

Individual assessment of the group of high users.

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Objective of the study.

The SAN case-control study disclosed a dose-dependent increase in risk of ESRD in 22 cases with a life-time analgesic ingestion of more than 2.5 Kg, calculated at index date 3 (5 years before admission to renal replacement therapy). As indicated at page 56 of the SAN report, it was suspected that, irrespective of the analgesic intake and when compared to controls, this group of patients would present more conditions predisposing to ESRD. Consequently an individual assessment was decided to investigate the evidence in favor of a causal relationship between the intake of analgesics and ESRD and the alternative possibility that the higher intake of analgesics could be indirectly associated to the risk of ESRD.

In the SAN study antipyretic analgesics and NSAIDs are considered together under the generic name “analgesics”. The renal risks attributed in the literature to both categories are however different. Schematically the following risks are described:

- ✓ *Short-term risks.* Most NSAIDs and some analgesics can under certain conditions lead to acute renal functional and/or structural damage. In the SAN study however cases with acute renal failure have been excluded by definition. Therefore, this type of acute renal damage will not be considered.
- ✓ *Long-term risks.* The data of the literature on the long term risks of chronic analgesic intake are inconsistent. In the 1995 edition of the authoritative Oxford Textbook of Clinical Nephrology [1] two different long-term risks are described:
 1. *Analgesic nephropathy (AN).* This is defined as “*a slowly progressive disease resulting from the daily use for many years of mixtures containing at least two antipyretics, anilides, and salicylates, usually together with caffeine or codeine (or both)*”. It is characterized by capillarosclerosis leading to papillary necrosis and secondary chronic interstitial nephritis [2].
 2. *A contribution to the development or the progression of existing chronic renal disease.* In contrast to AN which is attributed to the intake of special categories of antipyretic analgesics, all single or compound analgesics and NSAIDs have been suspected to contribute to the progression of existing renal diseases. This hypothetical influence has no clear clinical or pathological definition.

The possible contribution of these two different long-term risks to the evolution to ESRD will be examined successively on the basis of the data provided by the SAN investigators.

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Material and methods.

The following individual data were available for study:

- ✓ The patient questionnaire (Fragebogen I) as filled in by the interviewers .
- ✓ The medical questionnaire (Medizinischer Dokumentationsbogen FormII) as filled in by the physician responsible for the dialysis of the patient.
- ✓ A summary of the relevant medication data (Mengenangabe der Medikamente in mg) calculated by the SAN investigators at index date 1 (on admission for renal replacement therapy). For every relevant drug the number of units and grams was given.

Data were available on 22 cases and 19 controls selected from the SAN study on the basis of a lifetime analgesic intake exceeding 2.5 Kg at index date 3. It should be noted that in our study the intake of analgesics was estimated on the basis of index date 1 and that the headings “cases” and “controls” are used only to indicate clearly the origin of the selected files. The following table illustrates the repartition of the intake as reported in table 17 of the SAN report for index date 3 and the corresponding data when index date 1 is used.

Analgesic intake gram	Number of Cases		Number of Controls	
	<i>Index date 3</i>	<i>Index date 1</i>	<i>Index date 3</i>	<i>Index date 1</i>
2501-3000	3	0	8	3
3001-3500	5	2	6	5
3501-4000	2	4	1	0
4001-5000	4	3	2	6
5001-6000	2	0	1	1
>6000	6	13	1	4

This study was performed without access to the medical record and without contact with the physicians in charge of the patient. In particular, echographic and biopsy data were only available as yes/no scores on the medical questionnaire with some additional notes. It should be noted that most of these questionnaires were completed by the physician in charge of the dialysis and not by the nephrologist or internist who cared for the patient during the years preceding admission to dialysis. The accuracy of the responses to the medical questionnaires is therefore questionable. This is illustrated by the fact that in 19 out of these 22 cases of high users the physician denied having knowledge of abuse of analgesics. Without access to the complete medical record it is hazardous to question the diagnosis of the physician in charge, when appropriate some alternative suggestions will however be made on the individual case assessments.

Results:

1. Is there any evidence that extreme users of analgesics presented analgesic nephropathy (AN)?

To answer this question, the available data must be confronted with the clinical and pathological characteristics of this entity as described in the Oxford Textbook of Clinical Nephrology[1]. The intake of analgesics and the subdivision between Mono and Combi as reported in the SAN study was thus recalculated to bring it in line with the definition of analgesic nephropathy.

1. As analgesics only antipyretic analgesics (ASA, Salicylates, Aminophenazone etc..) were considered. NSAIDs were not included.
2. The amount of caffeine, codeine and other additives was not included in the calculations.
3. Combis were defined as the combination of at least two antipyretics, anilides and/or salicylates. (ASA with caffeine was not considered a Combi).
4. For the calculation of the total intake, only the intake spread over a period exceeding six months was taken into account. Occasional intakes for flu or toothache were not included.

The results of the recalculation of the “analgesics” intake according to these criteria are presented in the following table.

