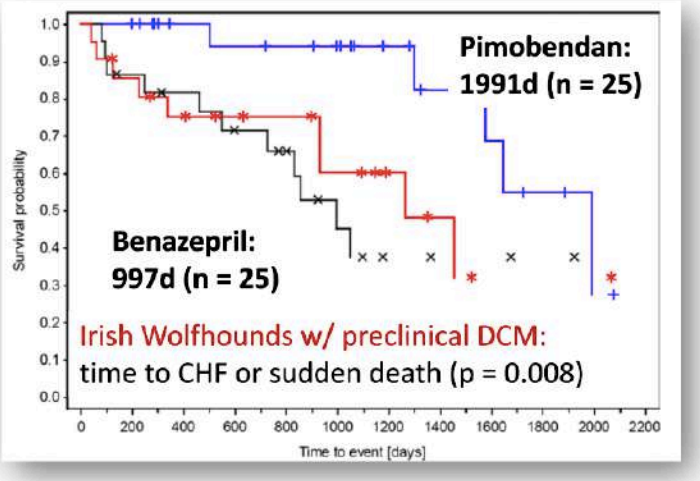
Stage C	Stage D
Oxygen supplementation	Oxygen supplementation
Sedation (butorphanol)	Sedation (butorphanol)
Furosemide	Furosemide
Pimobendan	Pimobendan
	+/- Dobutamine
	+/- Nitroprusside

My preferred ACEi dose is **0.5mg/kg PO q12hr** (round down). Benazepril is preferred if pre-existing azotemia.

Why pimobendan in DCM B2?

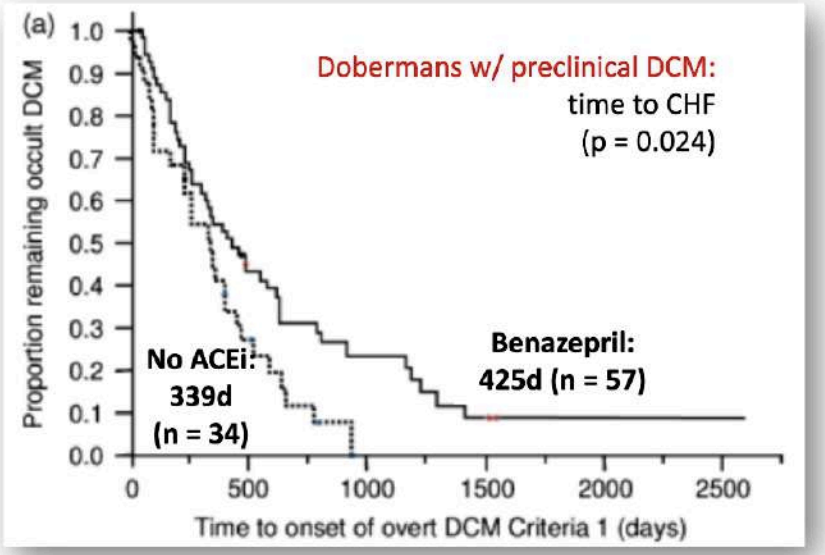


Summerfield JVIM 2014



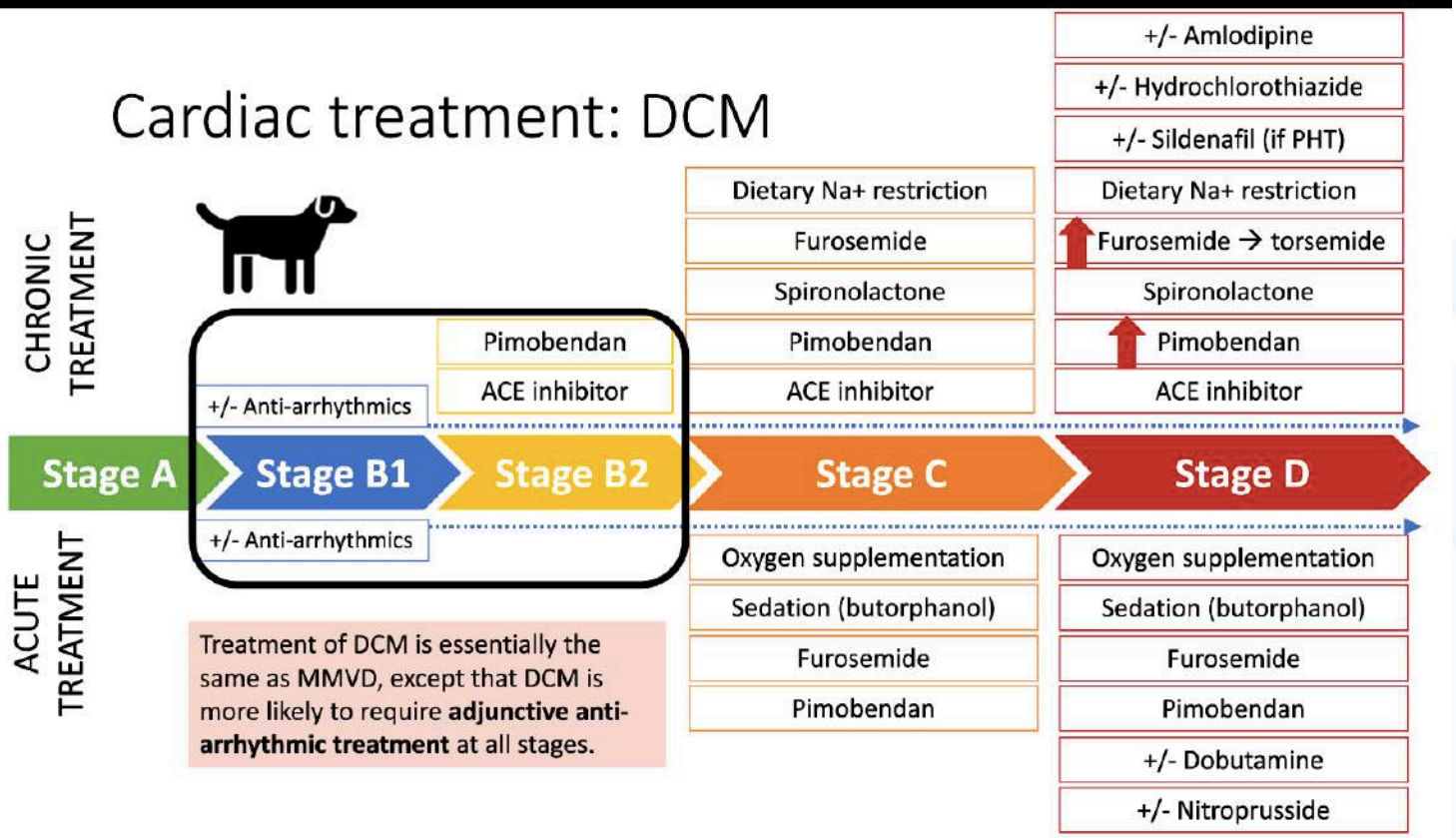
Vollmer JVIM 2016

Why ACEi in DCM B2?

