Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study

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Summary

Background Diabetes is regarded as a coronary heart disease risk equivalent—ie, people with the disorder have a risk of coronary events similar to those with previous myocardial infarction. We assessed whether chronic kidney disease should be regarded as a coronary heart disease risk equivalent.

Methods We studied a population-based cohort with measures of estimated glomerular filtration rate (eGFR) and proteinuria from Alberta, Canada. We used validated algorithms based on hospital admission and medical-claim data to classify participants with baseline history of myocardial infarction or diabetes and to ascertain which patients were admitted to hospital for myocardial infarction during follow-up (the primary outcome). For our primary analysis, we defined baseline chronic kidney disease as eGFR 15–59.9 mL/min per 1.73 m² (stage 3 or 4 disease). We used Poisson regression to calculate unadjusted rates and relative rates of myocardial infarction during follow-up for five risk groups: people with previous myocardial infarction (with or without diabetes or chronic kidney disease), and (of those without previous myocardial infarction), four mutually exclusive groups defined by the presence or absence of diabetes and chronic kidney disease.

Findings During a median follow-up of 48 months (IQR 25–65), 11 340 of 1 268 029 participants (1%) were admitted to hospital with myocardial infarction. The unadjusted rate of myocardial infarction was highest in people with previous myocardial infarction (18·5 per 1000 person-years, 95% CI 17·4–19·8). In people without previous myocardial infarction, the rate of myocardial infarction was lower in those with diabetes (without chronic kidney disease) than in those with chronic kidney disease (without diabetes; 5·4 per 1000 person-years, 5·2–5·7, vs 6·9 per 1000 person-years, 6·6–7·2; p=0·0001). The rate of incident myocardial infarction in people with diabetes was substantially lower than for those with chronic kidney disease when defined by eGFR of less than 45 mL/min per 1·73 m² and severely increased proteinuria (6·6 per 1000 person-years, 6·4–6·9 vs 12·4 per 1000 person-years, 9·7–15·9).

Interpretation Our findings suggest that chronic kidney disease could be added to the list of criteria defining people at highest risk of future coronary events.

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Introduction

Guidelines for lipid-lowering treatment mainly base initiation of treatment and therapeutic goals for LDL cholesterol on projected risk of coronary heart disease events. The US National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommends that LDL cholesterol be reduced to lower than 2·6 mmol/L in patients with coronary heart disease or an equivalent disorder. The term coronary heart disease risk equivalent refers to a characteristic that leads to a 10-year risk of coronary death or myocardial infarction that is equivalent to the risk associated with previous myocardial infarction (generally >20% risk). ATP III guidelines classify diabetes as a coronary heart disease risk equivalent, partly because data show that people with diabetes are at very high risk of cardiovascular events. An expert panel has suggested that chronic kidney disease should also be regarded as a coronary heart disease risk equivalent. People with chronic kidney disease have high rates of cardiovascular events, particularly when proteinuria is present. However, whether chronic kidney disease constitutes a coronary heart disease risk equivalent (compared with accepted criteria such as diabetes)—especially when proteinuria is included in the definition of chronic kidney disease—is unknown.

We used data from a large population-based cohort to examine the risk of hospital admission for myocardial infarction in people with previous myocardial infarction, diabetes mellitus, or chronic kidney disease compared with people without these disorders. We aimed to assess the merits of chronic kidney disease (with and without proteinuria) as a coronary heart disease risk equivalent.
See Online for appendix. We used the AKDN database—a selection of routine laboratory data from all patients in Alberta, Canada—to estimate risk of hospital admission for myocardial infarction, and a secondary outcome of all-cause death in individuals with previous myocardial infarction, diabetes, or chronic kidney disease. We identified adults aged 18 years and older whose serum creatinine was measured at least once as an outpatient between 2002 and 2009 and who did not have end-stage renal disease. Each patient’s first available serum creatinine measurement and the date it was taken were set as their index serum creatinine and index date, respectively. We excluded people with an index estimated glomerular filtration rate (eGFR) of lower than 15 mL/min per 1·73 m². Of the remaining patients, those who had been tested for proteinuria (dipstick urinalysis or albumin to creatinine ratio [ACR]) at least once within 6 months of their index creatinine measurement made up the cohort for all analyses with AKDN data (appendix).

