### Research

# Disability-free survival after major cardiac surgery: a population-based retrospective cohort study

Louise Y. Sun MD SM, Anan Bader Eddeen MSc, Thierry G. Mesana MD PhD

#### Abstract

**Background:** Cardiovascular research has traditionally been dedicated to "tombstone" outcomes, with little attention dedicated to the patient's perspective. We evaluated disability-free survival as a patient-defined outcome after cardiac surgery.

**Methods:** We conducted a retrospective cohort study of patients aged 40 years and older who underwent coronary artery bypass grafting (CABG) or single or multiple valve (aortic, mitral, tricuspid) surgery in Ontario between Oct. 1, 2008, and Dec. 31, 2016. The primary outcome was disability (a composite of stroke, 3 or more nonelective hospital admissions and admission to a long-term care facility) within 1 year after surgery. We assessed the procedure-specific risk of disability using cumulative incidence functions, and the relative effect of covariates on the subdistribution hazard using Fine and Gray models.

**Results:** The study included 72 824 patients. The 1-year incidence of disability and death was 2431 (4.6%) and 1839 (3.5%) for CABG, 677 (6.5%) and 539 (5.2%) for single valve, 118 (9.0%) and 140 (10.7%) for multiple valve, 718 (9.0%) and 730 (9.2%) for CABG and single valve, and 87 (13.1%) and 94 (14.1%) for CABG and multiple valve surgery, respectively. With CABG as the reference group, the adjusted hazard ratios for disability were 1.34 (95% confidence interval [CI] 1.21–1.48) after single valve, 1.43 (95% CI 1.18–1.75) after multiple valve, 1.38 (95% CI 1.26–1.51) after CABG and single valve, and 1.78 (95% CI 1.43–2.23) after CABG and multiple valve surgery, heart failure, creatinine 180 µmol/L or greater, alcohol use disorder, dementia and depression were independent risk factors for disability.

**Interpretation:** The cumulative incidence of disability was lowest after CABG and highest after combined CABG and multiple valve surgery. Our findings point to a need for models that predict personalized disability risk to enable better patient-centred care.

ardiac surgery is a growing field, with 2 million procedures currently being performed globally each year.<sup>1</sup> The last 2 decades have seen important advances in surgical and perioperative care and in improved patient survival.<sup>2-4</sup> On the other hand, as patients presenting for surgery become increasingly older and frail, they shift their goals and priorities toward how surgery might affect personal freedom and mobility, rather than longevity alone.<sup>5-9</sup> New or residual impairments after surgery are of particular concern to patients and clinicians alike, but the quality and standard of cardiac care has long been assessed by traditional "tombstone" measures such as mortality and major adverse cardiovascular events.<sup>5,8,10-12</sup> Patient-centred care represents a priority area for modern medical practice and research, and the facilitation of shared surgical decision-making could be improved by incorporating patient perspectives and patient-derived data.13-15

Our group has recently derived "disability-free survival" as a patient-defined outcome through a large-scale survey of more than 3000 patients with cardiovascular diseases.<sup>16</sup> According to patient preferences and values, disability was defined as the composite of stroke, recurrent nonelective hospital admissions and admission to a nursing home.<sup>16</sup> Before this outcome measure could be meaningfully used to inform patient-centred decision-making, its epidemiology and impact need to be described first at the population level. We therefore conducted the current study to evaluate disability-free survival after major cardiac surgery in a population-based cohort.

#### **Methods**

#### Design and study population

We conducted a population-based, retrospective cohort study in Ontario, Canada. We included adults residing in Ontario

Competing interests: None declared.

This article has been peer reviewed.

Correspondence to: Louise Sun, Isun@ottawaheart.ca

CMAJ Open 2021. DOI:10.9778/cmajo.20200096

aged 40 years or older and who had undergone CABG, or aortic, mitral or tricuspid valve surgery between Oct. 1, 2008, and Dec. 31, 2016 (Appendix 1, Supplementary Table 1, available at www.cmajopen.ca/content/9/2/E384/suppl/DC1). For those patients who underwent multiple cardiac procedures during the study period, we considered the first procedure to be the index procedure. Exclusion criteria were non-Ontario residency status, those with missing information regarding age and sex, and those who had concomitant arrhythmia, or pulmonic valve or thoracic aorta surgery. During the study period, Ontario was Canada's most populous province with a publicly funded, universal health care system that reimburses all covered services and providers.