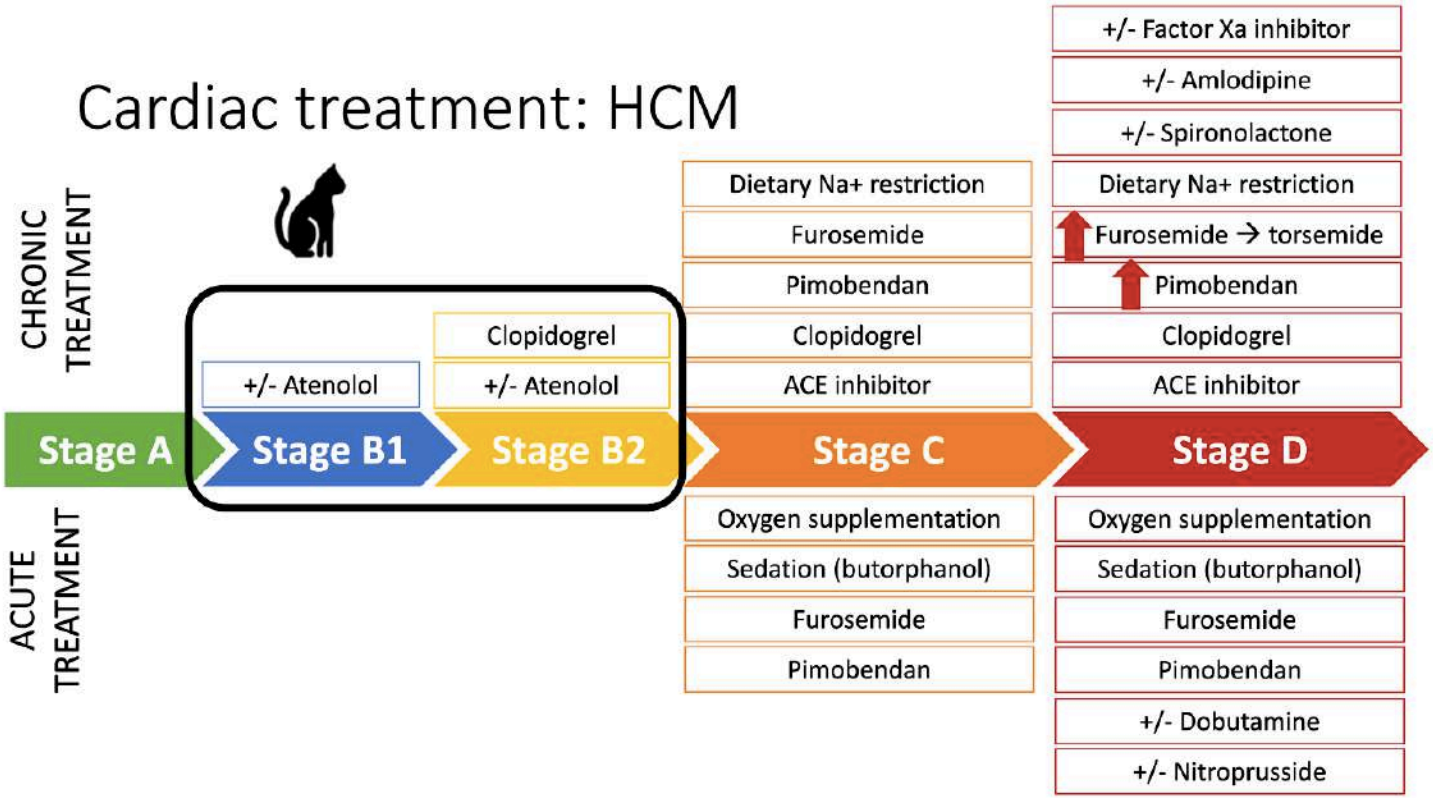


O'Grady JVIM 2009

Cardiac treatment: DCM

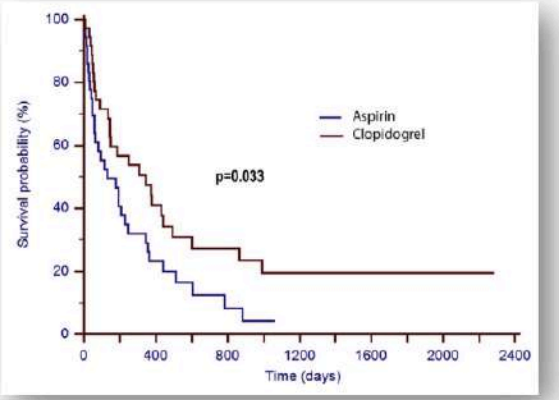


Cardiac treatment: HCM



Why clopidogrel in HCM B2?

- Risk of feline arterial thromboembolism (FATE) is related to degree of LA dilation
- Clopidogrel is superior to aspirin for (secondary) prevention of FATE
- Clopidogrel recommended in consensus guidelines for HCM stage B2

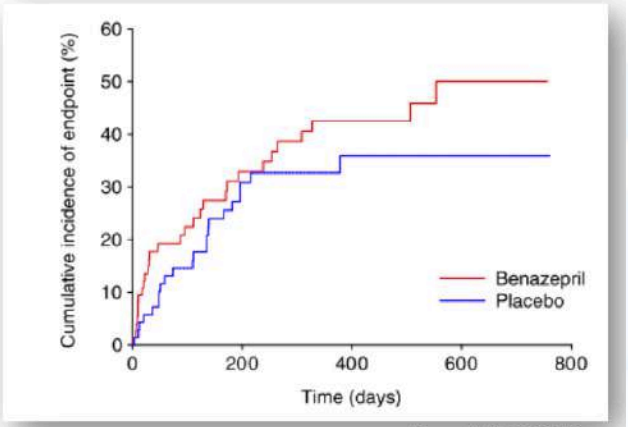


Hogan JVC 2015

ACVIM consensus statement guidelines for the classification, diagnosis, and management of cardiomyopathies in cats

Why not ACEi in HCM B2?

- No evidence of survival benefit in cats with HCM B2/C
  - Benazepril vs. no benazepril (Amberger JVC 1999, open-label)
  - Benazepril vs. placebo (King JVIM 2019)
- I consider ACEi in cats with severe LA dilation or LV remodeling (CHF "imminent")

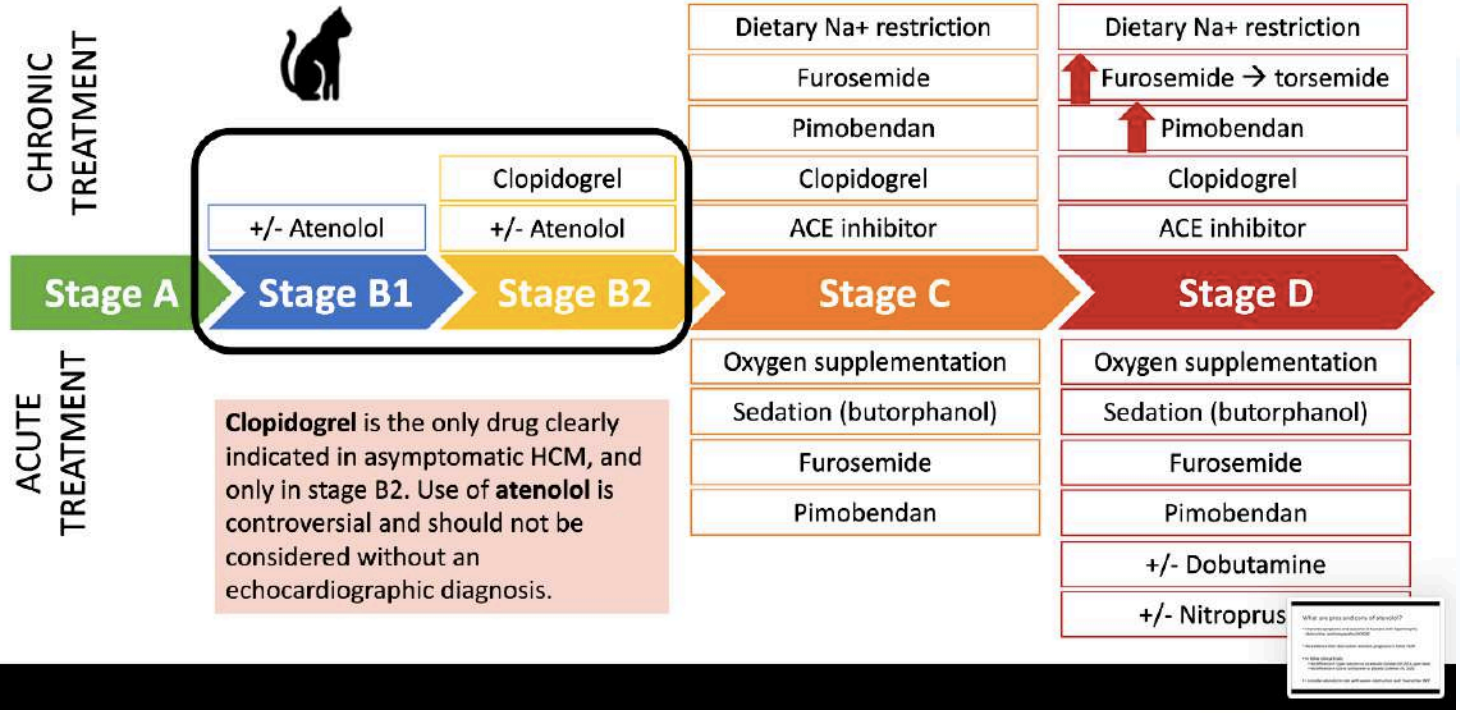


King JVIM 2019

What are pros and cons of atenolol?