We derived demographic and socioeconomic data for these participants from provincial health ministry records. The institutional review boards of the Universities of Calgary and Alberta approved the study.

Definitions for coronary heart disease risk equivalency criteria
We used a validated algorithm based on hospital admission data from 1994–2009 (appendix) to identify participants within our cohort with previous myocardial infarction. Because ATP III regards some types of cardiovascular disease as coronary heart disease risk equivalents, we also identified participants with previous stroke or transient ischaemic attack and those previously admitted for surgical or percutaneous coronary revascularisation (appendix). In sensitivity analyses, we regarded participants with cardiovascular disease—ie, one or more of previous myocardial infarction, stroke, transient ischaemic attack, or coronary revascularisation—as having a coronary heart disease risk equivalent, and compared them with participants with diabetes and chronic kidney disease. We used a validated algorithm based on medical claims for diabetes treatment and hospital admission data (appendix) to classify participants with diabetes at baseline. In sensitivity analyses, we used more specific criteria to identify diabetes: a glycated haemoglobin A₁c (HbA1c) concentration of greater than 6·5% measured within 6 months of index serum creatinine, irrespective of treatment or insurance-claim data. In this analysis, we classified participants as not having diabetes if their HbA1c concentration had not been measured.

The Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation is more accurate than the Modification of Diet in Renal Disease (MDRD)-GFR equation at estimation of GFR, particularly in people with eGFR of 45–60 mL/min per 1·73 m². Therefore, we used the CKD-EPI equation and a standardised serum creatinine assay in our primary analyses to estimate the baseline GFR for each participant. In sensitivity analyses, we used the MDRD-GFR equation and sex-specific serum creatinine cutoff points (≥137 μmol/L for men and ≥104 μmol/L for women) to identify reduced eGFR.

Our primary definition of chronic kidney disease was eGFR lower than 60 mL/min per 1·73 m², corresponding to stage 3 or 4 disease. We also considered four alternative definitions to assess the effect of increasingly severe kidney damage on the risk of adverse outcomes: eGFR lower than 60 mL/min per 1·73 m² or moderately or severely increased proteinuria (ACR ≥30 mg/g or urine dipstick ≥2+); eGFR lower than 45 mL/min per 1·73 m², corresponding to stage 3B or 4 chronic kidney disease; and eGFR lower than 45 mL/min per 1·73 m² with severely increased proteinuria.

In our primary analysis, we regarded chronic kidney disease (without diabetes) and diabetes (without chronic kidney disease) as mutually exclusive; however, in contemporary clinical practice, diabetes (with or without chronic kidney disease) is regarded as a coronary heart disease risk equivalent. Therefore, in sensitivity analyses, we assessed the rate of myocardial infarction in participants with chronic kidney disease (with or without diabetes) compared with those with diabetes (without chronic kidney disease).

Study outcomes
We followed up participants from the AKDN database from their index date until the study end (March 31, 2009). The primary outcome was first admission to hospital for myocardial infarction. The secondary outcome was all-cause mortality, identified from the Alberta Bureau of Vital Statistics. Finally, in the subset of participants admitted for myocardial infarction during follow-up, we assessed short-term (30 days after admission) and long-term (until end of follow-up) mortality after myocardial infarction.

NHANES 2003–06
We used NHANES 2003–06—a population-level study of a representative sample of US civilians (not living in institutions)—to estimate the number of US residents who would meet criteria for each risk group studied (previous myocardial infarction, or no previous myocardial infarction, but diabetes or chronic kidney disease or both). We included NHANES 2003–06 participants aged 20 years or older with complete information about serum creatinine (measured by following a standardised protocol) and ACR to assess proteinuria (see appendix for detailed inclusion criteria). We used established criteria to define a history of coronary heart disease, diabetes, and stroke.
Statistical analyses

For primary analyses, we considered five risk groups: people with previous myocardial infarction (with or without diabetes and chronic kidney disease), and four mutually exclusive groups of people without previous myocardial infarction (no diabetes and no chronic kidney disease, chronic kidney disease alone, diabetes alone, and both chronic kidney disease and diabetes). In clinical practice, criteria for coronary heart disease risk equivalents are applied without adjustment for covariates (such as age)—practitioners merely note whether the characteristic is present when assessing whether a patient has a coronary heart disease equivalent. Therefore, for our primary analysis we used Poisson regression to calculate unadjusted rates (per 1000 person-years) of myocardial infarction and all-cause mortality for each risk group. These rates are numerically equivalent to the traditional criteria for risk equivalency (expressed as the proportion of people who have an event over 10 years). If the Poisson assumption that variance equals the mean was not met, we used a negative binomial model.