	22 CASES		19 CONTROLS	
	<i>Total intake g.</i>	<i>Average g</i>	<i>Total intake g</i>	<i>Average g</i>
All analgesics	190.250	8.648	93.282	4.910
Antipyret. analg.	171.924	7.815	80.833	4.254
Difference	9.63%		13.35%	

All these intakes were calculated on the basis of index date 1. The differences are for the most part attributable to the intake of NSAIDs. Reporting these differences in grams tends to underestimate their significance, as the efficient doses of NSAIDs and of antipyretic analgesics are not identical. These results indicate that on average the intake of analgesics of the cases was nearly twice as high as the intake of the controls and that the control group had a relatively higher intake of NSAIDs than the cases. Annexed tables 1 and 2 illustrate the heterogeneity of these two groups.

The pattern of analgesic intake.

AN results from “...*the daily use for many years of mixtures containing at least two antipyretics, anilides, and salicylates...*[1].

The intake of antipyretic analgesics in the 22 cases with high consumption is shown in the annexed table 3. It is clear that more Mono preparations were used than Combis and that the intake was usually intermittent, often limited to a few tablets per day. A daily intake of analgesics was reported in 11 cases only (annexed table 4) and this concerned monos in 8 instances. Only 3 cases had thus a pattern of analgesic intake

corresponding to what is claimed responsible for AN. The corresponding data for the controls are reported in the annexed tables 5 and 6.

Clinical characteristics.

Analgesic nephropathy is a form of interstitial nephritis secondary to lesions in the papilla. There is little or no proteinuria. The kidneys are reduced in size, present an irregular contour and papillary calcifications can be present.

For the group of high users under evaluation, the available data on proteinuria and renal imaging are reported in the annexed table 7. Only one patient (case 10002847) presents kidneys reduced in size with bumpy contours. There were however no calcifications and proteinuria is mentioned, although the degree is not indicated. The only patient presenting papillary calcifications is case 10002895, a patient with insulin dependent diabetes mellitus and significant proteinuria. The clinical diagnosis was diabetic nephropathy and this can cause papillary calcifications.

In summary only one patient (case 10002847) presents echographic data compatible with analgesic nephropathy but unfortunately there are no data available on the degree of proteinuria.

In conclusion: The available data on these 22 cases with extreme use indicate that the pattern of analgesic intake deemed responsible for AN was found in only 3 patients and that only in one of these 3 cases the clinical data were compatible with AN . These findings are consistent with the fact that none of the patients were diagnosed by their physician as presenting AN. Analgesic nephropathy can thus be excluded as a significant cause of end stage renal failure in this group of “extreme users” of analgesics. This conclusion is in line with the recent study of Mihatsch who found that analgesic nephropathy disappeared progressively from the Basel autopsy data and with a study in Flanders[3] demonstrating the progressive disappearance of AN among the patients admitted to dialysis notwithstanding a continuous intake of mixed non-phenacetin analgesics. That phenacetin and not mixed antipyretic analgesics must be deemed responsible for AN is consistent with these data on high users from the SAN study.

2. Is there any evidence that the intake of analgesics and/or NSAIDs contributed to the development or the progression of existing chronic renal disease?

In contrast with AN which is well defined clinically and pathologically, a contribution of analgesic intake to the progression of existing renal diseases presents no distinctive clinical or pathological features. It is only substantiated by the results of epidemiological studies. The decrease in glomerular filtration rate or, as in the SAN study the evolution to ESRD, have been used as end-point for these studies. When the studies presenting major flaws are eliminated, the evidence provided is however weak and the data are inconsistent. When phenacetin is excluded, no other analgesic or NSAID or combination has been consistently linked with a progression to ESRD. In the clinical setting the recognition of this hypothetical influence of analgesics and NSAIDs is impossible and the aim of the present evaluation is therefore limited to examine if, besides the intake of analgesics, the present group of 22 extreme users presents risk factors sufficiently explaining the evolution to ESRD.

In contrast with the weak evidence for non-phenacetin analgesics, several other significant risk factors have been consistently identified. These are accepted as forming a scientifically sound basis for the prevention of evolution to ESRD[4-7]. It is on this basis that a common sense opinion will be given on the reasons for evolution to ESRD in these 22 cases and on the possible remaining role for non-phenacetin analgesics.

The following risk factors other than analgesics have been identified in several studies:

1. The type of kidney disease.

It is obvious that most kidney diseases can lead to end stage renal failure. By definition all of the cases and none of the controls presented end stage renal disease. Only one of the controls mentioned having suffered from pyelonephritis.

The risk of evolution to end stage and the rate of progression is obviously not the same for the different diseases. In a prospective study on 23,534 persons, the OR for treated diabetes was reported as 7.5 (4.8-11.7)[8]. Even within the same disease the rate of progression can be variable, as in the case of IgA nephropathy where clinical parameters as serum creatinine, proteinuria and hypertension can be used to predict disease progression [9].

These diseases can be incapacitating and stressful, leading to a high consumption of analgesics.

2. Sex.

Male patients present a higher incidence of glomerulonephritis. In general, risk factors for ESRD tend to be more significant in males than in females.

