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How much protection does clopidogrel provide to cats with hypertrophic cardiomyopathy?

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ABSTRACT

Cats with hypertrophic cardiomyopathy (HCM) have a risk of developing aortic thromboembolism (ATE). Clopidogrel reduces the risk of redeveloping ATE and delays recurrence of ATE in cats that have experienced an ATE episode. Consequently, cardiologists have recommended administering clopidogrel to cats as a primary preventative, suggesting that all cats with severe HCM be administered clopidogrel. However, clopidogrel is unpalatable in its manufactured format, making such administration problematic for many clients. Therefore, estimating the potential benefit of administration might help clinicians determine on a case-by-case basis the need to treat cats with clopidogrel. Relatively simple statistical analyses of currently available data, along with certain assumptions and extrapolations, allow such an estimation of benefit in terms of relative and absolute risk reduction conferred by clopidogrel. Using this approach, and provided certain assumptions are true, clopidogrel likely confers a reduction in risk of ATE in cats with moderate to severe HCM of approximately 3% to 4%. Given the difficulty of administering clopidogrel to cats, clinicians should weigh these relatively small potential benefits against the potential harms (difficulty of administration) and not necessarily insist that clients administer clopidogrel.

Keywords: cardiomyopathy, feline, medication, treatment, risk reduction

Hypertrophic cardiomyopathy (HCM) is the most common cardiac disease in adult cats. Three studies¹⁻³ have examined the natural history of HCM in cats, and all have concluded that the disease is slowly and variably progressive, with most cats having subclinical disease for many years. Approximately 10% of these cats have moderate to severe subclinical disease,⁴ which has a higher probability of developing complications such as congestive heart failure (CHF) or cardiogenic aortic thromboembolism (ATE). Approximately 15% to 25% of cats with HCM will eventually develop CHF over a 10-year period,¹⁻³ and 10% will develop ATE.¹⁻³

Almost all cats with HCM that develop ATE have severe disease (either subclinical or with CHF). Risk factors for ATE include large left atrial size, spontaneous echocardiographic contrast within the left atrium (indicative of poor atrial flow and red cell clumping), and poor left atrial function.^{5,6}

The FATCAT (Feline Aortic Thromboembolism Clopidogrel vs Aspirin Trial) study examined the

effect of administering clopidogrel (Plavix) to cats that had survived an initial ATE event for at least a month in preventing the risk of a subsequent ATE event, when compared to low-dose aspirin.⁷ Based on that study, the American College of Veterinary Internal Medicine consensus guidelines⁶ for diagnosis and treatment of feline HCM recommend administering clopidogrel to cats with increased risk of ATE (such as those factors mentioned earlier), whether or not the cat has experienced a previous event. The guidelines read, in part, as follows⁶:

Clopidogrel therefore is recommended in cats considered at risk of ATE (moderate to severe LA [Left Atrial] enlargement, low LA FS% [Left Atrial Fractional Shortening], low LA appendage velocities, SEC [Spontaneous Echocardiographic Contrast]; LOE [Level of Evidence] medium). Clopidogrel does not eliminate the risk of ATE, and thus other antithrombotic drugs can be considered in addition to clopidogrel in cats believed to be at very high risk of ATE (eg, clopidogrel plus aspirin, clopidogrel plus a PO [Per Os] factor Xa inhibitor, or clopidogrel plus aspirin plus a PO factor Xa inhibitor; LOE low).

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However, the guidelines provide no actual data about to what extent clopidogrel reduces the risk of ATE and claim that the evidence level for the recommendation is “moderate” (despite the absence of studies demonstrating a benefit in primary prevention).

Cats find clopidogrel unpalatable. Cats given clopidogrel “as is” will froth at the mouth profusely, gag, or vomit and will attempt to spit out the tablet. Therefore, it either requires compounding (into capsules that need to be swallowed intact) or must be hidden within other delivery systems, such as pill pockets. The drug needs to be administered indefinitely. Consequently, clients might find administering clopidogrel difficult or even impossible to cats considered to be at risk of ATE.

Evidence-based medicine argues that clinicians should weigh the benefits of any intervention, determined in clinical studies of study samples similar to the patient presenting to the clinician, against the costs/harms of such interventions—essentially, a cost-benefit analysis.⁸ The degree to which a clinician and client might accept a cost/harm depends, in part, on the magnitude of the benefit of the intervention—for a small benefit, the cost or harm might sway the client and clinician toward not intervening, whereas a large benefit might convince the client and clinician to persevere with the intervention despite the costs or harms.

With this approach, it would seem reasonable to try to determine the size of the benefit of administering clopidogrel to cats with moderate to severe HCM to reduce the risk of ATE and weigh that against the cost of administration (quality of life, stress to cat or client, client injury by the cat, etc). Such an analysis would help clinicians and clients make a more informed decision about instituting clopidogrel therapy in each cat.

To What Extent Does Clopidogrel Reduce the Risk of ATE in Cats With HCM?

The FATCAT study found that 19 of 39 (48%) cats that received clopidogrel experienced a recurrent ATE event; similarly, 27 of 36 (75%) cats that received aspirin also experienced a recurrent ATE event.⁶ This resulted in a relative risk reduction of 35% (95% CI, 5% to 45%; **Figure 1**). Put another way, cats administered clopidogrel had approximately 30% lower odds of experiencing a recurrent ATE event than cats administered aspirin. Furthermore, most cats in the study that experienced a recurrent ATE event did so within the first year (14/39 [38%] receiving clopidogrel; 23/36 [64%] receiving aspirin), resulting in a 1-year relative risk reduction of 44% (95% CI, 10% to 66%) and 56% lower odds of cats receiving clopidogrel experiencing a recurrent ATE event than cats receiving aspirin.