- Improves symptoms and outcome in humans with hypertrophic obstructive cardiomyopathy (HOCM)
- No evidence that obstruction worsens prognosis in feline HCM
- In feline clinical trials:
  - No difference in 5-year outcome vs. no atenolol (Schober JVC 2013, open-label)
  - No difference in QOL or activity level vs. placebo (Coleman JVC 2020)
- I consider atenolol in cats with severe obstruction and "overactive SNS"

Cardiac treatment: HCM



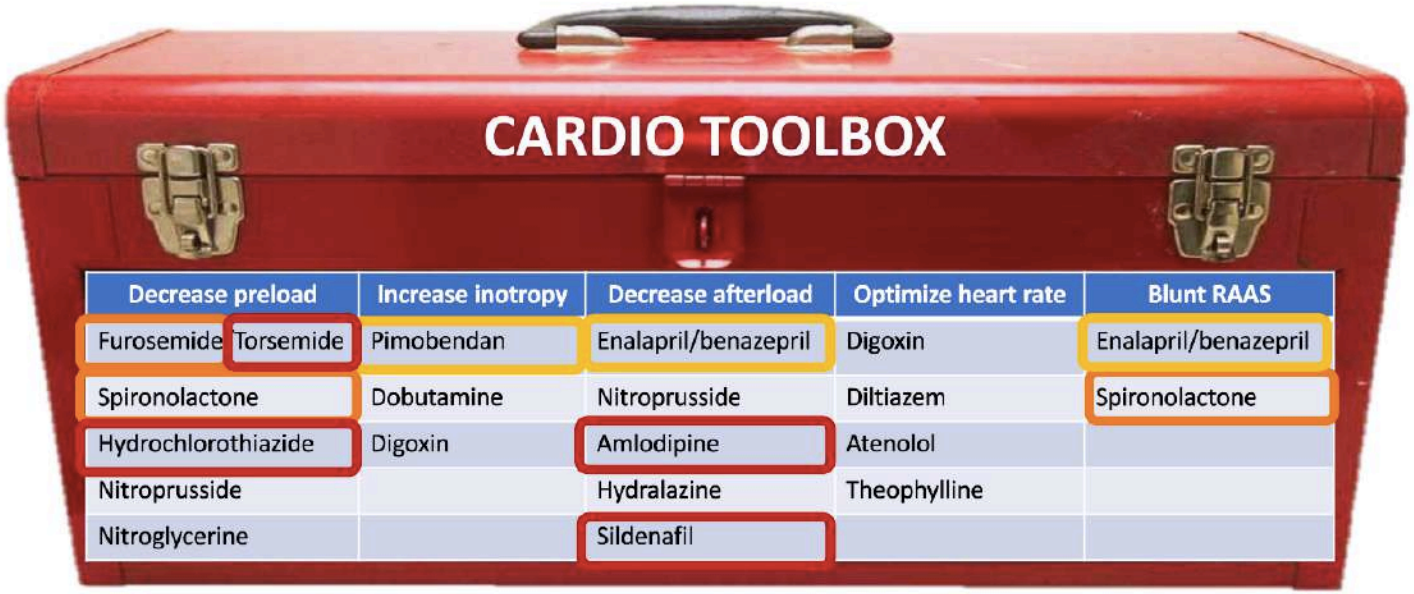
Once we know the stage, how do we treat?

Stage A | Stage B1 | Stage B2 | Stage C | Stage D

- Trajectory method
- Toolbox method
- Acronym method

Toolbox method

- Stage B2
- Stage C
- Stage D



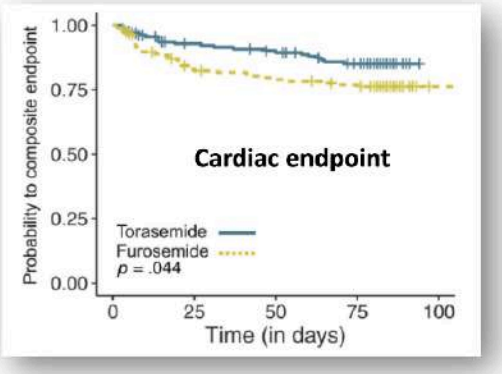
Decrease preload	Increase inotropy	Decrease afterload	Optimize heart rate	Blunt RAAS
Furosemide Torsemide	Pimobendan	Enalapril/benazepril	Digoxin	Enalapril/benazepril
Spironolactone	Dobutamine	Nitroprusside	Diltiazem	Spironolactone
Hydrochlorothiazide	Digoxin	Amlodipine	Atenolol	
Nitroprusside		Hydralazine	Theophylline	
Nitroglycerine		Sildenafil		

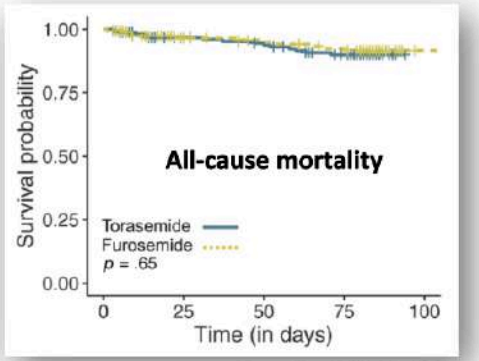
Acronym method

	Acute	Chronic
Stage B2		**"PA"** Pimobendan ACE inhibitor
Stage C	**"FOPS"** Furosemide Oxygen Pimobendan Sedation	**"Dogs Are For Special People"** Dietary Na+ restriction ACE inhibitor Furosemide Spironolactone Pimobendan
Stage D	**"FOPS"** + +/- Dobutamine +/- Nitroprusside	**"Dogs Are For Special People"** + ↑Furosemide or switch to torsemide ↑Pimobendan +/- Amlodipine +/- Hydrochlorothiazide +/- Sildenafil (if pulmonary hypertension)

Why do I choose quadruple therapy for canine CHF?

- **Furosemide (vs. torsemide)**
- Pimobendan
- ACE inhibitor
- Spironolactone

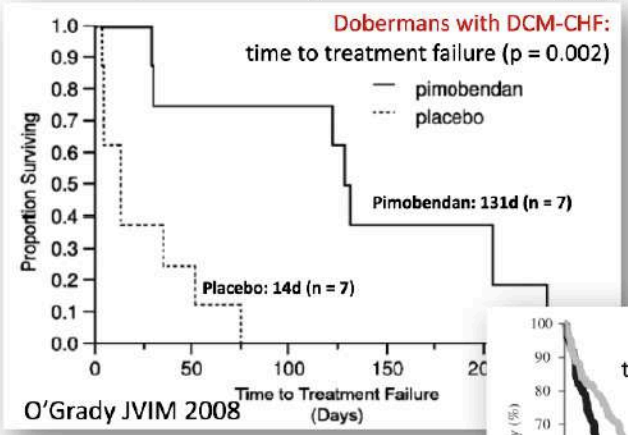


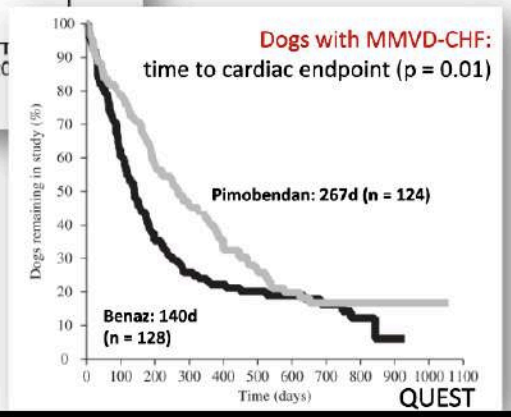


Besche JVIM 2020

Why do I choose quadruple therapy for canine CHF?