3. Vascular lesions.

Hypertension is a well known risk factor for ESRD.

In a prospective study of 23,534 persons hypertension was a significant risk factor for ESRD in men and in women. [8]:

✓ High normal BP	OR 3.0 (0.9-10.3)
✓ Stage 1 hypertension	OR 3.2 (1.0-10.4).
✓ Stage 2 hypertension	OR 5.7 (1.7-18.9)
✓ Stage 3 or 4 hypertension	OR 8.8 (2.6-30.3)

In a case-control study on 83 cases and 1190 controls the risk of ESRD in patients with hypertension was OR 3.07 (2.28-4.15)[10]

4. Obesity.

In a historical cohort study on 320,252 adult volunteers the following influence of Body Mass Index (BMI) on the risk for ESRD was found[11]:

BMI 25-29.9	Adjusted relative risk 1.87 (1.64-2.14)
BMI 30-34.9	Adjusted relative risk 3.57 (3.05-4.18)
BMI 35-39.9	Adjusted relative risk 6.12 (4.97-7.54)
BMI >40	Adjusted relative risk 7.07 (5.37-9.31)

5. Proteinuria.

The degree of proteinuria is one of the most significant indicators of the risk of ESRF and its reduction by ACE inhibitors or some NSAIDs significantly influences the outcome.

In a multiple risk factor interventional trial on 12,866 men followed over 25 yr the dipstick proteinuria was a predictor of ESRD. [12]

Dipstick proteinuria 1+ HR 3.1 (1.8-5.4).

Dipstick proteinuria >2 HR 15.7 (10.3-23.9)

6. Smoking.

Smoking in persons without renal disease influences renal function and damages the endothelium[13]. Smoking increases the risk of developing proteinuria and this effect is more marked in men [14]. Smoking is associated with an increased risk for chronic renal failure.

- ✓ A nationwide population-based case-control study [15] indicated the following risk:
 - >20 cigarettes/day OR 1.51 (1.06-2.15)
 - >40 years OR 1.45 (1.00-2.09).
 - >30 pack/years OR 1.52 (1.08-2.14)
- ✓ In a prospective study of 23,534 persons.[8], current smokers presented a higher risk of ESRD OR 2.6 (1.8-3.7).
- ✓ Case-Control study on 83 cases and 1190 controls [10]:
 - Current or past smoking OR 1.54 (1.14-2.07).

It could be expected that in the presence of renal and/or vascular diseases the effect of smoking would be exacerbated and result in an increased risk of ESRD [16]. Smoking increases the risk of developing diabetes[17]. Once the diabetes established, it increases the risk of microalbuminuria and diabetic nephropathy.

In patients with type 1 or 2 diabetes mellitus with normal renal function cigarette smoking decreases the glomerular filtration rate independent of confounding factors, including severity of proteinuria [18].

In the case-control study of Ibanez [10], smoking in the presence of diabetes increased the risk of end stage renal failure: OR 4.41 (1.45-13.38).

Not only diabetic nephropathy but also the evolution of other renal diseases is exacerbated by smoking. In a retrospective case-control study on 582 patients[16], in smoking men with IgA nephropathy or polycystic kidney disease the risk of progression to end stage renal failure was:

5-15 Packs/year OR 3.5 (1.3-9.6)

>15 Packs/year OR 5.8 (2.0-17)

In primary hypertension and no evidence of primary renal disease, smoking is the most powerful predictor of the loss of renal function. [19, 20].

7. (Ab)use of drugs.

In a case-control study 716 patients who started therapy for ESRD in 1991, were compared to 361 controls. After adjustment for age, sex, race, socioeconomic status, and history of hypertension and diabetes, persons who had ever used heroin or other opiates (any amount) were at increased risk for ESRD (adjusted odds ratio, 19.1; (1.7 - 208.7). The use of cocaine or crack and psychedelic drugs was also associated with ESRD, but these associations could not be separated from the effects of heroin. [21]

Risk factors in high users of analgesics.

The overall prevalence of the majors risk factors in Cases and Controls is indicated in the following table:

	Renal disease	Sex	Hypertens.	BMI>30	Proteinuria	Smoking >10P/Y	Drugs Coca/Her.
22 Cases	22 100%	13 Male 59%	21 95%	6 27%	14 (5 n.d.) 82%	12 (55%)	2 (9%)
19 Controls	1 5%-	10 Male 53%	6 32%	3 16%	-)	9 (47%)	

Details of the risk factors in the cases are given in the annexed table 8 and for the controls in table 9.

- ✓ In the cases the presence of **renal diseases** is not unexpected but the high number of diabetic patients (8 cases) and polycystic kidney disease (3 cases) is important to note as these diseases with a protracted evolution over many years are associated with painful conditions and stress.
- ✓ A remarkable finding is the presence of **hypertension** and vascular diseases in nearly all cases. This could possibly lead to headache and analgesic intake.
- ✓ Among the cases one in four is **obese**.
- ✓ **Proteinuria** is present in 82% of the cases for which results are available.
- ✓ At first sight **smoking** is nearly as frequent in cases as in controls. The risk for ESRD presented by smoking is however much higher in patients with diabetes, hypertension and in general vascular damage.
- ✓ **Drug abuse** is a significant risk factor. Only Cocaine and/or Heroin and not Cannabis have been considered.

