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Special Feature

Chronic kidney disease as cause of cardiovascular morbidity and mortality

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Abstract

To make an evidence-based evaluation of the relationship between kidney failure and cardiovascular risk, we reviewed the literature obtained from a PubMed search using pre-defined keywords related to both conditions and covering 18 years (1986 until end 2003). Eighty-five publications, covering 552 258 subjects, are summarized. All but three studies support a link between kidney dysfunction and cardiovascular risk. More importantly, the association is observed very early during the evolution of renal failure: an accelerated cardiovascular risk appears at varying glomerular filtration rate (GFR) cut-off values, which were $\geq$60 ml/min in at least 20 studies. Many studies lacked a clear definition of cardiovascular disease and/or used a single determination of serum creatinine or GFR as an index of kidney function, which is not necessarily corresponding to well-defined chronic kidney disease. In six studies, however, chronic kidney dysfunction and cardiovascular disease were well defined and the results of these confirm the impact of kidney dysfunction. It is concluded that there is an undeniable link between kidney dysfunction and cardiovascular risk and that the presence of even subtle kidney dysfunction should be considered as one of the conditions necessitating intensive prevention of this cardiovascular risk.

Introduction

In a landmark publication in 1974, Lindner *et al.* [1] first pointed out that patients treated by chronic renal replacement therapy are exposed to cardiovascular problems and suffer from accelerated and severe atheromatosis. More recently, the extent of the problem was re-emphasized by Foley *et al.* [2]. According to these authors, already a 5-fold increase in cardiovascular mortality risk is present in dialysis patients older than 75 years, but, more importantly, cardiovascular mortality is increased approximately 375 times in patients aged between 25 and 35 years [2]. In young adults dialysed for several years during childhood or adolescence, an exceptionally high prevalence of coronary calcifications is found for their age range [3]. In stage 5 chronic kidney disease (CKD) (end-stage), the overall risk for stroke increases 6-fold [4]. In patients with chronic kidney dysfunction, cardiovascular disease (CVD) is twice as common as in the general population and it advances at twice the rate [5]. In an essentially non-dialysed population from the UK with a serum creatinine (SCrea) $\geq$1.7 mg/dl ($\geq$150 μmol/l), standardized mortality was increased 2-fold *vs* the general population in those aged >65 years, 12-fold between the ages of 50 and 64 and even 36-fold between the ages of 16 and 49 [6].

Cardiac events in the dialysis population are characterized by a substantial mortality [7–9]. The expected remaining life time is shortened by $\geq$50% [10]. Life expectancy at the start of dialysis is comparable to, if not worse than, that of many cancers at the time of their diagnosis [11]. Even after successful revascularization for peripheral vascular disease, local recurrence rate is high and early [12].

These observations have an important socio-economic impact. In a multivariate analysis in dialysis patients, angina and peripheral vascular disease were among the most prominent reasons for hospitalization [13]. By the end of 2001, the dialysis population worldwide consisted of close to 1 500 000 patients [14], while it increases by $\geq$7% each year [14]. End-stage

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renal disease (ESRD) treatment is expected to cover, worldwide, 2 million patients in 2005 and 2.5 million in 2010. Even if these are seemingly small patient groups, the costs of dialysis, especially if indirect (hidden) costs related to the cardiovascular complications are included, make the socio-economic burden dramatic. More importantly, however, the problem starts long before dialysis is needed and this extends the population at risk $\geq$100-fold [15] (see below).

Our present study showed that (i) in the presence of an increased SCrea or a decreased glomerular filtration rate (GFR), morbidity and mortality because of CVD are markedly increased and vascular degradation is accelerated; (ii) the process of cardiovascular damage starts very early during progression in well-defined CKD, long before the dialysis stage is reached; (iii) the link between kidney dysfunction and CVD is an important global epidemiological entity with an extent comparable to the link observed between CVD and diabetes mellitus; (iv) apart from traditional cardiovascular risk factors, non-traditional factors specifically related to kidney failure *per se*, are very likely to play a causative role; (v) adequate preventive measures against CVD should be started early during the natural history of kidney dysfunction, but their application is hampered by the incorrect interpretation of renal function parameters, the delayed identification of kidney failure and the (too) late referral of patients with kidney dysfunction.

The primary aim of the present study was to offer a broad review of available studies referring to an enhanced cardiovascular risk in chronic renal failure patients. The second aim was to define at which stage of renal dysfunction cardiovascular problems were at first perceived.

Subjects and methods

To appreciate the relationship between changes in parameters of kidney function and cardiovascular risk, a literature search (PubMed) was undertaken with as keywords: 'cardio-vascular or cardiovascular or vascular or atheromatosis or atherosclerosis or atherogenesis or arteriosclerosis or stroke or outcome or survival or mortality' on one hand and 'renal or kidney or uremia or uraemia' on the other. This search was repeated at regular intervals (every 3 months) to update the database, with 31 December 2003 as final publication date for inclusion. In addition, the reference list of the retrieved publications was screened in order to add further missing publications to the database. This approach finally emanated in the retrieval of 85 publications, covering the period 1986–2003 (18 years in total).

The issue of kidney dysfunction as a cardiovascular risk marker was underscored recently in a comprehensive statement [16]. Another recent publication was restricted to reports published in 2003 [17]. Two seminal reviews reported on, respectively, 19 and 16 publications that are included in the present survey [18,19]. The present review extends the previous work by an almost complete retrieval of publications resulting in the identification of 40 additional references [6,20–58].

The retrieval was limited to studies containing at least one population with renal failure which was not yet on dialysis.