- Furosemide
- **Pimobendan**
- ACE inhibitor
- Spironolactone





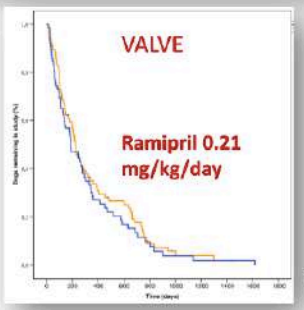
Why do I choose quadruple therapy for canine CHF?

- Furosemide
- Pimobendan
- **ACE inhibitor**
- Spironolactone

Table 1 Prospective, placebo- or drug-controlled, blinded clinical trials in veterinary cardiac disease.

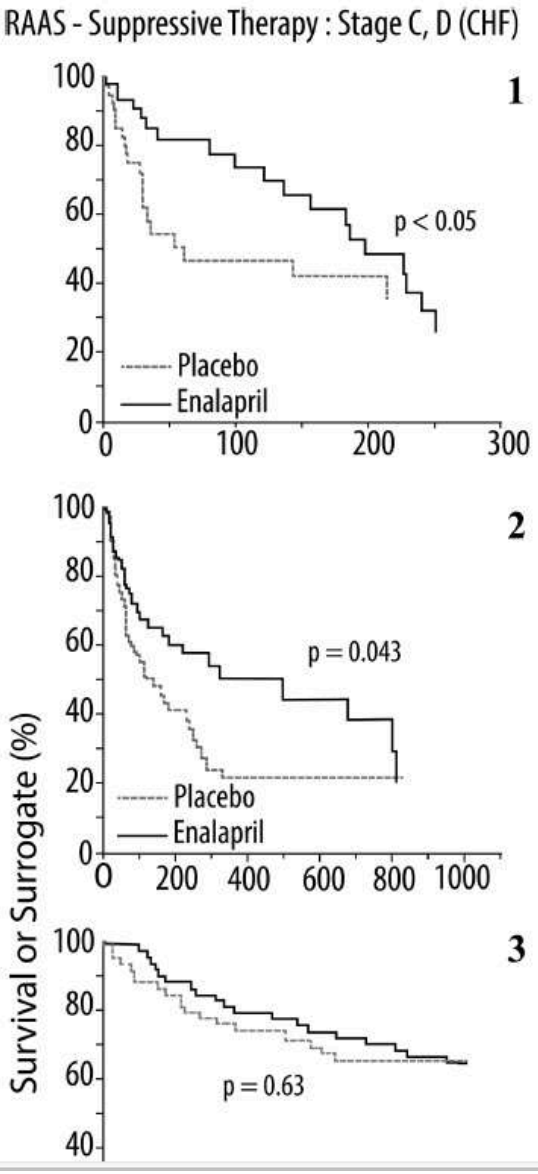
Trial, year, Reference	Number of patients	Disease studied (severity)	Drug[a]	Dosage	Follow-up time or median time to endpoint (Treatment group/ Placebo group)	Endpoint/outcome vs placebo or drug
IMPROVE (1995) [34]	58 (22 with MMVD)	MMVD, DCM, AI (NYHA 3–4)	Enalapril	=0.5 mg/kg SID to BID	21 days	Improved Mobility & Pulmonary edema scores, NYHA Class & PWP#
COVE (1995) [33]	211 (141 with MMVD)	MMVD, DCM	Enalapril	=0.5 mg/kg SID to BID	28 days	Improved clinical signs and QOL##
LIVE (1998) [31]	110 (67with MMVD)	MMVD, DCM (NYHA 3–4)	Enalapril vs placebo	=0.5 mg/kg SID to BID	160/87 days for MMVD dogs	Improved survival or removal from study for worsening signs
BENCH (1999) [32]	162 (61 with MMVD)	MMVD, DCM (NYHA 2–3)	Benazepril vs placebo	0.25–1 (mean 0.33) mg/kg SID	436/151 days for MMVD	Improved survival or removal from study for worsening signs and QOL[b]
FIRST (2004) [94]	128 (93 with MMVD)	MMVD, DCM (NYHA 2–4)	Imidapril (vs Enalapril)	Mean 0.25 mg/kg SID to BID Mean 0.5 mg/kg SID to BID	12 mos study	Similar QOL and survival to Enalapril[c]

Atkins & Haggstrom J Vet Cardiol 2012



Wess JVIM 2020

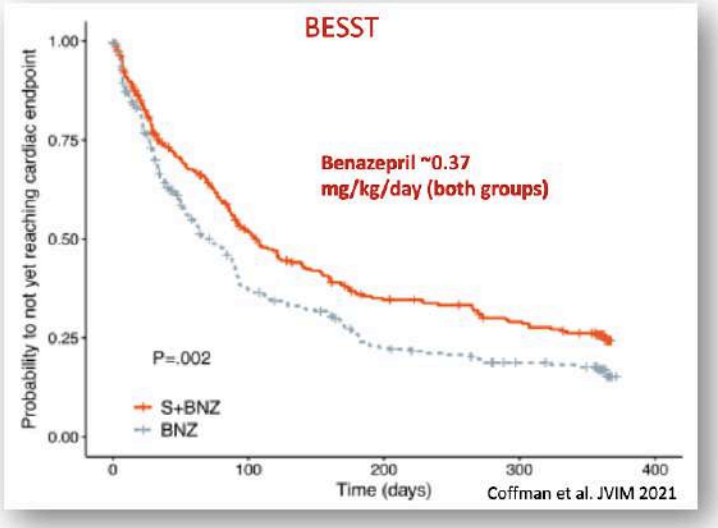
RAAS suppressive therapy Stages C, D



1. Ettinger et al JAVMA 1998, 213:1573
2. BENCH J.Vet Cardiol 1999, 1: 7-18
3. Besce et al JSAP 2007, 48: 265-270

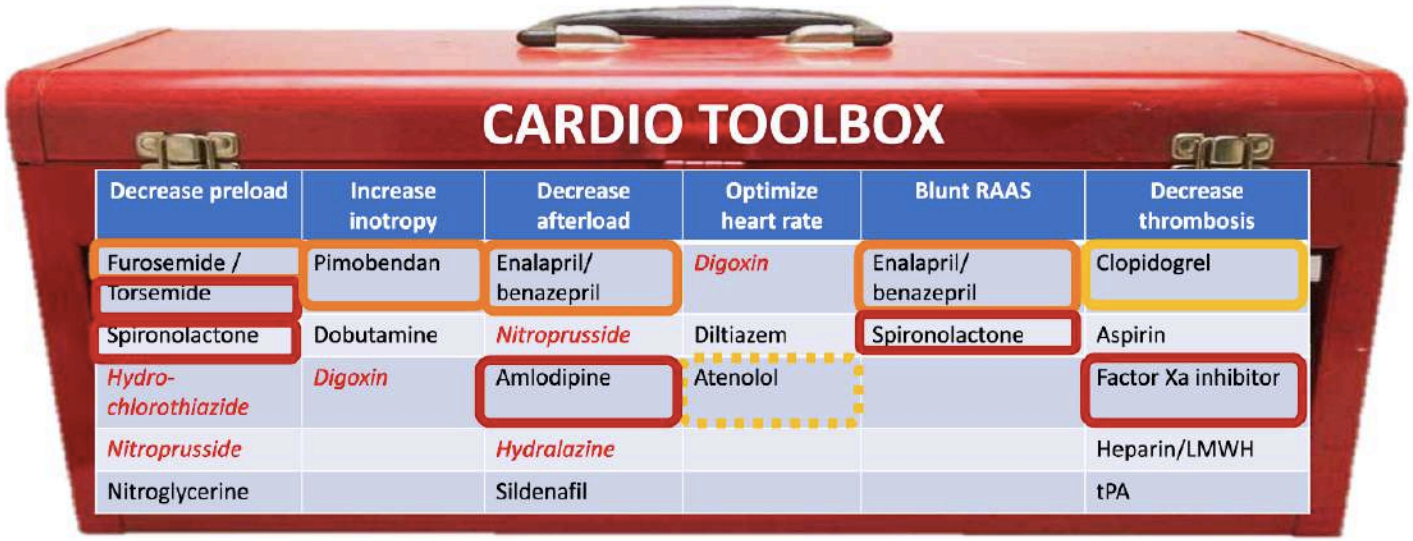
Why do I choose quadruple therapy for canine CHF?

