Coronary revascularization induces a shift from cardiac toward noncardiac mortality without improving survival in vascular surgery patients

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Objective: Although evidence has shown that ischemic heart disease (IHD) in vascular surgery patients has a negative impact on the prognosis after surgery, it is unclear whether directed treatment of IHD may influence cause-specific and overall mortality. The objective of this study was to determine the prognostic implication of coronary revascularization (CR) on overall and cause-specific mortality in vascular surgery patients.
Methods: Patients undergoing surgery for abdominal aortic aneurysm, carotid artery stenosis, or peripheral artery disease in a university hospital in The Netherlands between January 2003 and December 2011 were retrospectively included. Survival estimates were obtained by Kaplan-Meier and Cox regression analysis.
Results: A total of 1104 patients were included. Adjusted survival analyses showed that IHD significantly increased the risk of overall mortality (hazard ratio [HR], 1.50; 95% confidence interval, 1.21-1.87) and cardiovascular death (HR, 1.93; 95% confidence interval, 1.35-2.76). Compared with those without CR, patients previously undergoing CR had similar overall mortality (HR, 1.38 vs 1.62; $P = .274$) and cardiovascular mortality (HR, 1.83 vs 2.02; $P = .656$). Nonrevascularized IHD patients were more likely to die of IHD (6.9% vs 35.7%), whereas revascularized IHD patients more frequently died of cardiovascular causes unrelated to IHD (39.1% vs 64.3%; $P = .018$).
Conclusions: This study confirms the significance of IHD for postoperative survival of vascular surgery patients. CR was associated with lower IHD-related death rates. However, it failed to provide an overall survival benefit because of an increased rate of cardiovascular mortality unrelated to IHD. Intensification of secondary prevention regimens may be required to prevent this shift toward non-IHD-related death and thereby improve life expectancy. (J Vasc Surg 2015;61:1543-9.)

A number of reports have shown that long-term survival in patients undergoing vascular surgery procedures is as low as 25% after 10 years.[1] Cardiovascular causes account for the majority of early and late mortality after vascular surgery, surpassing 60%.[2] It is well known that patients undergoing vascular surgery are frequently affected by coronary artery disease, symptomatic or not.[3] Because the presence of ischemic heart disease (IHD) is associated with postoperative morbidity and mortality after noncardiac vascular surgery, IHD has been the subject of numerous studies regarding survival, preoperative evaluation, and perioperative management. Although evidence has shown that IHD in vascular surgery patients has a negative impact on the prognosis after surgery, it is unclear whether this is solely due to IHD-related death or due to non-IHD-related mortality risks as well.[4,5]

In an attempt to improve postoperative survival, several studies have investigated the effectiveness of coronary revascularization (CR) on the prognosis of patients undergoing noncardiac interventions.[6-14] The interpretation of these studies in terms of survival benefits is hampered by relatively short follow-up periods, small sample sizes, or heterogeneity within the studied population regarding patient and procedural risks. Retrospective data suggested that prior coronary bypass surgery was associated with a reduction of 30-day myocardial infarction and death rates.[6] However, subsequent randomized trials demonstrated that CR before vascular surgery does not improve survival.[7,8]

In light of these results and the systemic nature of atherosclerotic disease, we hypothesized that long-term survival will be similar between IHD patients with CR and IHD patients without CR because of a shift from IHD-related toward non-IHD-related mortality.[15-17] The objective of this study was to determine the prognostic implication of IHD and CR on long-term overall and cardiovascular mortality in patients undergoing vascular surgery.

METHODS

Patients. Patients undergoing elective open or endovascular surgery under general or locoregional anesthesia

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for abdominal aortic aneurysm, carotid artery stenosis, or peripheral artery disease in the Erasmus University Medical Center between January 2003 and December 2011 were retrospectively included. Identification was done with the use of operation codes and surgical reports. Because we were interested in the effect of IHD and prior CR on procedures that are accompanied by severe cardiac stress, patients undergoing percutaneous procedures (ie, percutaneous endovascular aneurysm repair, carotid artery stenting, and lower extremity revascularization) or procedures performed under local anesthesia were not included in this study. When a patient underwent multiple vascular procedures within the study period, the first operation in this period was defined as the index operation, and survival was assessed from that moment onward. Baseline characteristics were obtained from hospital records and included age, gender, cardiac history, other comorbidities, smoking status (current, former, or never), and body mass index (BMI). Patients were grouped according to their cardiac status before the index operation. IHD was considered if one of the following was present: reference to previous cardiac ischemic events in cardiology notes, prior coronary intervention, or evidence of myocardial ischemia in provocative preoperative tests (dobutamine stress echocardiography or myocardial scintigraphy). CR was defined as coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) at any time before the index vascular operation. Treatment indications for CR were in accordance with the American Heart Association guidelines (Appropriateness Criteria for Coronary Revascularization). Institutional approval for this study was obtained, and no informed consent was required according to local directives for retrospective studies. The study complies with the Helsinki Declaration on research ethics.