In order to avoid selection bias, we intentionally opted to include all retrieved studies, such as (I) studies using renal function as a continuous variable; (II) studies using sCrea as an index of renal function; (III) studies not adjusting for other cardiovascular risk factors; (IV) studies with overall mortality rather than cardiovascular mortality as an endpoint. All these characteristics are specified in Tables 1–3.

Likewise, no selection of cardiovascular endpoints was pursued and studies were included based on all possible endpoints, such as stroke, transient ischaemic attacks, myocardial infarction; coronary heart disease; unstable angina; coronary intervention (both surgical or percutaneous); admission to the coronary unit; vascular stenosis; atheroembolic disease; and cardiac death.

Studies were classified according to whether they had been conducted in patients with proven CVD, hypertension or chronic heart failure. Studies conducted in the elderly (>65 years old) were classified separately if patients were selected because of this age rather than because of one of the above-mentioned other risk factors together with age. A last separate set of studies was defined as having been undertaken in entirely unselected populations. These were still subdivided in two separate subgroups, one in known chronic renal failure patients and one based on one single renal function determination.

The primary endpoints of the studies contained in this survey are cardiovascular morbidity and mortality as well as overall mortality; in studies evaluating overall and cardiovascular mortality together, both showed remarkably parallel trends [47,55,59–65]. Those studies specifically focusing on cardiovascular morbidity or mortality are highlighted in bold in the corresponding tables (Tables 1–3).

Studies with as endpoints non-cardiovascular events or events only partially or indirectly related to CVD [66–79] and studies in transplant recipients were excluded [80–82], although also these studies convincingly pointed to a relation with kidney dysfunction (17 studies covering 366 720 subjects). The following were considered as only partially or indirectly related to CVD: ventilation time, length of stay in the coronary care unit, post-operative stay, need for blood transfusion, bleeding, overall adverse events, cardiac arrhythmia or immediate in-hospital mortality following vascular surgery or intervention, acute coronary syndrome, general or heart valve surgery or admission to the coronary care unit.

Studies on the relationship of proteinuria/albuminuria with CVD [83] were also considered to be beyond the scope of this survey, although such a relationship is increasingly being recognized [16].

For those studies determining relative mortality risk (RR) in function of GFR, those two factors were correlated with each other in a separate analysis. A separated regression analysis was undertaken for those studies in which RR was close to 1 and in those with an overt increased mortality. The confluence point of the two regression lines was plotted. Data referring to clearance analysis by Cockroft and Gault or by the modification of diet in renal disease (MDRD) formula and data from studies in which adjustments were made for other cardiovascular risk factors were identified by specific symbols and analysed separately. Data from 24 studies were submitted to this analysis.

Table 1. Studies in populations selected on the presence of proven CVD: study characteristics

Author	Year	Selection criterion	*n*	Age[a]	F-U[b]	Cut-off clear[c]	Cut-off SCrea[d]	Adjust[e]
Friedman [32]	1991	STR	492	>59	1.5		120.0 (1.36)	Yes
Matts [61]	**1993**	**MI**	**417**	**51**	**>7.0**		**80.0 (0.90)**	**Yes**
Nygard [33]	1997	CHD	587	62	4.6		120.0 (1.36)	Yes
Gottlieb [34]*	1998	MI	201752	73	2.0		124.0 (1.40)	Yes
Anderson [84]	**1999**	**CABG**	**3902**	**64**	**0.1**		**132.6 (1.50)**	**No**
McCullough [85]**	2000	CCU	9544	63	6.7	81.5[f,g]		Yes
Brooks [101]	**2000**	**CI**	**3610**	**62**	**5.0**	**ND[h]**	**ND[h]**	**Yes**
Rubenstein [86]	**2000**	**PCI**	**3334**	**68**	**4.6**		**132.6 (1.50)**	**No**
Beattie [87]**	**2001**	**MI**	**[1724]**	**63**	**8.3**	**63.1[f,g]**		**Yes**
Hemmelgarn [88]	2001	PCA	16989		2.0		203.3 (2.30)	Yes
Schlipak [89]	**2001**	**CHD**	**2763**	**67**	**4.1**	**60.0[f]**	**106.1 (1.20)**	**Yes**
Szczech [90]	2001	CI	59576	65	3.0		221.0 (2.50)	Yes
Ting [35]	**2001**	**PCI**	**2626**	**67**	**2.0**		**265.2 (3.00)**	**Yes**
Asinger [36]	**2001**	**PCI**	**154**	**60**	**2.0**		**177.0 (2.00)**	**No**
Al Suwaidi [60]	**2002**	**CHD**	**37925**	**72**	**0.5**	**70.0[f]**		**Yes**
Szczech [59]	**2002**	**CHD**	**3608**	**63**	**7.0**		**132.6 (1.50)**	**Yes**
Best [91]	2002	PCI	5327	69	3.0	70.0[f]		Yes
Beddhu [92]***	**2002**	**PCA**	**8600**	**63**	**8.0**	**57.0[i]**		**Yes**
Gruberg [93]	**2002**	**PCI**	**5084**	**67**	**1.0**	**Cont[f,j]**	**132.6 (1.50)[k]** **124.0 (1.40)[l]**	**Yes**
Januzzi [37]	**2002**	**CCU**	**1537**	**67**	**Tran[m]**	**75.0[f]**		**No**
Wright [94]	2002	MI	3106	73	5.0	75.0[f]		Yes
Walsh [95]	2002	MI	483	71	1.0	**Cont[f,g,j]**	132.6 (1.50)	Yes
McCullough [53]	**2002**	**CP**	**817**	**64**	**0.1**	**47.0[f,g]**		**Yes**
Sorensen [99]	2002	MI	6252	69	6.0	55.0[f]		Yes
Shlipak [100]*	2002	MI	[130099]	77	1.0	55.0[f]	132.6 (1.50)	Yes
Reis [102]	**2002**	**CHD**	**784**	**60**	**Tran[m]**	**80.0[f]**	**106.1 (1.20)**	**Yes**
Kaplan [57]	**2002**	**MI**	**2677**	**64**	**3.4**		**120.0 (1.36)**	**Yes**
Gruberg [96]	2003	CHD	1265	71	1.0	50.0[f]		Yes
Reinecke [97]	2003	PCI	1049	63	3.2		115.0 (1.30)	Yes
Wison [98]	**2003**	**CHD**	**2503**	**63**	**Tran[m]**	**76.8[f,n]**		**Yes**
Zebrack [38]***	**2003**	**PCA**	**[1484]**	**65**	**3.0**	**60.0[i]**		**Yes**
Reddan [39]	2003	CHD	4584	63	5.0	90.0[f]		No
Keeley [40]	2003	CHD	4758	64	7.0	60.0[i]		Yes
Conlon [41]	2003	RAS	1235		4.0		Cont[j]	Yes
Naidu [42]	2003	PCI	4602	64	1.0		Increased[o]	Yes
HPSCG[p] [43]	**2003**	**OAD**	**20536**	**63**	**5.0**		**130.0 (1.47)[k]** **110.0 (1.25)[l]**	**No**
Sadeghi [52]	**2003**	**PCI**	**1933**	**65**	**1.0**	**60.0[f]**		**Yes**
Langston [54]	2003	MI	508	74	1.0	60.0[f]		Yes
Scolari [55]	2003	AERD	95	71	7.0	50.0[i]		Yes
Hillege [56]	**2003**	**MI**	**298**	**59**	**1.0**	**81.0[f]**		**Yes**

