

Analgesic Nephropathy and Renal Replacement Therapy in Australia: Trends, Comorbidities and Outcomes

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Background and objectives: This study examined age-specific incidence and prevalence of renal replacement therapy attributed to analgesic nephropathy from 1971 through 2005 and adjusted comorbidity prevalence and survival of patients who had analgesic nephropathy and were on renal replacement therapy (compared with control subjects without diabetes).

Design, setting, participants, & measurements: This retrospective cohort study, using data from the Australia and New Zealand Dialysis and Transplant registry, included all patients who were aged 35 to 84 yr and started long-term renal replacement therapy in Australia from 1971 through 2006.

Results: Of 31,654 incident renal replacement therapy patients, 10.2% had analgesic nephropathy. Incidence and prevalence of renal replacement therapy attributed to analgesic nephropathy decreased earlier and faster among younger (age <55 yr) patients. Prevalence of analgesic nephropathy among 75- to 84-yr-old renal replacement therapy patients is still increasing. Compared with control subjects without diabetes, comorbidities (coronary artery, cerebrovascular, peripheral vascular, and chronic lung diseases) were more prevalent among patients with analgesic nephropathy at renal replacement therapy start. All-cause, cardiovascular, infection, and cancer mortality were higher among patients who had analgesic nephropathy and were on renal replacement therapy. For both comorbidities and mortality, the associations were stronger in younger patients.

Conclusions: Trends in renal replacement therapy attributed to analgesic nephropathy differed by age. Patients with analgesic nephropathy have more comorbidities and poorer survival on renal replacement therapy, especially among younger patients.

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Classical analgesic nephropathy (AN) is characterized by reduced GFR, pyuria, hematuria, proteinuria, tubular dysfunction, hypertension, and papillary necrosis (1). Associated features include urinary tract transitional cell carcinomas (TCC) (2), accelerated atherosclerosis, peptic ulcer disease, and pigmentation and premature aging of the skin.

AN is caused by long-term ingestion of combination analgesics that contain phenacetin or its main metabolite, paracetamol, in combination with aspirin, caffeine, or codeine (3,4). Combination analgesic use was prevalent in the 1960s and 1970s in Australia, parts of Europe (Scandinavia, Belgium, and Switzerland), and Canada. In Australia, combination analgesics were easily available as Vincent's or Bex powders (phenacetin with aspirin and caffeine). Regular use exceeded 10% of the population in some states (5), especially among middle-aged women with chronic headache (2,6–8). Phenacetin was removed from combination analgesic powders in 1967 (Vincent's) and 1975 (Bex), respectively and totally banned in 1977. Over-

the-counter sales of all combination analgesics were banned in 1979 (9).

Although a Swiss cohort study documented higher risks for cardiovascular morbidity and mortality in combination analgesic users (10), it is uncertain whether this was due to their chronic kidney disease. The impact on the survival of patients who have AN and are on renal replacement therapy (RRT) is also unclear. In this study, we used data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry to examine for (1) trends in the incidence and prevalence of RRT attributed to AN during the period 1971 through 2005; (2) comorbidity prevalence at RRT start, comparing patients with and without AN; and (3) survival on RRT, comparing patients with AN and other nondiabetic nephropathy.

Materials and Methods

The ANZDATA Registry has been collecting data on long-term RRT patients from all renal units in Australia since 1963. All patients who started long-term RRT at age 35 to 84 yr in Australia from 1971 to 2006 were included in this study.

Trends

We calculated age-specific incidence and prevalence rates of RRT using annual population figures (1971 through 2005) from the Australian Bureau of Statistics. Age was divided into 10-yr age groups (35 to 44, 45 to 54, 55 to 64, 65 to 74, and 75 to 84).

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Comorbidities

Prevalence of comorbidities at RRT start were compared between patients with and without AN. Nonskin cancers were divided into TCC and non-TCC. Data on smoking history (current, ex-, or nonsmoker) and comorbidities (coronary artery, cerebrovascular, peripheral vascular, and chronic lung disease) at RRT start were collected only for patients who started RRT from April 1, 1991. These were based on reports from each nephrology unit with no further verification. Comorbidities were coded as present or absent with no indications of severity or duration. There were no major changes in classification methods during the study period. Analyses of cigarette smoking and comorbidities were limited to patients without diabetes only.