#### Data sources

We used the administrative health care databases from ICES with information on all Ontario residents, and the detailed clinical registry data from CorHealth Ontario. CorHealth Ontario maintains a prospective registry of all patients who undergo invasive cardiac procedures in Ontario. All 20 advanced cardiac hospitals in Ontario participate in the registry. It captures demographic characteristics and comorbidity- and procedural-related information and has been validated through selected chart audits. In addition, ejection fraction and angiographic data in the CorHealth Ontario database undergo core laboratory validation.<sup>17</sup>

We identified individuals who underwent the specified cardiac procedures from the CorHealth Ontario registry, and linked them deterministically to the ICES administrative databases by using encrypted unique confidential codes. Specifically, we linked the date and type of cardiac procedures, physiologic and comorbidity data from CorHealth Ontario with the Canadian Institute for Health Information's Discharge Abstract Database (comorbidities and hospital admissions) and Same Day Surgery database (comorbidities), the Ontario Health Insurance Plan database (physician service claims), the Registered Persons Database (ascertainment of vital statistics), the Continuing Care Reporting System (admissions to long-term care facilities) and the Canadian Census. The administrative databases have been validated for many outcomes, exposures and comorbidities, including heart failure, chronic obstructive pulmonary disease, asthma, hypertension, myocardial infarction and diabetes.<sup>18-21</sup>

#### Comorbidities

We identified comorbidities from the CorHealth Ontario registry and supplemented the information with data from the Discharge Abstract Database, Same Day Surgery database and Ontario Health Insurance Plan using *International Classification of Diseases, 10th Revision* codes<sup>22</sup> within 5 years before the index procedure, according to validated algorithms.<sup>18,20,23–25</sup> We estimated socioeconomic status based on patients' neighbourhood median income in the Canadian Census, and determined their residence (rural v. urban) using the definitions from Statistics Canada.<sup>26</sup> We ascertained emergent procedural status from the CorHealth Ontario registry, as cases requiring operative intervention within 48 hours of acute presentation to hospital. We identified height, weight and body mass index from the CorHealth Ontario registry and used it to define class 3 or severe obesity (weight > 159 kg or body mass index  $\geq$  40).<sup>16,25,27,28</sup> We identified frailty status using the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator, which is an instrument that uses administrative data and is designed and validated for research of frailty-related outcomes and use of resources.<sup>28–33</sup>

#### Outcomes

The primary outcome was disability, defined as patientderived composite of stroke, de novo nursing home admission and recurrent nonelective hospital admissions for 3 or more episodes occurring within 1 year of surgery.<sup>16</sup> Secondary outcomes consisted of all-cause death and each individual component of disability. We identified stroke requiring hospital admission using a validated algorithm with 70% sensitivity and 99% specificity.<sup>34</sup> We ascertained nonelective hospital admissions using the Discharge Abstract Database, and long-term care admissions using the Continuing Care Reporting System.

#### Statistical analysis

Continuous variables were expressed as mean (standard deviation) and categorical variables as number (proportions). We assessed outcomes through Dec. 31, 2017. Patients were censored when they lost possession of a valid Ontario health insurance card. We defined disability-free survival as survival time from the date of index surgery until the date of a disability-defining event, death or last followup, whichever occurred earlier. For patients who had recurrent nonelective hospital admissions, we considered disability to have occurred on the date of the first admission. To account for death as a competing risk, we estimated the cumulative incidence of disability over time using cumulative incidence functions (CIFs), and the relative effect of covariates on the subdistribution hazard using a Fine and Gray model. We explored whether sex had a modifying effect on the relation between disability and type of surgery, by using a multiplicative interaction term of sex x type of surgery within each of the multivariable time-to-event models. Post hoc, we also examined the cumulative incidence of disability, death, and the composite of these end points, as stratified by age.

We performed analyses using SAS 9.4 (SAS Institute), with statistical significance defined by a 2-sided p value of < 0.05. We used the adjusted hazard ratio (HR) and associated 95% confidence intervals (CIs) to describe the measure of association.

#### **Ethics approval**

The use of data in this project was authorized under section 45 of Ontario's *Personal Health Information Protection Act*, which does not require review by a research ethics board.<sup>35</sup>

#### Research

#### **Results**

The study included 72 824 patients. A flow diagram detailing the process used to select the study cohort is provided in Appendix 1, Supplementary Figure 1. The baseline patient characteristics according to type of surgery are summarized in Table 1. Isolated CABG accounted for 72.2% of the provincial procedure volume. These were most likely to be performed in younger men with a history of previous myocardial infarction and percutaneous coronary intervention, and least likely to have been performed in those with heart failure.

