

# Determination of CADESI-03 thresholds for increasing severity levels of canine atopic dermatitis

Thierry Olivry\*, Ralf Mueller†, Tim Nuttall‡, Claude Favrot§ and Pascal Prélard¶ for the International Task Force on Canine Atopic Dermatitis\*\*

\*Department of Clinical Sciences and Center for Comparative Medicine and Translational Research, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina, USA

†Medizinische Tierklinik, Ludwig-Maximilians University, Munich, Germany

‡Faculty of Veterinary Science, The University of Liverpool Small Animal Teaching Hospital, Leahurst Campus, Neston, UK

§Clinic for Small Animal Internal Medicine, Dermatology Unit, Vetsuisse Faculty, University of Zürich, Zürich, Switzerland

¶Clinique Advetia, Paris, France

Correspondence: Thierry Olivry, DrVet, PhD, Department of Clinical Science, North Carolina State University, College of Veterinary Medicine, Research Building, 4700 Hillsborough Street, Raleigh, NC 27606, USA. E-mail: Thierry\_Olivry@ncsu.edu

\*\*As of 1 January 2008, The International Task Force on Canine Atopic Dermatitis was composed, in alphabetical order, of Emmanuel Bensignor (F), Didier Carlotti (F), Douglas J DeBoer (USA), Claude Favrot (CH), Craig Griffin (USA), Richard Halliwell (Chair; UK), Bruce Hammerberg (USA), Peter Hill (UK), Toshiro Iwasaki (J), Hilary Jackson (UK), Sadatoshi Maeda (J), Kenichi Masuda (J), Rosanna Marsella (USA), Ralf Mueller (D), Tim Nuttall (UK), Thierry Olivry (USA), Pascal Prélard (F), Candace Sousa (USA) and Ton Willemsse (NL).

clinicians subjectively rated the severity of AD as 'in remission', 'mild', 'moderate' or 'severe', and a CADESI-03 score was then determined. In all, 158 CADESI-03 values were recorded and divided among the four disease severity categories. Receiver-operating characteristics (ROC) curves were generated at increasing cut-off values to determine the benchmark that would offer optimal sensitivity and specificity between adjacent categories. Cut-offs of 16, 60 and 120 are proposed at the interface of remission, mild, moderate and severe categories, respectively. Proposed intervals therefore are: remission: 0–15; mild AD: 16–59; moderate AD: 60–119; and severe AD:  $\geq 120$ . This Task Force recommends that, whenever applicable and relevant, subgroup analyses of outcome measures, based on disease severity as determined with these cut-off CADESI-03 values, be preplanned for clinical trials enrolling dogs with AD. Such subgroup analyses could help determine whether specific interventions might be more effective in a particular subset of atopic dogs.

Accepted 6 March 2008

## What is known about the topic of this paper

- The CADESI-03 is a disease severity scale that has been validated for clinical trials enrolling dogs with atopic dermatitis.
- At this time, cut-off values of CADESI-03 that separate disease severity categories are not known.

## What this paper adds to the field of veterinary dermatology

- This study establishes CADESI-03 values that can serve as benchmarks to separate mild, moderate and severe atopic dermatitis categories.

## Abstract

To evaluate the extent and severity of skin lesions in clinical trials enrolling dogs with atopic dermatitis (AD), the International Task Force on Canine Atopic Dermatitis recently recommended the use of the third version of the CADESI. This version of the CADESI was found to exhibit acceptable content, construct, criterion, inter- and intraobserver reliability and sensitivity to change. The current study was aimed at determining optimal CADESI-03 cut-off points to separate AD severity categories for future clinical trials. One hundred and eight dogs with AD were selected based on current diagnosis standards. At one or more visits,

## Introduction

In an attempt to better determine the effect of interventions for treatment of atopic dermatitis (AD) in dogs, clinician investigators have relied on the subjective assessment of various parameters that usually include pruritus and skin lesions. Over time, various severity scales have been used to grade the extent and severity of cutaneous lesions in clinical trials enrolling dogs with AD. Unfortunately, until recently, none of the proposed morbidity scales had been evaluated for variability, reliability and sensitivity to change. From 2004 to 2006, a committee of the International Task Force on Canine Atopic Dermatitis (ITFCAD) reviewed all existing scales used in humans and dogs with AD and a third version of the CADESI (Canine Atopic Dermatitis Extent and Severity Index) was generated by expanding previous ones.<sup>1,2</sup> This revised version – CADESI-03 – was found to possess adequate content, construct, criterion, inter- and intraobserver reliability and sensitivity to change to justify its recommendation for assessment of atopic skin lesions in clinical trials.<sup>3</sup> The CADESI-03 scale presently consists of the evaluation of the severity (0–5) of four different lesions at 62 body sites.