[a]Age: mean value, mean of means or medians of different groups, or mean of ranges; lower limit if preceded by '>'; [b]F-U: mean/median follow-up in years; shortest reported follow-up if preceded by '>'; [c]cut-off clear: highest clearance value [creatinine clearance or equivalent of GFR (ml/min)] for which a deterioration in cardiovascular status was observed *vs* the control ('normal kidney function') group; [d]cut-off SCrea: lowest sCrea value [μmol/l (mg/dl)] for which a deterioration in cardiovascular status was observed *vs* the control ('normal kidney function') group; [e]adjust: adjustment for comorbid factors; [f]Cockroft–Gault; [g]normalized per 72 kg body weight; [h]ND: renal failure not defined; [i]MDRD formula; [j]kidney function parameter(s) used as continuous variable; [k]men; [l]women; [m]trans-sectional study; [n]normalized per 1.73 m^2; [o]increased: the cut-off for kidney failure is an 'increased' sCrea without further specification; [p]Heart Protection Study Collaborative Group [Occlusive Arterial Disease without known diabetes (14 573 subjects) or diabetes mellitus (5963 subjects)].

STR, stroke; MI, myocardial infarction; CHD, coronary heart disease, unstable angina; CCU, admission to the coronary unit; CI, coronary intervention (both CABG and PCI); CP, chest pain; RAS, renal artery stenosis; OAD, occlusive arterial disease; AERD, atheroembolic renal disease.

*–***Both studies were undertaken in the same population or database (*Cooperative Cardiovascular Project; **Henry Ford Hospital Cardiac Intensive Care Unit Database; ***Intermountain Heart Study). Only the study with the highest number of patients is taken into account for calculating the total number of analysed subjects; the omitted numbers are cited in square brackets.
Studies in bold have a cardiovascular endpoint.

It should be realized that there are a number of limitations to our present approach, such as the unlimited introduction of publications into the database without selection and the descriptive aim pursuing an encyclopaedic listing of related studies rather than aiming at an in-depth pathophysiological interpretation of the reported data. Furthermore, the approach did not follow the rigid conditions requested for a meta-analysis.

Table 2. Studies in populations selected on the presence of at least one cardiovascular risk factor or of chronic heart failure, or on age: study characteristics