It can be concluded that this group of high users of analgesics presented a large number of major risk factors explaining the evolution to ESRD. In addition, the combination of these risk factors is known to greatly increase the risk. As already mentioned an additional influence of analgesic use on the progression of the disease cannot be demonstrated nor excluded by a clinical study of individual cases.

Reasons for taking analgesics.

These patients obviously present a chronic incapacitating disease with a variety of complaints and this could explain some inconsistency in the answers when asked for the reasons for taking analgesics.

Among the high consumers of analgesics there are more cases than controls. The main reasons indicated for taking analgesics are summarized in the following table.

	n	Headache/migraine	Rheuma	Fever, Cold etc.
Cases	22	18 (82%)	4	10
Controls	19	16 (84%)	4	4

Headache is in the two groups the main reason for taking analgesics. If the cases consumed more analgesics than the controls the obvious explanation seems to be that they had more headache. The stress related to the existence of serious diseases as diabetes or polycystic disease could in itself provide an explanation. This is consistent with the observation that, when compared to the lifetime intake of analgesics at index date 3, the intake at index date 1 increased more in cases than in controls (see table in “material and methods”). In addition, comparison between the detailed list of problems and complaints of cases and controls (annexed tables 10 and 11), indicates more reasons for headache in the cases. Hypertension is reported in all but one of the cases against 6 cases only in the controls. Stress, depression, hypertension etc... can lead to headache and high consumption of analgesics.

General conclusions

1. AN was not diagnosed by the physician in charge.
One case (10002847) could be compatible with analgesic nephropathy but the data are incomplete and previous phenacetin intake is not excluded. The relationship between analgesic use and ESRD in this one case can be classified as “unassessable” according to the WHO criteria.
On the basis of the available data from the questionnaires there is no direct or indirect evidence of analgesic nephropathy in the remaining 21 cases, for whom the relationship is classified as “unlikely” according to the WHO criteria.
2. The reasons for taking analgesics in cases and controls are remarkably similar. Both report headache as the main reason. Both have in common a series of “neurotic complaints”, use of drugs, heavy smoking etc. suggesting a predisposition to abuse. When compared to the controls, the cases present in addition the diseases directly responsible for the ESRD such as diabetes, polycystic kidney disease and other vascular involvements known for their multiple and sometimes painful complications. These diseases, aggravated by multiple concomitant risk factors determined the evolution to ESRD and could provide additional reasons for taking analgesics. There is no reason to postulate an additional causal role of analgesics in the progression to ESRD.

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Table 1.

	All "analgesics"	Antipyretic analgesics	Difference	Difference
	Gram	Gram	Gram	%
20004437	34.118	30.812	3.306	9,69%
10000135	24.823	19.208	5.615	22,62%
10002759	15.521	14.933	588	3,79%
10002847	12.892	10.767	2.125	16,48%
10000010	12.560	12.318	242	1,93%
20004540	8.326	6.464	1.862	22,36%
10001264	7.746	7.524	222	2,87%
10001879	7.354	6.879	475	6,46%
10000460	6.803	6.129	674	9,91%
10001674	6.676	6.547	129	1,93%
10003427	6.482	6.436	46	0,71%
10000449	6.325	6.193	132	2,09%
20004531	6.180	5.092	1.088	17,61%
10002222	4.922	4.668	254	5,16%
10000115	4.211	4.082	129	3,06%
10002895	4.189	4.074	115	2,75%
20004549	3.699	2.658	1.041	28,14%
10001279	3.690	3.689	1	0,03%
10003593	3.628	3.628	0	0,00%
10001218	3.580	3.503	77	2,15%
10002925	3.380	3.380	0	0,00%
10000140	3.145	2.940	205	6,52%
Total	190.250	171.924	18.326	9,63%
Average	8648	7815	833	9,63%

Cases. Intake of “analgesics” as reported in the SAN Study and intake of “antipyretic analgesics”. (Data at Index date 1)

Table 2

	All "analgesics"	Antipyretic analgesics	Difference	Difference
	Gram	Gram	Gram	%
C10002215	16.888	16.188	700	4,14%
C10001491	7.765	156	7.609	97,99%
C10002044	6.569	6.502	67	1,02%
C20004560	6.209	6.209	0	0,00%
C10003784	5.566	4.742	824	14,80%
C10001539	4.638	4.624	14	0,30%
C10000721	4.453	3.701	752	16,89%
C10003797	4.388	4.320	68	1,55%
C20004629	4.036	3.907	129	3,20%
C10000626	4.035	4.035	0	0,00%
C10000865	4.002	3.554	448	11,19%
C10001265	3.480	3.480	0	0,00%
C20004377	3.364	3.364	0	0,00%
C10001314	3.145	2.964	181	5,76%
C10002619	3.141	3.112	29	0,92%
C10001722	3.120	1.715	1.405	45,03%
C20004892	2.904	2.904	0	0,00%
C20004525	2.819	2.602	217	7,70%
C20004730	2.760	2.754	6	0,22%
Total	93.282	80833	12449	13,35%
Average	4.910	4254	656	13,36%

Controls. Intake of “analgesics” as reported in the SAN Study and intake of “antipyretic analgesics”. (Data at index date 1).