- Furosemide
- Pimobendan
- ACE inhibitor
- **Spironolactone**



Toolbox method

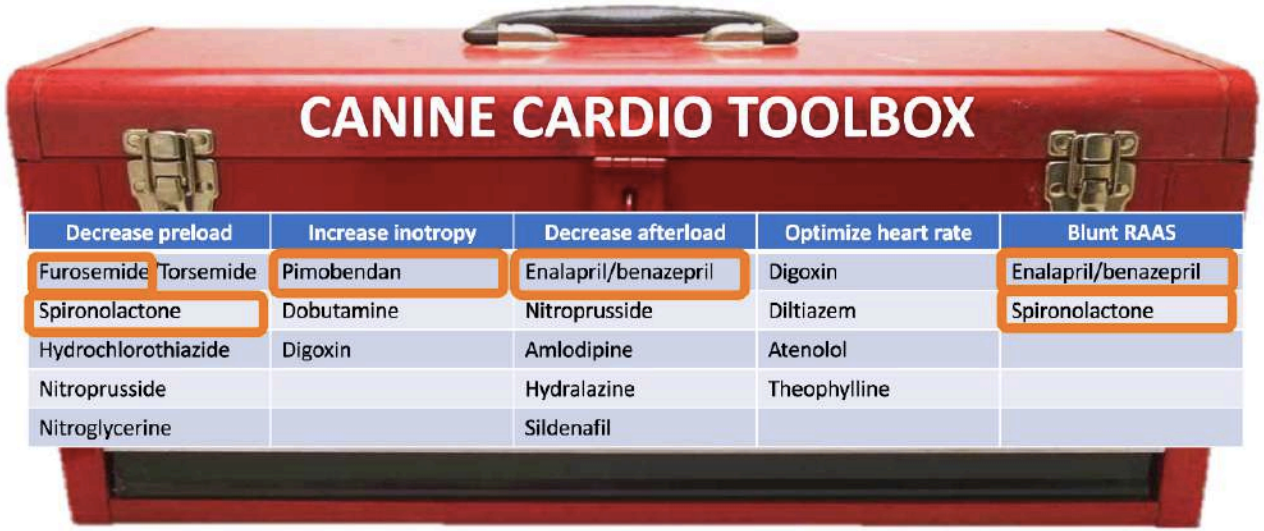
- Stage B2
- Stage C
- Stage D



CARDIO TOOLBOX

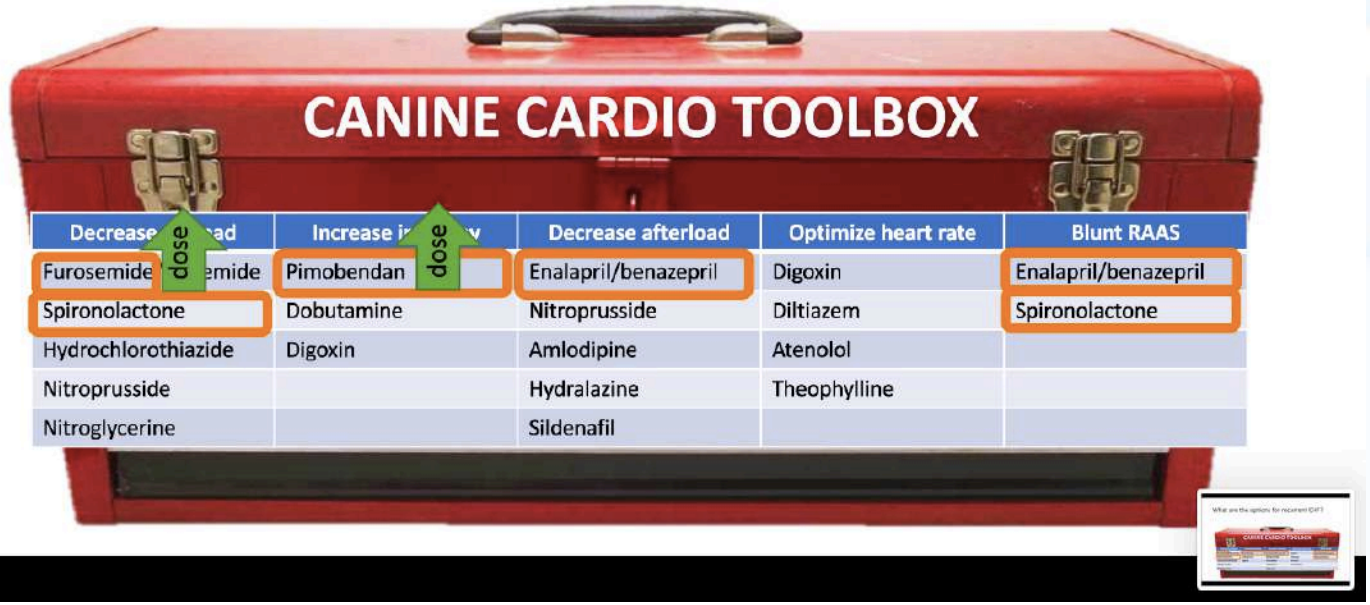
Decrease preload	Increase inotropy	Decrease afterload	Optimize heart rate	Blunt RAAS	Decrease thrombosis
Furosemide / Torsemide	Pimobendan	Enalapril/ benazepril	*Digoxin*	Enalapril/ benazepril	Clopidogrel
Spironolactone	Dobutamine	*Nitroprusside*	Diltiazem	Spironolactone	Aspirin
Hydro-chlorothiazide	*Digoxin*	Amlodipine	Atenolol		Factor Xa inhibitor
Nitroprusside		*Hydralazine*			Heparin/LMWH
Nitroglycerine		Sildenafil			tPA

What are the options for recurrent CHF?