Author	Year	Selection criterion	*n*	Age[a]	F-U[b]	Cut-off clear[c]	Cut-off SCrea[d]	Adjust[e]
A. Cardiovascular risk factor								
Bulpitt [20]	1986	HT	5451	51	4.3		Cont[j]	Yes
Schulman [63]	**1989**	**HT**	**10940**	**50**	**5.0**		**150.4 (1.70)**	**Yes**
Flack [64]	**1993**	**HT**	**4830**	**46**	**6.0**		**Cont[j]**	**Yes**
Rossing [24]	1996	DM	939	39	10.0		Cont[j]	Yes
Pahor [25]	**1998**	**HT**	**4336**	**72**	**4.0**		**101.7 (1.15)**	**No**
Mann [105]	**2001**	**DM[q]**	**9287**	**67**	**4.5**	**65.0[f]**	**124.0 (1.40)**	**Yes**
Ruilope [62]	**2001**	**HT**	**18591**	**63**	**3.8**	**60.0[f]**	**132.6 (1.50)**	**Yes**
Schillaci [106]	**2001**	**HT**	**1829**	**51**	**4.0**		**83.0 (0.94)[k]** **70.0 (0.79)[l]**	**Yes**
Wang [31]	**2001**	**HT**	**1880**	**67**	**3.0**		**80.0 (0.90)**	**Yes**
De Leeuw [108]	**2002**	**HT**	**4688**	**70**	**4.1**		**90.0 (1.02)**	**Yes**
B. Chronic heart failure								
Packer [21]	1991	CHF	1088	64	1.5		115.0 (1.30)	No
Madsen [22]	1994	CHF	190	66	2.1		121.0 (1.37)	No
Spinar [23]	1996	CHF	300	58	1.0		Cont[j]	Yes
Feenstra [26]	1998	CHF	2246	77	0.4		115.0 (1.30)	Yes
McAlister [27]	1999	CHF	566	66	1.4		130.0 (1.47)	Yes
Opasich [28]	2000	CHF	3327	64	1.0		221.0 (2.50)	Yes
Dries [103]*	**2000**	**LVD**	**[5834]**	**63**	**2.8**	**60.0[f]**		**Yes**
Cowie [29]	**2000**	**CHF**	**220**	**76**	**1.3**		**Cont[j]**	**Yes**
Hillege [104]	2000	CHF	1906	65	3.3	76.0[f]		Yes
Al Ahmad [30]*	2001	LVD	6635	60	2.8	75.0[i,n]	221.0 (2.50)	Yes
Mahon [107]	2002	CHF	585	65	2.6	63.9[f]		Yes
Kearney [109]	2002	CHF	553	63	5.0		111.0 (1.26)	Yes
McClellan [110]	2002	CHF	646	76	1.0		132.6 (1.50)[k] 124.0 (1.40)[l]	Yes
C. Aged								
Damsgaard [44]	1990	Age	216	67	6.0		Cont[j]	Yes
Manolio [111]**	**1996**	**Age**	**[5201]**	**74**	**3.3**		**132.6 (1.50)**	**Yes**
Alcorn [45]**	**1996**	**Age**	**[4575]**	**>65**	**5.0**		**80.0 (0.90)**	**Yes**
Fried [112]**	1998	Age	[5201]	73	5.0		106.1 (1.20)	Yes
Bursztyn [46]	1999	Age	448	70	6.5		Cont[j]	Yes
Schlipak [113]**	**2002**	**Age**	**5808**	**75**	**Tran[m]**	**60.0[f]**	**132.6 (1.50)[k]** **115.0 (1.30)[l]**	**Yes**
Manjunath [65]**	**2003**	**Age**	**[4893]**	**73**	**4.3**	**90.0[i,n]**		**Yes**
Fried [47]**	**2003**	**Age**	**[5808]**	**74**	**7.3**		**97.3 (1.10)**	**Yes**

[a–e, i–n]For explanation refer to Table 1; [q]diabetes mellitus and/or CVD.

HT, hypertension; DM, diabetes mellitus; CHF, chronic heart failure; LVD, left ventricular dysfunction.

*Both studies were undertaken in the same population or database (SOLVD). **All six studies were undertaken in the same population or database (Cardiovascular Health Study). Only the study with the highest number of patients is taken into account for calculating the total number of analysed subjects; the omitted numbers are cited in square brackets.
Studies in bold have a cardiovascular endpoint.

Results

Studies in populations selected on the presence of proven CVD

Data are presented in Table 1.

In this section, 40 studies are included, representing 425 312 patients [32–43,52–57,59–61,84–102]. Of these studies, 19/40 (47.5%) had overall mortality as an endpoint, compared with 21/40 (52.5%) studies with cardiovascular morbidity or mortality as an endpoint. The cardiovascular conditions used to define this population were coronary heart disease in nine studies (22.5%), myocardial infarction in 10 studies (25.0%), percutaneous coronary intervention (PCI) in eight studies (20.0%), post-coronary angiography (PCA) in three studies (7.5%), admission in the coronary care unit and coronary intervention [both PCI and coronary artery bypass graft (CABG)], each in two studies (5.0%), and renal artery stenosis, chest pain, occlusive arterial disease, atheroembolic renal disease, left CABG and stroke, each in one study (2.5%).

Considering these studies together, median age was 64 years (range: 51–77 years) and median follow-up time was 3 years (range: 0.1–8.3 years). The median cut-off value of renal function linked to an increased cardiovascular risk was 60.0 ml/min for GFR or one of its surrogates (calculations according to Cockroft and Gault or one of the MDRD formulae) (highest value: 90.0 ml/min) [39] and 1.47 mg/dl (131.3 μmol/l) for

Table 3. Studies in entirely unselected populations: study characteristics

Author	Year	Selection criterion	*n*	Age[a]	F-U[b]	Cut-off clear[c]	Cut-off SCrea[d]	Adjust[e]
A. Studies in known chronic renal failure								
Jungers [48][r]	**1997**	**–**	**147**	**65**	**5.4**	**50.0[f,n]**		**Yes**
Jungers [49][r]	**1998**	**–**	**980**	**63**	**Nor[s]**	**50.0[f,n]**		**No**
Levin [50][r]	**2001**	**–**	**313**	**56**	**Tran[m]**	**75.0[f]**		**No**
Landray [120][r]	**2001**	**–**	**369**	**62**	**Tran[m]**	**44.0[f]**	**130.0 (1.47)**	**No**
Sarnak [121][r]	**2002**	**–**	**1342**	**50**	**Tran[m]**	**Cont[j,t]**		**No**
Drey [6]	2003	–	1076		5.5		300.9 (3.40)	Yes
B. Studies based on a single determination of renal function								
Wannamethee [114]	**1997**	**–**	**7690**	**50**	**14.7**		**116.0 (1.31)**	**Yes**
Culleton [115]	1999	–	2837	54	11.0		132.6 (1.50)[u]	Yes
Garg [116]	**2002**	**–**	**2352**		**16.1**		**122.0 (1.38)[k]** **104.0 (1.18)[l]**	**Yes[v]**
Muntner [117]	**2002**	**–**	**6354**	**55**	**14.0**	**90.0[i]**		**Yes**
Henry [118]	**2002**	**–**	**631**	**64**	**8.7**	**72.2[i,n]**		**Yes**
Manjunath [119]*	**2003**	**–**	**15350**	**56**	**6.2**	**90.0[i,n]**		**Yes**
Abramson [51]*	**2003**	**–**	**[13716]**	**54**	**Nor[s]**	**60.0[f]**		**Yes**
Jurkovitz [58]*	**2003**	**–**	**[13329]**	**54**	**Nor[s]**		**132.6 (1.50)[k]** **106.1 (1.20)[l]**	**Yes**