Definitions. Diabetes mellitus was recorded if diabetes was mentioned in the medical history or if patients used insulin or oral antidiabetics. Hypertension was defined as blood pressure >140/90 mm Hg or use of antihypertensive medication. A history of cancer was defined as past or current malignant neoplastic disease, except for basal cell carcinoma. Renal insufficiency was defined as an estimated glomerular filtration rate <60 mL/min as calculated from preoperative serum creatinine levels using the Modification of Diet in Renal Disease formula. Smoking status and BMI were derived from the medical records.

Follow-up. Survival status was obtained by inquiry of the civil registry. The latest date of follow-up was considered December 31, 2012.

Cause of death. Data regarding the causes of death were obtained from the Dutch Central Bureau of Statistics (CBS). A database containing all relevant patient characteristics from the hospital records was anonymized and imported into the CBS and was subsequently linked to the Dutch death registries. Because of CBS regulation, data analysis was performed only by authorized researchers (K.U., F.B.G.) in a secure environment at the CBS head office. Before data were approved to be used for publication purposes, all output was independently checked for privacy violations by two separate reviewers. The cause of death was defined as the cause for the initial health deterioration that subsequently resulted in death. This approach is similar to the strategy employed for the overall Dutch population death registrations and reports. Autopsy was not regularly performed. The causes of death were grouped according to the International Classification of Diseases, Tenth Revision. The following codes were used: for cardiovascular death, I10-I79; for IHD-related death, I20-I25, I50; and for non-IHD cardiovascular death, I10-I19, I26-I49, I51-I79 (Supplementary Table, online only). Because IHD is the principal etiology of heart failure, death due to heart failure-related causes was classified as IHD-related death.[18,19]

End points. The primary end points were long-term overall and cardiovascular mortality. Secondary end points were IHD-related and non-IHD-related cardiovascular mortality.

Statistical methods. Baseline characteristics were described as counts and percentages (dichotomous variables) or means and standard deviations (continuous variables). Differences at baseline were determined by Pearson χ^2 analysis and one-way analysis of variance testing, where appropriate. For survival analyses, patients were grouped according to their cardiac medical history. Patients' overall survival was initially assessed by Kaplan-Meier analyses. Cox proportional hazards models were constructed to study the impact of IHD and the influence of invasive treatment on overall and cardiovascular survival in an adjusted manner. Multivariate analyses included demographics (ie, age and gender), comorbidities (ie, diabetes, hypertension, a history of cancer, renal insufficiency, and BMI), and behavioral risk factors (ie, smoking). To determine the prognostic implications of invasive and noninvasive treatment strategies for IHD (ie, CABG or PCI), the overall IHD group was subdivided into a non-CR group and a CR group. The non-IHD group was designated the reference category for the Cox regression analyses. Differences in cardiovascular death distribution (ie, different proportions of IHD-related and non-IHD-related death) were tested with the use of χ^2 analyses. All tests were two sided, and significance was considered a P value $< .05$. Statistical analysis was performed with the IBM SPSS Statistics 20 (IBM Inc, Chicago, Ill).

RESULTS

Between January 2003 and December 2011, a total of 1107 patients received surgical treatment for abdominal aortic aneurysm, carotid artery stenosis, or peripheral artery disease. Three patients (0.3%) were excluded because of unobtainable follow-up due to emigration. Among the resulting 1104 patients, 499 (45.2%) had a history of IHD. Within the IHD group, CR was performed preoperatively in 245 cases (22.2%).