Compared with those who underwent combined CABG and valve procedures, those who underwent isolated valve surgery were younger and were more likely to have preserved left ventricular ejection fraction and a lower burden of comorbidities, as evidenced by a lower Charlson Comorbidity Index. Further, those who underwent combined CABG and multiple valve surgery were among the frailest and burdened with the highest number of comorbidities.

As we did not observe a statistically significant interaction effect between sex and type of surgery (interaction p = 0.07), subsequent analyses were not stratified by sex.

#### **Disability-free survival**

Table 2 and Supplementary Table 2 in Appendix 1 summarize the cumulative incidence of disability, death and individual disability-defining events according to surgery type. Graphical representations of these events and their subcomponents are provided by surgery type in Figures 1 and 2, and Supplementary Figures 2–4 in Appendix 1. Figure 3 shows the cumulative incidence of disability, death and the combination of these events for all surgeries.

The incidence proportions of disability and death were as follows: 2431 (4.6%) versus 1839 (3.5%) in the CABG-only group; 677 (6.5%) versus 540 (5.2%) in the single valve group; 118 (9.0%) versus (10.7%) in the multiple valve group; 718 (9.0%) versus 734 (9.2%) in the CABG and single valve group; and 87 (13.1%) versus 94 (14.1%) in the CABG and multiple valve group. Overall, the 1-year cumulative incidence of disability was lowest in patients who underwent isolated CABG and highest after CABG and multiple valve surgery. Disability occurred more frequently than death in the year after isolated CABG and single valve surgery. Of those who developed disability, 755 (18.7%) subsequently died within the year after surgery.

#### Disability and patient age

Post hoc, we evaluated the impact of patient age on disability, death and the combination of these events. The cumulative incidence of these events was lowest in adults aged 40–49 years and 50–59 years, and was incrementally higher for each decade above the age of 60 years (Appendix 1, Supplementary Figures 5–7).

#### **Disability-defining events**

The cumulative incidence of stroke, recurrent nonelective hospital admissions and long-term care admissions varied

by type of surgery (Table 1 and Appendix 1, Supplementary Figures 2–4). Specifically, the rates of all 3 events were lowest after isolated CABG, highest after combined CABG and multiple valve reconstruction, and were similar after multiple valve surgery and CABG combined with single valve surgery.

#### **Disability risk factors**

The multivariable predictors of disability are summarized in Table 3. With isolated CABG as the reference group, the adjusted subdistribution HRs for disability were 1.34 (95% CI 1.21-1.48) for single valve, 1.43 (95% CI 1.18-1.75) for multiple valve, 1.38 (95% CI 1.26-1.51) for CABG and single valve, and 1.78 (95% CI 1.43-2.23) for CABG and multiple valve reconstruction. Other statistically significant risk factors of disability were age, female sex, emergent operative status, low income, a history of hypertension, atrial fibrillation, myocardial infarction, heart failure, cerebrovascular disease, peripheral arterial disease, current smoker, chronic obstructive pulmonary disease, diabetes, anemia, renal insufficiency, liver disease, alcohol use disorder, dementia, depression and cancer. Of these, CABG and multiple valve surgery, heart failure, baseline creatinine 180 µmol/L or greater, alcohol use disorder, dementia and depression were the most clinically significant predictors of disability.

#### Interpretation

In this population-based study, we systematically described the incidence and risk factors of patient-defined disability after common cardiac procedures. We found that the cumulative incidence of disability was lowest after isolated CABG and highest after CABG and multiple valve surgery. Disability occurred more frequently than death in the year after isolated CABG and single valve surgery. Combined CABG and multiple valve surgery, heart failure, baseline creatinine 180 µmol/L or greater, alcohol use disorder, dementia and depression were important predictors of disability in the year after cardiac surgery.

