The Progressive Cost of Complications in Type 2 Diabetes Mellitus

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Background: A substantial proportion of the costs of diabetes treatment arises from treating long-term complications, particularly cardiovascular and renal disease. However, little is known about the progressive cost of these complications. Firmer knowledge would improve diabetes modeling and might increase the financial and organizational support for the prevention of diabetic complications.

Methods: We analyzed 9 years of clinical data on 11,768 members of a large group-model health maintenance organization who had probable type 2 diabetes mellitus. We ascertained the presence of cardiovascular and renal complications, staged the members progression, and estimated their incremental costs by stage.

Results: We found no significant differences between men and women in the prevalence or staging of complications. Per-person costs increased over baseline ($2033) by more than 50% ($1087) after initiation of cardiovascular drug therapy and/or use of a cardiologist, and by 360% ($7352) after a major cardiovascular event. Abnormal renal function increased diabetes treatment costs by 65% ($1337); advanced renal disease, by 195% ($3979); and end-stage renal disease, by 771% ($15,675). Both cardiovascular and renal diseases were more common among older subjects, but age did not affect the additional costs of these complications. Women had substantially higher medical care costs after controlling for age and presence of complications. Incremental cost estimates based solely on “labeled” events significantly underestimate true incremental cost.

Conclusions: In an aggregate population, the greatest cost savings would be achieved by preventing major cardiovascular events. For individuals, the greatest savings would be achieved by preventing progression to stage 3 renal disease.
PARTICIPANTS AND METHODS

RESEARCH SETTING AND STUDY POPULATION

Participants were members of Kaiser Permanente Northwest Division (KPNW), a large, not-for-profit, group-model HMO that provides comprehensive, prepaid coverage to about 20% of the Portland, Ore, population. Subscribers are representative of the area population as a whole.7

Information on patient admissions, pharmacy dispensations, outpatient visits, laboratory tests, and outside claims and referrals is kept at KPNW in databases that are linked through unique health record numbers given to each member at the time of his or her first enrollment in the health plan. The KPNW diabetes registry contains a continuous census of more than 25,000 members with diabetes diagnosed since January 1, 1987. Internal validation studies have shown the registry to be over 99% sensitive and 99% specific for diagnosed diabetes. Subjects included in the present analysis were limited to the 11,768 registrants with probable type 2 diabetes mellitus and a full year of health plan eligibility in 1995. Those who became members after 1995 were excluded, as were those who died or left the plan prior to that year. Members were presumed to have type 2 diabetes mellitus if they entered the registry after age 45 years or entered earlier and had no insulin dispensed within 2 years of entry. The average length of time in the registry for study subjects was 5.3 years (median, 5 years).

IDENTIFICATION OF COMPLICATIONS

We screened 9 years of clinical data for the years 1987 through 1995 to ascertain the presence of cardiovascular and renal complications and to stage their progression. We assigned subjects with complications to the highest stage for which their histories qualified them. We defined the 3 cardiovascular and renal complication stages as follows: stage 0, no evidence of cardiovascular disease or treatment; stage 1, pre-event treatment, ie, taking cardiovascular drugs or having a history of at least 2 specialty visits to a cardiologist; and stage 2, postevent disease, history of 1 or more major cardiac, cerebrovascular, or peripheral vascular events such as myocardial infarction, stroke, revascularization procedure, or hospitalization for congestive heart disease. (Please refer to the Appendix for a description of the specific codes used in the staging algorithm.)

The cardiovascular drugs that qualified subjects for stage 1 cardiovascular disease included drugs for risk-factor control such as antihyperlipidemics and antihypertensives, as well as drugs to treat symptomatic cardiovascular disease such as digoxin and antianginal medications. Most of the stage 1 drugs are used for both treatment and risk-factor control. Although angiotensin-converting enzyme (ACE) inhibitors are also used to prevent the progression of diabetic renal disease, these drugs are included among the stage 1 cardiovascular drugs because of their frequent use to control hypertension.

