Critical appraisal Gelzer et al., 2009– Randomized controlled trial questions

Introduction	
Are the aims clearly stated?	Yes
Methods	
Is the study design suitable for the aims?	Yes. • Crossover trial is appropriate when condition is relatively stable over time • Crossover trial allows for increased statistical power from a smaller sample size because each patient serves as its own control
Which population was studied?	18 medium and large breed dogs (>15kg) presented to Cornell University Hospital for Animals (USA) with advanced heart disease and rapid (>140 beats per minute, BPM) atrial fibrillation (AF) • 10 dogs had dilated cardiomyopathy • 7 dogs had degenerative valve disease • 1 dog had AV valve dysplasia • 15/18 dogs were in congestive heart failure (CHF) at enrollment.
Were the treatments randomly allocated? If yes, how was the randomization done?	Yes. A random number generator was used to assign treatment group (treatment order)
Were the groups comparable prior to intervention?	Patients served as their own controls (crossover design). Additional notes: The time intervals of treatment blocks (2 weeks) substantially exceeded the half-lives of diltiazem and digoxin in dogs, minimizing risk of carryover effect. Additionally, the authors compared changes in heart rates (HR) between treatment sequences (monotherapy to combination,

	combination to monotherapy) and found no differences, suggesting no carryover effects.
Was the person who administered the interventions blinded?	Not stated.
Is it clear what measurements were carried out in the study?	Yes. • 60 second ECG to confirm atrial fibrillation • Holter monitor recordings • Serum digoxin and diltiazem levels
Were the correct measurements chosen? Do they reflect (or are they strongly related to) the outcome of interest?	Yes Yes • Good evidence that Holter measurements are a reasonable measure of ventricular rate control
Were previously established validated methods used to make the measurements? (e.g. Glasgow pain score, International Units etc)	Yes • Holter monitoring is a well validated technique • Serum levels of digoxin and diltiazem were measured using standard assays.
What outcomes were measured?	Holter outcomes: • Hourly HR average and 24 hour average HR. • HR also categorized into percentiles of time spent <100, 100-140, >140 BPM. • Serum digoxin levels (fluorescent polarization assay, Cornell) • Serum diltiazem (HPLC, commercial lab)
Are the outcomes clinically relevant?	Yes Tachyarrhythmia with atrial fibrillation can decrease cardiac output and increase pulmonary wedge pressures in humans, exacerbating or causing CHF. Additionally, experimental models of chronic tachycardia (including those using dogs) result in ventricular dysfunction. Rate control is standard of care in people who are

	not candidates for conversion to sinus arrhythmia. No studies on long term outcomes for rate control had been done in dogs but extrapolation from the human literature is well accepted by veterinary cardiologists.
Were the outcomes assessed blind?	Yes. Automated Holter analysis verified by Holter examiner who was blinded to treatments
Are the statistical methods described?	Yes
Was the statistical significance level stated?	Yes , with appropriate correction for multiple comparisons
Was the sample size justified?	No
Was ethical approval obtained?	Yes
Are the methods described in enough detail that you could repeat them?	Yes
Results	
Were the basic data adequately described?	Yes
Do the numbers add up? Are all subjects accounted for?	Yes Yes
Was the statistical significance (p value) stated in the results? Is this consistent with the methods? (It should be stated in the sample size or power calculation)	Yes Yes

Were any side effects of the intervention reported if applicable?	Yes Assessed for signs of digoxin toxicity and clinically significant arrhythmias
What were the main findings/key results?	All three treatments (digoxin, diltiazem, and diltiazem-digoxin) reduced average Holter heart rate: • Digoxin (DG) 24 BPM median reduction • Diltiazem (DT) 28 BPM median reduction • Diltiazem-digoxin (DGDT) 60 BPM median reduction Proportions achieving target average rates: • DG: 5/11 dogs HR<160, 2/11 HR<140. • DT: 4/9 dogs HR<160, 3/9 dogs HR <140. • DGDT: 18/18 dogs HR <160. 12/18 HR<140. DGDT provided statistically significantly greater reduction in average heartrate and time spent (60%) within target heart rate ranges (<140 BPM) than DG or DT monotherapy (ca. 12% each). Diltiazem and digoxin as monotherapies were not significantly different in rate reduction. No correlation was found between digoxin serum levels and HR control. No correlation was found between diltiazem serum level and HR control. Serum digoxin in therapeutic range (0.5-2 ng/ml) in 17/18 dogs at dose of ~0.005 mg/kg (range .0035-0.0071 mg/kg) PO BID. No clinical signs of DG toxicity observed. Extended release diltiazem (DiltXR) used at 3 mg/kg (range 2.4-5.65 mg/kg) PO BID resulted in serum level range of 10-134 ng/ml. Most dogs in study had asymptomatic ventricular arrhythmias with one dog having pauses of up to

	5.7 seconds followed by ventricular escape beats. No dogs required treatment for ventricular arrhythmia.
Discussion and conclusion	
What do the main findings/key results mean?	In dogs >15 kg, with tachycardia from atrial fibrillation secondary to heart disease, a combination of digoxin to diltiazem in combination may achieve better ventricular rate control than use of diltiazem alone. Adverse side effects (primarily from decreased cardiac output secondary to use of negative inotropes or from digitalis toxicity) are expected to be uncommon at the doses used although ventricular arrhythmias can be seen. In this study, rate control was not attempted prior to resolution of CHF thus caution would be advised in using negative inotropes prior to stabilization of congestive heart failure.
Are the negative findings discussed? How are the negative findings interpreted?	Yes The lack of correlation between digoxin and diltiazem serum levels with ventricular rate control could reflect small sample size and an underpowered study, particularly given that authors were only able to successfully measure diltiazem levels in half of the study participants. Additionally, the authors note that rate control is not a proven proxy for improved survival.
Does the discussion reflect the results?	Yes
Interpretation	
What are the clinical implications of this study?	A combination of digoxin and diltiazem in controlling fast atrial fibrillation is likely to yield better ventricular rate control than diltiazem used alone. Digoxin doses used in this study for dogs >15 kg did not lead to symptoms of digoxin toxicity

Are the subjects in the study similar to those in the BET/your own?	and few adverse cardiac or other side effects were observed. However, CHF should be treated prior to initiation of pharmacologic rate control. Yes
General	
Who funded this study?	Doberman Pinscher Foundation and Cornell University

Comments:

The diltiazem formulation used in this study was an extended release formulation which may not currently be available and may be too large for dogs <40 kg. Standard release diltiazem dosed at 1 mg/kg TID is commonly substituted for extended release diltiazem by many cardiologists.