# Metabolic alterations in dialysis patients

Drechsler, C.

CHAPTER 6

# Wasting is strongly associated with sudden cardiac death in hemodialysis patients

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## Abstract

**Background:** Wasting is common in patients with end-stage renal disease (ESRD), and often accompanied by cardiovascular disease and inflammation. The cardiovascular risk profile meaningfully changes in ESRD, and little is known about the impact of wasting on specific clinical outcomes.

**Objective:** This study examined the effects of wasting on the various components of cardiovascular outcome, and on deaths due to infection in hemodialysis patients.

**Design:** Patients participating in the German Diabetes and Dialysis Study (4D Study) were categorized according to the presence or absence of wasting, defined by both a BMI ≤23 kg/m$^2$ and albumin level ≤3.8g/dl. By Cox regression analyses, the associations of wasting with sudden cardiac death (SCD; n=160), myocardial infarction (MI; n=200), combined cardiovascular events (CVE; n=469), and deaths due to infection (n=128) were investigated during 4 years of follow-up.

**Results:** Compared to the patients without wasting (n=1147), patients with wasting (n=108) had a 3 fold increased risk of SCD (HR 3.0, 95% CI 2.0-4.5), which hardly attenuated after multivariable adjustment (HR 2.5, 95% CI 1.6-3.8). There were trends for increased risks of stroke and deaths due to infection, while MI was not affected. The risk of CVE was significantly increased by 60% ($HR_{adj}$ 1.6 (1.2-2.1)) and mainly explained by the effect of wasting on SCD.

**Conclusions:** Wasting was strongly associated with SCD, but not with MI in diabetic hemodialysis patients. Non-atherosclerotic cardiac disease potentially plays a major role to account for the increased CVE in patients with wasting, suggesting the need for novel treatment strategies.

## Introduction

In advanced stages of chronic kidney disease (CKD), patients increasingly develop wasting. Wasting is a severe syndrome characterized by poor food intake, low muscle mass, inflammation and the development of comorbidities. It has also been referred to as the malnutrition-inflammation-atherosclerosis (MIA) or malnutrition-inflammation-complex syndrome (MICS)(1;2). In general, patients suffering from wasting experience an excessive risk of cardiovascular disease and death(3-6). However, little is known about the impact of wasting on specific clinical events, accounting for the poor overall outcome.

The pattern and composition of mortality risk is changing in advanced stages of CKD. While myocardial infarction represents the most frequent cause of death in the general population, sudden cardiac death (SCD) is the major occuring event in dialysis patients(7), which as a single cause accounts for one quarter of all deaths(8;9). Risk factors playing an important role in the pathogenesis of SCD include increased levels of cytokines, endothelial dysfunction and oxidative stress. Cardiac and vascular damage are predisposing conditions for SCD, with heart failure and left ventricular hypertrophy playing a major role(10;11). Furthermore, endocrine disorders, including insulin resistance and glycemic state, meaningfully increase the incidence of SCD, but are not associated with myocardial infarction(12). Similarly, all these conditions have been found important implications in the wasting syndrome(2;6). It may therefore be hypothesized that wasting is specifically associated with SCD rather than myocardial infarction in hemodialysis patients.

The concurrent presence of inflammation in the wasting syndrome has often been demonstrated. Furthermore, the immune system in patients with wasting has been shown compromised(13-15). Whether this translates into higher rates of inflammatory and infectious deaths, remains largely unknown however.

To that end, we investigated the association of wasting as represented by low body mass index (BMI) and hypoalbuminemia with the risk of SCD, myocardial infarction, stroke, combined cardiovascular events (CVE) and death due to infection in hemodialysis patients. We analyzed data from the German Diabetes

Dialysis Study (4D Study: Die Deutsche Diabetes Dialyse Studie), which evaluated atorvastatin in 1255 patients with type 2 diabetes mellitus on maintenance hemodialysis(9).