We defined 4 stages of renal disease: stage 0, no evidence of disease—normal laboratory test results or no laboratory tests; stage 1, abnormal test results—at least 1 microalbuminuria test value higher than 45 mg/dL or at least 1 quantitated 24-hour test value for urinary protein higher than 165 mg/24 h; stage 2, advanced nephropathy—serum creatinine level higher than 141 µmol/L (1.6 mg/dL), creatinine clearance under 0.83 mL/s (50 mL/min) on at least 2 separate occasions, or an inpatient diagnosis indicating advanced renal disease; and stage 3, end-stage renal disease—renal transplantation or long-term hemodialysis.

ascertainment of costs of care within kpnw

We based our costing method on procedures developed and validated by the Kaiser Permanente Center for Health Research.4 This method creates standard costs for units of medical care (defined in the outpatient setting as office visits and in the inpatient setting as direct hospital service components). Costs are identified from aggregate departmental expenditures rather than from procedure-specific charges or prices. Administrative costs and other indirect and joint costs are allocated to units of direct service using a variety of algorithms developed either by the organization (in the case of outpatient visits and ancillary costs) or by the Center for Health Research (in the case of KPNW-produced

For renal disease treatment, costs increased $1337 with the onset of stage 1. Progression to advanced renal disease short of end stage increased the incremental costs of renal disease treatment by an additional $2642, to a cumulative $3979. Progression to the final stage of renal disease—chronic hemodialysis or a history of renal transplantation—raised treatment costs dramatically, to $15,675 over the costs of uncomplicated diabetes.

Table 2 describes the prevalence of cardiovascular and renal complications by age and sex. Overall, we detected advanced or end-stage renal disease (stages 2 and 3) in 11% of subjects. Significant cardiovascular disease was much more prevalent—29% had stage 2 disease. Additionally, the data in Table 2 reveal a trend toward more advanced disease with advancing age in both men and women. For example, advanced or end-stage renal disease was rare among 30- to 49-year-old women but affected 17% of women older than 70 years. Advanced cardiovascular disease was present in only 6% of the 30- to 49-year-old women but in 46% of the women older than 70 years. We found no significant differences between men and women in the prevalence or staging of complications.

Table 1. Age and Sex Distribution of Study Subjects

<table>
<thead>
<tr>
<th>Age Groups, y</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>997  (17)</td>
<td>946 (16)</td>
<td>1943 (17)</td>
</tr>
<tr>
<td>20-29</td>
<td>3196 (53)</td>
<td>2909 (50)</td>
<td>6105 (52)</td>
</tr>
<tr>
<td>30-69</td>
<td>1785 (30)</td>
<td>1935 (33)</td>
<td>3720 (32)</td>
</tr>
<tr>
<td>Total</td>
<td>5978 (51)</td>
<td>5790 (49)</td>
<td>11,768</td>
</tr>
</tbody>
</table>

*Data are given as number of subjects (percentage).
inpatient services). We multiplied standard unit costs by volume of use to obtain total costs over an interval of time. The expenditures of KPNW include essentially all of the costs of acute inpatient care received by its members and nearly 100% of outpatient costs (fewer than 10% of members use an out-of-plan service in any given year). We adjusted all costs to reflect 1993 prices.

OUTPATIENT COSTS WITHIN KPNW

We included visit-associated imaging and testing in the costs of outpatient visits. Standard unit visit costs were calculated separately by type of clinician (physician vs physician assistant and/or nurse practitioner) and by specialty, based on a special study of outpatient costs conducted in 1993. We obtained the total visit costs by multiplying the number of visits per department per clinician type by the appropriate unit cost.