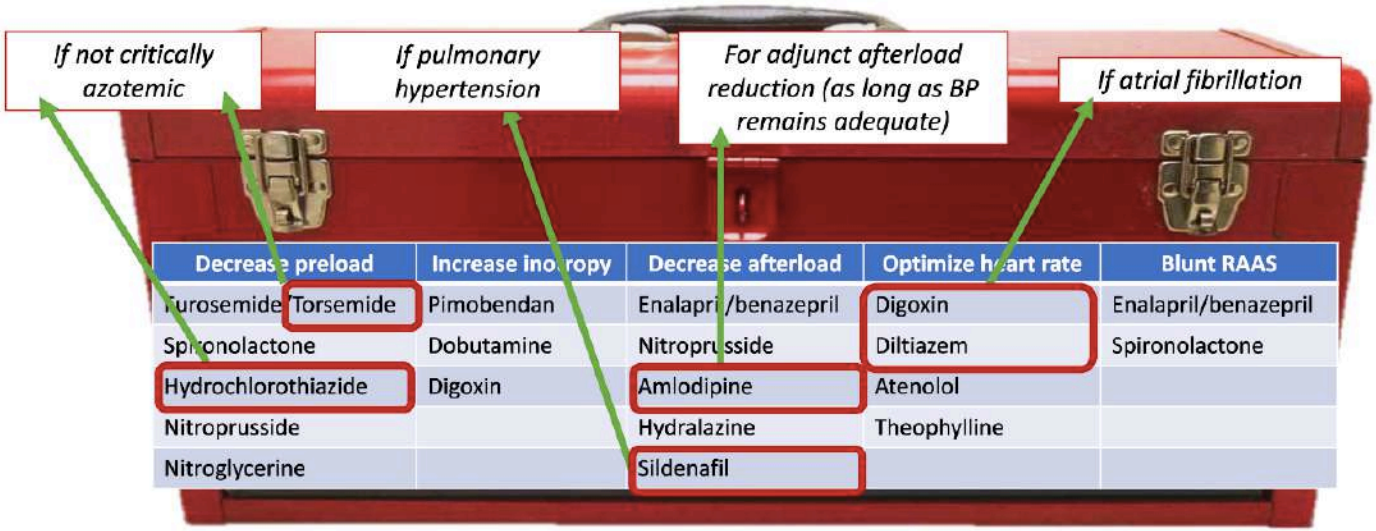
Decrease preload	Increase inotropy	Decrease afterload	Optimize heart rate	Blunt RAAS
Furosemide Torsemide	Pimobendan	Enalapril/benazepril	Digoxin	Enalapril/benazepril
Spironolactone	Dobutamine	Nitroprusside	Diltiazem	Spironolactone
Hydrochlorothiazide	Digoxin	Amlodipine	Atenolol	
Nitroprusside		Hydralazine	Theophylline	
Nitroglycerine		Sildenafil		

What are the options for recurrent CHF?



Decrease preload	Increase inotropy	Decrease afterload	Optimize heart rate	Blunt RAAS
Furosemide	Pimobendan	Enalapril/benazepril	Digoxin	Enalapril/benazepril
Spironolactone	Dobutamine	Nitroprusside	Diltiazem	Spironolactone
Hydrochlorothiazide	Digoxin	Amlodipine	Atenolol	
Nitroprusside		Hydralazine	Theophylline	
Nitroglycerine		Sildenafil		

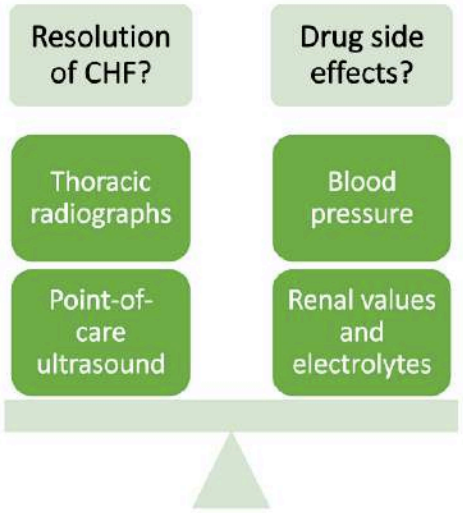
What are the options for refractory CHF (stage D)?

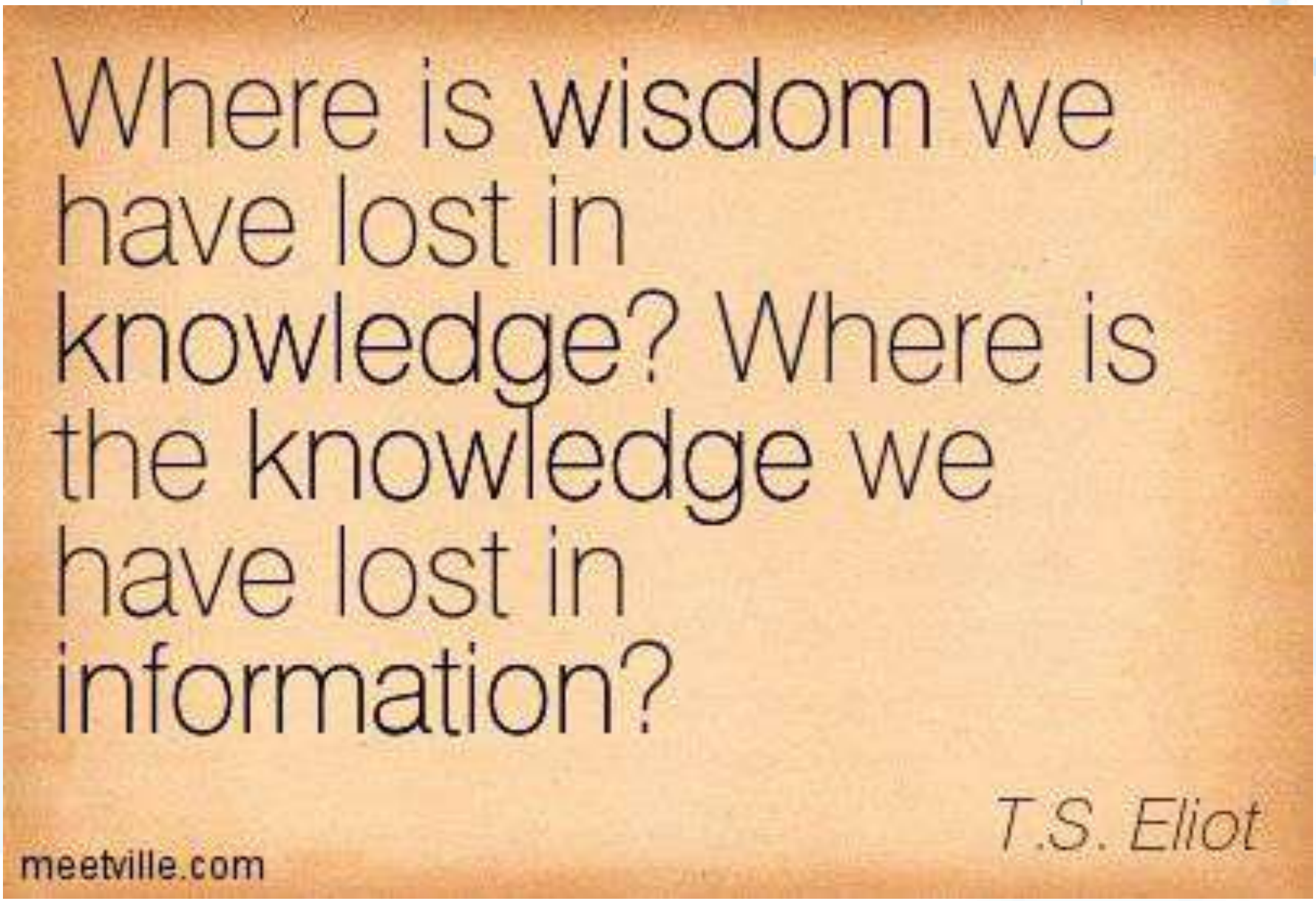


Decrease preload	Increase inotropy	Decrease afterload	Optimize heart rate	Blunt RAAS
Furosemide/Torsemide	Pimobendan	Enalapril/benazepril	Digoxin	Enalapril/benazepril
Spironolactone	Dobutamine	Nitroprusside	Diltiazem	Spironolactone
Hydrochlorothiazide	Digoxin	Amlodipine	Atenolol	
Nitroprusside		Hydralazine	Theophylline	
Nitroglycerine		Sildenafil		

Monitoring cardiac therapy involves assessing for resolution of CHF and screening for drug side effects

Side effects of diuretics:	Side effects of vasodilators:
Polyuria/polydipsia Dehydration Azotemia Electrolyte imbalances	Hypotension