As shown in a recent study enrolling dogs with AD,<sup>4</sup> there are interventions that appear more effective in dogs with lower CADESI scores compared to those with higher lesion extent and severity. As a result, when designing future clinical trials, it might be worthwhile considering the

comparison of outcome measures in dogs with variable disease severity. Moreover, based on the knowledge of AD pathogenesis and/or mechanism of action of the molecule(s) of interest, investigators might wish to test the efficacy of a particular intervention in dogs with either mild, moderate or severe AD. Indeed, drugs with relatively 'low' anti-inflammatory or antipruritic potencies may be better suited for the treatment of mild canine AD, while those with potent effect would be better designed for decreasing signs and symptoms in dogs with severe disease. Furthermore, interventions aimed at preventing flares of AD might be more suitable for dogs whose disease is in remission – or of mild severity – while such an approach would likely fail in dogs with higher disease activity. Finally, having common benchmarks for frequently used scales would allow better comparison of data between clinical trials reporting the effect of similar interventions, an increasing necessity at the age of systematic reviews, meta-analyses and evidence-based veterinary dermatology.

The concepts highlighted above illustrate the need to generate usable benchmarks to separate dogs in remission from those suffering from mild, moderate or severe AD. The study described herein aimed at determining CADESI-03 cut-off values that allow the distinction of these three AD severity categories.

## Materials and methods

### Canine subjects and CADESI categorization

Clinician members of the ITFCAD selected dogs with AD diagnosed according to standard methods.<sup>5</sup> All dogs were deemed devoid of obvious skin infections at the time of examination. Each atopic dog could be selected one or more times, before and/or after being treated with anti-inflammatory drugs. At each evaluation visit, clinicians assessed the severity of AD (remission, mild, moderate or severe) before determining the CADESI-03 value at that time.<sup>3</sup> The estimation of the degree of AD severity was made subjectively, taking into account the extent and intensity of all skin lesions present at the time of examination. All CADESI-03 scores were then grouped within each of the four severity categories, each subject contributing one or more value.

### Determination of disease severity thresholds

To determine AD disease severity thresholds (i.e. CADESI-03 cut-off values), receiver-operating characteristic (ROC) curves were generated using statistics software (Prism 4.0, GraphPad, San Diego, CA, USA). CADESI-03 values of each of the three AD categories (mild, moderate and severe) were compared to the ones in the category immediately below using increasing CADESI-03 cut-off points. At each of these threshold values, sensitivities (i.e. the fraction of dogs from the upper category that had CADESI-03 above the cut-off value) and specificities (i.e. the proportion of dogs from the lower category that had CADESI-03 below the cut-off value) were calculated, and ROC curves (sensitivities vs. [1 minus specificities]) were generated.<sup>6</sup> The 'best' CADESI-03 cut-off point between the two categories was chosen to be the closest to the upper left corner 'ideal' value, the latter exhibiting 100% sensitivity and specificity (i.e. 1.0 and 0.0 xy coordinates).<sup>6</sup> This chosen CADESI-03 cut-off value is associated, therefore, with the best combination of sensitivity and specificity to separate values from adjacent severity categories.

## Results

### Canine subjects

In all, 108 dogs with AD were selected. Ages ranged from 2.5 months to 13.0 years (mean: 5.0; median: 4.5 years) and the female:male ratio was 0.7. Eight dogs were listed

as crossbred and the other ones were identified as purebred. The following five breeds had more than five dogs included in this study: German shepherd dog (15 dogs), Labrador (11), West Highland white terrier (10), golden retriever (9) and boxer (7); all of these breeds are deemed predisposed to develop AD.<sup>7</sup>

### CADESI categorization

In 77 out of 108 subjects (81%), only one disease severity and CADESI-03 pair was determined, while in 21 dogs (19%), multiple assessments were made at two or more consecutive visits. *In toto*, 158 data pairs were obtained, 68 of them (43%) assessed in dogs not receiving any anti-inflammatory treatment. Details of the spread of CADESI-03 values for each severity category can be found in Table 1 and Fig. 1. Even though overlap of data points occasionally occurred between adjacent categories, their 95% confidence intervals (CI) – or even the 99% CI (data not shown) – never coincided (Table 1). CADESI-03 values passed a normality test in each of the four categories, as shown by the remarkable similarity between means and medians in each group.

