

# COST-EFFECTIVENESS OF KETOSTERIL TREATMENT IN DIALYSIS PATIENTS

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## BACKGROUND

The number of patients with chronic kidney diseases (CKD) is increasing worldwide and current trends in the prevalence of end-stage renal disease (ESRD) indicate that the population of ESRD patients around the globe is exceed 2 million patients. This increase in CKD patients is being driven by an aging population plus an increase in the incidence of diabetes and other diseases causing kidney damage. Besides being a major health problem, CKD represents a major economic problem around the globe because of the high cost of renal replacement therapy (dialysis and transplantation). For these reasons and because there is a shortage of kidneys for transplantation, new methods of preventing and treating CKD must be developed to reduce the need of renal replacement therapy and to improve the overall health of patients with CKD.

Keto acids are amino acids without nitrogen. The non-essential keto acids metabolized without urea production. The ketoacid supplementation of a low protein diet is a great leap forward in CKD treatment. There are numerous evidences on the favorable nutritional effects of Ketosteril (ketoacid-aminoacid) treatment in dialysis patients. Better quality of life and overall survival are attainable through improved nutritional status, which is also proved in practice.

## OBJECTIVES

It is increasingly recognized that conclusions drawn from classical clinical trials are not always a useful aid for decision-making - assessing the value of a drug or technology requires an understanding of its impact on current management in a practical, real-life setting. Our aim was to evaluate the real life cost-effectiveness of Ketosteril treatment in dialysis patients in comparison with CKD treatment without Ketosteril treatment.

## METHODS

A cohort calculation was presented on the basis of a representative patient and valid database from the Hungarian National Health Insurance Fund and Administration (NHIFA). NHIFA database uniquely includes health care utilization data (pharmaceutical, in- and outpatient care services, labs, diagnostics, medical aids, sickness benefit) of the total population of Hungary. Since 2004, all financed health care services are strictly validated and use the same database structure.

Our retrospective analysis contains data of January 2004-January 2010 for all dialyzed patients with chronic kidney disease (ICD code N17-19) as main diagnosis. Ctree() function of party package in R statistical program was used to determine empirical survival curves for patients treated with or without Ketosteril. Total direct costs of health care services were taken into account. Unit costs were calculated on official list prices. All eligible costs items were cumulated during the end of study period or death. In case of death life years' loss were calculated on the basis of Hungarian age specific life expectancy. Clinical evidences and expert opinion regarding the influent factors for death were used to define potential covariates of our survival analysis. Explorative statistical investigation (measures of correlation and association) was performed to identify the relevant covariates with significant effect on survival time. Altogether 86 variables - like: age, gender, type of dialysis, co-morbidities, co-medications, death, Ketosteril dosage - were investigated.

The study population was selected through the following inclusion criteria:

- continuous haemodialysis treatment after second quarter of 2004. Continuous treatment was defined as experiences of haemodialysis at least every third day.
- at the active arm, Ketosteril naive patients were enrolled with at least three months continuous Ketosteril therapy (at least 1000 tablets prescriptions) parallel haemodialysis treatment,
- patients with at least two health care services (inpatient or outpatient care services) on relevant ICD-10 code (N18-19), during the study period,

Patients were excluded as follows:

- transplantation during the whole study period
- death after starting haemodialysis in a five months period

CART module of R program was used (Classification And Regression Trees) to gain survival curves for relevant patient population subgroups. The algorithm of CART is selecting under the potential covariates to perform patients subgroup with statistically different survival curves. The selection is recursive and hierarchical, which assured the clarification of the covariant association.

Significantly ( $p < 0,05$ ) different survival curves on real life data were integrated to a Microsoft Excel platform decision-tree model where the health-economy analysis was performed. Costs and health outcomes were registered and compute monthly. The Hungarian yearly discount rate of 5% was used for both costs and outcomes. The time horizon was clarified on the basis of the mean follow up period. Exchange rate was 300 HUF/€. Main outcome of the analysis was incremental cost of life years gained (LYG). The pharmaco-economic analysis was conducted from a payer perspective.

## RESULTS

Primary 14 347 CKD patients were detected, but after selection criteria altogether 13 615 patients' data were enrolled, that included 1 008 patients with Ketosteril treatment with a mean follow up of 53 months.

In case of categorical covariates Fisher test was performed, while numerical covariates were analysed with correlation (both Pearson and Spearman correlation coefficient were calculated).

**Table 1. OR of categorical covariates on death ( $p < 0,05$ )**

Covariate	OR [CI 95%]
Ketosteril treatment	0,55 [0,50-0,61]
Ketosteril treatment (more than 1000 tablets prescribed)	0,46 [0,40-0,52]
SHPT diagnosis before renal replacement therapy	0,43 [0,25-0,74]
SHPT or ROD diagnosis and treatment	0,32 [0,30-0,34]
EPO prescription	0,27 [0,25-0,30]
Cardiovascular disease diagnosis before renal replacement therapy	1,37 [1,27-1,47]
Osteoporosis diagnosis before renal replacement therapy	1,76 [1,59-1,94]
Stroke diagnosis before renal replacement therapy	1,12 [1,01-1,23]