Survival on RRT

Patients were followed up to death; loss to follow-up; or December 31, 2006. Survival of patients with AN was compared with patients with nondiabetic nephropathy and without AN. Analysis was limited to the first 5 yr of RRT to ensure comparability among patients who started in different eras, because patients with AN were more likely to be from earlier eras and hence have longer follow-up. Patients who started RRT after 2000 were excluded to ensure that analyses were based on actual 5-yr survival data. Cause-specific mortality (cardiovascular, infection, cancer, withdrawal, and other causes) was also examined.

Comparisons of categorical outcome variables were by χ^2 test and multivariate logistic regression. Comparisons of continuous outcome variables were by *t* test. Overall and cause-specific patient survival, with and without censoring at first transplantation, was analyzed using Cox proportional hazard models. Multivariate models were adjusted for age at RRT start, era of RRT start, gender, and indigenous status. Interactions

with age, era, and gender were specifically sought for. Analyses of comorbidity were also adjusted for smoking history (current, ex-, or nonsmoker) and its interaction was sought for. Statistical analyses were performed using Stata 10 (StataCorp, College Station, TX). *P* < 0.05 was considered statistically significant. Point estimates of rates, odds ratios, and hazard ratios are presented with 95% confidence intervals.

Results

Demographic Characteristics

The study population included 31,654 patients; their demographic characteristics are shown in Table 1. Numbers of incident RRT patients are shown in Table 2. The proportion of incident RRT patients attributed to AN decreased markedly during this period. Overall, 10.2% of incident RRT was attributed to AN. AN patients were older (*P* < 0.001) and more likely to be female (*P* < 0.001). The age difference was greater in recent eras: In 1971 through 1975, mean ages of patients with and without AN were 47.9 and 47.7 yr, respectively, whereas in 2001 through 2006, they were 62.0 and 70.4 yr, respectively. The proportions of women among patients with and without AN and were 78 and 37%, respectively, in 1971 through 1975 and 83 and 39%, respectively, in 2001 through 2006.

Incidence and Prevalence

Figure 1 shows incident RRT rates from non-AN causes increasing during 1971 through 2005, whereas that from AN

Table 1. Characteristics of patients aged 35 to 84 yr starting RRT in Australia, 1971 through 2006^a

Characteristic	AN	Non-AN	<i>P</i>
<i>n</i> (%)	3231 (10.2)	28423 (89.8)	
Female (%)	84	38	<0.001
Age (yr; mean [SD])	59.9 (10.3)	58.7 (12.5)	<0.001
Indigenous (%)	0.8	7.7	<0.001
Era of RRT start (%)			
1971 through 1975	9	3	
1976 through 1980	15	5	
1981 through 1985	17	6	
1986 through 1990	16	10	<0.001
1991 through 1995	17	15	
1996 through 2000	14	23	
2001 through 2006	13	38	
Comorbidities at RRT start ^b			
diabetes (%)	11	38	<0.001
coronary artery (%) ^c	51	34	<0.001
cerebrovascular (%) ^c	20	13	<0.001
peripheral vascular (%) ^c	31	18	<0.001
chronic lung (%) ^c	26	16	<0.001
current/ex-smokers (%) ^c	51	54	<0.001
History of cancer at RRT start			
transitional cell (%)	5.5	1.1	<0.001
other nonskin cancers (%)	5.9	7.9	<0.001

^aAN, analgesic nephropathy; RRT, renal replacement therapy.

^bPatients who started RRT from April 1, 1991 only.

^cPatients without diabetes only.

Table 2. Number of incident RRT patients in Australia 1971 through 2005, by age at RRT start and cause of end-stage kidney disease

Year	Age (yr)					Total
	35 to 44	45 to 54	55 to 64	65 to 74	75 to 84	
1971 through 1975						
non-AN	295	417	147	12	0	871(75%)
AN	92	160	43	3	0	298(25%)
1976 through 1980						
non-AN	354	493	346	88	2	1283(72%)
AN	96	207	164	23	1	491(28%)
1981 through 1985						
non-AN	460	517	580	236	19	1812(77%)
AN	51	168	246	71	3	539(23%)
1986 through 1990						
non-AN	576	689	880	626	68	2839(85%)
AN	10	103	243	138	9	503(15%)
1991 through 1995						
non-AN	737	965	1226	1213	252	4393(89%)
AN	3	63	218	218	32	534(11%)
1996 through 2000						
non-AN	925	1303	1509	1954	835	6526(94%)
AN	0	20	125	226	81	452(6%)
2001 through 2005						
non-AN	1235	1938	2483	2935	2108	10,699(96%)
AN	2	9	64	201	138	414(4%)