We repeated these analyses in strata defined by baseline age (<65 years or ≥65 years), sex, and statin use (in participants aged ≥65 years, for whom drug data were available). Finally, to assess the contribution of other clinical characteristics to the potential value of chronic kidney disease as a coronary heart disease risk equivalent, we did further exploratory analyses with multivariable Poisson regression that adjusted for baseline age, sex, socioeconomic status, and comorbidities (any solid cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, hemiplegia/paraplegia, HIV/AIDS, liver disease, metastatic solid tumour, peptic ulcer disease, peripheral vascular disease, and rheumatic disease) assessed by validated algorithms on the basis of insurance claims and hospital admission data. These models were used to calculate relative rates (per 1000 person-years) of the two outcomes for each risk group, compared with a reference group of people with no history of myocardial infarction, no diabetes, and no chronic kidney disease (eGFR ≥60 mL/min per 1·73 m²).

We used sampling weights for NHANES 2003–06 calculations to account for unequal probabilities of selection, over-sampling, and non-response in estimations of the number of Americans who met criteria for each risk group. We did analyses of AKDN data with Stata/MP 11 software and calculated how many US citizens would meet criteria for each risk group with SUDAAN (version 9.1).

### Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Previous myocardial infarction* (n=12 960)</th>
<th>No previous myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>Diabetes and CKD (n=15 368)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>66·1 (12·5)</td>
</tr>
<tr>
<td><strong>Aboriginal people</strong></td>
<td>3471 (26·8%)</td>
</tr>
<tr>
<td><strong>Socioeconomic status†</strong></td>
<td>211 (1·6%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>648 (5·0%)</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>427 (3·3%)</td>
</tr>
<tr>
<td><strong>Previous percutaneous coronary revascularisation</strong></td>
<td>3898 (30·1%)</td>
</tr>
<tr>
<td><strong>Previous surgical coronary revascularisation</strong></td>
<td>5497 (42·4%)</td>
</tr>
<tr>
<td><strong>eGFR (mL/min per 1·73m²)</strong></td>
<td>2126 (16·4%)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>9366 (72·3%)</td>
</tr>
<tr>
<td><strong>Socioeconomic status†</strong></td>
<td>1274 (16·8%)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>1420 (11·0%)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>10 385 (80·1%)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>19 444 (15·0%)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>631 (4·9%)</td>
</tr>
<tr>
<td><strong>Statin use‡</strong></td>
<td>4258 (63·2%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). Totals do not always add to 100% because of rounding. Chronic kidney disease is defined as eGFR lower than 60 mL/min per 1·73 m², with or without proteinuria. Proteinuria is defined as: normal (albumin to creatinine ratio [ACR] <30 mg/g or negative urine dipstick result), moderately increased (ACR 30–300 mg/g or urine dipstick trace or 1+), or severely increased (ACR >300 mg/g or urine dipstick ≥2+). CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. *Includes participants with or without diabetes and chronic kidney disease. †Low socioeconomic status was defined by yearly family income of lower than CAD39 250; participants were classed as in receipt of social assistance according to Government of Alberta health-care insurance records. ‡Data for statin use were available only for the 196 700 participants aged 65 years or older; the numbers of patients aged 65 years or older in each group are as follows: previous myocardial infarction, n=6896; diabetes and CKD, n=12 075; CKD, n=43 409; diabetes, n=21 757; no diabetes or CKD, n=112 563.
Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows baseline characteristics of the 1 268 029 participants who met the inclusion criteria in each risk group. Participants with previous myocardial infarction or chronic kidney disease were substantially older than those with diabetes (table 1). During median follow-up of 48 months (IQR 25–65), 11 340 (1%) participants were admitted to hospital with myocardial infarction, and 47 712 (4%) died.