## REFERENCES

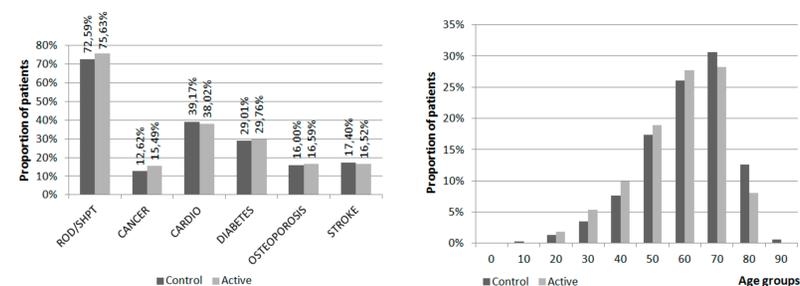
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**Table 2. Ketosteril treatment (nr of prescribed table) effect on the survival time ( $p < 0,05$ )**

Definition of survival time	Pearson_R	Spearman_R
Time from first CKD diagnosis	0,22	0,26
Time from first renal replacement therapy	0,21	0,28

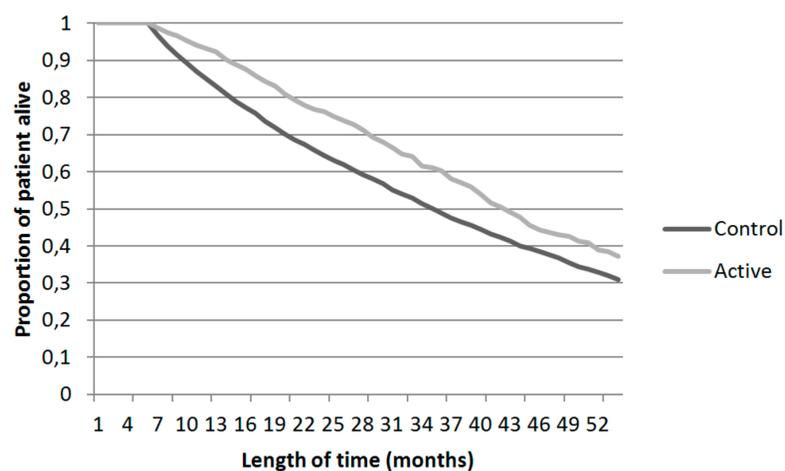
Distributions of covariates with significant effect were measured in the modeling arms, to capture differences between the compared patients groups. As Figure 1 show, probability distribution was comparable by age groups, gender (47% wo and 48% female w Ketosteril) and comorbidity between the two study population. Since these parameters showed a homogenous distribution and have the same effect on both therapeutically arms, these effect were not involved into the modeling phase.

Figure 1. Distribution of co-morbidities and age in the modelling arms



The survival analysis detected significant ( $p < 0,05$ ) benefit with Ketosteril treatment (Figure 2).

Figure 2. Survival curves in the modelling arms



Cost analysis of NHFA data showed higher average monthly costs on the Ketosteril arm, as it is apparent at Table 3. The daily Ketosteril treatment cost (12 tabs/diem) was 5,49 €, and the average prescribed table was 3 824 per patients. On the basis of that 1 748,11 € treatment cost was calculated for Ketosteril in the active arm.

**Table 3. Monthly cost per categories in the modeling arms**

MONTHLY SERVICES	Active arm	Control arm
Dialysis	899,06 €	771,88 €
Drugs (without Ketosteril)	124,53 €	93,82 €
Active inpatient care	64,67 €	62,90 €
Chronic care beds	1,81 €	2,78 €
Outpatient care	10,76 €	7,71 €
Labor Costs	8,88 €	6,30 €
Sickness benefit	4,34 €	4,59 €
SUM	1 114,05 €	949,99 €

Total costs and outcomes were calculated for 1000 subjects in the model. Results are presented in Table 4.

**Table 4. Results of the modeling**

	Active arm	Control arm	Difference
Sample size	1 000	1 000	
TOTAL EXPENDITURE	42 636 673,42 €	32 265 100,86 €	10 371 572,56 €
TOTAL EXP., DISCOUNTED	39 883 218,68 €	30 286 716,11 €	9 596 502,57 €
LYLs	7 943,71	8 842,98	899,27
LYLs, DISCOUNTED	7 244,50	8 214,27	969,77

The average total cost per patient was 9 596 € higher with Ketosteril treatment (39 883 € vs 30 287 €). Mean increases in LYGs were 0,97 with Ketosteril treatment (7,24 years vs 8,21 years). ICER was 11 698 €/LYG.

## CONCLUSIONS

Ketosteril treatment was associated to greater clinical benefits and higher costs in dialysis patients based on real world data analysis of Hungarian patients. Considering the unofficial willingness-to-pay threshold of 25 000 €/LYG in the Hungarian setting, Ketosteril represents a cost-effective option in comparison with non-Ketosteril treatment.

Our results limited by the main purpose of the NHIFA registry that is the administration of health services founded by public services. For that reason patient and disease specifics are not fully taken into account which is the main limitation of the study. Another limitation of this study is that the time frame for some analyses is relatively short. Real-world data analysis has a natural limitation itself compared to the randomized clinical trial analysis.