decreased since the early 1980s. The trends varied by age. Non-AN incidence rates were stable among 35- to 44-yr-olds, increased gradually among 45- to 54-yr-olds and more rapidly among older patients. AN-related incidence rates started declining from the mid-1970s among 35- to 44-yr-olds, from the early 1980s among 45- to 54-yr-olds, and from the early 1990s among 55- to 65-yr-olds. Among 65- to 74-yr-olds, incidence increased until the mid-1990s before decreasing from 44.0 per million (1996) to 24.3 per million (2005). Among 75- to 84-yr-olds, incidence started rising only in the early 1990s to 33.0 per million (1999) before declining to 26.2 per million (2005).

The prevalence of RRT patients attributed to AN started decreasing only from the early 1990s (Figure 2). Again, the decline started later among older patients, and prevalence among 75- to 84-yr-olds is still increasing. Overall, 20.0, 21.6, 12.8, 5.2, and 3.5% of RRT patients in 1971, 1981, 1991, 2001, and 2005, respectively, were attributed to AN.

Comorbidities at RRT Start

Among 22,656 patients who started RRT from April 1, 1991, patients with AN were less likely to be current or ex-smokers (51 versus 54%; $P = 0.03$); however, after adjustment for demographic factors, the association with smoking varied by gender ($P = 0.006$ for interaction): AN was associated with smoking in women (adjusted odds ratio [aOR] 1.79; 95% confidence interval [CI] 1.57 to 2.04; $P < 0.001$) but not in men (aOR 0.93; 95% CI 0.70 to 1.25; $P = 0.64$). Among 14,554 (64%) patients who did not have diabetes and

started RRT from April 1, 1991, patients with AN had higher prevalence of coronary artery disease, cerebrovascular disease, peripheral vascular disease, and chronic lung disease (Table 1) at RRT start. In multivariate models, the associations were stronger among younger patients ($P < 0.05$ for interaction with age), as shown in Table 3. Associations with chronic lung disease also varied by smoking status ($P = 0.002$ for interaction), being stronger for current smokers (aOR 2.12; 95% CI 1.47 to 3.05; $P < 0.001$) than ex-smokers (aOR 1.38; 95% CI 1.10 to 1.74; $P = 0.006$) or nonsmokers (aOR 1.37; 95% CI 1.02 to 1.83; $P = 0.03$). There were no significant interactions with gender or era of RRT start.

At RRT start, patients with AN were more likely to have had TCC (5.1 versus 1.1%; $P < 0.001$), even after adjustment for demographic factors (aOR 5.51; 95% CI 4.34 to 6.99; $P < 0.001$); however, they were less likely to have had other nonskin cancers (5.9 versus 7.9%; $P < 0.001$), even after adjustment for demographic factors (aOR 0.82; 95% CI 0.70 to 0.97; $P = 0.02$). When additional adjustment for smoking was made for patients who started RRT from April 1, 1991, the association with TCC remained (aOR 4.77; 95% CI 3.58 to 6.35; $P < 0.001$) but that with other nonskin cancers was no longer statistically significant (aOR 0.87; 95% CI 0.71 to 1.06; $P = 0.18$). Among patients without TCC before RRT start, incidence (per 1000 patient-years) of new TCC was 5.5 (95% CI 4.5 to 6.8) and 1.0 (95% CI 0.9 to 1.2) in patients with and without AN, respectively. This association remained significant after adjustment for demographic