The unadjusted rate of myocardial infarction during follow-up was higher in people with a history of myocardial infarction (18·5 per 1000 person-years, 95% CI 17·4–19·8) than in those without previous myocardial infarction but with diabetes (5·4 per 1000 person-years, 5·2–5·7) or chronic kidney disease (6·9 per 1000 person-years, 6·6–7·2; figure 1). In people without previous myocardial infarction, the rate of myocardial infarction during follow-up was lower for those with diabetes but without chronic kidney disease than in those with chronic kidney disease but without diabetes (5·4 per 1000 person-years, 95% CI 5·2–5·7, vs 6·9 per 1000 person-years, 6·6–7·2; p<0·0001; figure 1). Results were similar when the MDRD-GFR equation and sex-specific serum creatinine cutoff points were used to identify reduced GFR (appendix).

When we used a more stringent criterion of an eGFR of lower than 45 mL/min per 1·73 m² (especially with coexisting proteinuria) to define chronic kidney disease, the rate of myocardial infarction during follow-up in people with chronic kidney disease (compared with those with diabetes) was higher than in the primary analysis (appendix). In all analyses, the rate of first myocardial infarction was higher in people with both chronic kidney disease and diabetes than in those with either disorder alone (figure 1; appendix).

When rate of myocardial infarction in people with chronic kidney disease (either with or without diabetes), was compared with diabetes (without chronic kidney disease), the rate of myocardial infarction was significantly higher in people with chronic kidney disease than in those with diabetes (8·0 per 1000 person-years, 95% CI 7·7–8·3, vs 5·4 per 1000 person-years, 5·2–5·7; p<0·0001; appendix).

When diabetes was defined by HbA₁c concentration of greater than 6·5%, findings were similar to our primary analysis—ie, the likelihood of myocardial infarction was greatest in patients with previous myocardial infarction, followed by those with both diabetes and chronic kidney disease, and lowest in patients without either chronic kidney disease or diabetes (appendix). Results were consistent when the broader definition of previous cardiovascular disease was used rather than previous myocardial infarction alone (appendix). Sensitivity analyses had qualitatively similar results to primary analyses when we considered all-cause death during follow-up rather than incident myocardial infarction (figure 1 and appendix).

Finally, we did further exploratory analyses that adjusted for age, sex, socioeconomic status, and comorbidity. These analyses showed that such adjustment decreased the relative rate of myocardial infarction to a greater extent in people with chronic kidney disease than in those with diabetes, suggesting that demographic and clinical characteristics account for some of the cardiovascular risk associated with chronic kidney disease (table 2). However, adjusted relative rates of myocardial infarction were similar for people with chronic kidney disease and severely increased proteinuria to those for people with diabetes (appendix).

The proportion of participants who died within 30 days of admission for myocardial infarction was significantly higher for people with chronic kidney disease (but no diabetes or previous myocardial infarction [233 of 1667 [14%]] than for those with diabetes but no chronic kidney disease or previous myocardial infarction [151 of 1809 [8%]; p=0·0001; 30 days of admission for myocardial infarction] for those with a history of myocardial infarction (102 of 993 [10%; p=0·0053). Similarly, the unadjusted relative rate of mortality after admission for myocardial infarction (until end of follow-up) was significantly higher for participants with chronic kidney disease than for those without.

Figure 1: Unadjusted rates of clinical outcomes in each risk group

Unadjusted rates and 95% CIs of myocardial infarction (A) and all-cause mortality (B) per 1000 person-years. Chronic kidney disease is defined as estimated glomerular filtration rate lower than 60 mL/min per 1·73 m² with or without proteinuria. CKD=chronic kidney disease. *Includes participants with or without diabetes and chronic kidney disease.

Articles

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with diabetes (p<0·0001) or previous myocardial infarction (p<0·0001; figure 2).

8245 participants of NHANES 2003–06 met our age and data criteria for assessment of the projected number of adults in the USA classified in each risk group. If chronic kidney disease were added to the list of coronary heart disease risk equivalents, the number of US adults with one or more risk equivalents would increase to a substantially greater extent if chronic kidney disease were defined by eGFR of lower than 60 mL/min per 1·73 m² alone (11·975 million US adults) than if a more stringent definition based on combinations of reduced eGFR and proteinuria were used (eg, 0·788 million US adults with eGFR <60 mL/min per 1·73 m² and proteinuria). CRTa=chronic kidney disease. eGFR=estimated glomerular filtration rate.

**Discussion**

In this population-based cohort of nearly 1·3 million people, the unadjusted rate of hospital admission for myocardial infarction during follow-up was substantially lower for people with diabetes or chronic kidney disease than for those with a history of myocardial infarction. However, the rate of first myocardial infarction during follow-up was slightly higher in those with chronic kidney disease (but without diabetes) than in those with diabetes (without chronic kidney disease), especially when we used lower thresholds of eGFR (<45 mL/min per 1·73 m²) or proteinuria to define chronic kidney disease.