[a–e, i–n]For explanation refer to Table 1; [r]these studies contained no real control group, but incidence of CVD was strikingly higher than in the general population; [s]risk rates normalized per number of observation years; [t]GFR; [u]significant relationship with kidney failure only in men; [v]significant relation disappeared after adjustment for traditional risk factors.
*All three studies were undertaken in the same population or database (ARIC). Only the study with the highest number of patients is taken into account for calculating the total number of analysed subjects; the omitted numbers are cited in square brackets.
Studies in bold have a cardiovascular endpoint.

SCrea [lowest value: 0.90 mg/dl (80 µmol/l); values in men and women combined] [61]. The median of the values linked to an increased cardiovascular risk for the MDRD formula (57 ml/min) was slightly lower than for the Cockroft and Gault formula (65.5 ml/min), reflecting the divergent clinical and mathematical bases for both formulae. The results of 34 studies (85.0%) were adjusted for other cardiovascular risk factors.

The first publication for this specific subgroup was published in 1991, when Friedman *et al.* [32] described that survival was more compromised with a higher SCrea, in 492 elderly subjects post-stroke.

The study by Shlipak *et al.* [89] published in 2001 and the one by Reis *et al.* [102] were restricted to women and showed the same trend as studies covering both genders.

The study by Szczech *et al.* [59] as well as the study conducted by the Heart Protection Study Collaborative Group [43] evaluated patients with and without diabetes mellitus separately, but showed parameters of kidney failure to be a discriminating factor in both arms.

This section contains five study populations including more than 20 000 subjects, all convincingly underscoring a link of signs of enhanced cardiovascular damage with parameters corresponding to a decrease of renal function [34,43,60,90,100]. Two of these studies contained more than 100 000 subjects, but were conducted in the same study population [34,100].

Studies in populations selected on the presence of at least one traditional cardiovascular risk factor, including old age, or of chronic heart failure

Data are presented in Table 2.

In this section, 31 studies are included, representing 87 505 patients [20–31,44–47,62–65,103–113].

Table 2 is subdivided into three sections: (A) patients selected because of the presence of at least one cardiovascular risk factor (either hypertension or diabetes mellitus) (10 studies in 62 771 subjects; respectively, two and eight studies with diabetes and hypertension as determinant); (B) patients selected because of the presence of chronic heart failure or left ventricular dysfunction (13 studies in 18 262 subjects); and (C) patients selected because of old age (eight studies in 6472 subjects). Aged patients were confined to this part of the survey (corresponding to section C of Table 2) if no additional selection criterion was present. In Table 1 and sections A and B of Table 2, patient groups of similar old age are considered, but in these studies, patients were selected in addition because of the presence of at least one vessel lesion, one cardiovascular risk factor or chronic heart failure [22,25–27,29,31,34,35,37,54,55,60,86,89,91,93–96,99, 100,105,108,110].

Of the 31 studies contained in this section, 16/31 (51.6%) had overall mortality as an endpoint, compared with 15/31 (48.4%) studies with cardiovascular morbidity or mortality as an endpoint. Considering these studies together, median age was 66.0 years

(range: 39–77 years) and median follow-up time was 3.9 years (range: 0.4–10.0 years). The median cut-off value of renal function for showing increased cardiovascular risk was 63.9 ml/min for GFR or one of its surrogates (highest value: 90.0 ml/min) [65] and 1.3 mg/dl (115 μmol/l) for SCrea [lowest value overall: 0.9 mg/dl (80 μmol/l); in women: 0.79 mg/dl (70 μmol/l)] [31,45,106]. The results of 28 studies (90.3%) were adjusted for other cardiovascular risk factors.

To the best of our knowledge, the very first study to describe a relationship between parameters of kidney function and CVD is included in this section and was published by Bulpitt *et al*. in 1986 [20].

The largest population in this section was reported by Ruilope *et al*. ($n = 18\,790$) [62] in a reanalysis of the Hypertension Optimal Treatment (HOT) Study.

In the study by Opasich *et al*. [28], patients with chronic congestive heart failure and a SCrea >2.5 mg/dl (>220 μmol/l) had a markedly higher mortality. This is the only study in this section where the difference in mortality was not significant, possibly because of the low number of patients with parameters corresponding to kidney failure (2.8% of the population; $n = 93$).

Studies in unselected populations

Data are presented in Table 3.

In this section, 14 studies are included, representing a total of 39 441 patients [6,48–51,58,114–121]. Of note, in all studies reported in Tables 1 and 2 and in seven of the 14 studies in Table 3, the enrolment in different strata is based on a single determination of SCrea, GFR or surrogate of GFR. These levels do not necessarily correspond to different degrees of severity of chronic kidney dysfunction, as they might have been influenced by instant factors, such as (de)hydratation, drug intake (non-steroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors), recent radio-contrast investigations, etc. The seven studies of this type in Table 3 are classified under 'kidney dysfunction not defined' (35 214 subjects). Six studies covering 4227 subjects are based on defined CKD and are considered separately [6,48–50,120,121].