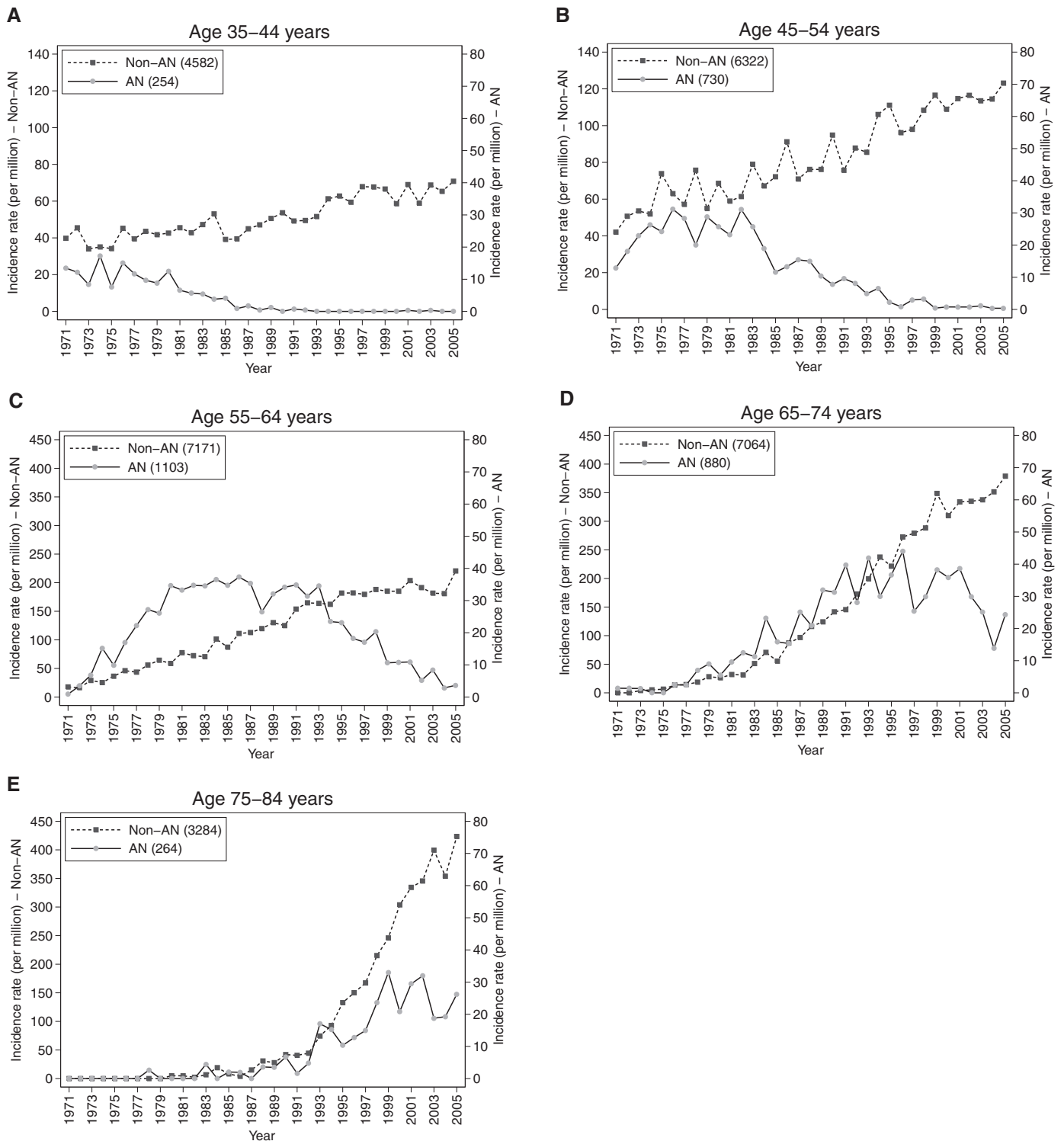


Figure 1. Age-stratified incidence of new renal replacement therapy (RRT) patients from analgesic nephropathy (AN) and other causes in Australia, 1971 through 2005. Note different scales of y axes.

factors (aOR 4.61; 95% CI 3.35 to 6.34; $P < 0.001$). As shown in Figure 3, after the first 3 mo of RRT, unadjusted incidence rates (per 1000 patient-years) in patients with AN was fairly constant for the first 10 yr (0 to 5 yr 5.7 [95% CI 4.4 to 7.5]; 5 to 10 yr 6.0 [95% CI 4.0 to 9.1]) and was somewhat lower beyond 10 yr (3.9 [95% CI 2.0 to 7.4]). Incidence rates in patients without AN decreased

slightly with time on RRT (0 to 5 yr 1.2 [95% CI 1.0 to 1.4]; 5 to 10 yr 0.8 [95% CI 0.5 to 1.1]; >10 yr 0.7 [95% CI 0.4 to 1.2]).