**Table 1.** CADESI-03 values in atopic dogs with varying disease severity

|             | No. | Mean | Median | 95% confidence interval |
|-------------|-----|------|--------|-------------------------|
| Remission   | 29  | 13   | 9      | 8–18                    |
| Mild AD     | 43  | 34   | 31     | 27–42                   |
| Moderate AD | 57  | 75   | 77     | 66–84                   |
| Severe AD   | 29  | 230  | 230    | 195–266                 |

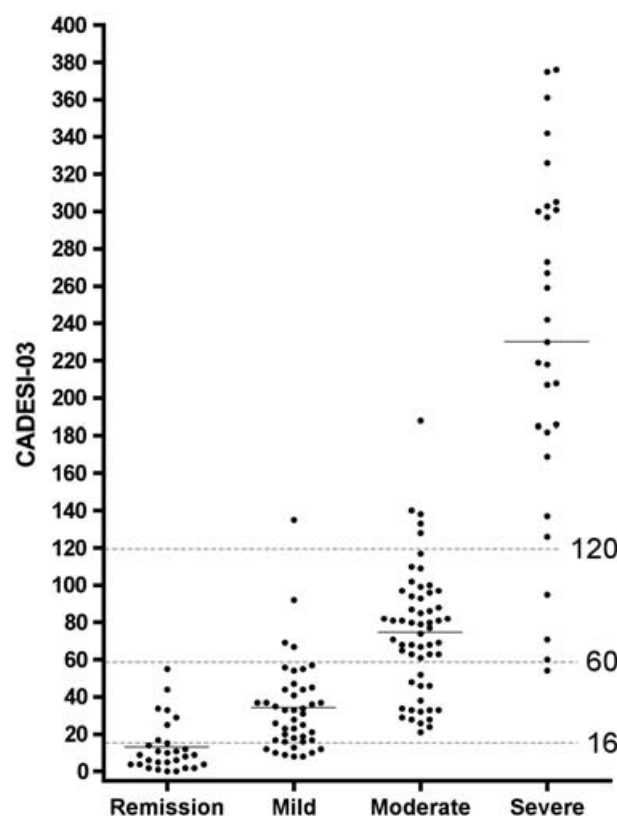


**Figure 1.** Scatter plot of CADESI-03 values in each disease severity category, Bar = mean.

### Determination of disease severity thresholds

To determine the best possible cut-off point, data from adjacent categories were compared to each other using the upper and lower categories as 'active' and 'control' groups, respectively. ROC curves were generated using increasing hypothetical CADESI-03 cut-offs (Fig. 2). In each graph, the upper left-most data set represented CADESI-03 value that exhibited the best combination of sensitivity and specificity, and this value therefore was chosen as 'best' cut-off point. For example (upper curve in Fig. 2), at the cut-off of 16, dogs with mild AD were most likely to have a CADESI-03 superior to this benchmark (sensitivity analysis), while those with disease in remission were most likely to have values inferior to it (specificity analysis). The same concepts applied to the interfaces of moderate versus mild (cut-off: 60) and severe versus moderate (cut-off: 120). Of interest is that the greater overlap of data between mild and remission categories was reflected with the poorest sensitivity/specificity combination (76 and 80%, respectively) of the three interfaces at the cut-off point of 16. At the other two interfaces, sensitivity and specificity combinations were higher (91% and 78% for moderate vs. mild; 89 and 82% for severe vs. moderate).

Using the cut-offs of 16, 60 and 120 for benchmarks of mild, moderate and severe AD category, 114 of 158 (72%) CADESI-03 measurements fell into their adequate severity group, while 42 (27%) fell in an adjacent one. Only two measurements (1%) fell in a nonadjacent disease severity category.

### Discussion

In this study, clinicians with expertise diagnosing AD in dogs subjectively scored the severity of this disease before assessing the extent and intensity of skin lesions using the previously validated CADESI-03 scale as described before.<sup>3</sup> From 108 dogs with AD, 158 data pairs were obtained. ROC curves were used to compare CADESI-03 values between adjacent severity categories. Cut-off points of 16, 60 and 120 were found to possess the highest sensitivity–specificity combinations between remission, mild, moderate and severe AD categories, respectively.