## Subjects and methods

***Study Design and Participants***

As described previously(16), the 4D study was a prospective randomized controlled trial including 1255 patients with type 2 diabetes mellitus, age 18 – 80 years, and on hemodialysis for less than 2 years. Between March 1998 and October 2002, patients were recruited in 178 dialysis centres in Germany. After a run-in period of 4 weeks, patients were randomly assigned to double-blinded treatment with either 20mg atorvastatin (n=619) or placebo (n=636) once daily. Study visits took place three times before randomization (visit 1-3), at randomization (visit 4), and at four weeks (visit 5) and every six months (visit 6 etc.) after randomization until the date of death, censoring, or end of the study in March 2004. The primary endpoint of the 4D study was defined as a composite of death from cardiac causes, stroke and myocardial infarction, whichever occurred first. Death from cardiac causes comprised fatal myocardial infarction (death within 28 days after a myocardial infarction), SCD, death due to congestive heart failure, death due to coronary heart disease during or within 28 days after an intervention, and all other deaths ascribed to coronary heart disease. Patients who died unexpectedly and did not present with a potassium level greater than 7.5 mmol per liter before the start of the three most recent sessions of hemodialysis were considered to have had sudden death from cardiac causes. 4D Study endpoints were centrally adjudicated by three members of the endpoint committee blinded to study treatment and according to pre-defined criteria.

For the present analysis, SCD, myocardial infarction (including fatal and non-fatal events), stroke (fatal and non-fatal), the primary endpoint of combined CVE and death due to infection were chosen to be separate outcome measures. An additional endpoint comprised all combined CVE except SCD. The study was

conducted in accordance with the ethical standards, approved by the medical ethical committee, and all patients gave their written informed consent before inclusion.

***Data collection***

Information on age, gender and smoking status was obtained through patient interviews. Smoking status was classified as never, former or current. Comorbidities, including the presence of coronary artery disease and congestive heart failure, as well as the duration of diabetes mellitus and dialysis treatment were reported by the patients´ nephrologist. Blood pressure was measured in sitting position. Body mass index was calculated as weight (kg) divided by height (m) squared. All laboratory measurements of the 4D-Study were performed centrally at the Department of Clinical Chemistry, University of Freiburg, Germany. Concentrations of serum albumin, C-reactive protein, hemoglobin, calcium, phosphate, LDL, HDL and total cholesterol were measured in blood samples taken at baseline at study visit 3 (1 week before randomization). Albumin was measured photometrically using the anionic dye bromcresol green on a Roche Modular clinical chemistry analyser (Roche Diagnostics, Mannheim, Germany). Calibrators and quality control materials were also obtained by Roche Diagnostics. Inter-assay coefficients of variance were <5%. All blood samples were taken before the start of dialysis sessions and administration of drugs.

***Statistical Analysis***

The study population was categorized according to the presence or absence of wasting. Since wasting represents an unspecific condition with a number of contributing factors, and due to the absence of guidelines for classification(17), we used BMI and serum albumin concentration as commonly available markers in line with suggestions recently been given by an expert panel. Wasting was defined 1) by a BMI ≤23kg/m$^2$, 2) by albumin levels ≤3.8g/dl, and 3) the combination of both a BMI ≤23kg/m$^2$ and albumin ≤3.8g/dl. The latter represented the main categorization used for the present study. Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) as appropriate, and categorical variables were expressed as percentages.

First, we assessed the association of wasting as defined by the combination of both a low BMI and low albumin with SCD. Absolute (incidence) rates were calculated as the number of events occuring per 100 person years of follow-up. Kaplan-Meier curves were performed in each group, and the log rank test was computed to compare the curves. By Cox regression analyses, hazard ratios and corresponding 95% confidence intervals were calculated, and adjusted for the confounders age, sex, atorvastatin treatment, duration of dialysis, smoking, coronary artery disease, congestive heart failure, systolic blood pressure, levels of LDL-cholesterol, haemoglobin, C-reactive protein, HbA1c, calcium and phosphate. Second, we performed additional Cox regression analyses with inclusion of potential intermediate variables, including left ventricular hypertrophy, levels of NT-pro-BNP. Third, we determined the relation of wasting with further cardiac and vascular outcomes, i.e. myocardial infarction, stroke, and cardiovascular events combined (CVE). Fourth, wasting was investigated regarding the risk of death due to infections. For the robustness of our results, wasting was furthermore analysed using the separate definitions by low BMI, or by low albumin. Finally, we investigated potential interaction of wasting with atorvastatin in the effect on the specified endpoints, and repeated all analyses stratified by treatment. All p-values are reported two-sided. Analyses were performed using SPSS version 16.0.