Survival on RRT

All 17,343 (84%) patients with nondiabetic nephropathy of the 20,541 who started RRT from 1971 through 2000 were

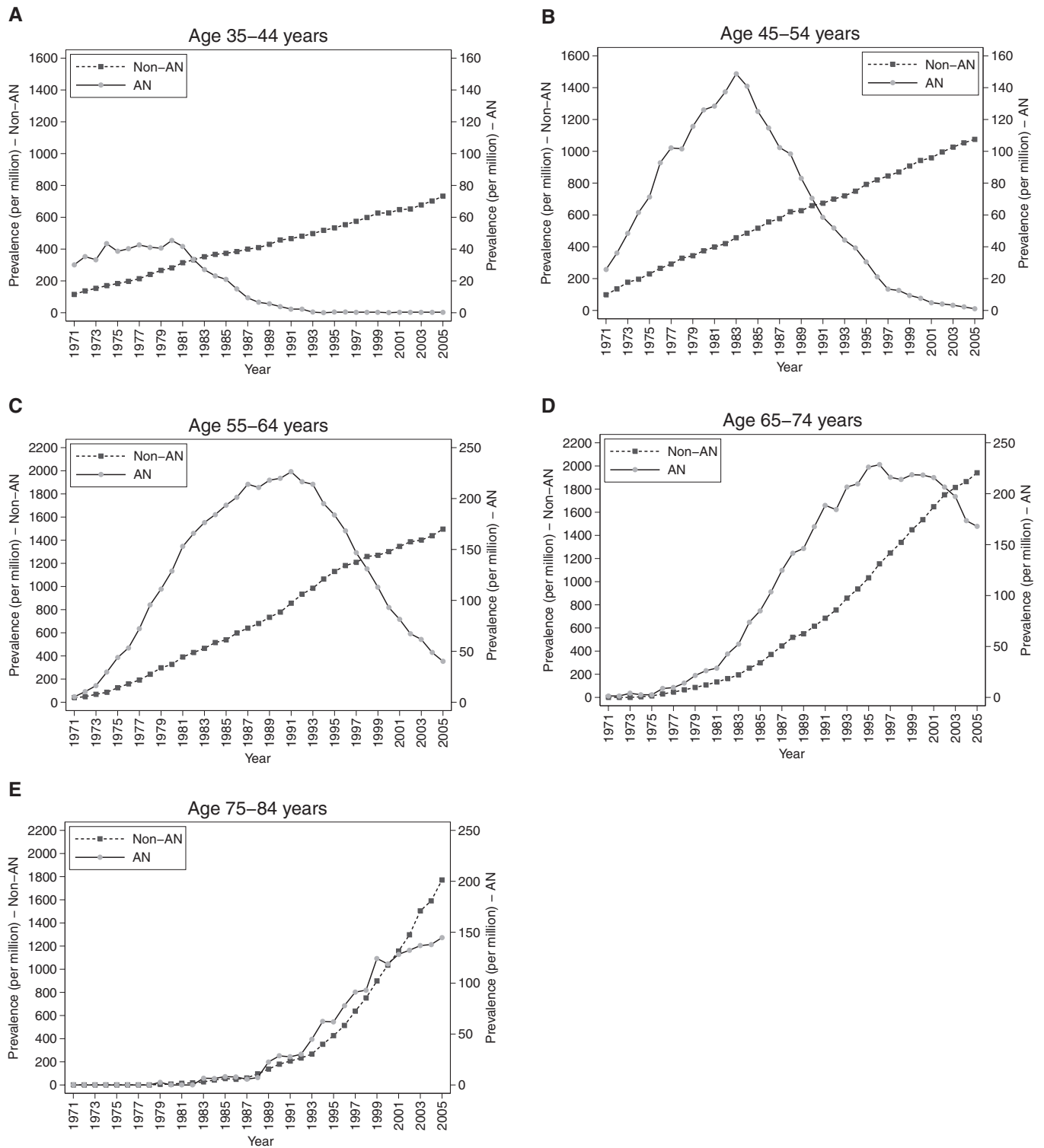


Figure 2. Age-stratified prevalence of RRT patients from AN and other causes in Australia, 1971 through 2005. Note different scales of y axes.

included in analyses of 5-yr patient survivals, with 8290 deaths. Unadjusted survival rates for patients with and without AN were 70 and 77%, respectively, at 2 yr and 40 and 54%, respectively, at 5 yr from RRT start. Overall, AN was associated with poorer survival, particularly among younger patients ($P < 0.001$ for interaction with age; Table 4).