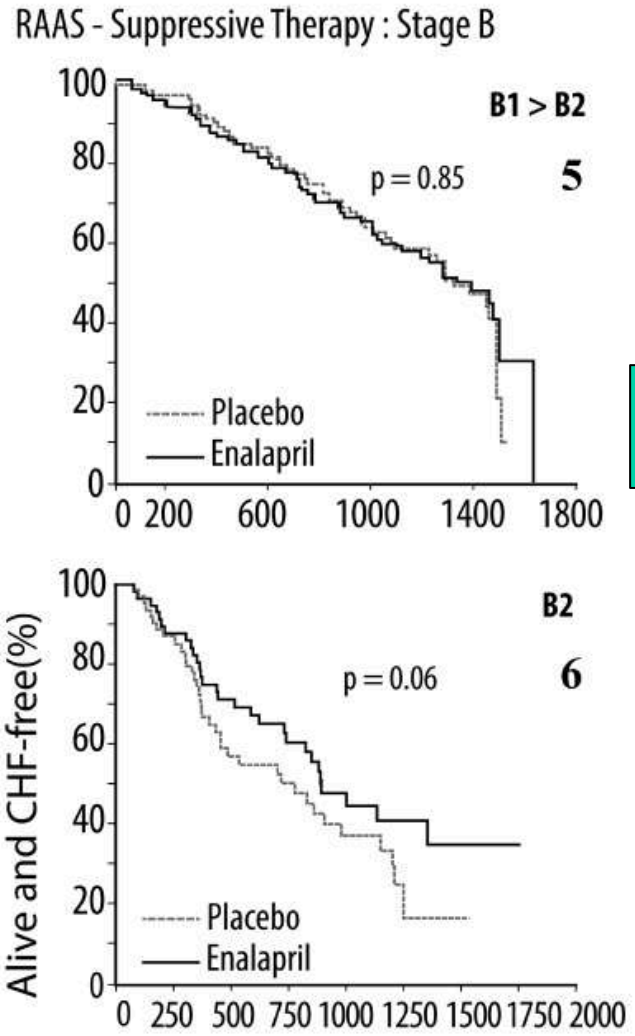

Where is wisdom we have lost in knowledge? Where is the knowledge we have lost in information?
T.S. Eliot
meetville.com

Questions?

Recommendations for treatment of Stage B2

- Pimobendan is recommended at a dosage of 0.25-0.3 mg/kg PO q12h.[44,55] (Class I, LOE: strong)
- Dietary treatment is recommended. Principles guiding dietary treatment at this stage include mild dietary sodium restriction and provision of a highly palatable diet with adequate protein and calories for maintaining optimal body condition.[56] (Class IIa, LOE: weak)
- Angiotensin converting enzyme inhibitors (ACEI): For patients in Stage B2 on either initial examination, or in which the LA has increased markedly in size on successive monitoring examinations, 5 (of 10) panelists recommend treatment with ACEI.[57–59] (Class IIa in geographic regions where ACEI are low cost, LOE: weak)

Suppressive therapy: Stage B

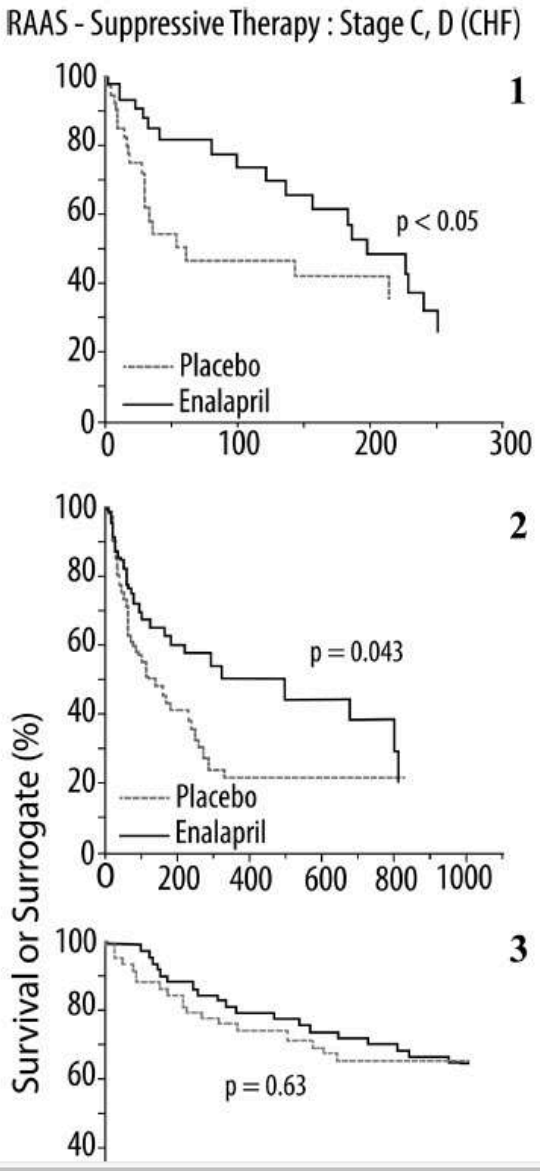


5. Kvart et al JVIM 2002, 16: 80-88
6. Atkins et al JAVMA 2007, 231: 1061-1069

Recommendations for treatment of Stage C

- Continue or start ACEI (eg, enalapril or benazepril, 0.5 mg/kg PO q12h) or an equivalent dosage of another ACEI, if approved for this use. Measurement of serum creatinine and electrolyte concentrations 3-14 days after beginning an ACEI is recommended for animals with Stage C heart failure. Concern for development of acute kidney injury is warranted should serum creatinine concentrations increase by ≥30% of the baseline concentration. (Class I, LOE: weak)
- Spironolactone (2.0 mg/kg PO q12 - 24 h) is recommended as an adjunct for chronic treatment of dogs in Stage C heart failure. The primary benefit of spironolactone in this situation is thought to be aldosterone antagonism.[74,75] (Class I, LOE: moderate)
- Continue pimobendan, 0.25-0.3 mg/kg PO q12h.[76,77] (Class I, LOE: strong)

RAAS suppressive therapy Stages C, D



1. Ettinger et al JAVMA 1998, 213:1573
2. BENCH J.Vet Cardiol 1999, 1: 7-18
3. Besce et al JSAP 2007, 48: 265-270

VALVE study by Wess et al 2021

DOI: 10.1111/jvim.15863

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access

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Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial

Gerhard Wess[1] | Jan-Gerd Kresken[2] | Ralph Wendt[3] | Juliane Gaugele[1] | Markus Killich[1] | Lisa Keller[1] | Julia Simak[1] | Peter Holler[1] | Alexander Bauer[4] | Helmut Küchenhof[4] | Tony Glaus[5]

[1]Clinic of Small Animal Medicine, Ludwig-Maximilians-Universität, Munich, Germany

[2]Clinic for Small Animals Kaiserberg, Duisburg, Germany

[3]Tierärztliche Überweisungspraxis Kirschenwäldchen, Wetzlar, Germany

[4]Statistical Consulting Unit, StaBLab, Department of Statistics, Ludwig-Maximilians-Universität, Munich, Germany

[5]Division of Cardiology, Department of Small Animals, Vetsuisse Faculty, University of

Abstract

Background: Triple therapy (TT) consisting of furosemide, pimobendan, and an angiotensin-converting enzyme inhibitor (ACEI) frequently is recommended for the treatment of congestive heart failure (CHF) attributable to myxomatous mitral valve disease (MMVD). However, the effect of adding an ACEI to the combination of pimobendan and furosemide (dual therapy [DT]) so far has not been evaluated prospectively.

Hypothesis: Triple therapy will extend survival time compared to DT in dogs with

Letter by Atkins et al.