When these threshold values were used to separate disease categories, approximately 70% of the CADESI-03 scores fell into the range associated with the category that had been subjectively determined for that subject at that visit. Twenty-seven percent of scores fell in an adjacent category. These observations highlight the principal limitation of this study; there is no clinical or laboratory parameter – or combination of parameters – that can be used to reliably determine the severity of AD in dogs. As a result, clinicians only had recourse to their observational and interpretational skills to assess disease severity. It is foreseeable, and even likely, that a dog with relatively few skin lesions but marked pruritus might have been

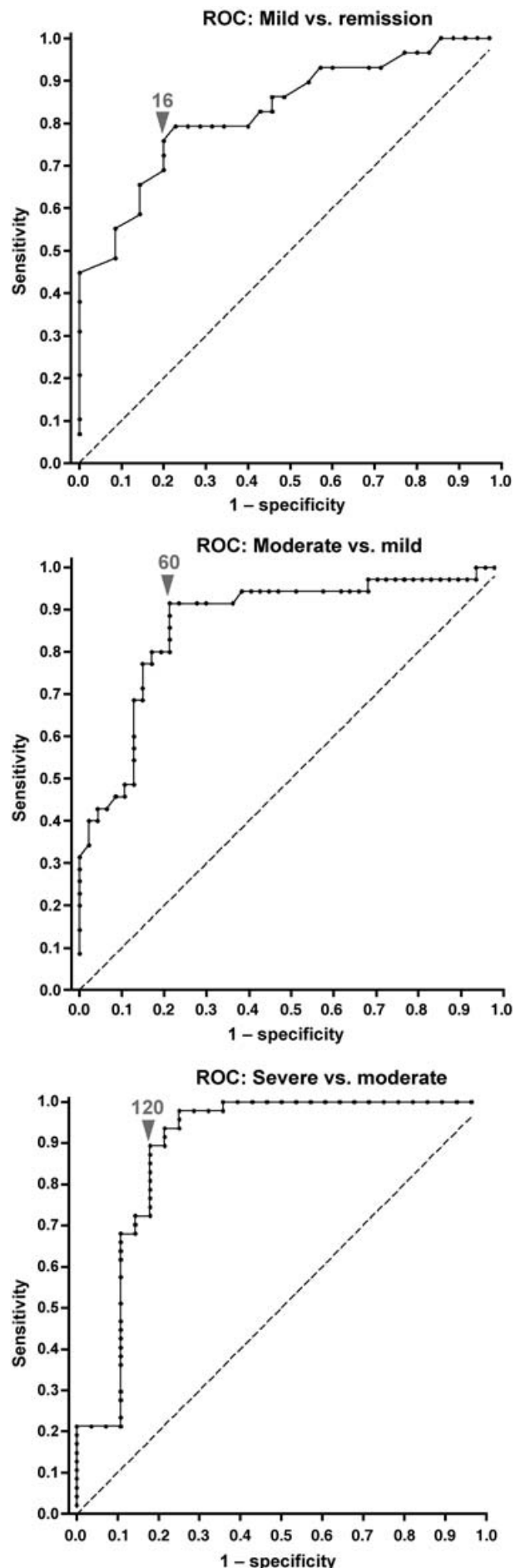


**Figure 2.** Receiver-operating characteristic (BOC) curves. CADESI-03 values from each atopic dermatitis severity category were compared to data from the category immediately below at increasing CADESI-03 cut-off points. Sensitivities and (1 - specificity) curves were plotted, and the best possible cut-off point was determined as the upper left-most point. The no-discrimination line is represented as the dotted bisectrix.

assessed as suffering from moderate – or even severe AD. This phenomenon likely explains the 16 observations of dogs (~10% of data pairs) assessed as suffering from moderate AD but having CADESI-03 values that fell below 60. Conversely, a dog with widespread or pronounced skin lesions, albeit with low pruritus, could have been assessed as having only mild or moderate AD. This situation was rarely seen, however.

A second limitation of this study is highlighted by the overlap of CADESI-03 values between the 'remission' and 'mild AD' categories. This convergence of data may be due to the relative difficulty of subjectively estimating the degree of mild erythema or to a possible lack of sensitivity of the CADESI-03 lesions 'lichenification' and 'self-induced alopecia'. Indeed, these lesions may not return to normal values (scores of '0' or '1') for weeks despite a lack of inflammation or pruritus at the time of examination. As a result, a dog may have no longer active AD, but its CADESI-03 score might remain higher than the benchmark chosen herein.