The causes of death in the first 5 yr were cardiovascular (48%), infections (16%), cancer (8%), withdrawal (15%), and other causes (13%). The risks for different causes of death varied significantly ($P < 0.001$ for interaction with cause of death). AN was associated with deaths from cardiovascular disease, infection, cancer, and other causes but not from treat-

Table 3. Adjusted odds ratio, stratified by age, of patients with AN and without diabetes for comorbidities at RRT start (compared with control subjects without diabetes), 1991 through 2006^a

Age (yr)	Adjusted odds ratio (95% CI)			
	Coronary Artery Disease (n = 5075)	Cerebrovascular Disease (n = 1929)	Peripheral Vascular Disease (n = 2725)	Chronic Lung Disease (n = 2420)
35 to 84 (n = 14,503)	1.69 (1.48 to 1.93) ^b	1.22 (1.04 to 1.44) ^c	1.54 (1.33 to 1.78) ^b	1.48 (1.27 to 1.73) ^b
35 to 54 (n = 4614)	4.19 (2.57 to 6.82) ^b	2.44 (1.20 to 4.99) ^b	3.73 (2.09 to 6.66) ^b	3.71 (2.20 to 6.23) ^b
55 to 64 (n = 3228)	1.86 (1.45 to 2.40) ^b	1.58 (1.13 to 2.20) ^b	2.08 (1.56 to 2.79) ^b	1.48 (1.09 to 1.99) ^c
65 to 74 (n = 4196)	1.38 (1.14 to 1.68) ^b	1.06 (0.84 to 1.35)	1.22 (0.98 to 1.52)	1.33 (1.05 to 1.68) ^c
75 to 84 (n = 2465)	1.59 (1.18 to 2.14) ^b	1.15 (0.82 to 1.62)	1.45 (1.06 to 1.98) ^c	1.33 (0.91 to 1.94)

^aAdjusted for age, era, gender, indigenous status, and smoking history. Significant interactions with age for all comorbidities. n = number of patients in multivariate analyses. CI, confidence interval.

^bP < 0.01.

^cP < 0.05.

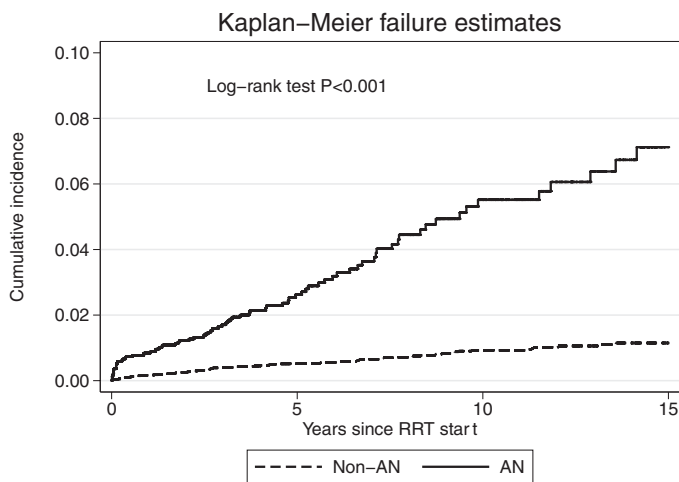


Figure 3. Kaplan-Meier cumulative incidence of new transitional cell carcinoma (TCC) in patients on RRT.

ment withdrawal. The risks for cardiovascular, cancer, and other causes of death varied significantly with age ($P < 0.01$ for interaction with age). Overall and age-stratified adjusted hazard ratios are shown in Table 3. Censoring at first transplantation did not substantially affect results. There were no significant interactions with gender or era of RRT start. TCC occurred in 2.4% of deaths and 38.3% of cancer deaths in patients with AN and in 0.7% of deaths and 9.3% of cancer deaths in patients without AN ($P < 0.001$ for comparisons between groups).

Discussion

Our study expanded on previously reported trends in Australia (11,12). After the ban on over-the-counter combination analgesic sales in 1979, incidence of RRT attributed to AN fell rapidly among younger patients. In older patients, rates were unchanged or increased for up to 25 yr before starting to decline. These trends could be explained by cohort effects. Significant combination analgesic exposure was unlikely in individuals who were younger than 30 yr in 1979, hence the

negligible incidence of RRT attributed to AN among 35- to 44-yr-olds since the late 1980s. Older people could have had significant combination analgesic exposure before 1979; therefore, the incidence of RRT attributed to AN continued to rise among older patients up to the 1990s.