INPATIENT COSTS WITHIN KPNW

We captured 4 inpatient use parameters to calculate inpatient costs: (1) number of days in a critical care unit, (2) number of days in routine care, (3) number of minutes in an operating room, and (4) number of minutes in a recovery room. All clinician inpatient costs and hospital indirect costs (including personnel, utilities, depreciation, and fixtures) were first allocated to the relevant cost center. Total annual expenditures per cost center were then divided by the total volume of output to estimate the average cost per unit of use. These time-based cost coefficients were then multiplied by the number of units of services consumed, totaled, and combined with inpatient imaging costs to obtain an estimate of the total inpatient cost of caring for an individual for a given admission or year.

COSTS INCURRED AT NON-KPNW FACILITIES

To ascertain the costs of care in non-KPNW facilities, we analyzed the claims paid for procedures, hospitalizations, and professional and related services. For inpatient and outpatient use provided both in non-KPNW facilities and by non-KPNW clinicians, we used as costs the amounts that KPNW actually paid to vendors. Inpatient and outpatient pharmaceutical costs approximated 1995 retail costs in the local market, deflated to 1993 dollars.

STATISTICAL METHODS

To identify the most valid analytic method, we tested 3 regression techniques: a 2-part model, a transformation model, and an ordinary least squares (OLS) model. The 2-part model employed logistic regression to determine the probability of use (cost > 0), followed by an OLS, or gamma regression, of total annual cost for the year 1995 for subjects with costs greater than 0. The predicted expense was then multiplied by the probability of use to obtain predicted cost, adjusted for the probability of use. The transformation model involved normalizing the distribution of total annual cost by taking the natural log (cost plus an arbitrary constant value). The logarithmic transformation adequately normalized the dependent variable so that the regression assumptions were met, but the coefficients obtained from this model were not directly translatable into dollars. In addition, after retransformation, the model did not predict as well as untransformed OLS. We concluded, as did Hornbrook and Goodman, that OLS was as good as, or better than, the other techniques in terms of both predictive accuracy and interpretability.

We therefore present 2 OLS models in this report. The first model regressed total annual cost per person on cardiovascular complication level, renal complication level, age, and sex. We included subject age and sex as independent variables to estimate the incremental costs of complications in addition to the costs attributable to sex-specific aging. We also estimated a second model that added a “renal × cardiovascular” interaction term. This model accounts for the known epidemiological interaction between diabetic, renal, and cardiovascular disease18 and tests whether the incremental costs of cardiovascular and renal disease are more or less than additive when both complications are present.

We used the SAS Statistical Analysis System version 6.12 (SAS Institute, Cary, NC) for all statistical analyses. All the statistical tests that we report are 2-sided. The term statistically significant implies a P < .05.

Unadjusted total treatment expenditures per person categorized by age, sex, and complication level are given in Table 3. Subjects without renal disease had higher average treatment costs than those without cardiovascular disease, presumably because the former group included a substantial complement of subjects with cardiovascular disease. Overall, treatment expenditures across cardiovascular disease stages were consistently associated with age and were similar by stage in men and women. Unadjusted costs of end-stage renal disease, however, decreased with age and were dramatically higher for women in all age groups.

Table 4 gives the results of regressing the total treatment cost per person categorized by age, sex, cardiovascular complication stage, and renal complication stage. In this model, the coefficient on a complication stage represents the estimated total cost involved in treating that stage, compared to the cost without any stage of the complication (stage 0). Table 4 also displays the marginal treatment cost per stage, which is the treatment cost incurred by progression to the current stage from the next lower stage.

Age was a nonsignificant predictor of the cost of complications in the multivariate model. However, expenditures for women exceeded expenditures for men by an average of $1105, controlling for age and stage of complication. The OLS model was highly statistically significant and explained 10.3% of the total variance in costs.

In Table 5, we report the results of a regression model that adds interaction terms between all 3 stages of cardiovascular disease and all 4 stages of renal disease. Our intentions here were to improve model fit by acknowledging the possibly causal associations between renal and cardiovascular disease in diabetes, and to obtain adjusted estimates of the incremental costs of renal disease stages, given alternative stages of cardiovascular.
cicular disease. As expected, we observed statistically significant interactions between stages of cardiovascular disease and stages of renal disease. The model with interactions provided a slightly better fit, explaining 10.6% of the variation in costs. However, estimates for sex, age, and the cost of uncomplicated diabetes were similar to those obtained from the model without interactions.