As a minor observation, it is worth noting that the CADESI-03 values graded in this study ranged from '0' in dogs whose atopic signs were deemed in remission to '376', in a dog with severe AD. Even though the maximal theoretical score of this CADESI-03 is 1240 (five degrees of severity  $\times$  four lesions  $\times$  62 sites), more than two-thirds of the possible scores may never be reached, as such high values would represent a pet with atopic disease of a severity unacceptable for most pet owners.

It is the hope of this Task Force that the benchmarks proposed herein will be used in future clinical trials and mechanistic studies enrolling dogs with AD. These cut-off points would be helpful for subgroup analyses to test the efficacy of interventions and/or the association of biomarkers in dogs with increasing AD severity. It is likely that some therapeutic interventions, because of their variable potencies, might be more effective in dogs with varying morbidity. Additionally, using similar disease severity, CADESI-03 thresholds will augment the likelihood and usefulness of

pooling data from various clinical trials in meta-analyses. Such action would increase the level of evidence of efficacy of interventions to treat canine AD, one of the most common skin diseases of dogs.

## Acknowledgements

The authors thank Emmanuel Bensignor, Didier Carlotti, Hilary Jackson and Rosanna Marsella who also contributed original patient data to this study.

## Availability for download

The CADESI-03 template is available for free download, in two formats, at the bottom of the following site: [http://www.cvm.ncsu.edu/docs/thierry\\_olivry.html](http://www.cvm.ncsu.edu/docs/thierry_olivry.html)

## References

1. Olivry T, Guaguère E, Héripret D. Treatment of canine atopic dermatitis with the prostaglandin E1 analog misoprostol: An open study. *Journal of Dermatological Treatment* 1997; 8: 243–7.
2. Olivry T, Rivierre C, Jackson HA et al. Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. *Veterinary Dermatology* 2002; 13: 77–87.
3. Olivry T, Marsella R, Iwasaki T et al. Validation of CADESI-03, a severity scale for clinical trials enrolling dogs with atopic dermatitis. *Veterinary Dermatology* 2007; 18: 79–96.
4. Ricklin Gutzwiller ME, Reist M, Peel JE et al. Intradermal injection of heat-killed mycobacterium vaccae in dogs with atopic dermatitis: a multicentre pilot study. *Veterinary Dermatology* 2007; 18: 87–93.
5. DeBoer DJ, Hillier A. The ACVD task force on canine atopic dermatitis (XV): fundamental concepts in clinical diagnosis. *Veterinary Immunology and Immunopathology* 2001; 81: 271–6.
6. Browner WS, Newman TB, Cummings SR. Designing a new study: III. diagnostic tests. In: Hulley SB, Cummings SR, eds. *Designing Clinical Research: an Epidemiologic Approach*. Baltimore, MD: Williams & Wilkins, 1988: 87–97.
7. Sousa CA, Marsella R. The ACVD task force on canine atopic dermatitis (III): genetic factors. *Veterinary Immunology and Immunopathology* 2001; 81: 153–8.

**Résumé** Pour évaluer l'étendue et la sévérité des lésions cutanées dans les essais cliniques portant sur les chiens souffrant de dermatite atopique (AD), l'International Task Force on Canine AD a récemment recommandé l'utilisation de la troisième version du CADESI. Cette version du CADESI a été rapportée comme valable sur son contenu, sa construction, la reproductibilité inter- et intra-examineur et sa sensibilité. L'étude présentée ici avait pour but de déterminer les valeurs seuils du CADESI-03 pour diviser des catégories de sévérité d'AD pour les études ultérieures. Cent huit chiens à AD ont été inclus en se basant sur les critères diagnostiques classiques. A une ou plusieurs visites, des cliniciens ont subjectivement classé l'AD en 'rémission', 'faible', 'modérée' ou 'sévère', et un score CADESI-03 a été réalisé. Au total, 158 valeurs de CADESI-03 ont été établies et divisées dans les 4 catégories de sévérité. Des courbes ont été réalisées à des valeurs seuils exponentielles pour déterminer la valeur qui permettait la meilleure sensibilité et spécificité entre les différentes catégories. Des valeurs de 16, 60 et 120 sont proposées à l'interface des sévérités rémission, faible, modérée et sévère. Les intervalles proposés sont donc: AD en rémission: 0–15; AD faible: 16–59; AD modérée: 60–119; AD sévère:  $\geq 120$ . Ce groupe de travail recommande que, lorsque applicable et valable, des analyses d'efficacité se basant sur ces sous-groupes, comme déterminé dans cette étude à partir du CADESI-03, soient prévues dans les essais cliniques portant sur l'AD. Ces analyses en sous-groupes pourraient aider à déterminer si un traitement est plus efficace pour un type particulier de chien atopique.