## Results

### *Patient characteristics*

Between March 1998 and October 2002, a total of 1255 patients were included into the 4D study, and had their BMI and albumin levels assessed at baseline. The mean follow-up period was 3.96 years (median 4.0 years) on atorvastatin and 3.91 years (median 4.08 years) on placebo. During follow-up, 469 patients reached the primary endpoint of combined CVE. A total of 617 patients died, of whom 160 patients died of SCD, and 128 patients died of infection. Furthermore, 200 patients experienced a fatal or non-fatal myocardial infarction, and 103 patients experienced a stroke (fatal or non-fatal).

In the study population (n=1255), the mean (SD) age was 65.7 (8.3) years, and 54% of the patients were male. A total of 189 patients had a BMI ≤ 23kg/m$^2$, and 1066 had a BMI > 23kg/m$^2$. Albumin levels were ≤3.8g/dl in 668 patients, and >3.8g/dl in 587 patients. According to our main classification of wasting based on the combination of both parameters, a total of 108 patients were categorized as suffering from wasting (i.e. having a BMI ≤ 23kg/m$^2$ and albumin ≤3.8g/dl). The baseline patient characteristics are shown in Table 1. Patients with wasting had a higher burden of coronary artery disease, congestive heart failure, left ventricular hypertrophy (LVH), and markedly higher levels of N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) compared to patients without wasting.

**Wasting and the risk of sudden cardiac death**

In the whole study group, the incidence rate of SCD was 4.5 events/100 person years (py). Compared to patients without wasting, who had an incidence rate of 4.0/100py, patients with wasting had a highly increased incidence rate of 11.8/100py (Table 2 and Figure 1A).

By Cox regression analyses, the unadjusted hazard to experience SCD was 3 fold higher in patients with wasting as compared to those without wasting (hazard ratio (HR) 3.0, 95% confidence interval (CI) 2.0-4.5). This association remained strong after adjustment for confounders (HR (95% CI) 2.5 (1.6-3.8)). To evaluate potential intermediate variables, we additionally included LVH, by which the adjusted hazard ratio for SCD was further reduced to 2.4 (1.5-3.7). When log NT-pro-BNP was added to the model, the association was attenuated to a hazard ratio of 2.1 (1.4-3.3). Addition of both potential intermediate variables to the same model resulted in a hazard ratio of 2.1 (1.3-3.3).

Findings were similar, when wasting was analysed using separate definitions by a low BMI, or by a low albumin in additional analyses. The hazard of SCD was more than 2 fold increased in patients with a BMI ≤ 23kg/m$^2$, as compared to those with a BMI >23kg/m$^2$. Similarly, patients with an albumin ≤ 3.8g/dl had a 80% higher hazard of SCD compared to patients with an albumin >3.8g/dl. The associations persisted after adjustment for confounders (Table 2).

**Table 1:** Patient characteristics according to the presence or absence of wasting at baseline; study population n=1255