However, after adjustment for age, socioeconomic status, and comorbidity, the rate of first myocardial infarction was lower in people with chronic kidney disease (eGFR <60 mL/min per 1·73 m²) than in those with diabetes. This finding suggests that some of the increased risk associated with reduced eGFR is attributable to old age, which often accompanies chronic kidney disease. Nonetheless, even after further adjustment for sex, socioeconomic status, and comorbidity, people with stage 3–4 chronic kidney disease and concomitant severe proteinuria had similar rates of first myocardial infarction to those for people with diabetes.

ATP III guidelines include diabetes as a coronary heart disease risk equivalent for three reasons. First, results from a study2 showed that 1059 people with diabetes but no previous myocardial infarction had a similar age-adjusted risk of heart disease to 1359 people with a history of myocardial infarction. Our findings show that the risk of myocardial infarction in people with chronic kidney disease and proteinuria is similar to or greater than the risk in those with diabetes. Second, people with diabetes have substantially higher mortality after myocardial infarction than do the general population,23,24 emphasising the potential value of prevention of coronary events. The rate of mortality after myocardial infarction in our study was significantly higher in participants with chronic kidney disease than in those with diabetes. Third, investigators of clinical trials showed that statin treatment safely improved outcomes in people with diabetes.25 A large trial has shown benefits of cholesterol-lowering therapy in people with advanced chronic kidney disease,26 supporting existing data showing that statins improve cardiovascular outcomes in mild chronic kidney disease. Thus, arguments supporting the inclusion of diabetes in the highest risk category for coronary heart disease seem to also apply to people with proteinuric chronic kidney disease. However, our data show that diabetes alone and chronic
kidney disease alone (with or without proteinuria) do not increase the rate of myocardial infarction to the same extent as does a history of coronary disease, and therefore do not support the use of the term coronary heart disease risk equivalent for either disorder. Nevertheless, the risks of both myocardial infarction and all-cause death in people with both diabetes and chronic kidney disease were similar to or higher than those in people with previous myocardial infarction.

Because people with diabetes are already thought to be in the highest risk category for coronary heart disease, the addition of chronic kidney disease to the criteria for this category should affect only people without diabetes. However, a focus on this lower risk subset—ie, those with chronic kidney disease but not diabetes—underestimates the potential value of chronic kidney disease as a prognostic marker for coronary heart disease. When people with chronic kidney disease with and without diabetes were grouped together, the unadjusted rate of myocardial infarction during follow-up in those with previous myocardial infarction was similar to the rate in those with the most stringent definition of chronic kidney disease (eGFR <45 mL/min per 1·73 m² and proteinuria). Similarly, if future guidelines base risk assessment on the presence or absence of several characteristics, reduced GFR with concomitant proteinuria should be considered for inclusion.

Inclusion of people without diabetes but with chronic kidney disease in the highest risk group for coronary heart disease would imply that (as for people with diabetes), most people in this population should receive lipid-lowering treatment. Although we did not assess the proportion of people with chronic kidney disease who had LDL cholesterol of 2·6 mmol/L or higher, findings from previous studies suggest that most would meet this criterion and would thus be candidates for statin treatment.

Several small studies suggest that the risk of coronary events is lower in people with diabetes than in those with previous myocardial infarction. However, previous studies assessing the potential merit of chronic kidney disease as a coronary heart disease equivalent have reached conflicting conclusions, possibly because of their small size, shortage of data for proteinuria, and focus on less severe chronic kidney disease (eGFR 30–59·9 mL/min per 1·73 m²) than that tested in our analysis (panel).

Our study’s large size, rigorous methods, and comprehensive sensitivity analyses overcome these limitations, but it does have weaknesses. All participants had their serum creatinine measured as outpatients as part of routine clinical care in one Canadian province, potentially limiting the extent to which we can generalise these results. Furthermore, median follow-up was only 4 years. Although rates per 1000 person-years are numerically equivalent to the proportion of participants who have an event over 10 years, further study is needed to assess whether our findings apply throughout long-term follow-up. As in other related studies, our primary analysis focused on previous myocardial infarction. However, results were similar when histories of stroke and coronary revascularisation were added to the criteria used to identify people with a coronary heart disease risk equivalent.