Considering these studies together, the median age of the patients was 55.5 years (range: 50–65 years) (i.e. markedly younger than in the previous sections A and B) and the median follow-up time was 9.85 years (range: 5.4–16.1 years) (i.e. markedly longer than in the previous sections). The median cut-off value of renal function linked to increased cardiovascular risk was 72.2 ml/min for GFR or one of its surrogates (highest value: 90.0 ml/min) [117,119] and 1.42 mg/dl (126.0 μmol/l) for SCrea [lowest value overall: 1.31 mg/dl (116 μmol/l); in women: 1.18 mg/dl (104 μmol/l)] [114,116]. The results of 10 studies (71.4%) were adjusted for other cardiovascular risk factors.

In the study by Culleton *et al*. [115], an impact of mild changes in renal function parameters on overall mortality was found only in men. This partial gender-related lack of significance might, in part, be attributed to the small number of patients with renal dysfunction in the gender strata ($n = 270$ for women).

Garg *et al*. [116] undertook an analysis of the data from the first National Health and Nutrition Examination Study (NHANES I) in 2352 adults. The hazard ratio related to moderate indices of kidney failure lost significance after correction for traditional risk factors. This is the only study included in the present survey, where a loss of significance after adjustment is observed.

When in more recent studies GFR was used as a renal function index, a relation of cardiovascular risk with kidney failure parameters was corroborated each time [117–119].

Also in the study by Abramson *et al*. [51], GFR-defined chronic renal failure resulted in a higher incidence of stroke, but most strikingly if combined with anaemia. Similar results were published, based on the same population, for risk of coronary events [58]. Of note, in at least four other studies, however, adjustment for anaemia did not neutralize the statistical weight of renal failure [47,54,65,85].

Overall summary of the data

Overall, 552 258 subjects were considered in 85 studies. All studies based on larger population sizes (>5000 subjects) [20,30,34,43,47,51,58,60,62,63,85,88,90–93, 99, 100,103,105,111–114,117,119] and/or based on adequate parameters of kidney function (GFR) [20,23, 24,29,30,37–41,44,46,48–56,60,62,64,65,85,87,91,92,94, 96,98–100,103,104,107,113,117–119,121] showed a significant relationship between the markers of renal dysfunction and overall mortality and/or cardiovascular morbidity or mortality.

One of the most relevant findings of this analysis is that the increase in cardiovascular risk occurs very early during the evolution of chronic renal failure (Figure 1), irrespective of the method of determination of renal function.

In 40 studies (Table 1), subjects were selected because of the presence of at least one cardiovascular abnormality, whereas in 31 other studies (Table 2), subjects were selected because of the presence of at least one traditional risk factor, including old age, or chronic heart failure. One might argue that this type of selection does not relate to kidney dysfunction *per se*. Of note, however, most of the patients attending nephrology clinics have similar comorbidities. In addition, results were similar in 14 studies in unselected populations (Table 3). In these populations, the hidden presence of the above-mentioned risk factors is not excluded, however. The results in these low cardiovascular risk populations with well-defined CKD point in the same direction of enhanced risk related to kidney dysfunction as the studies in the remaining populations. However, the link is somewhat less straightforward.

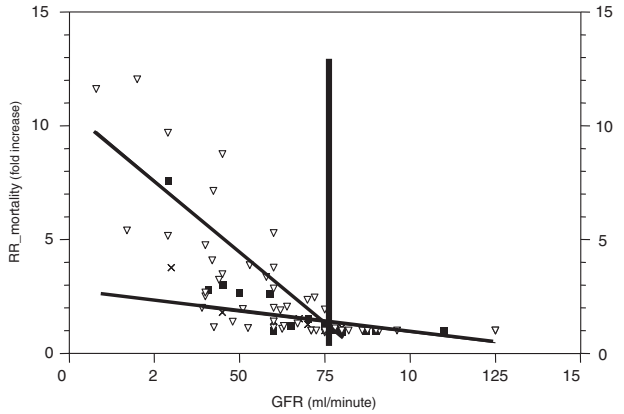

Fig. 1. Relative risk of mortality (RR_mortality) *vs* GFR. Twenty-four studies were included in this analysis. The points plotted in the graph correspond to the values available in the publications included in the present review. The majority of studies used Cockroft and Gault formulae to estimate clearance (open triangles). Studies using the MDRD formula are indicated by the closed squares and unadjusted studies by the crosses. Two different parts of the graph can be identified clearly: one constituted of those points related to an increased mortality (which are associated with a lower renal function) and those with a RR of mortality close to 1 (which are associated with a nearly normal renal function). Both clusters follow a linear distribution. The linear regression has been calculated separately for these two areas of the graph and the regression lines plotted [respectively: $y = (0.1262x) + 10.77$, $r = 0.645$, $P < 0.001$; $y = (-0.1018x) + 2.727$, $r = 0.574$, $P < 0.004$]. The confluence point of the obtained regression lines represents the level at which a change in the slope is observed: to a given decrease in GFR corresponds a higher increase in RR mortality. This threshold point corresponds to a GFR of 75 ml/min, supporting the results reported in the publications analysed and indicating that an intensive follow-up and prevention of CVD should be aimed at very early when renal function decays. Recalculation of the threshold points with only studies based on Cockroft and Gault, or only with adjusted studies, also resulted in values between 74 and 76 ml/min.