| Characteristic | wasting | | BMI (kg/m²) | | Albumin (g/dl) | |
|---|---|---|---|---|---|---|
| | BMI ≤ 23 & albumin ≤3.8 (n=108) | BMI > 23, albumin > 3.8 (n=1147) | ≤23 (n=189) | >23 (n=1066) | ≤3.8 (n=668) | >3.8 (n=587) |
| Age *years* | 68 (8) | 65 (8) | 67 (8) | 65 (8) | 67 (8) | 65 (8) |
| Gender *% male* | 52 | 54 | 58 | 53 | 48 | 61 |
| BMI *kg/m²* | 21.1 (1.5) | 28.2 (4.6) | 21.1 (1.5) | 28.7 (4.3) | 27.7 (5.1) | 27.4 (4.5) |
| Atorvastatin treatment *%* | 53 | 49 | 47 | 50 | 50 | 49 |
| Systolic BP *mmHg* | 147 (22) | 145 (22) | 149 (23) | 145 (22) | 145 (23) | 146 (21) |
| Diastolic BP *mmHg* | 74 (11) | 76 (11) | 75 (12) | 76 (11) | 75 (11) | 76 (11) |
| Smoker / Ex-smoker *%* | 48 | 40 | 51 | 39 | 36 | 45 |
| Duration of diabetes *years* | 16.9 (7.8) | 18.2 (8.9) | 17.3 (8.2) | 18.3 (8.9) | 18.2 (8.8) | 18.0 (8.8) |
| Time on dialysis *months* | 6.5 (5.5) | 8.4 (7.0) | 7.8 (6.5) | 8.4 (7.0) | 7.3 (6.3) | 9.4 (7.3) |
| History of | | | | | | |
| CAD *%* | 42 | 28 | 37 | 28 | 30 | 28 |
| CHF *%* | 53 | 34 | 44 | 34 | 39 | 31 |
| arrhythmia *%* | 21 | 19 | 21 | 18 | 19 | 19 |
| PVD *%* | 57 | 44 | 53 | 43 | 47 | 42 |
| LVH *%* | 28 | 11 | 29 | 10 | 13 | 12 |
| Laboratory parameters | | | | | | |
| Total cholesterol *mg/dl* | 203 (37) | 221 (43) | 211 (38) | 221 (43) | 216 (43) | 223 (42) |
| LDL cholesterol *mg/dl* | 116 (28) | 126 (30) | 123 (30) | 126 (30) | 124 (31) | 128 (29) |
| HDL cholesterol *mg/dl* | 39 (15) | 36 (13) | 40 (16) | 35 (12) | 36 (13) | 37 (14) |
| Albumin *g/dl* | 3.55 (0.25) | 3.84 (0.29) | 3.77 (0.33) | 3.83 (0.30) | 3.59 (0.20) | 4.07 (0.17) |
| Hemoglobin *g/dl* | 10.7 (1.3) | 10.9 (1.4) | 10.9 (1.4) | 10.9 (1.4) | 10.7 (1.4) | 11.1 (1.3) |
| Calcium *mmol/l* | 2.3 (0.2) | 2.3 (0.2) | 2.3 (0.2) | 2.3 (0.3) | 2.3 (0.2) | 2.3 (0.2) |
| Phosphate *mmol/l* | 5.79 (1.83) | 6.05 (1.59) | 5.96 (1.77) | 6.04 (1.58) | 5.93 (1.66) | 6.14 (1.54) |
| HbA1c *%* | 6.5 (1.2) | 6.7 (1.3) | 6.5 (1.2) | 6.8 (1.3) | 6.8 (1.3) | 6.6 (1.2) |
| Adiponectin *mg/l* | 20.3 (15.5) | 15.9 (9.0) | 20.4 (13.7) | 15.5 (8.7) | 16.5 (10.8) | 16.0 (8.6) |
| NT-pro-BNP *pg/ml* | 6941 (2043-22302) | 3143 (1373-8375) | 6403 (2145-21800) | 2977 (1336-7711) | 3690 (1570-10220) | 2905 (1290-8049) |
| C-reactive protein *mg/l* | 5.5 (1.7-16.2) | 4.9 (2.4-12.0) | 4.1 (1.7-12.0) | 5.1 (2.5-12.5) | 6.4 (2.8-15.8) | 3.9 (2.0-8.4) |

Values are presented as means (SD) or median (interquartile range) or %.
Abbreviations: BP, blood pressure; HbA1c, glycated hemoglobin A1c;
CAD, coronary artery disease; CHF, congestive heart failure; PVD, peripheral vascular disease, LVH, left ventricular hypertrophy
LDL, low density lipoprotein; HDL, high density lipoprotein; NT-pro-BNP, N-terminal-pro-B-type-natriuretic peptide