As in most previous studies, we classified people as having chronic kidney disease on the basis of one serum creatinine value, which might have led to incorrect classification of some participants. Because such misclassification would tend to underestimate the risk associated with chronic kidney disease, the potential value of kidney disease as a risk equivalent might be higher than is suggested by our results. Although some investigators have suggested that the CKD-EPI equation might not be suitable for people with diabetes, most suggest that the CKD-EPI equation is the best available formulae to estimate GFR. Additionally, results were similar in analyses with alternative definitions of reduced eGFR and chronic kidney disease, suggesting that this issue is unlikely to have affected our results. Finally, the traditional definition of coronary heart disease risk equivalency is based on the incidence of

Panel: Research in context

Systematic review
We searched PubMed from Jan 1, 1950, to March 10, 2012, without language restrictions with the search terms (“kidney” OR “renal”) AND “risk equivalent”, and examined the reference lists of articles identified in the search. We reviewed observational studies examining the implications of regarding chronic kidney disease as a coronary heart disease risk equivalent, with or without comparison with diabetes. We identified several high-quality studies examining this issue; however, all were small, focused on stage 3 chronic kidney disease (estimated glomerular filtration rate [eGFR] 30–59·9 mL/min per 1·73 m²), and did not consider the additional risk associated with concomitant proteinuria. As a result, all are inconclusive.

Interpretation
Our large cohort size, and the fact that we took proteinuria into account, allowed us to reliably estimate coronary risk in people with and without chronic kidney disease, diabetes, and previous myocardial infarction. The incidence of future myocardial infarction was similar in people with diabetes (but without chronic kidney disease) and those with stage 1–4 chronic kidney disease (but without diabetes). When more advanced chronic kidney disease was considered (eg, eGFR <45 mL/min per 1·73 m², especially with severely increased proteinuria), the rate of myocardial infarction was significantly higher in those with chronic kidney disease than in those with diabetes. These findings suggest that chronic kidney disease could be added to the list of criteria defining people at highest risk of coronary events.
myocardial infarction or cardiovascular death. Because we did not assess cardiovascular death, we focused instead on the clinically relevant outcome of hospital admission for myocardial infarction. Results for all-cause mortality and our primary outcome were similar, suggesting that this limitation is unlikely to have affected our conclusions.

Rates of hospital admission for myocardial infarction and the risk of death after such an event in people with chronic kidney disease without diabetes were similar to or higher than rates in those with diabetes (without chronic kidney disease). These findings suggest that chronic kidney disease could be added to the list of criteria defining people at highest risk of future coronary events.

References


Designation of a disorder as a coronary heart disease risk equivalent would imply that the disorder leads to a 10-year risk of coronary death or myocardial infarction that is at least as high as after myocardial infarction (ie, usually exceeding 20%).\(^1\) Guidelines therefore recommend lipid-lowering therapy (in addition to therapeutic lifestyle changes) for most adults with a coronary heart disease risk equivalent.\(^1,2\) Evidence points to a strong association between coronary heart disease and chronic kidney disease.\(^3\) In The Lancet, Marcello Tonelli and colleagues\(^4\) address a natural question arising from epidemiological data: does chronic kidney disease constitute a coronary heart disease risk equivalent?

Tonelli and colleagues used data from the Alberta Kidney Disease Network (AKDN) in Canada. The study assessed almost 1.3 million individuals, not on dialysis, with a median follow-up of 48 months. The primary definition of chronic kidney disease was an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m\(^2\), estimated with the Chronic Kidney Disease Epidemiological Collaboration equation.\(^5\)

The primary outcome was first admission to hospital for myocardial infarction, ascertained by linking AKDN to a medical claims database of all Alberta residents. The investigators compared incident event rates in patients with previous myocardial infarction with individuals in four mutually exclusive groups defined by the presence or absence of chronic kidney disease and diabetes (which under current guidelines is considered a risk equivalent).\(^5\) The ability to use data from such a sizable study population in a real-world setting is one of the study’s major strengths. One inevitable limitation is the shortage of information about individuals’ medications and the extent of cardiovascular risk factor control, particularly blood pressure.