Table 3

		SEX	Antipyretic analgesics intake								Reason for intake		Mono %
			Combi			Mono			Total Gram	Total n years			
			Gram	Tabl/day	Days/year	Gram	Tabl/day	Days/year					
10000135	Diab nephropathy	M				19.208	1 to 10	14 to 365	19.208	26	Headache, Paresthesia	100%	
10000460	Diab nephropathy	F	5.254	4	108	875	3	25	6.129	24	Headache	14%	
10001264	Diab nephropathy	M	803	3 to 4	72 to 208	6.721	2 to 10	156 to 208	7.524	24	Headache	89%	
10001279	Diab nephropathy	M				3.689	1 to 3	24 to 365	3.689	30	Headache. Thombosis prevention	100%	
10001879	Diab nephropathy	M				6.879	2 to 3	7 to 365	6.879	28	Phantom pain, headache	100%	
10002895	Diab nephropathy	M	1.390	2	12 to 30	2.682	2	12 to 90	4.074	30	Headache	66%	
10003427	Diab nephropathy	F				6.436	2 to 3	42 to 365	6.436	25	Pain. Headache	100%	
10002759	Diabetes, Cyclosp. tox?	M				14.933	2 to 10	6 to 365	14.933	14	Headache Arthralgia	100%	
10000010	Polycystic K D	F	12.318	15	365				12.318	6	Headache Prevention	0%	
10001674	Polycystic K D	M				6.547	2	365	6.547	19	Headache Arthralgia	100%	
20004540	Polycystic K D	M	6.464	3	144				6.464	34	Headache	0%	
10000115	Focal Glomer.	M	1.002	4	24	3.080	4	48	4.082	25	Headache Migraine	75%	
10000449	IgA nephritis	M				6.193	4 to 2	365	6.193	20	Headache. Thombosis prevention	100%	
10002925	Glomerulonephritis	M				3.380	3	365	3.380	7	Headache	100%	
10002222	Lupus Glomnephritis	F				4.668	2 to 4	36 to 104	4.668	19	Headache	100%	
20004549	Rec. Pyelonephritis?	F	2.658	3 to 4	12 to 30				2.658	15	Pain (NSAID)	0%	
20004437	Int.Neph. Heroin?	F	30.812	6	365				30.812	32	Headache	0%	
10000140	Renal infarction	M				2.870	2	4 to 147	2.940	20	Headache	98%	
10001218	Malignant Hypert.	M				3.503	3 to 4	182	3.503	17	Headache	100%	
10003593	Amyloidosis	F				3.628	2	156	3.628	25	Fever?	100%	
10002847	?	F	10.767	8	365				10.767	11	Headache	0%	
20004531	?	F	234	2	10	4.858	3	10 to 56	5.092	25	Cold	95%	
Total			71.702			100.150			171.924			58%	

Cases. Details of intake of antipyretic analgesics.

Table 4.

		SEX	Antipyretic analgesics intake						n years	Reason for intake	
			Combi			Mono					
			Gram	Tabl/day	Days/year	Gram	Tabl/day	Days/year			
10000135	Diab nephropathy	M				19.130	1 to 10	365	3 + 16	Headache, Paresthesia	3y Metamizol, 16y ASA
10001279	Diab nephropathy	M				2.953	1	365	17	Thombosis prevention	500 ASA
10001879	Diab nephropathy	M				6.601	2 to 3	365	5 + 11	Phantom pain	5y Metamizol, 11y ASA
10003427	Diab nephropathy	F				4.872	2	365	25	Pain	500 ASA
10002759	Diabetes, Cyclosp. tox?	M				14.823	2 to 10	365	8	Arthrosis	8y ASA 500, 7y Tramadol
10000010	Polycystic K D	F	12.318	15	365				6	Headache and Migraine	6y ASA-Paracetamol
10001674	Polycystic K D	M				6.547	2	365	19	Headache Arthralgia	ASA
10000449	IgA nephritis	M				6.193	2 to 4	365	20	Headache. Thombosis prevention	10y Propyphenazon, 17y ASA 500
10002925	Glomerulonephritis	M				3.380	3	365	7	Headache	ASA 500
20004437	Int.Neph. Heroin?	F	30.812	6	365				32	Headache	32 y ASA,Paracetamol.
											11y Propyphenazon, Paracetamol
10002847	?	F	10.767	8	365				11	Headache	Phenazon, ASA, Paracetamol

Cases. Patients with daily intake of antipyretic analgesics during more than 6 months.