**Table 2:** Absolute incidence rates, and hazard ratios with 95% confidence intervals (HR, 95% CI) for sudden cardiac death, myocardial infarction, the primary endpoint of combined cardiovascular events, and the primary endpoint except for sudden cardiac death according to the presence or absence of wasting at baseline; n=1255

| Outcome | wasting | | BMI | | albumin | |
|---|---|---|---|---|---|---|
| | BMI≤23 & albumin ≤3.8 (n=108) | BMI>23 and/or albumin >3.8 (n=1147) | ≤23 (n=189) | >23 (n=1066) | ≤3.8 (n=668) | >3.8 (n=587) |
| ***Cardiovascular events*** | | | | | | |
| Incidence rate / 100py | 23.8 | 13.6 | 19.6 | 13.4 | 16.3 | 12.5 |
| Crude HR (95% CI) | 1.8 (1.3-2.4) | 1 | 1.5 (1.2-1.9) | 1 | 1.4 (1.1-1.6) | 1 |
| Adj.[1] HR (95% CI) | 1.6 (1.2-2.1) | 1 | 1.4 (1.1-1.8) | 1 | 1.2 (1.01-1.5) | 1 |
| ***Sudden death*** | | | | | | |
| Incidence rate / 100py | 11.8 | 4.0 | 8.2 | 3.9 | 5.8 | 3.3 |
| Crude HR (95% CI) | 3.0 (2.0-4.5) | 1 | 2.1 (1.5-3.0) | 1 | 1.8 (1.3-2.5) | 1 |
| Adj.[1] HR (95% CI) | 2.5 (1.6-3.8) | 1 | 1.9 (1.3-2.8) | 1 | 1.6 (1.1-2.2) | 1 |
| ***Stroke*** | | | | | | |
| Incidence rate / 100py | 4.3 | 2.9 | 3.2 | 2.9 | 4.1 | 2.0 |
| Crude HR (95% CI) | 1.5 (0.8-2.9) | 1 | 1.1 (0.6-1.9) | 1 | 2.2 (1.5-3.4) | 1 |
| Adj.[1] HR (95% CI) | 1.6 (0.8-3.2) | 1 | 1.2 (0.7-2.2) | 1 | 2.0 (1.3-3.1) | 1 |
| ***Myocardial infarction*** | | | | | | |
| Incidence rate / 100py | 6.2 | 5.9 | 4.8 | 6.1 | 5.8 | 6.1 |
| Crude HR (95% CI) | 1.1 (0.6-1.9) | 1 | 0.8 (0.5-1.2) | 1 | 1.0 (0.7-1.3) | 1 |
| Adj.[1] HR (95% CI) | 1.0 (0.5-1.7) | 1 | 0.8 (0.5-1.2) | 1 | 0.9 (0.7-1.3) | 1 |
| ***Cardiovascular events except sudden death*** | | | | | | |
| Incidence rate / 100py | 11.2 | 9.3 | 10.9 | 9.1 | 10 | 8.9 |
| Crude HR (95% CI) | 1.2 (0.8-1.9) | 1 | 1.2 (0.9-1.6) | 1 | 1.2 (0.95-1.5) | 1 |
| Adj.[1] HR (95% CI) | 1.2 (0.8-1.8) | 1 | 1.2 (0.9-1.7) | 1 | 1.1 (0.9-1.4) | 1 |
| ***Death due to infection*** | | | | | | |
| Incidence rate / 100py | 6.3 | 3.4 | 4.8 | 3.4 | 4.5 | 2.8 |
| Crude HR (95% CI) | 2.0 (1.2-3.5) | 1 | 1.5 (0.9-2.3) | 1 | 1.8 (1.3-2.6) | 1 |
| Adj.[1] HR (95% CI) | 1.5 (0.8-2.6) | 1 | 1.2 (0.8-2.0) | 1 | 1.7 (1.1-2.5) | 1 |