Baseline characteristics. Baseline characteristics per study group (ie, non-IHD, non-CR IHD, and CR IHD) are listed in Table I. Vascular surgical patients with IHD were older, were more frequently of male gender, and had

Table I. Baseline characteristics

Variable	*Non-IHD (n = 605)*	*Non-CR IHD (n = 254)*	*CR IHD (n = 245)*	P *value*
Demographics				
Female gender	174 (29)	47 (19)	36 (15)	<.001
Age, years	67.4 (±10.2)	70.0 (±9.6)	69.4 (±9.3)	.001
Prior medical history				
Diabetes mellitus	112 (19)	65 (26)	67 (27)	.006
History of cancer	98 (16)	45 (18)	41 (17)	.868
Peripheral arterial occlusive disease	251 (41)	108 (43)	123 (50)	.062
Renal insufficiency	126 (21)	76 (30)	82 (33)	<.001
Cerebrovascular disease	238 (39)	100 (39)	94 (38)	.962
Hypertension	375 (62)	190 (75)	190 (78)	<.001
History of vascular interventions	133 (22)	64 (25)	63 (26)	.406
IHD Characteristics				
Myocardial infarction	0	186 (73)	189 (77)	—
Angina	0	91 (36)	202 (83)	—
CABG/PTCA	0	0	245 (100)	—
Environmental risk factors				
Smoking	257 (43)	97 (38)	75 (31)	.005
BMI, kg/length^2	25.7 (±4.1)	26.2 (±4.3)	26.9 (4.1)	.001

BMI, Body mass index; *CABG,* coronary artery bypass graft; *CR,* coronary revascularization (ie, CABG or PTCA); *IHD,* ischemic heart disease; *PTCA,* percutaneous transluminal coronary angioplasty.

Baseline characteristics are described as counts and percentages (dichotomous variables) or means and standard deviations (continuous variables).

a higher BMI than those without IHD. Furthermore, diabetes, renal insufficiency, and hypertension were more common among patients with IHD. Finally, current smoking was more frequently observed among non-IHD patients.

Overall mortality. During a median follow-up of 4.1 years (interquartile range, 2.3-5.9), 164 (27.1%), 108 (42.5%), and 91 (37.1%) deaths occurred in the non-IHD, non-CR IHD, and CR IHD groups, respectively (Table II). Kaplan-Meier analyses showed a significant difference in the postoperative prognosis between non-IHD and IHD patients, with an expected survival at 5 years of 74% and 62%, respectively ($P < .001$; Fig 1). There was no significant difference in survival between IHD patients without CR and IHD patients with CR (60% and 62% at 5 years for non-CR and CR IHD groups, respectively; $P = .167$). IHD was confirmed as an independent risk factor for all-cause mortality in Cox regression analysis compared with vascular surgical patients without a history of IHD (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.21-1.87; Table III). Regarding survival for the groups separately, compared with the non-IHD group, the non-CR IHD group (HR, 1.62; 95% CI, 1.26-2.08) and the CR IHD group (HR, 1.38; 95% CI, 1.05-1.80) were burdened by additional survival hazards. However, there was no significant difference in overall survival between the revascularized and the nonrevascularized IHD groups ($P = .274$).

Cardiovascular mortality. Causes of death could be obtained for all but one patient (99.7%). Cardiovascular disease was reported as the cause of death in 53 cases (32.5%) in the non-IHD group and in 46 cases (42.6%) and 42 cases (46.2%) in the non-CR and CR IHD groups, respectively (Table II). Adjusted analysis showed that patients with IHD were at higher risk of cardiovascular death compared with patients without IHD (HR, 1.93; 95% CI, 1.35-2.76; Table III). Both the nonrevascularized group (HR, 2.02; 95% CI, 1.34-3.04) and the revascularized group (HR, 1.83; 95% CI, 1.19-2.81) had an increased risk of cardiovascular death compared with the non-IHD group. Equivalent to overall survival, cardiovascular survival between the non-CR and CR groups was similar ($P = .656$).