Table 5

		SEX	Antipyretic analgesics intake								Reason for intake	Mono % of total
			Combi			Mono			Total Gram	Total n years		
			Gram	Tabl/day	Days/year	Gram	Tabl/day	Days/year				
C10000626	1954	M				4.035	1	365	4.035	23	Lower backpain	100%
C10000721	1953	M	3.319	3	48 to 52	382	3	9	3.701	29	Headache Backpain	10%
C10000865	1962	F				3.554	4 to 5	24 to 72	3.554	20	Migraine	100%
C10001265	1966	M				3.480	6	48	3.480	25	Headache	100%
C10001314	1963	F	1.064	2	84	1.900	3	168	2.964	15	Headache	64%
C10001491	1977	F				156	2 to 4	3 to 16	156	16	Headache	100%
C10001539	1958	F				4.624	1 to 2	20 to 365	4.624	17	Headache	100%
C10001722	1964	M				1.715	3 to 4	12 to 365	1.715	13	Backpain	100%
C10002044	1972	F	783	2	108	5.719	2 to 4	108 to 156	6.502	16	Headache Migraine	88%
C10002215	1956	F	6.002	2	365	10.186	1 to 3	365	16.188	19	Headache	63%
C10002619	1965	M				3.112	1 to 2	104 to 156	3.112	24	Migraine Arthralgia	100%
C10003784	1951	M				4.742	2	24 to 104	4.742	21	Headachee	100%
C10003797*	1960	F				4.320	4	144	4.320	16	Migraine	100%
C20004377	1956	M				3.364	3 to 5	21 to 30	3.364	33	Grip. Inf.	100%
C20004525	1959	M	1.296	4	108	1.306	2 to 4	24 to 108	2.602	28	Headache Inflamm.	50%
C20004560	1957	F				6.209	2 to 4	40 to 96	6.209	39	Headache	100%
C20004629	1953	M	231	1 to 2	5 to 84	3.676	1 to 2	3 to 120	3.907	16	Headache	94%
C20004730	1960	F				2.754	2	132	2.754	26	Headache	100%
C20004892	1957	M				2.904	3to 4	8 to 40	2.904	30	Headache	100%
Total			12.695			68.138			80.833			84%

**Controls. Details of intake of antipyretic analgesics.
(* Patient with pyelonephritis).**

Table 6

	Born	SEX	Antipyretic analgesics intake							Total n years	Reason for intake	
			Combi			Mono						
			Gram	Tabl/day	Days/year	Gram	Tabl/day	Days/year				
C10000626	1954	M				4.035	1	365	4.035	23	Lower backpain	Paracetamol
C10001539	1958	F				4.569	2	365	4.624	15	Headache	10 y Aspirin, 5 y Paracetamol
C10001722	1964	M				1.507	4	365	1.715	13	Backpain	Propyphenazon
C10002215	1956	F	6.002	2	365	10.186	1 to 3	365	16.188	19	Headache	19 y Thomapyrin, 19 y Aspirin.

Controls with daily intake of antipyretic analgesics during more than 6 months.

Table 7

		SEX	BORN	Antipyr. analg.	Years	Proteinuria		Echo					CT	Biopsy	
						Gram	<2g/24h	>2g/24h	Reduced size	Bumpy contour	Papillary calcificati	Ohne Befund			No interpretation
10000135	Diab nephropathy	M	1957	19.208	26		Yes	Not Done					No		
10000460	Diab nephropathy	F	1957	6.129	24	Unknown	Unknown				Yes		No	Yes	
10001264	Diab nephropathy	M	1967	7.524	24	Yes			Yes				Decreased parenchyma. Cysts	No	
10001279	Diab nephropathy	M	1952	3.689	30	Yes							Echogenic parenchyma. Unsharp limit parenchym-pyelon	No	
10001879	Diab nephropathy	M	1959	6.879	28	Yes							Parenchyma reduced. Density increased	No	
10002895	Diab nephropathy	M	1952	4.074	30		Yes	Yes		Yes				No	
10003427	Diab nephropathy	F	1955	6.436	25	Yes							Right nephrostomy. 1 cyst in left kidney	No	
10002759	Diabetes, Cyclosp. tox?	M	1958	14.933	14	Unknown	Unknown	Not Done					No		
10000010	Polycystic K D	F	1952	12.318	6	No	No						Kidney diameter 20 cm Multiple cysts up to 7cm	No	
10001674	Polycystic K D	M	1962	6.547	19	No	No						Congenital polycystic kidney	No	
20004540	Polycystic K D	M	1966	6.464	34	Unknown	Unknown						Polycystic kidney	No	
10000115	Focal Glomer.	M	1970	4.082	25		Yes							No	Yes
10000449	IgA nephritis	M	1965	6.193	20	Yes		Yes					Isolated cysts	No	Yes
10002925	Glomerulonephritis	M	1966	3.380	7		Yes	Yes						No	Yes
10002222	Lupus Glomnephritis	F	1968	4.668	19		Yes	Yes						No	Yes
20004549	Rec. Pyelonephritis?	F	1960	2.658	15	Yes		Yes						MRT	
20004437	Int.Neph. Heroin?	F	1958	30.812	32		Yes	Yes						No	Yes
10000140	Renal infarction	M	1958	2.940	20	No	No						Solitary kidney 16 cm High resistance in vessels	No	
10001218	Malignant Hypert.	M	1964	3.503	17	Yes							Normal size bilat. Verwaschener parenchym.Cyst r pyelon	No	Yes
10003593	Amyloidosis	F	1980	3.628	25	Unknown	Unknown	Yes						No	
10002847	?	F	1957	10.767	11	Unknown	Unknown	Yes	Yes					No	
20004531	?	F	1955	5.092	25		Yes	Yes						No	

Cases. Diagnostic data for AN.