Anecdotal experience (T.H.M. personal observations) suggested that renal function often markedly improved after cessation of combination analgesics. In some studies, renal function improved or stabilized after combination analgesic cessation (13–15); however, these studies were small (<50 patients), with relatively short follow-up (<5 yr). Our study suggests continuing renal deterioration after combination analgesic cessation, resulting in end-stage kidney disease up to 30 yr later. Continuing renal deterioration may also be caused by secondary factors, such as residual hypertension and renovascular disease. Although combination analgesics remained available by prescription, anecdotal evidence suggests that regular use was uncommon, although evidence is lacking.

Other factors could have artifactually maintained incidence of RRT attributed to AN (16). The age, medical, and social criteria for starting RRT have become more relaxed. Deaths from competing causes such as cardiovascular disease have decreased. Earlier RRT start meant that some patients who would otherwise have died before starting RRT would then die only after starting RRT. These factors increase the number of patients who need and start RRT; however, their effects could be avoided by autopsy studies. In Switzerland, the autopsy prevalence of AN declined from 3 to 0.2% between 1980 and 2000 (1), suggesting a real decline after controls on combination analgesics.

Another possible factor is misdiagnosis of AN. Diagnoses reported by the individual units were not routinely confirmed by requests for radiologic or other investigations that may have been performed. Despite interests in using computed tomography to diagnose classical AN (17,18), diagnosis is still often by drug history supported by radiologic signs (papillary calcification or necrosis), which by themselves are nonspecific. Cases of nonsteroidal anti-inflammatory drugs contributing to end-stage kidney disease could also have been labeled as AN,

Table 4. Adjusted HR, stratified by age, for 5-yr mortality of patients who had AN and were on RRT (compared with control subjects with nondiabetic nephropathy), 1971 through 2000^a

Age (yr)	All-Cause Mortality (n = 8290)	Cause-Specific Mortality				
		Cardiovascular (n = 3960)	Infection (n = 1359)	Cancer (n = 624)	Withdrawal (n = 1250)	Other (n = 1098)
35 to 84 (n = 17,343)	1.26 (1.19 to 1.34) ^b	1.26 (1.16 to 1.38) ^b	1.34 (1.17 to 1.54) ^b	1.31 (1.05 to 1.65) ^c	1.15 (0.99 to 1.34)	1.30 (1.11 to 1.53) ^b
35 to 44 (n = 2998)	1.90 (1.51 to 2.41) ^b	2.11 (1.45 to 3.07) ^b	1.81 (1.19 to 2.75) ^b	1.86 (0.59 to 5.85)	2.34 (0.77 to 7.12)	1.51 (0.85 to 2.68)
45 to 54 (n = 4308)	1.24 (1.08 to 1.41) ^b	1.17 (0.95 to 1.44)	1.26 (0.94 to 1.69)	1.05 (0.60 to 1.83)	1.30 (0.79 to 2.13)	1.45 (1.08 to 1.95) ^c
55 to 64 (n = 4795)	1.36 (1.23 to 1.51) ^b	1.27 (1.09 to 1.47) ^b	1.40 (1.09 to 1.81) ^b	1.37 (0.94 to 1.98)	1.34 (0.98 to 1.84)	1.67 (1.26 to 2.20) ^b
65 to 74 (n = 4072)	1.10 (0.99 to 1.22)	1.13 (0.97 to 1.32)	1.28 (0.98 to 1.67)	1.27 (0.85 to 1.88)	0.99 (0.78 to 1.25)	0.87 (0.62 to 1.23)
75 to 84 (n = 1170)	1.15 (0.93 to 1.41)	1.31 (0.99 to 1.74)	1.01 (0.54 to 1.88)	1.05 (0.39 to 2.80)	1.14 (0.79 to 1.63)	0.59 (0.24 to 1.44)

^aAdjusted for age, era, gender, and indigenous status. Significant interaction with age for all-cause, cardiovascular, infection, and other causes of death. n = number of patients in multivariate analyses.

^bP < 0.01.