In the primary analysis, unadjusted rates of incident myocardial infarction in adults with chronic kidney disease or diabetes, at 6.9 (95% CI 6.6–7.2) and 5.4 (5.2–5.7) per 1000 person-years, respectively, were less than half of the rate in adults with previous myocardial infarction, at 18.5 (17.4–19.8) per 1000 person-years. When the definition of chronic kidney disease was restricted to an eGFR of less than 45 mL/min per 1.73 m\(^2\) and severe proteinuria, unadjusted rates exceeded 10 per 1000 person-years. However, after adjusting for age, sex, and comorbidities, the relative rate for individuals with chronic kidney disease was lower than for people with diabetes or previous myocardial infarction. Consequently, Tonelli and colleagues’ analysis does not support classification of chronic kidney disease as a coronary heart disease risk equivalent. Much of the coronary risk in patients with chronic kidney disease is probably mediated by chronic exposure to cardiovascular risk factors.

Despite negative findings for the primary outcome, compelling reasons are provided to consider lipid-lowering therapy in patients with chronic kidney disease. The researchers report that unadjusted mortality rates after myocardial infarction in adults with chronic kidney disease (3.6 per 1000 person-years) were higher than were those in adults with a history of myocardial infarction (2.7 per 1000 person-years) or diabetes (1.9 per 1000 person-years). Previous investigations showed increasing morbidity and mortality after myocardial infarction with worsening kidney function.\(^6\) Tonelli and colleagues offer new insight by comparing individuals with chronic kidney disease with those who have a history of myocardial infarction, on a very large scale. Their findings emphasise the importance of primary prevention, particularly because patients with chronic kidney disease comprise a large proportion of patients who have myocardial infarction. In one registry, 30.5% of ST-elevation and 42.9% of non-ST-elevation
myocardial infarctions were in adults with an eGFR of less than 60 mL/min per 1·73 m².7

The disparity between mortality rates after myocardial infarction in patients with and without chronic kidney disease might be partly related to processes of care. Compared with patients without chronic kidney disease, those with the disease are less likely to undergo revascularisation or receive medications such as β blockers, aspirin, and clopidogrel.7 A fear of worsening kidney function might have influenced clinical decision making, because patients with an eGFR of 15–30 mL/min per 1·73 m² had lower rates of revascularisation than did patients with end-stage renal disease.7

Another important consideration in chronic kidney disease is whether treatment with statins improves outcomes. So far, only the Study of Heart and Renal Protection (SHARP) trial has focused on patients with moderate-to-severe kidney disease.4 In SHARP, more than 9000 adults without known coronary heart disease were randomly assigned to simvastatin 20 mg plus ezetimibe 10 mg (to minimise risks of statin-related toxicity) or placebo. Most participants had an eGFR between 15 and 60 mL/min per 1·73 m², and about a third were on dialysis. As established in other major statin trials, simvastatin 20 mg plus ezetimibe 10 mg reduced atherosclerotic events. This reduction (17%) was proportional to the reduction in LDL (which reduced, on average, by 0·85 mmol/L). The results of SHARP suggest that low-dose statin therapy is safe and helps to reduce the incidence of atherosclerotic events in adults with stages 3 and 4 chronic kidney disease.

Ultimately, the relative importance of risk-equivalent status depends in part on geography. In the UK, practice guidelines reserve statin therapy mainly for high-risk patients.7 By contrast, patients in the USA whose 10-year estimated cardiovascular risk is below 20% are recommended for statin therapy on the basis of their LDL concentration and estimated coronary heart disease risk.1 Using higher LDL cutoffs than are currently recommended, one study estimated that more than 60% of adults with chronic kidney disease (including those with previous myocardial infarction or diabetes) already qualify for statins according to US guidelines.3 However, about 35–40% of patients with chronic kidney disease stages 3–5, and 41% of dialysis patients, are thought to receive statins.10 With an update of the US guidelines due before the end of 2012, the indications for statins will possibly broaden and include more adults with stages 3–5 chronic kidney disease at lower coronary heart disease risk.

Finally, Tonelli and colleagues report that adults with both diabetes and proteinuric chronic kidney disease have incident myocardial infarction rates that well exceed those of patients with previous myocardial infarction. These findings emphasise the original construct put forth by the Steno-2 study—ie, aggressive control of glucose, blood pressure, and lipids reduces rates of chronic kidney disease progression and cardiovascular mortality in patients with nephropathy from type 2 diabetes.11

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