Table 8

	Diagnosis	SEX	Vascular risk		BMI	Proteinuria		Smoking			Drugs
			Hypertensio	Arteriopathy		<2g/24hrs	>2g/24hrs	Ever	Still smokin	Pack/years	
10000135	Diab nephropathy	M	Yes		23,29		Yes	Yes	Yes	33	
10000460	Diab nephropathy	F		Yes	33,95	Unknown		Yes		4,5	
10001264	Diab nephropathy	M	Yes	Yes	22,41	Yes					Cocain
10001279	Diab nephropathy	M	Yes		29,63	Yes		Yes		18	
10001879	Diab nephropathy	M	Yes		28,58	Yes		Yes		57,5	
10002895	Diab nephropathy	M	Yes	Yes	19,34		Yes	Yes	Yes	18	
10003427	Diab nephropathy	F	Yes		31,20	Yes					
10002759	Diabetes, Cyclosp. tox?	M	Yes	Yes	23,37	Unknown		Yes	Yes	20	
10000010	Polycystic K D	F	Yes		26,26			Yes	Yes	15,5	
10001674	Polycystic K D	M	Yes		25,93						
20004540	Polycystic K D	M	Yes		22,63	Unknown					
10000115	Focal Glomer.	M	Yes		21,43		Yes	Yes	Yes	18,75	
10000449	IgA nephritis	M	Yes		36,59	Yes					
10002925	Glomerulonephritis	M	Yes		30,78		Yes				
10002222	Lupus Glomnephritis	F	Yes		23,34		Yes				
20004549	Rec. Pyelonephritis?	F	Yes		22,28	Yes		Yes		13,5	Cannabis
20004437	Int.Neph. Heroin?	F	Yes		23,14		Yes	Yes	Yes	60	Heroin, Cocain
10000140	Renal infarction	M	Yes	Yes	32,41			Yes		14	
10001218	Malignant Hypert.	M	Yes		24,49	Yes		Yes	Yes	11	
10003593	Amyloidosis	F	Yes		14,82	Unknown					
10002847	?	F	Yes		33,02	Unknown		Yes	Yes	28	
20004531	?	F	Yes		25,22		Yes	Yes		0,25	

Cases. Risk factors

Table 9

	Diagnosis	SEX	Vascular risk		BMI	Proteinuria	Smoking			Drugs
			Hypertension	Arteriopathy			Ever	Still smoking	Pack/years	
C1000626		M			30,19	unknown	Yes	Yes	5	
C1000721		M			24,22	unknown	Yes	Yes	31	
C1000865	Cystitis	F			19,84	unknown				
C1001265		M			25,15	unknown	Yes	Yes	13,5	
C1001314		F			25,99	unknown				
C1001491		F			26,17	unknown	Yes		8,5	
C1001539		F	Yes		23,53	unknown	Yes	Yes	25	
C1001722		M	Yes		41,91	unknown	Yes	Yes	44	Hash
C1002044		F			36,73	unknown				
C1002215		F			24,30	unknown	Yes	Yes	15	
C1002619		M		Yes	19,49	unknown	Yes	Yes	18	
C1003784	TBC	M			24,30	unknown	Yes	Yes	41	
C1003797	Cystitis.Pyelonephritis.	F			27,06	unknown				
C20004377		M	Yes		28,09	unknown	Yes	Yes	32	
C20004525		M			22,68	unknown	Yes	Yes	43,5	Hash, Ecstasy
C20004560		F	Yes		22,52	unknown				?
C20004629		M	Yes		22,59	unknown				
C20004730		F			27,94	unknown				
C20004892		M	Yes		27,78	unknown				

Controls. Risk factors.