Table 5 presents the results of the interaction model in 3 columns. Column A reports the estimated additional costs associated with each combination of complications. (No value is given for the cost of end-stage renal disease in cardiovascular stage 0 because too few subjects occupied this cell to yield a stable estimate. In addition, many other cells had stable but nonsignificant estimates due to small sample size.) Column B displays the costs per cell that the interactive model predicted apart from the contributions of the interaction terms. Finally, column C shows the net effect of each interaction. Although many of the interaction term coefficients were not significantly different from 0, a general pattern emerged: renal disease imposed higher-than-average additional costs in subjects with postevent (stage 2) cardiovascular disease, and lower-than-average additional costs in the presence of stage 1 and stage 2 cardiovascular disease. Considering only the statistically significant interactions, all but one of the interaction effects were small, less than $1000. The one exception involved subjects in the highest stage of both cardiovascular and renal disease. This combination of complications exhibited substantially higher costs ($3734) than would have been expected without an interaction.

Studies show that, on a population basis, cardiovascular disease is the most costly complication of type 2 diabetes mellitus. Moreover, in an estimated 86% of persons with type 2 diabetes mellitus, cardiovascular disease is the cause of death. Renal disease appears to be the next most costly complication, accounting for at least 10% of the incremental costs of diabetes in popula-
Cardiovascular and renal disease are closely related, and there is mounting evidence that they are both strongly associated with insulin resistance. In addition, microalbuminuria strongly predicts the development of cardiovascular disease. Consistent with these reports, 75% of the population we studied were under treatment for cardiovascular risk factors or had evidence of cardiovascular disease, whereas only 23% had evidence of abnormal renal function, including 11% who had either advanced or end-stage renal disease.

The purpose of the present study was to estimate the additional medical care costs imposed by cardiovascular and renal disease in persons with type 2 diabetes mellitus and to understand how these additional costs grow as cardiovascular and renal disease progress. The independent contribution of cardiovascular disease to individual cost ranged from about $1100 for those persons taking cardiovascular drugs and/or with a history of visits to a cardiologist, to about $7400 for persons who had experienced a major cardiovascular, cerebrovascular, or peripheral vascular event. The additional cost of care associated with early signs of renal disease was similar, about $1300. This cost rose to an additional $4000 with the development of advanced renal dysfunction and to $15 700 with the onset of chronic renal failure. When renal failure (or a history of transplantation) occurred in the presence of postevent cardiovascular disease, costs increased an additional $3700 per person-year.

Costs of renal disease were lower than average in subjects with less advanced cardiovascular disease, probably because the primary pharmacologic treatment for microalbuminuria and proteinuria was ACE-inhibitor therapy. In our staging algorithm, ACE-inhibitor use was the single most common reason a subject was included in cardiovascular stage 1. Therefore, treatment of microalbuminuria and proteinuria could have added little to the cost of treating stage 1 cardiovascular disease. Also, by definition, no subject with microalbuminuria or proteinuria in stage 0 cardiovascular disease received an ACE inhibitor.

Later stages of cardiovascular and renal disease were more common in older subjects, but age did not modify the additional cost of treating these complications. Treatment was about as expensive in younger subjects as in older subjects. However, women had substantially higher medical care costs—about $1100 higher—after controlling for age and the presence of complications. The explanation for this sex difference is unclear.