It is of note that studies from all over the world came to the same conclusion. In addition to Europe and Northern America, which are the most common geographical areas where this type of study is conducted, reports from China [31], Israel [46] and New Zealand [32] are also included. Hence, the relation between kidney dysfunction and cardiovascular risk seems to be universal.

Some of the enclosed studies were not undertaken primarily to evaluate the connection between kidney dysfunction and cardiovascular problems, but were e.g. evaluations of drug effects, which amongst other elements contained a comparison between patients with and without kidney dysfunction [20–22, 26,28,33,34,37,43]. Also, these studies came to the same conclusions as those specifically considering the relationship of kidney dysfunction and cardiovascular risk.

It might be argued that even if in total more than 550 000 subjects were considered in the 85 publications reported, the fraction of patients with kidney dysfunction contained in these studies might be much smaller, if not irrelevant. For that reason, the specific number of subjects with parameters corresponding to kidney dysfunction was also considered. For this subanalysis, overall, data from 74 studies were available. Among those, 26% of subjects in total conformed with preset parameters corresponding to kidney dysfunction, defined as the stratum or the sum of strata characterized by a higher sCrea and/or a lower GFR than the reference (control) group. If we accept that the vast majority of these study populations are recruited among subjects with at least one known cardiovascular problem [Tables 1 and 2 (section B)] or cardiovascular risk factor (Table 2, sections A and C), it might be hypothesized from the above that approximately one-quarter of these populations additionally suffer from a certain degree of renal dysfunction which only adds to their cardiovascular risk.

Of note, 71 of the 85 studies under consideration were adjusted for other cardiovascular risk factors. In only one study was the significant weight of renal failure lost [116].

Discussion

Our present study showed that (i) in the presence of an increased SCrea or a decreased GFR, morbidity and mortality because of CVD are markedly increased and vascular degradation is accelerated; (ii) the process of cardiovascular damage starts very early during progression in well-defined CKD, long before the dialysis stage is reached; (iii) the link between kidney dysfunction and CVD is an important global epidemiological entity with an extent comparable to the link observed between CVD and diabetes mellitus; (iv) apart from traditional cardiovascular risk factors, non-traditional factors specifically related to kidney failure *per se*, are very likely to play a causative role; and (v) adequate preventive measures against CVD should be started early during the natural history of kidney dysfunction, but their application is hampered by the incorrect interpretation of renal function parameters, the delayed identification of kidney failure and the (too) late referral of patients with kidney dysfunction.

Methodological considerations regarding the analysed literature

A substantial proportion of the cited studies are post-hoc analyses of interventional trials or observational studies. In this section, methodological aspects related to study design and choice of outcome variables are discussed. These more likely obscured or weakened rather than amplified the association of impaired renal function with CVD.

Retrospective analyses of the effect of a variable (in this case a renal function parameter) on the endpoints are generally underpowered, because these studies were not designed to detect such effects. Since renal failure *per se* enhances certain traditional risk factors, adjusted risks or hazard ratios may overcorrect

for these factors and equally will underestimate a true relationship.

In most studies, a single determination of a surrogate marker for GFR is studied. A well-known problem with single determinations is regression dilution bias, a statistical phenomenon whereby the extreme values of high and low GFR (or surrogates) are more likely to over- or underestimate the real values; thus, once more attenuating the relationship of increasing cardiovascular risk with decreasing renal function. The frequently used surrogate markers for GFR, such as sCrea, may be increased by multiple instant factors, whereas an artefactual decrease is rare and in essence only related to spurious cases of fluid overload. This unequal distribution of errors may increase the scatter in the relationship with cardiovascular risk. Attempts to overcome this problem by calculating GFR causes the difficulty that known cardiovascular risk factors, such as age, weight and gender, are included a second time as predictor variables, so that the use of classical multivariate methods probably overcorrects for these factors. Categorization (renal failure or not) of a continuous variable (GFR) generally further decreases the power to detect a relationship with the outcome variable. Additionally, most studies a priori assume a linear relationship between GFR and CVD risk. The lack of exploration of non-linear relationships and interactions between chronic renal failure and other factors may result in a larger scatter (and weaker relationship) of the data when fitting the statistical model.

It is known that creatinine values vary across clinical laboratories and that all estimates of GFR from creatinine equations (Cockroft and Gault or MDRD formula) result in biased estimates if the sCrea assay used in a specific study is calibrated differently from that in the study which validated the method for estimating GFR. Systematic bias is relatively unimportant in investigations of the relationship between CVD and renal function within a study, but hampers comparison across studies and limits the interpretation of specific GFR cut-off points.

In addition, it should be realized that, apart from these drawbacks, sCrea is only a crude index of renal function and that GFR values, even if calculated, are more valid. For that reason, the method of renal function estimation was clearly specified in the tables. Studies based on sCrea were not excluded, however, to avoid selection bias (see 'Subjects and methods').

Studies considering mortality instead of cardiovascular morbidity as the endpoint may also lose power to detect a relationship, since mortality rates are much lower than cardiovascular incidence rates. Moreover, when all-cause mortality is considered rather than cardiovascular mortality, the relationship may become blurred by non-cardiovascular deaths.

Altogether, multiple aspects related to methodological design may influence the results in a way that they tend to weaken rather than strengthen the relationship between renal dysfunction and CVD. That such a strong relationship is nevertheless found only further corroborates the impact of this pathophysiological association.