[1] model 1: adjusted for age, sex, atorvastatin treatment, systolic blood pressure, coronary artery disease, congestive heart failure, smoking, duration of dialysis, levels of LDL cholesterol, hemoglobin, C-reactive protein, HbA1c, calcium and phosphate

***Wasting and risk of myocardial infarction, stroke and combined cardiovascular events***

In contrast, no association of wasting with myocardial infarction was found. The incidence rate of myocardial infarction was 5.9/100 py in the whole study group, and not markedly different in the presence (6.2/100py) or absence of wasting (5.9/100py) (Figure 1B). The crude hazard ratio for myocardial infarction associated with wasting was 1.1 (0.6-1.9). Similarly, the multivariable adjusted hazard ratio was 1.0 (0.5-1.7). When non-fatal and fatal MI were analyzed separately, the results were confirmed showing no association between wasting and myocardial infarction. The results were furthermore consistent throughout all definitions of wasting used.

The presence of wasting affected the risk of stroke by trend, but not significantly (Table 2). In the additional analyses, low levels of albumin (below 3.8 g/dl) were associated with a twofold increased risk of stroke, while a low BMI (<23 kg/m$^2$) irrespective of the inflammatory status had no influence.

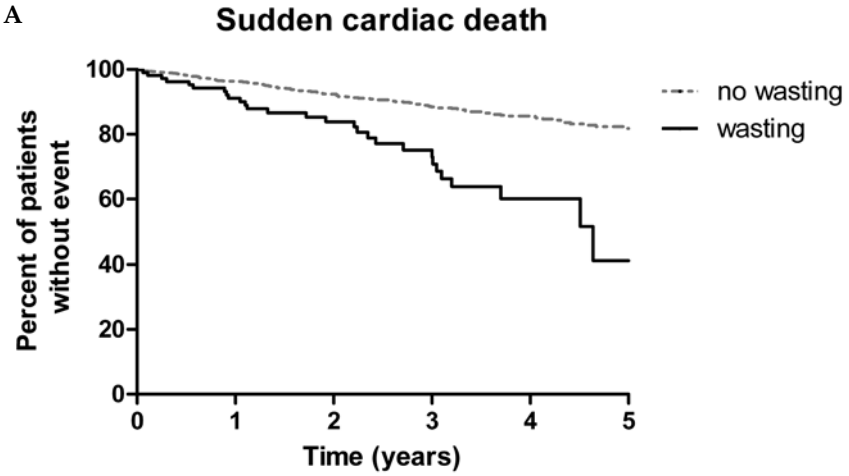
The endpoint of combined CVE was markedly increased in patients suffering from wasting (Table 2 and Figure 1C). Affected patients had an adjusted 60% higher risk of combined CVE as compared to patients without wasting. Additional analyses revealed that this relation was mainly explained by the impact of wasting on SCD, since no association was found for combined CVE except SCD. The findings were consistent in the additional analyses using BMI or albumin separately for the definition of wasting.

***Wasting and risk of death due to infection***

Deaths due to infection were increased in patients suffering from the wasting syndrome. They had a twofold increased risk compared to non-affected patients, but this association was significantly attenuated after multivariable adjustment. Similarly to what was seen for strokes, the inflammatory component of the wasting syndrome as represented by a low albumin appeared to strongly increase the risk, while a low BMI separately had no influence.

To strengthen our results, we eliminated any potential influence by atorvastatin treatment and repeated all analyses in the placebo group only. The results were similar, indicating no effect modification and supporting the use of the complete data.