### Table 4. Estimates of the Independent Contributions to Health Care Cost of Renal and Cardiovascular Complications in Type 2 Diabetes Mellitus, Based on Linear Regression*

<table>
<thead>
<tr>
<th>Characteristic orComplication†</th>
<th>Cumulative Contribution to Cost, $ (Parameter Estimate)</th>
<th>Marginal Cost per Stage, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept (no CVD or renal disease)</td>
<td>2033‡</td>
<td>2033</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>−67</td>
<td></td>
</tr>
<tr>
<td>Sex: female</td>
<td>1105‡</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular complication stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preventive treatment</td>
<td>1087‡</td>
<td>1087</td>
</tr>
<tr>
<td>Postevent</td>
<td>7352‡</td>
<td>6265</td>
</tr>
<tr>
<td>Renal complication stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>1337‡</td>
<td>1337</td>
</tr>
<tr>
<td>Advanced</td>
<td>3979‡</td>
<td>2642</td>
</tr>
<tr>
<td>ESRD</td>
<td>16 675‡</td>
<td>13 033</td>
</tr>
</tbody>
</table>

*The following regression model was used: cost = intercept + β1 age + β2 female + β3 (CVD stage i) + β4 (renal stage j) + error. Adjusted R² = 10.3%.
†CVD indicates cardiovascular disease; ESRD, end-stage renal disease.
‡Significantly different from 0 based on 2-sided test at level α = .05.
§Estimates are unstable owing to few cases in these categories.

### Table 5. Joint Additional Contributions to Cost of Renal and Cardiovascular Complications*

<table>
<thead>
<tr>
<th>Joint Complication Groups</th>
<th>Contribution to Cost With Interactions‡</th>
<th>Contribution to Cost Assuming No Interaction (B)</th>
<th>Net Interaction Cost (A−B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept (no cardiovascular or renal disease)</td>
<td>2105‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sex: female</td>
<td>1066‡</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>−59</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>No cardiovascular treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>−12</td>
<td>1337</td>
<td>−1349</td>
</tr>
<tr>
<td>Advanced renal complications</td>
<td>3515‡</td>
<td>3979</td>
<td>−464‡</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>15 675‡</td>
<td>13 033</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular complications—preventive treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No renal complications and no tests</td>
<td>1206‡</td>
<td>1087</td>
<td>119‡</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>2139</td>
<td>2424</td>
<td>−285</td>
</tr>
<tr>
<td>Advanced renal complications</td>
<td>3483</td>
<td>5066</td>
<td>−1583</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>8886</td>
<td>16 762</td>
<td>−7876</td>
</tr>
<tr>
<td>Cardiovascular complications—after the event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No renal complications and no tests</td>
<td>6711‡</td>
<td>7352</td>
<td>−641‡</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>9300‡</td>
<td>8689</td>
<td>611‡</td>
</tr>
<tr>
<td>Advanced renal complications</td>
<td>12 030</td>
<td>11 331</td>
<td>699</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>26 761‡</td>
<td>23 027</td>
<td>3734‡</td>
</tr>
</tbody>
</table>

*All data are given in 1993 dollars. NA indicates not applicable.
†The following regression model was used to generate column A: cost = intercept + β1 age + β2 female + β3 (CVD stage i) + β4 (renal stage j) + β5 (CVD stage i and renal stage j) + error. Adjusted R² = 10.6%. CVD indicates cardiovascular disease.
‡Parameter estimate significantly different from 0 based on 2-sided test at level α = .05.
§Estimates are unstable owing to few cases in these categories.
Our estimates of the costs of cardiovascular disease are much lower than a recent report of empirical estimates of the costs of cardiovascular disease in diabetes.7 In their report, Gilmer et al12 estimated the costs of treating hyperglycemia controlling for the presence of cardiovascular disease (including hypertension), which added an estimated $11,326 in treatment costs per person-year (1995 dollars), assuming a glycosylated hemoglobin value of 8.0%. However, Gilmer et al calculated costs from charges, whereas our estimates are based on actual costs.