IHD-related and non-IHD-related cardiovascular mortality. IHD-related death occurred 13 times (8.0%) in the non-IHD group during the follow-up period. In the

Table II. Mortality and the causes of death for the study groups separately

Cause of death	*Non-IHD (n = 605)*	*Non-CR IHD (n = 254)*	*CR IHD (n = 245)*
All cause	164[a]	108	91
Cancer	54 (33.1)	23 (21.3)	20 (22.0)
Cardiovascular	53 (32.5)	46 (42.6)	42 (46.2)
IHD related	13 (8.0)	28 (25.9)	15 (16.5)
Non-IHD cardiovascular	40 (24.5)	18 (16.7)	27 (29.7)
Cerebrovascular disease	14 (8.6)	<5 (<4.6)[b]	<5 (<5.5)
Other arterial disease	17 (10.4)	13 (12.0)	17 (18.7)
Non-IHD[c]	6 (3.7)	<5 (<4.6)	6 (6.6)
Other[d]	<5 (<3.1)	<5 (<4.6)	<5 (<5.5)
COPD	10 (6.1)	<5 (<4.6)	5 (5.5)
Digestive system	10 (6.1)	<5 (<4.6)	<5 (<5.5)
Other causes	36 (22.1)	32 (29.6)	22 (24.2)

COPD, Chronic obstructive pulmonary disease; *CR,* coronary revascularization; *IHD,* ischemic heart disease.

Percentages are relative to the total obtained deaths per study group.

[a]Cause of death was obtained for 163 of 164 patients (99.3%).

[b]Numbers <5 were not provided to protect privacy.

[c]For example, valvular heart disease and cardiomyopathy.

[d]Hypertensive and pulmonary circulatory disease.

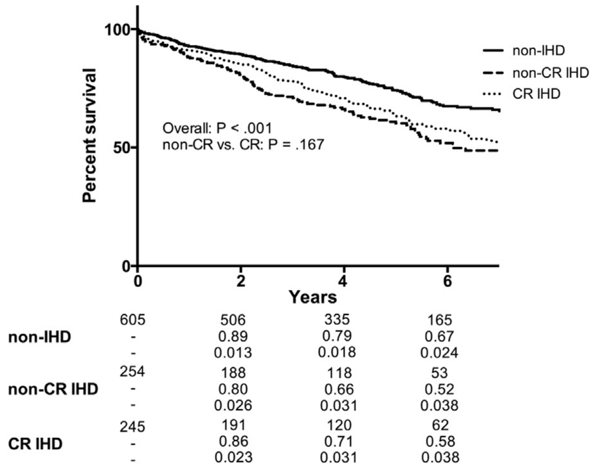

Fig 1. Kaplan-Meier analyses for overall survival. *CR,* Coronary revascularization; *IHD,* ischemic heart disease.

Table III. Cox regression analyses for overall and cardiovascular mortality

	Univariate			*Multivariate*		
	HR	*95% CI*	P *value*	*HR*	*95% CI*	P *value*
Overall death						
Overall IHD	1.64	1.33-2.01	<.001	1.50	1.21-1.87	<.001
Non-CR	1.80	1.41-2.29	<.001	1.62[a]	1.26-2.08	<.001
CR	1.48	1.15-1.92	.003	1.38[a]	1.05-1.80	.019
Cardiovascular death						
Overall IHD	2.24	1.59-3.15	<.001	1.93	1.35-2.76	<.001
Non-CR	2.36	1.59-3.50	<.001	2.02[b]	1.34-3.04	.001
CR	2.12	1.41-3.18	<.001	1.83[b]	1.19-2.81	.006

CI, Confidence interval; *HR,* hazard ratio; *IHD,* ischemic heart disease.
HRs for the two IHD groups separately were established in a model with the non-IHD group as reference category.
[a]Overall survival between the non-CR and the CR IHD groups did not differ ($P = .274$).
[b]Cardiovascular survival between the non-CR and the CR IHD groups did not differ ($P = .656$).

nonrevascularized and revascularized IHD groups, IHD-related death was determined in 28 (25.9%) and 15 (16.5%) cases, respectively (Table II, Fig 2). Death due to cardiovascular causes other than IHD was ascertained in 40 (24.5%), 18 (16.7%), and 27 (29.7%) cases. The distribution of the cardiovascular cause of death subgroups, IHD related and non-IHD related, was significantly different between the non-IHD and the non-CR IHD groups. Patients with a history of IHD were more likely to die of IHD-related causes, whereas the majority of cardiovascular death among non-IHD patients was unrelated to coronary artery disease ($P < .001$). No significant divergences were found in the cardiovascular death distributions between the non-IHD and the CR IHD groups ($P = .235$). The distribution between nonrevascularized and revascularized IHD patients, however, differed significantly. Cardiovascular death in the non-CR IHD group was predominantly due to IHD-related causes, whereas the majority of cardiovascular death among revascularized patients was due to non-IHD-related disease ($P = .018$).