**A**

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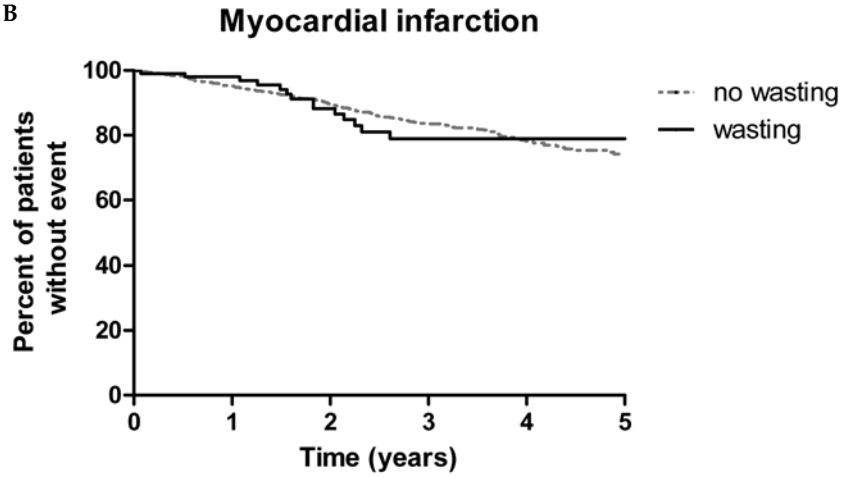

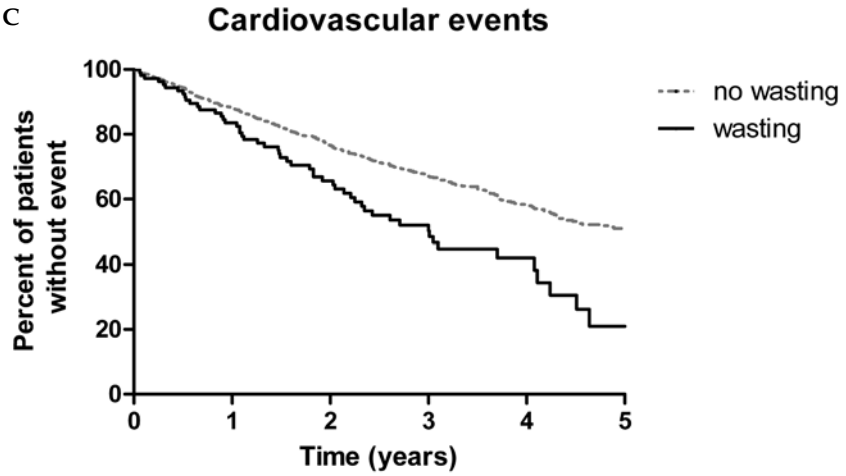


**Figure 1 A-C:** Kaplan-Meier curves for the time to A) sudden cardiac death, B) myocardial infarction, C) the primary endpoint of combined cardiovascular events in subgroups of patients according to the presence or absence of wasting.

## Discussion

We investigated the effect of wasting on particular components of cardiovascular outcome, and death due to infection in a large prospective cohort of hemodialysis patients with type 2 diabetes mellitus. Within 4 years of follow-up, the presence of wasting was significantly associated with a three-fold increased risk of sudden cardiac death, and by trend with stroke and deaths due to infection. In contrast, the presence of wasting did not affect the risk of myocardial infarction. Furthermore, the strong impact of wasting on sudden cardiac death mainly explained the increased hazard of combined cardiovascular events in the wasting syndrome, being 60% higher in patients with wasting as compared to patients without wasting.

Wasting is common in patients with CKD and becoming most prevalent in end-stage renal disease. Estimated 18-75% of dialysis patients are suggested to show evidence of the wasting syndrome, depending on the measured parameters,