Practical epidemiological considerations

After it had been established that dialysis patients are prone to accelerated atheromatosis [1], it has been suggested more recently that the cardiovascular system becomes affected in renal failure well before the stage of dialysis is reached [122]. This suggestion is strongly corroborated by this present survey. The smallest impairments in renal function associated with a significant increase in cardiovascular risk are a GFR of 90 ml/min/1.73 m^2 [39,65,117,119] and a sCrea of 0.90 mg/dl (80 μmol/l) (Figure 1) [31,45,61]. The median cut-off GFR in each of Tables 1–3 was situated at $\geq$60 ml/min/1.73 m^2, which corresponds to a loss of kidney function by a maximum 50%.

This problem of cardiovascular risk associated with kidney dysfunction, hence, affects a larger section of the general population than until recently suspected (Table 4). Based on recent data collected in the United States, ~4.7% of the overall population suffers from a deterioration of GFR by $\geq$50% [123]. The vast majority of those (92%) has a GFR between 60 and 30 ml/min (CKD stage 3), of whom >90% are non-diabetics [123]. One should be careful with extrapolating these data from the USA to the rest of the world, but, unfortunately, to the best of our knowledge, no data from outside the USA are available as yet. However, even if the number of patients at risk would be substantially lower outside the USA, which is rather unlikely, the group size of potentially affected individuals seems to be not much different from those attributed to diabetes mellitus [124,125]. In spite of this, the cardiovascular risk associated with kidney dysfunction is not always recognized as such by society and even not by the nephrological community. Extending this problem to a population which is much larger than the group currently treated by dialysis also extends the socio-economic implications (Table 4) and underscores the urgent need for intervention to detect kidney dysfunction and to intensify the management of CVD when it is present.

Most patients with kidney dysfunction also bear one or more traditional cardiovascular risk factors and a major pathophysiological role might be attributed to these factors [126,127]. They undeniably have a negative clinical impact and should, if possible, be treated appropriately. In several correlation analyses, however, the statistical weight of traditional risk factors was weak to absent [50,105,128,129]. While submitting the uraemia population to a Framingham risk analysis, the real observed risk is far greater than the calculated one based on the traditional risk factors [121,128,130,131], which hardly differs from the risk in the general population [121,128,131]. Statistical adjustment for a host of comorbid factors in 71 studies does not neutralize the relation of cardiovascular

Table 4. Potential subjects at risk[a]

	Worldwide	USA	Europe
Overall population	6 000 000 000	389 000 000	800 000 000
GFR < 60 ml/min (4.7%)[b]	282 000 000	18 283 000	37 600 000
Stage 5 (ESRD[c])	1 750 000	335 000	350 000

[a]Approximative figures; [b]based on epidemiological data collected in the USA [123]; [c]based on worldwide data for 2001 [14] – ESRD corresponds to the need for renal replacement therapy (according to the current classifications: stage 5).

risk with renal failure [6,20,23,24,26–35,38,40–42, 44–48,51–65,85,87–115,117–119].

The risk factors which were most frequently adjusted were age (69/71 studies), gender (56), diabetes mellitus (55), vascular disease (52), blood pressure (49), left ventricular dysfunction (49), medication (39), smoking (36) and lipid status (32). Therefore, it is likely that non-traditional risk factors (as yet identified as well as non-identified) are at play as well.

Prominent candidates in such a role are uraemic retention solutes [128], which accumulate because the kidneys fail to eliminate them. Their accumulation in kidney failure might impose a mechanistically similar damaging effect as the one provoked by glycation products in diabetes [132]. Interestingly, several supportive studies suggest a relation between uraemic retention solutes and CVD: oxidative stress products [133–137]; pro-coagulant factors [48,135,138]; interleukin-6 [139]; phosphate and calcium–phosphate product [140–143]; asymmetric dimethylarginine [144,145]; parathyroid hormone [146,147]; neuropeptide Y [148]; homocysteine [48,149–154]. Also, sympathetic overactivity plays a prominent pathophysiological role [155].

However, at present, the evaluation of the factors responsible for increased CVD is far from complete and has been concentrated on those factors that had already been incriminated in the general population. It seems very much appropriate to extend our studies to those factors specific for renal failure. Recently identified but until then unsuspected compounds, such as phenylacetic acid, indoxyl sulphate, guanidine, methylguanidine, guanidinosuccinic acid, guanidinoacetic acid and *p*-cresol [156–158], underscore that many responsible compounds might have, as yet, gone unrecognized. Therefore, a more systematic evaluation and classification of known uraemic solutes [159] should be undertaken, to allow the development of more directed therapeutic approaches.

This review was conducted to make an objective evaluation in how many available studies in the literature the link between kidney dysfunction and CVD was confirmed. Confirmation was obtained from 85 studies covering more than 550 000 subjects, clearly showing this relationship, independent of geographic or ethnic factors. Differences in cardiovascular risk are already present at the very early phase of renal impairment; those can only be detected by sensitive methods of renal function assessment (GFR), which are therefore necessary and fully justified.

The epidemiological features observed bring this problem to the highest level of importance, along with other major conditions, such as diabetes mellitus and hypertension.

Much remains to be done, however, to improve the prevention of CVD associated with renal failure. The main aspects, with a predictable positive impact, that require our particular attention include:

a. Sensibilization regarding the problem and improvement of the awareness about its existence.
b. Inclusion in the follow-up of patients with cardiovascular risk of sensitive parameters assessing renal function and in patients with kidney dysfunction of parameters of cardiovascular risk.
c. Improvement of the interpretation of parameters of kidney (dys)function.
d. Sensibilization of the general population and general practitioners and improvement of collaboration between all healthcare providers to facilitate a timely referral of these patients to the nephrologist.
e. Application of the rules of secondary prevention in the presence of even moderate renal dysfunction.

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References

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