Table 10

	All "analgesics" Gram.	Antipyretic analgesics	Years usus	F9,6	F10	F11	F20 Häufiger Beschwerden										F21 Über längere Z				F22 Prob		F26 Hauptgrund	
				Arteriopathy	Psych.-neuro Stör	Hypertension	Magen-Darmbeschw	Herz-Kreislaufbesch	übelkeit, Erbrechen	Depression	Angst	Schlafst.	Schläfrigkeit	Reizbarkeit	Stress	Essstörungen	Rheumatische B	Chron Ruckenschm.	Migraine	Headache	Stress	Vorbeug.Kopfschm		
10000135	24.823	19.208	26			Yes	Yes							Yes							Yes		Headache	Grippe
10000460	6.803	6.129	24	Yes			Yes	Yes	Yes		Yes	Yes	Yes	Yes				Yes	Yes			Headache	Migraine	
10001264	7.746	7.524	24	Yes		Yes	Yes						Yes			Yes			Yes			Headache	Backpain,	
10001279	3.690	3.689	30			Yes		Yes	Yes	Yes	Yes		Yes			Yes	Yes					Headache	Thromb profyl	
10001879	7.354	6.879	28			Yes	Yes		Yes				Yes						Yes			Phantompain	Headache	
10002895	4.189	4.074	30	Yes		Yes								Yes				Yes	Yes			Headache	Grippe	
10003427	6.482	6.436	25			Yes		Yes					Yes			Yes	Yes		Yes			Rheuma		
10002759	15.521	14.933	14	Yes	Yes	Yes										Yes	Yes					Arthralgia	Backpain,	
10000010	12.560	12.318	6		Yes	Yes				Yes							Yes			Yes		Headache	Migraine	
10001674	6.676	6.547	19			Yes						Yes				Yes	Yes	Yes	Yes		Yes	Rheuma	headache	
20004540	8.326	6.464	34		Yes	Yes				Yes	Yes											Headache	Grippe	
10000115	4.211	4.082	25			Yes	Yes							Yes				Yes	Yes		Yes	Headache		
10000449	6.325	6.193	20			Yes	Yes		Yes			Yes							Yes			Headache	Grippe	
10002925	3.380	3.380	7			Yes	Yes						Yes	Yes					Yes	Yes		Headache		
10002222	4.922	4.668	19			Yes			Yes			Yes				Yes		Yes			Yes	Headache	Cold	
20004549	3.699	2.658	15			Yes																Headache	Cold	
20004437	34.118	30.812	32			Yes	Yes						Yes		Yes	Yes	Yes					Headache	Grippe	
10000140	3.145	2.940	20	Yes		Yes																Headache	Cold	
10001218	3.580	3.503	17			Yes								Yes				Yes	Yes			Headache	Fever	
10003593	3.628	3.628	25			Yes	Yes					Yes	Yes					Yes	Yes			Fever		
10002847	12.892	10.767	11			Yes														Yes		Heavy Pain	Headache	
20004531	6.180	5.092	25			Yes												Yes				Dysmen.	Gripp	

Cases. Complaints and reasons for using analgesics.

Table 11

	All "analgesics" Gram	Antipyr. Analges. Gr.	Years usus	F9,5	F10	F11	F20 Häufiger Beschwerden										F21 Über längere Z				F22 Prob		F26 Hauptgrund				
				Arteriopathy	Psych.-neuro Stör	Hypertension	Magen-Darmbeschw	Herz-Kreislaufbesch	übelkeit, Erbrechen	Depression	Angst	Schlafst.	Schläfrigkeit	Reizbarkeit	Stress	Essstörungen	Rheumatische B	Chron Ruckenschm.	Migraine	Headache	Stress	Vorbeug.Kopfschm					
C10000626	4.035	4.035	23															Yes	Yes							Low backpain	
C10000721	4.453	3.701	29									Yes							Yes		Yes					Headache	Backpain
C10000865	4.002	3.554	20																	Yes						Migraine	
C10001265	3.480	3.480	25																							Headache	Grippe
C10001314	3.145	2.964	15										Yes						Yes	Yes	Yes					Headache	
C10001491	7.765	156	16		Yes				Yes			Yes		Yes					Yes	Yes	Yes	Yes	Yes			Headache	
C10001539	4.638	4.624	17			Yes													Yes	Yes	Yes					Headache	
C10001722	3.120	1.715	13			Yes						Yes	Yes	Yes					Yes							Backpain	
C10002044	6.569	6.502	16																	Yes	Yes					Headache	Migraine
C10002215	16.888	16.188	19									Yes	Yes	Yes							Yes	Yes	Yes			Headache	
C10002619	3.141	3.112	24	Yes			Yes	Yes				Yes	Yes		Yes			Yes	Yes	Yes	Yes	Yes				Migraine	Arthralgia
C10003784	5.566	4.742	21																Yes	Yes	Yes	Yes				Headache	
C10003797	4.388	4.320	16		Yes		Yes	Yes	Yes	Yes	Yes							Yes	Yes	Yes	Yes		Yes			Migraine	
C20004377	3.364	3.364	33		Yes	Yes				Yes	Yes	Yes	Yes	Yes							Yes					Grip. Inf.	
C20004525	2.819	2.602	28				Yes					Yes	Yes	Yes	Yes	Yes	Yes				Yes	Yes				Headache	Inflamm.
C20004560	6.209	6.209	39			Yes																				Grippe	Headache
C20004629	4.036	3.907	16		Yes	Yes	Yes				Yes								Yes		Yes	Yes	Yes			Headache	Dysequilibrium
C20004730	2.760	2.754	26				Yes												Yes	Yes						Headache	
C20004892	2.904	2.904	30			Yes																				Headache	

Controls. Complaints and reasons for using analgesics.