Our method (basing estimates on aggregate departmental expenditures) and our results also differ from the approach of O’Brien et al,13 whose estimates were based on precoded per-event costs derived from sources such as hospital discharge databases, clinical guidelines, government reports, fee schedules, and peer-reviewed literature. Because O’Brien et al could not ascertain unprecoded costs, their estimates of early-stage costs are much lower than ours—less than $100 per year for both microalbuminuria and gross proteinuria. (They did not estimate early cardiovascular disease costs.) For end-stage renal disease, however, their annual estimate was dramatically higher, $53,700 compared with our $15,700. The primary reasons for this discrepancy are the use of Medicare payment data by O’Brien et al, rather than actual costs, and their inclusion of all expenditures incurred by Medicare for persons with end-stage renal disease, not just the incremental payments incurred in treating the condition.

Our estimates may also be compared with aggregate estimates of the costs of renal and cardiovascular complications in defined populations.2 Populationwide costs of treating renal and cardiovascular disease can be calculated from our results by weighting the cumulative costs of each disease stage by the inverse of its prevalence. Table 6 summarizes the results of such calculations by complication and by stage of complication. For cardiovascular disease, our results imply an average per-person cost of $2,629, mostly attributable to the cost of treating postevent (stage 2) disease. This amount is considerably higher than the best comparable published estimates of cardiovascular costs. For example, from a report by Huse et al1 on the 1986 cost of treating type 2 diabetes mellitus, based on national US samples, it is possible to calculate a per-person cost associated with cardiovascular disease of $664 per year. Glauber and Brown3 estimated that the medical care costs associated with cardiovascular disease among persons with diabetes totaled at least $8,587 per person per year in 1988. More recently, Selby et al2 estimated that cardiovascular disease accounts for 26% of the total incremental medical care costs of diabetes (costs caused by diabetes treatment over and above costs that would otherwise have been incurred by persons of similar age and sex), or $908 per person with diabetes per year in 1994 dollars.

For renal disease treatment, our results yielded an aggregate population cost per person of $719, much lower than for cardiovascular disease. Again, however, this result exceeds earlier estimates, such as the $18 calculable from Huse et al and the $370 estimated by Selby et al.2

Previous studies of the aggregate costs of complications in populations with diabetes yielded lower estimates because they attributed costs to complications only when available data explicitly associated an expenditure with a diagnosis.13 For example, the cost of a hospitalization was attributed to cardiovascular disease if the first listed discharge diagnosis was acute myocardial infarction. However, these studies would have missed, for example, the contribution of cardiovascular disease to the need for podiatric care. Our results strongly suggest that incremental cost estimates based solely on labeled use will dramatically underestimate true incremental cost.

Despite the higher costs of renal disease in affected subjects, our results indicate that substantially more money would be saved on a population basis by preventing the development or progression of cardiovascular disease rather than renal disease. This is because late-stage cardiovascular disease is much more common than late-stage renal disease. In addition, our analysis indicates that the aggregate annual cost of preventing cardiovascular events in type 2 diabetes mellitus is, at most, only about one fifth the cost of caring for persons after they have had such events. This supports the view that the prevention of cardiovascular disease is cost-effective in type 2 diabetes mellitus. On the other hand, the aggregate annual cost of treating end-stage renal disease is relatively low, $157 per person-year. Investments in the prevention of end-stage renal disease probably do not contribute greatly to cost savings.

Our analysis has several limitations. First, we have not included complications other than cardiovascular and renal disease. Some bias may have resulted from these omissions. Additional studies with more comprehensive and detailed data are needed to provide estimates of the costs of treating additional complications.