DISCUSSION

The results of this study confirm that prior IHD is a significant prognostic factor for long-term overall and cardiovascular survival after vascular surgery. Interestingly, patients with previous CR had similar total cardiovascular mortality but proportionally less ischemic cardiac-related deaths compared with patients with a history of IHD but no prior revascularization. However, prior CR did not provide a survival benefit for patients with IHD. This indicates that coronary intervention had an impact on the occurrence of subsequent cardiac events but failed to provide protection for cardiovascular death in general.

Our findings are in line with the study by Back et al,[12] who showed that although perioperative cardiac factors are the primary determinants of life expectancy, patients with a history of CR did not have a better survival after major arterial reconstruction. In addition, the Coronary Artery Revascularization Prophylaxis (CARP) and DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V trials demonstrated that even preoperative CR in patients with extensive myocardial ischemia on preoperative cardiac testing failed to improve postoperative survival compared with best medical treatment alone in patients undergoing elective vascular surgery.[7-9,20] These studies formed the basis for the current standpoint that CR before major noncardiac surgery should not routinely be performed.[21]

As hypothesized, overall mortality and the death rate distribution among the main categories, including cardiovascular and cancer-related death, were similar in the non-CR and CR IHD groups. Further, we found that cardiovascular death in patients with established IHD who had not been treated for coronary stenosis by CABG or PCI was most frequently due to ischemic cardiac events. However, those who underwent prior coronary treatment more often died of noncardiac ischemic events, the majority of which were related to peripheral arterial rather than cerebrovascular disease. Thus, in spite of the impact on cardiac events, treatment of IHD induces a shift in the cause, rather than providing protection against cardiovascular death. Such a shift in mortality from IHD-related toward non-IHD-related death implicates that a history of IHD in vascular surgery patients should be regarded as a sign of advanced atherosclerotic disease. This is in agreement with several previous studies showing that vascular patients are often burdened by advanced atherosclerotic disease, whether or not they are symptomatic, in multiple vascular beds.[22,23] Also, it has been shown that the rates of ischemic events in other vascular beds are higher in vascular patients with a history of IHD compared with those without.[24-26]

In view of the risks conferred by advanced atherosclerotic disease, intensification of cardiovascular risk management may be a potential means to reduce noncardiac cardiovascular health hazards and to improve postoperative

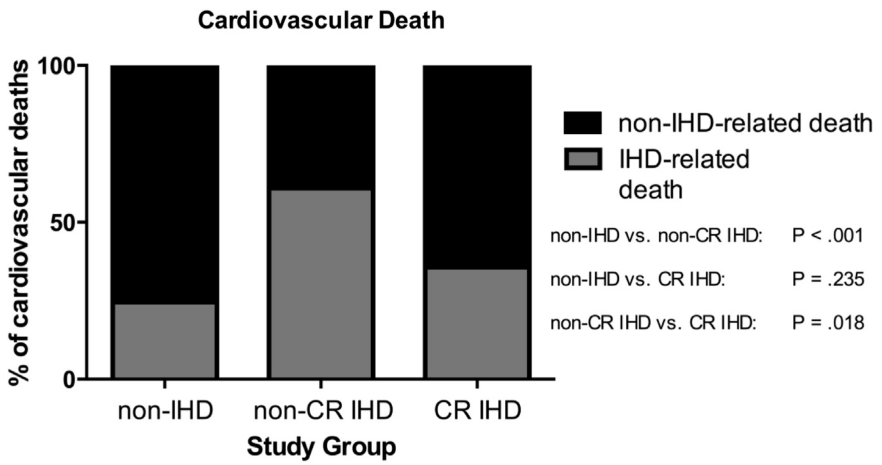

Fig 2. Proportions of specific cardiovascular death causes among the different study groups. Percentages are relative to the total cardiovascular deaths per study group. *CR,* Coronary revascularization; *IHD,* ischemic heart disease.