The first assumption we need to make is that the benefit of clopidogrel in cats that have already demonstrated their propensity to develop ATE translates similarly to cats that have not yet had an ATE event (ie, that the benefit in preventing recurrence—so-called secondary prevention—is the same as the benefit in preventing an initial event—primary prevention; Figure 1). It might be higher, it might be lower, it might be the same. We will, for the sake of this analysis, assume that the benefit is similar—approximately a 35% relative risk reduction.

The second assumption we need to make is that aspirin has little effect at preventing ATE in cats with HCM. Indeed, studies^{9,10} of aspirin in cats (uncontrolled case series) suggest that aspirin has no observable effect on ATE occurrence.

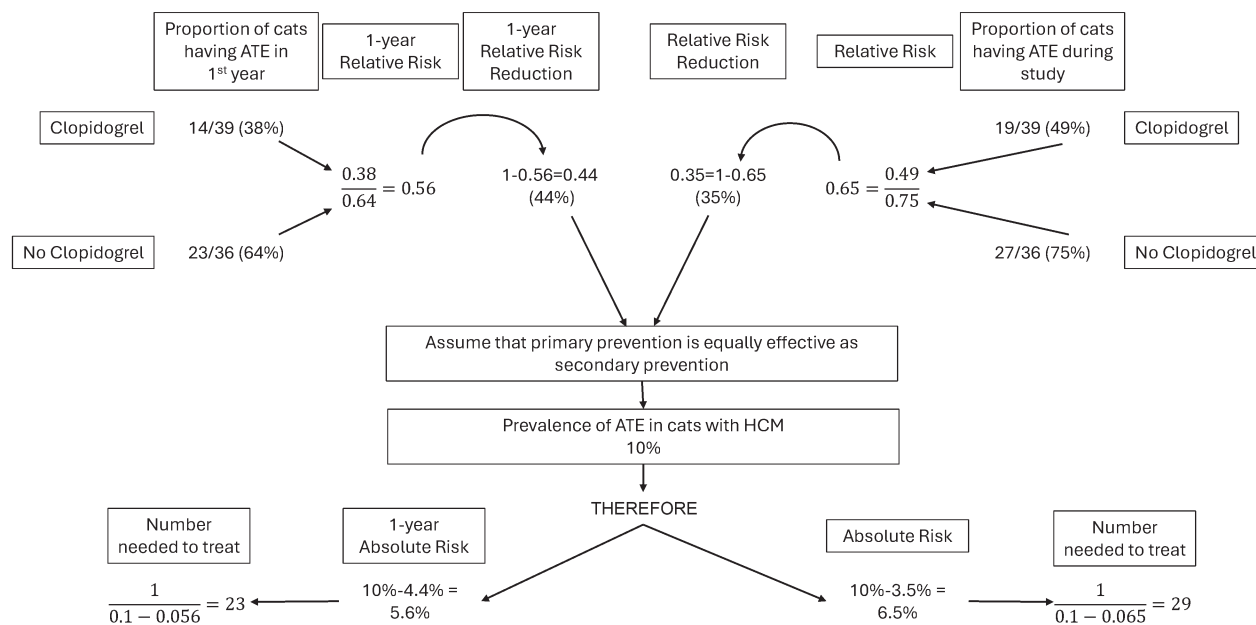


Figure 1—A flowchart depicting the calculation steps involved in determining the absolute risk reduction and the number of cats that need to be treated to prevent 1 aortic thromboembolism (ATE) event. HCM = Hypertrophic cardiomyopathy.

Consequently, it seems reasonable to assume that aspirin either has no effect on outcomes or might actually worsen outcomes.

What Is the Baseline Risk of Developing ATE in Cats With HCM?

By knowing the baseline risk for ATE in cats with moderate to severe HCM, we can calculate the absolute risk reduction offered by administering clopidogrel. Remember, that 10% of apparently healthy cats, examined at random, will have moderate to severe disease (Figure 1). This is the target population for considering treatment. Of these, approximately 10% will experience an ATE event at some point, meaning that 90% will not benefit from the drug. Of course, identifying the 10% of cats that will experience an ATE event is not possible, so clinicians tend to prescribe it to all these cats.

What Is the Absolute Risk Reduction of Developing ATE in Cats With HCM?

If the baseline risk is 10% and we have a relative risk reduction of 35%, then the absolute risk reduction is 3.5% (Figure 1). Similarly, if we have a relative risk reduction of 44%, then the absolute risk reduction is 4.4%. This means that approximately 5.6% to 6.5% of cats at risk of ATE would suffer the event even if being administered clopidogrel, whereas 10% of cats at risk not being administered clopidogrel would suffer an ATE event. Viewed a different way, you would need to treat some 23 to 29 cats considered at risk to prevent 1 ATE event.

Should All Cats With Moderate to Severe HCM Be Prescribed Clopidogrel?

Consequently, the decision to prescribe clopidogrel to a cat with moderate to severe HCM should not be taken lightly, and clinicians should not consider it mandatory or even recommended. There is likely a small benefit for at-risk cats, but the harms of administration should also inform the decision. Therefore, clinicians should not be disappointed if clients decide not to administer clopidogrel to their cats and should not feel that they are practicing less-than-ideal medicine.

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