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LETTER TO THE EDITOR

Letter to the editor regarding "Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial"

Dear Editors,

The manuscript entitled *Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial*[1] reports a study which sought to answer the question "could pimobendan be all that is needed beyond loop diuretics to manage congestive heart failure (CHF) in myxomatous mitral valve disease (MMVD)?" This was done by prospectively comparing the efficacy of pimobendan + ramipril + furosemide (triple treatment) to pimobendan + furosemide (double treatment) to treat new-onset CHF caused by MMVD.

While agreeing with the authors that this question has merit, we share several comments and questions regarding applicability of their study results to current practice. During the VALVE trial, worsening signs of CHF were primarily managed with progressively larger diuretic dosages, as opposed to other potential pharmacological interventions such as greater renin-angiotensin-aldosterone system (RAAS) suppression, alternative diuretic use, higher pimobendan dos-

in the study. This is important because it is known that RAAS suppression before the onset of CHF has favorable effects on cardiac remodeling.[2]

Although unknowable by the authors at the time of the VALVE trial design, other studies completed during the 10-year duration of the VALVE trial have demonstrated significant benefit from greater, longer, and more broad-spectrum RAAS suppression (eg, higher or q12h ACEI dosing and mineralocorticoid antagonist [MRA] inclusion) in treating proteinuria and CHF.[3-5]

Because the VALVE trial was performed under Good Clinical Practice guidelines, owner adherence to the trial protocol was quantified. It would be useful to know whether those measurements identified "adherence parity" between the 2 treatment groups, thus eliminating 1 potential source of unintentional bias.

Ramipril, a narrow-spectrum RAAS suppressant (ie, it causes no direct MRA effect), was tested as an "add-on" to drugs providing symptomatic relief (pimobendan and furosemide). Although the

Atkins et al write…..criticism of the VALVE

While agreeing with the authors that this question has merit, we share several comments and questions regarding applicability of their study results to current practice. During the VALVE trial, worsening signs of CHF were primarily managed with progressively larger diuretic dosages, as opposed to other potential pharmacological interventions such as greater renin-angiotensin-aldosterone system (RAAS) suppression, alternative diuretic use, higher pimobendan dosing, and arterial vasodilator treatment. While the angiotensin-converting enzyme inhibitor (ACEI) ramipril (VASOTOP) was begun at a once daily dosage according to label recommendation, the initial furosemide dosage (median, 8 mg/kg/d), high by current clinical standards, was increased to as much as 15 mg/kg/d, before predefined treatment failure was reached; ramipril dosage was increased (doubled) in only 3 dogs. Spironolactone dosing was left to the clinicians' discretion (added to baseline treatment in only 13 dogs, 8 in the triple

Atkins et al write…..criticism of the VALVE

Ramipril, a narrow-spectrum RAAS suppressant (ie, it causes no direct MRA effect), was tested as an "add-on" to drugs providing symptomatic relief (pimobendan and furosemide). Although the absence of an MRA as part of the test article is understandable because of the timing of the VALVE study design, its absence impairs our understanding of the potential role that true RAAS suppression (ie, more RAAS suppression than ACE inhibition alone) might play in managing CHF caused by MMVD. It is now known that incomplete RAAS suppression (aldosterone breakthrough) is common with either ACEI or angiotensin II receptor blockers (ARB) in normal dogs challenged with furosemide or amlodipine[5,6]; with ACEI in natural MMVD before CHF (without furosemide)[5,7]; and in MMVD with CHF in dogs receiving ACEI and furosemide.[5,7] Furthermore, inclusion of MRAs in therapeutic protocols has improved survival in CHF caused by

Atkins et al write…..

Although the VALVE results are surprising and interesting, a conclusion that they obviate the need for ACEI treatment in the management of CHF from MMVD is not justified. We believe this study to be hypothesis generating, rather than pivotal. A larger study, employing methodology that provides evidence of more complete RAAS inhibition with contemporary adjunctive heart failure treatment is needed to provide pivotal data upon which to guide practice.

Atkins et al authors…..

Clarke Atkins, DVM, DACVIM (Small Animal Internal Medicine, Cardiology)[1]

Bruce Keene, DVM, MSc, DACVIM (Cardiology)[1]

Teresa C. DeFrancesco, DVM, DACVIM (Cardiology), DACVECC[1]

Sandra Tou, DVM, DACVIM (Small Animal Internal Medicine, Cardiology)[1]

Valérie Chetboul, DVM, MSc, PhD, DECVIM-CA (Cardiology)[2]

Étienne Côté, DVM, DACVIM (Small Animal Internal Medicine, Cardiology)[3]

Stephen Ettinger, DVM, DACVIM (Small Animal Internal Medicine, Cardiology), FACC, FAHA, CCRP[4]

Philip R. Fox, DVM, MSc, DACVIM (Cardiology), ECVIM-CA (Cardiology), DACVECC[5]

Robert L. Hamlin, DVM, PhD, DACVIM (Small Animal Internal Medicine, Cardiology)[6]

Jonathan P. Mochel, DVM, MS, PhD, DECVPT, AAVPT Fellow[7]

Jean-Louis Pouchelon, DVM[2]

Rebecca L. Stepien, DVM, MS, DACVIM (Cardiology)[8]

[1]*Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina*

[2]*Alfort Cardiology Unit (UCA), National Veterinary School of Alfort (ENVA), Maisons-Alfort, France*

[3]*Department of Companion Animals, Atlantic Veterinary College, University of Prince Edward Island, Charlottetown, Prince Edward Island, Canada*

[4]*Textbook of Veterinary Internal Medicine, VetCorp, Inc., Laguna Beach, California*

[5]*Department of Cardiology, The Animal Medical Center, New York, New York*

[6]*Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio*

[7]*Department of Biomedical Sciences, College of Veterinary Medicine, Iowa State University, Ames, Iowa*

[8]*Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, Wisconsin*

Response to Atkins et al. letter

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LETTER TO THE EDITOR

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Response to letter to the editor regarding "Efficacy of adding ramipril (VAsotop) to the combination of furosemide (Lasix) and pimobendan (VEtmedin) in dogs with mitral valve degeneration: The VALVE trial"

Dear editor,

We appreciate the interest in our VALVE trial by Dr Atkins and others. The authors open an important discussion and raise several interesting questions that we would like to address. However, we would like to point out that their letter to the editor appears to start with a misunderstanding. The aim or the primary hypothesis of the VALVE trial was not to address whether pimobendan "is all that is needed beyond loop diuretics to manage CHF in MMVD." The only aim of the VALVE trial was to answer the question in dogs with MMVD that had reached the stage of congestive heart failure (CHF), ACVIM stage C or D, *if the addition of an angiotensin converting enzyme inhibitor (ACEI)*

This raised the question as to whether ACEI were beneficial in dogs with MMVD before the development of congestion and before the use of diuretics. Nevertheless, ACEI inhibitors continued to be widely used in dogs with preclinical MMVD (ACVIM stage B) for many years, and still are.

Then came the SVEP trial, a prospective randomized study which failed to show any benefit of enalapril in dogs with MMVD, when administered before the clinical occurrence of congestion.[8] There was no measurable benefit demonstrated, neither in dogs with normal heart size (which today would be called ACVIM stage B1), nor in dogs with demonstrable compensatory left ventricular volume overload

Wess and Glaus respond……

We fully agree with Atkins and colleagues that our VALVE trial does not provide the final answer concerning RAAS suppression in dogs with MMVD and CHF. However, the VALVE trial is a large, prospective, randomized, multicenter study with a very high event rate that did not show any survival benefit with respect to the use of an ACEI in dogs with advanced MMVD. Therefore, given the data available today, we cannot in good faith recommend adding an ACEI to the basic treatment consisting of furosemide and pimobendan in dogs with MMVD in ACVIM stage C.

Gerhard Wess DMV, PhD, DACVIM (Cardiology), DECVIM-CA (Internal Medicine, Cardiology)[1]
Tony Glaus PhD, DMV, DACVIM (Small Animal Internal Medicine), DECVIM-CA (Internal Medicine, Cardiology)[2]
VALVE Investigators