outcome in these high-risk individuals. Although the effectiveness of secondary prevention measures for reducing overall and cardiovascular death is well established, studies have demonstrated that adherence to the guidelines is <60%.[27] A lack of knowledge and the attitude of both patients and physicians have been implicated in playing a causal role.[28,29] Therefore, improving the attitude of patients and physicians regarding the importance of atherothrombotic risk and secondary prevention is worthwhile. In addition to stimulating guideline adherence, stricter management of the cardiovascular risk factors should be considered. For example, tight control of blood pressure (ie, ≤130-135 mm Hg), as opposed to relaxed control (ie, ≤140 mm Hg), might be associated with a reduction in cardiovascular morbidity and mortality.[30,31] Moreover, lowering blood pressure by as little as 10 mm Hg has been reported to reduce the lifetime risk for cardiovascular and stroke-related death by 25% to 40%.[32] Similar associations have been found for both blood glucose and lipid levels.[33-35]

The limitations of this study are inherent to its retrospective nature. Because all symptomatic IHD patients were grouped into a single IHD group, we could not differentiate between prognostic differences in relation to severity of IHD. Previous studies have questioned whether survival benefits from CR are generalizable.[36] Evidence suggests that survival benefits from CR before vascular surgery are most significant among severely affected coronary patients.[6] In addition, no difference was made on the basis of the time between CR and the index operation. Prior research has shown that the protective effect of CR for adverse cardiac events diminishes as time progresses.[11,37] This suggests that the demonstrated shift from IHD-related toward non-IHD-related cardiovascular mortality will be more apparent in vascular patients who have undergone recent CR. Our study could not discriminate between CABG and PCI in survival benefit analysis. Finally, stratified analysis for each surgical indication separately was not performed because of the limited event rates in the subgroups and the consequent lack of statistical power.

CONCLUSIONS

This study adds new insights into the implications of IHD on long-term survival in vascular surgery patients. Our data confirm the significance of IHD for postoperative survival of these patients as well as the effectiveness of CR in the reduction of cardiac ischemic events. However, we also show that treatment of IHD alone is insufficient to improve life expectancy in these high-risk patients. Patients with prior revascularization for IHD indeed have reduced risks of fatal cardiac ischemic events, but this does not translate into an overall survival benefit because they have a greater risk of dying of cardiovascular causes unrelated to IHD. Further research is warranted to determine whether more aggressive secondary prevention regimens are justified to prevent the shift toward non-IHD-related health hazards and thus improve postoperative survival in patients with advanced atherosclerotic disease.

AUTHOR CONTRIBUTIONS

Conception and design: KU, ER, FB, HV
Analysis and interpretation: KU, ER, SH, FL, EB
Data collection: KU, FB
Writing the article: KU, ER, SH, FL
Critical revision of the article: KU, ER, FL, FB, EB, RS, HV
Final approval of the article: KU, ER, SH, FL, FB, EB, RS, HV
Statistical analysis: KU, SH
Obtained funding: Not applicable
Overall responsibility: HV

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Supplementary Table (online only). Causes of death definitions in accordance with the *International Classification of Diseases, Tenth Revision (ICD-10)* classification

ICD-10	*Description*
Cancer-related death	
C00-C75	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, hematopoietic, and related tissue
C76-C80	Malignant neoplasms of ill-defined, secondary, and unspecified sites
C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic, and related tissue
C97-C97	Malignant neoplasms of independent (primary) multiple sites
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms
D37-D48	Neoplasms of uncertain or unknown behavior
Cardiovascular death	
IHD-related cardiovascular death	
I20-I25	Ischemic heart disease
I50-I50	Heart failure
Non-IHD-related cardiovascular death	
I10-I15	Hypertensive disease
I26-I28	Pulmonary heart disease and diseases of the circulatory system
I30-I49	Other forms of heart disease
I51-I52	Other forms of heart disease
I60-I69	Cerebrovascular disease
I70-I79	Diseases of arteries, arterioles, and capillaries
Chronic obstructive pulmonary disease-related death	
J40-J47	Chronic lower respiratory diseases
Digestive system-related death	
K00-K14	Diseases of oral cavity, salivary glands, and jaws
K20-K31	Diseases of esophagus, stomach, and duodenum
K35-K38	Diseases of appendix
K40-K46	Hernia
K50-K52	Noninfective enteritis and colitis
K55-K64	Other disease of intestines
K65-K67	Diseases of peritoneum
K70-K77	Diseases of liver
K80-K87	Disorders of gallbladder, biliary tract, and pancreas
K90-K93	Other diseases of the digestive system

IHD, Ischemic heart disease.