age and comorbidities(18). Wasting is characterized by a low body weight, low protein-energy stores, muscle loss and low concentrations of albumin and other proteins(19). In dialysis patients, many factors may affect nutritional status and the development of wasting, such as uremia induced low appetite, hormonal disturbances, metabolic acidosis, oxidative stress and comorbidities(17;20). In the context of its multifactorial character, wasting has also been referred to as „malnutrition-inflammation-complex (MICS)" syndrome, „malnutrition-inflammation-atherosclerosis (MIA)" syndrome, or „malnutrition-inflammation-cachexia" syndrome (1;2). The single contributions of the wasting components are difficult to assess, considering the variety of factors and their complex interactions. Pathways and specific outcome effects are therefore crucial to get further insights into which wasting factors and wasting mechanisms may -relatively to others- be most important to serve as promising targets for novel intervention strategies. Little is known so far on specific outcomes associated with wasting, and our study is the first to address this question in a large cohort of dialysis patients who experienced a high incidence of pre-specified and centrally adjudicated endpoints. Our finding that wasting was strongly associated with SCD is supported by previous research outlined in the literature. One study investigating risk factors for SCD in dialysis patients found markers of inflammation including albumin, hsCRP and IL-6 of major importance (21). Inflammation is commonly involved in the wasting syndrome and may increase the risk of sudden death via the development of premature atherosclerosis and cytokine-induced plaque instability(22), or by direct effects on the myocardium and electrical conduction system(23). Cytokines are also involved in the modulation of ion channel function and the generation of arrhythmias (24;25), as well as in the aggravation of sympathetic tone, leading to tachycardia and cardiac electrical instability. In our study, patients with wasting exhibited to a considerable extent left ventricular hypertrophy and increased levels of adiponectin and NT-pro-BNP. These factors are known to be strong predictors of SCD and may, at least in part, represent wasting related to structural changes in the heart(11;26-28). In this context, our study may offer novel treatment strategies for patients with wasting. Given that current treatments are limited, new therapeutic options are urgently needed. Our

finding that patients with the wasting syndrome are at increased risk of SCD suggests that the patients may be considered for particular treatments to prevent SCD, including ß-blocker or implantable cardioverter defibrillator therapy (29;30). Given that wasting is considered to contribute to atherosclerosis (6;31), our finding of no relation between wasting and the risk of myocardial infarction came rather as a surprise. Despite a significant burden of coronary artery disease in patients with wasting (about 40% at baseline), wasting did not translate into a higher risk of myocardial infarction as a major ischemic complication. Stroke risk, which is less related to atherosclerosis compared to myocardial infarction showed a remarkable trend for an association with wasting. It is of major interest, that the increased cardiovascular events seen in patients with wasting are mainly explained by the effect of wasting on SCD. Therefore, although a lot of attention is paid to atherosclerosis in the wasting syndrome, other factors like structural heart disease may be even more important, resulting in a relative excess of SCD. In addition, our findings may be particularly important concerning the paradoxical associations often seen for metabolic or nutritional status and outcome in dialysis patients. By now, explanations for the survival benefits largely seen for dialysis patients with obesity included time effects (short follow-up), age, differences among populations and reverse causation (32;33). While obesity is known to be a risk factor for myocardial infarction (34), our study shows that the latter may potentially be overruled by excessive incidences of SCD in patients with beginning or obvious wasting. This in turn may lead to a relative underrepresentation of (e.g. obesity induced) myocardial infarctions.

Finally, our results showing increased deaths due to infection in patients with wasting strengthen the notion that inflammation meaningfully impacts and contributes to the patients´ mortality. In line with findings on compromised immune status and higher rates of infections (13-15), wasting continues to translate into poor infection-specific outcome.

Potential limitations of the study need to be acknowledged. It was a post-hoc analysis within a selected cohort of German patients with type 2 diabetes mellitus on hemodialysis. Therefore, the relationship between the presence of wasting and risk may not be generalisable to other patient populations. Yet, it may be assumed

that the results also hold true for non-diabetic hemodialysis patients, similarly suffering from wasting. The group of patients with wasting, defined by using a BMI ≤ 23kg/m$^2$ was relatively small, and results may become stronger with larger numbers of patients in future studies. The specific outcomes, among which SCD, and their association with wasting to be analyzed was the main strength of this study. In this context, the long-term follow-up, adequate sample size and high incidence of pre-specified and centrally adjudicated endpoints are further to be mentioned.

In conclusion, the presence of wasting was strongly associated with sudden cardiac death, but not with myocardial infarction in diabetic hemodialysis patients. Non-atherosclerotic cardiovascular disease potentially plays a major role to account for the increased cardiovascular events in patients with wasting. In addition to current treatment, patients with the wasting syndrome should be targeted in the prevention of sudden cardiac death. Apart from regular examinations, patients with wasting may be considered for further treatments including ß-blocker or implantable cardioverter defibrillator therapy(29;30).

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