Second, our ability to stage disease was limited by the clinical data available to us electronically. This resulted in a relatively crude staging, and clinical ascertainment undoubtedly lagged behind the physiological appearance of disease in many subjects. Fortunately or unfortunately, however, the costs of treating complications primarily occur after clinical diagnosis, so our cost estimates are probably better than our epidemiological staging. A related limitation was imposed by the necessity of using drug-use data to ascertain cardiovascular

### Table 6. Estimated Aggregate Incremental Annual Cost by Stage of Cardiovascular and Renal Complications*

<table>
<thead>
<tr>
<th>Complication Stage</th>
<th>Aggregate Cost</th>
<th>Average Cost per Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular disease</td>
<td>30,932,776</td>
<td>2,629</td>
</tr>
<tr>
<td>Preventive treatment</td>
<td>5,862,935</td>
<td>498</td>
</tr>
<tr>
<td>Postevent treatment</td>
<td>25,069,841</td>
<td>2,130</td>
</tr>
<tr>
<td>Any renal disease</td>
<td>8,457,543</td>
<td>719</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>1,916,301</td>
<td>163</td>
</tr>
<tr>
<td>Advanced renal complications</td>
<td>4,695,432</td>
<td>399</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>1,845,811</td>
<td>157</td>
</tr>
</tbody>
</table>

*All data are given in 1993 dollars.
stage 1. Because ACE inhibitors are used for hypertension control and other cardiovascular purposes, as well as to control nephropathy, we underestimated the incremental cost of nephropathy in stage 0 and stage 1 cardiovascular disease.

Third, care should be taken when applying our estimates to other settings. Our study site was a well-established, not-for-profit group-model HMO with a successful history of cost control, in a low-cost region of the country, operating in a competitive local market. Unit costs might well be higher in other settings. On the other hand, use of services might be lower in systems that imposed high copayments and deductibles, or where access to care is limited for other reasons. Physicians in KPNW are encouraged to use aggressive methods of treatment and prevention. In other settings, factors such as costs, patient profile, access to care, and aggressiveness of treatment are likely to influence findings.

Finally, our models may have overestimated the incremental contribution of cardiovascular and renal disease as complications of diabetes to some degree, because persons without diabetes also experience cardiovascular and renal disease. This problem is inconsiderant for renal disease, because renal disease is tens of times more prevalent in patients with diabetes than in those without diabetes. Cardiovascular disease, however, is only 3 to 5 times more prevalent in diabetes.3,14 Perhaps 20% to 30% of our estimated costs of treating cardiovascular disease would have occurred in these subjects in the absence of diabetes.

These limitations notwithstanding, we believe that the present study provides the best estimates to date of the additional costs imposed by treatment of the 2 most costly complications of type 2 diabetes mellitus, both in individuals who develop them and in the aggregate. Our estimates suggest that, on an individual basis, the largest cost savings would be achieved by preventing the progression to stage 3 renal disease and especially by preventing end-stage renal disease in persons postevent cardiovascular disease. On an aggregate population basis, the greatest savings would be achieved by preventing major cardiovascular events. Recent studies show that aggressive treatment of hypertension and hyperlipidemia is successful in reducing microvascular and macrovascular complications.15-19 Novel therapeutic interventions in type 2 diabetes mellitus—especially those such as the thiazolidinediones that attack underlying processes of the insulin-resistance syndrome—should be evaluated for their ability to prevent cardiovascular and renal complications as well as for their antihyperglycemic effects.

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STAGES OF CARDIOVASCULAR DISEASE

Stage 0: No evidence of complication.
Stage 1: Pre-event treatment—taking cardiovascular drugs or a history of at least 2 specialty visits to a cardiologist. Cardiovascular drugs include antihyperlipidemics and antihypertensives as well as drugs used to treat the symptoms of cardiovascular disease.
Stage 2: Postevent cardiovascular disease—hospitalization data indicating a major active cardiac, cerebrovascular, or peripheral vascular event. This includes history of coronary artery bypass graft, coronary angioplasty, heart transplantation, carotid endarterectomy, amputation, or peripheral artery bypass, as well as any of the following International Classification of Diseases, Ninth Revision discharge diagnoses:

(a) 402.91 - Hypertensive heart disease with congestive heart failure
(b) 428.xx - Heart failure
(c) 410.xx - Acute myocardial infarction
(d) 411.xx - Other acute and subacute forms of ischemic heart disease
(e) 412.xx - Old myocardial infarction
(f) 413.xx - Angina pectoris
(g) 414.xx - Other forms of chronic ischemic heart disease
(h) 431.xx - Intracerebral hemorrhage
(i) 432.xx - Unspecified intracranial hemorrhage
(j) 433.xx - Occlusion and stenosis of precerebral arteries
(k) 434.xx - Occlusion of cerebral arteries
(l) 435.xx - Transient cerebral ischemia
(m) 436.xx - Acute but ill-defined cerebrovascular disease
(n) 437.xx - Other cerebrovascular disease
(o) 784.30 - Aphasia or history of carotid endarterectomy
(p) 250.70 - Diabetes with peripheral circulatory disorders
(q) 440.00 - Atherosclerosis
(r) 441.00 - Aortic aneurysm
(s) 443.90 - Unspecified peripheral vascular disease
(t) 444.xx - Arterial embolism and thrombosis
(u) 785.40 - Gangrene
(v) 707.10 - Chronic ulcer of lower limbs, except decubitus

STAGES OF RENAL DISEASE

Stage 0: Normal—normal laboratory test results or no laboratory tests.
Stage 1: Abnormal—abnormal laboratory tests suggesting microalbuminuria or early proteinuria; at least 1 microalbumin test value higher than 45 µmol/L or inpatient, or more 24-hour protein quantitated urine test values higher than 165 mg for a 24-hour period.
Stage 2: Advanced Nephropathy—serum creatinine levels higher than 141 µmol/L (1.6 mg/dL) or creatinine clearance under 0.83 mL/s (50 mL/min) or inpatient.

APPENDIX

STAGES OF RENAL DISEASE

Stage 0: No evidence of complication.
Stage 1: Pre-event treatment—taking cardiovascular drugs or a history of at least 2 specialty visits to a cardiologist. Cardiovascular drugs include antihyperlipidemics and antihypertensives as well as drugs used to treat the symptoms of cardiovascular disease.
Stage 2: Postevent cardiovascular disease—hospitalization data indicating a major active cardiac, cerebrovascular, or peripheral vascular event. This includes history of coronary artery bypass graft, coronary angioplasty, heart transplantation, carotid endarterectomy, amputation, or peripheral artery bypass, as well as any of the following International Classification of Diseases, Ninth Revision discharge diagnoses:

(a) 402.91 - Hypertensive heart disease with congestive heart failure
(b) 428.xx - Heart failure
(c) 410.xx - Acute myocardial infarction
(d) 411.xx - Other acute and subacute forms of ischemic heart disease
(e) 412.xx - Old myocardial infarction
(f) 413.xx - Angina pectoris
(g) 414.xx - Other forms of chronic ischemic heart disease
(h) 431.xx - Intracerebral hemorrhage
(i) 432.xx - Unspecified intracranial hemorrhage
(j) 433.xx - Occlusion and stenosis of precerebral arteries
(k) 434.xx - Occlusion of cerebral arteries
(l) 435.xx - Transient cerebral ischemia
(m) 436.xx - Acute but ill-defined cerebrovascular disease
(n) 437.xx - Other cerebrovascular disease
(o) 784.30 - Aphasia or history of carotid endarterectomy
(p) 250.70 - Diabetes with peripheral circulatory disorders
(q) 440.00 - Atherosclerosis
(r) 441.00 - Aortic aneurysm
(s) 443.90 - Unspecified peripheral vascular disease
(t) 444.xx - Arterial embolism and thrombosis
(u) 785.40 - Gangrene
(v) 707.10 - Chronic ulcer of lower limbs, except decubitus

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tient diagnosis indicating advanced renal disease based on the following International Classification of Diseases, Ninth Revision discharge diagnoses:
(a) 585.xx - chronic renal failure
(b) 86.00 - unspecified renal failure
Stage 3: End-stage renal disease—renal transplantation or long-term hemodialysis.

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