**Resumen** Para evaluar la extensión y severidad de las lesiones de piel en las pruebas clínicas con perros con dermatitis atópica (AD), el grupo internacional de trabajo en Dermatitis Atópica recientemente recomendó el uso de una tercera versión de CADESI. Esta versión de CADESI tiene contenido, construcción, criterio, fiabilidad inter e intra-observadores y sensibilidad aceptables. Este estudio tenía el propósito de

determinar los puntos óptimos de separación de las diferentes categorías de dermatitis atópica en la nueva versión de CADESI. Ciento ocho perros con dermatitis atópica fueron seleccionados en base a las presentes indicaciones del diagnóstico. Tras una o más visitas los clínicos veterinarios valoraron subjetivamente la severidad de la dermatitis atópica como 'en remisión', 'ligera', 'moderada' o 'intensa', y se determinó un valor para el CADESI-03. En total se dieron 158 valores de CADESI-03 divididos en la cuatro categorías de intensidad de la enfermedad. Con ellos se generaron curvas de características de receptor operador (ROC) con valores de corte en incremento para determinar el punto que ofrecería una sensibilidad y especificidad óptimas entre las diferentes categorías. Se proponen valores de corte de 16, 60 y 120 en las transiciones entre categorías en remisión, ligera, moderada e intensa, respectivamente. Los intervalos propuestos son pues: remisión 0–15; dermatitis atópica ligera 16–59; moderada 60–119 e intensa  $\geq 120$ . Este grupo de trabajo recomienda que en pruebas clínicas de dermatitis atópica, y cuando sea aplicable y de importancia, se preplanifiquen análisis de subgrupos en la valoración de resultados basados en la intensidad de la enfermedad determinada por estos puntos de corte. El mencionado análisis de subgrupos podría ayudar a determinar si particulares intervenciones médicas son más efectivas en una subpoblación particular de perros con dermatitis atópica.

**Zusammenfassung** Um das Ausmaß und den Schweregrad von Hautveränderungen bei klinischen Studien, die Hunde mit atopischer Dermatitis (AD) verwenden, zu evaluieren, hat die Internationale Task Force für Canine AD unlängst die Verwendung einer dritten Version des CADESI empfohlen. Es wurde befunden, dass diese Version des CADESI einen akzeptablen Inhalt hatte, gut aufgebaut war, einen Beurteilungsmaßstab, sowie Verlässlichkeit zwischen den Ermittlern und innerhalb eines Ermittlers und Empfindlichkeit für Veränderung aufwies. Die vorliegende Studie zielte darauf ab, optimale CADESI-03 Cut-Off Punkte zu bestimmen, um für zukünftige klinische Untersuchungen einzelne AD Kategorien nach Schweregraden zu trennen. Einhundertacht Hunde mit AD wurden nach momentanen diagnostischen Standards ausgewählt. Bei einer oder mehreren Visiten stuften die Kliniker den Schweregrad der AD subjektiv ein in 'in Remission', 'mild', 'moderat' oder 'schwer', woraufhin ein CADESI-03 Wert bestimmt wurde. Insgesamt wurden 158 CADESI-03 Werte festgehalten und zwischen den vier Krankheitskategorien mit unterschiedlichen Schweregraden aufgeteilt. Die 'Receiver Operator Characteristics' (ROC) – Kurven wurden bei zunehmenden Cut-Off Werten erstellt, um den Richtwert, der optimale Sensibilität und Spezifität zwischen angrenzenden Kategorien bot, zu bestimmen. Cut-off Werte von 16, 60 bzw. 120 wurden an den Übergängen der Kategorien Remission, mild, moderat bzw. schwer vorgeschlagen. Die beabsichtigten Intervalle sind daher: Remission: 0–15; milde AD: 16–59; moderate AD: 60–119; und schwere AD:  $\geq 120$ . Diese Task Force empfiehlt, dass, so oft es anwendbar und relevant ist, eine Untergruppenanalyse der Messergebnisse, basierend auf dem Schweregrad der Krankheit, der durch die Cut-Off CADESI-03 Werte bestimmt wird, für klinische Versuche bei Hunden mit AD vorausgeplant wird. Derartige Auswertungen der Untergruppen könnten dabei helfen herauszufinden, ob spezielle Interventionen bei einer bestimmten Untergruppe von atopischen Hunden effektiver sein könnten.