^cP < 0.05.

despite their differences; however, there were high levels of awareness of AN among Australian nephrologists throughout the study period. Although no systematic survey has been done, it is likely that many (if not most) diagnoses of AN would have been supported by extrarenal manifestations, radiologic investigations (intravenous urograms in the early days, ultrasonography and computed tomography more recently), or other evidence (e.g., histologic examination of sloughed renal papillae); therefore, we believe that misdiagnosis is unlikely to be a major explanation of the observed trends.

Whether nonphenacetin combination analgesics caused AN remains uncertain. In Australia, the delay between removing phenacetin from Bex (1975) and banning all over-the-counter combination analgesic sales (1979) was short; therefore, we could not adequately distinguish between the effects of these two measures. Similar age-specific trends were seen in Belgium (19) and Switzerland (20). In the former, phenacetin combination analgesics were gradually removed between 1967 and 1981 and banned in 1987, but nonphenacetin combination analgesics remained available over the counter. In the latter, phenacetin combination analgesics were banned in 1981 through 1983, whereas nonphenacetin combination analgesics remained available. A review found insufficient epidemiologic and pharmacologic evidence to support an association between nonphenacetin combination analgesics and AN (21), but debates remain (3).

Associations of AN with cardiovascular disease have been reported. A 20-yr cohort study found that women who took phenacetin combination analgesics had relative risks of 1.8 for cardiovascular disease and 2.9 for cardiovascular deaths (10); however, analyses were not adjusted for renal dysfunction, a strong cardiovascular risk factor (22). By comparing within a cohort with end-stage kidney disease, we partly accounted for renal disease. We could not account for the duration and severity of renal dysfunction or survivor bias. Ascertainment bias, where comorbidities were more intensively looked for among patients with AN, is also possible; however, we think that these biases could not fully account for the strength and consistency of the associations, especially in younger patients.

Another potential bias is bias by indication, whereby combination analgesics were used to relieve symptoms of cardiovascular disease, such as chest pain or claudication; however, in Australia, the main reasons for use were headaches and musculoskeletal pain (although claudication may mimic this). Combination analgesic use was then often maintained for their psychotropic effects and to prevent headaches from caffeine (and possibly phenacetin) withdrawal (23,24). We believe that this bias is unlikely to be an important explanation for the associations.

Patients with diabetes were excluded because its strong association with cardiovascular disease may obscure the impact of AN. The strength of the associations decreased with age, perhaps as a result of higher background comorbidity rates in older patients. For example, in patients without AN, 11% of the 35- to 54-yr age group and 49% of the 75- to 84-yr age group had coronary artery disease. Patients who had AN and started RRT at a younger age may also have had greater combination analgesic exposure or be more susceptible to combination analgesic effects. The association with chronic lung disease has not been previously described and was also seen in nonsmokers. This could be due to pathogenic mechanisms similar to cardiovascular disease or be confounded by environmental or occupational factors for which we could not adjust.

Patients with AN had poorer survival on RRT, even after adjustment for demographic factors. We used diabetic nephropathy as a surrogate to exclude patients with diabetes from the comparison group, because diabetes status was not collected before 1991. Patients with diabetes have much worse survival on RRT (25), and their inclusion may obscure the effects of AN. Previous studies of cardiovascular mortality of patients who had AN and were on RRT did not adjust for patient characteristics (26) or adjusted for age only (20). Results were conflicting. Our study found that patients with AN remained at higher risk for cardiovascular death even after starting RRT.

The increased risk for TCC in AN is widely known (27). In one study, 3.7% of patients with AN received a diagnosis of TCC after transplantation (0.32% in patients without AN), de-

spite pretransplantation screening (28). Another study found a 14.1% incidence of TCC in posttransplantation patients with AN, with case fatality rate of 64% (29). In our study, patients with AN had a 32% higher risk for cancer deaths, more than one third of which were in those with TCC; however, TCC contributed to only 2.4% of deaths of patients with AN in the first 5 yr of RRT.

Conclusions

Controls on combination analgesics led to significant decreases in incidence and prevalence of patients who had AN and were on RRT; however, these were delayed, especially in older patients, because of several factors. We also demonstrated the higher cardiovascular risks in patients with AN and their continuing impact on survival after starting RRT, particularly in younger patients. This study illustrates that the RRT burden attributed to a particular cause is not relieved immediately after its elimination and may continue to increase for some time.

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Disclosures

None.

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