Traditional revascularization trials have sometimes been referred to as "tombstone trials"<sup>6</sup> because of their focus on death and complications. However, a survey of cardiovascular patients indicated that important outcomes identified by patients were in fact very different compared with those from the clinician's view.<sup>16</sup> Our findings suggest that most patients who experience disability after cardiac surgery will continue to live with disability. Thus, the incorporation of patient perceptions and values into the design of outcome measures has been proposed as a priority area for cardiovascular research. Such a paradigm shift has been shown to increase the relevance of the research to the end user, speed up the uptake of research into practice and empower patients to make better-informed decisions.<sup>36</sup>

To date, few studies have directly engaged surgical patients to determine what outcomes were meaningful to them, as important end users of the research. Such studies include surveys of noncardiac surgery patients to rank

#### Table 1: Baseline characteristics, stratified by type of surgery\*

VariableIsolated CABG $n = 52 546$ Single valve; $n = 10 368$ Multiple valves§ $n = 7936$ CABG + multiple valves§ $n = 665$ Age, yr, mean + SD $65.9 \pm 9.8$ $675 \pm 11.2$ $68.3 \pm 11.4$ $72.6 \pm 9.0$ $72.5 \pm 9.1$ $40-64$ $22.925(43.6)$ $3996(38.3)$ $458(35.0)$ $1460(18.4)$ $129(19.4)$ $65-74$ $116 626(35.4)$ $3197(30.8)$ $395(30.2)$ $2795(53.2)$ $216(32.5)$ $75-64$ $10 220(19.4)$ $2201(27.0)$ $388(29.6)$ $3128(39.4)$ $269(40.5)$ $2 85$ $775(15)$ $401(3.9)$ $68(5.2)$ $553(7.0)$ $51(7.7)$ Rural residence $8204(15.6)$ $1756(16.9)$ $203(15.5)$ $1457(18.4)$ $143(21.5)$ Income quintile		No. (%) of patients†						
Age, yr, mean $\pm$ SD65.9 $\pm$ 9.867.5 $\pm$ 11.268.3 $\pm$ 11.472.6 $\pm$ 9.072.5 $\pm$ 9.140-6422.925 (43.6)3969 (38.3)458 (35.0)1440 (18.4)129 (19.4)65-7418.626 (35.4)3197 (30.8)396 (30.2)2795 (35.2)216 (32.5)75-6410.220 (18.4)2801 (27.0)388 (29.6)3128 (39.4)289 (40.5) $\pm$ 85775 (15.)401 (3.9)68 (5.2)553 (7.0)51 (7.7)Rural residence8204 (15.6)1756 (16.9)203 (15.5)1457 (18.4)143 (21.5)I (lowest)10.003 (19.0)1728 (16.7)245 (18.7)1370 (17.3)102 (15.3)210.724 (20.4)1999 (18.9)257 (19.6)1608 (20.3)148 (22.3)310.627 (20.2)2117 (20.4)249 (19.0)1609 (20.3)157 (23.6)410.714 (20.4)2214 (21.4)257 (19.6)1705 (21.5)127 (19.1)5 (highpest)10.144 (19.4)2310 (22.3)282 (22.3)1617 (20.4)129 (19.4)Missing294 (0.5)40 (0.4)9 (0.7)27 (0.3) $\leq 5^{**}$ Hypertension46 111 (87.8)7954 (77.7)1007 (76.9)7185 (90.5)555 (89.5)Atrial fibrillation2373 (4.5)1343 (13.0)304 (23.2)990 (12.5)155 (23.3)Recent MI20.684 (39.4)422 (4.1)56 (4.2)1659 (20.9)132 (19.8)Previous PC18773 (16.7)617 (6.0)70 (5.3)1004 (12.7)68 (10.2)Previous PC18773 (16.7) <td>Variable</td> <td>Isolated CABG <math>n = 52546</math></td> <td>Single valve‡ <i>n</i> = 10 368</td> <td>Multiple valves§ <math>n = 1309</math></td> <td>CABG + single valve‡ n = 7936</td> <td>CABG + multiple valves§ n = 665</td>	Variable	Isolated CABG $n = 52546$	Single valve‡ <i>n</i> = 10 368	Multiple valves§ $n = 1309$	CABG + single valve‡ n = 7936	CABG + multiple valves§ n = 665		
40-64     22 925 (43.6)     3969 (38.3)     458 (35.0)     1460 (18.4)     129 (19.4)       65-74     16 626 (35.4)     3107 (30.6)     335 (30.2)     275 (35.2)     216 (32.5)       75-64     10 220 (19.4)     2801 (27.0)     388 (29.6)     3128 (39.4)     289 (40.5)       ≥ 85     775 (15)     401 (3.9)     66 (5.2)     553 (7.0)     51 (7.7)       Pural residence     8204 (15.6)     1756 (16.9)     203 (15.5)     1457 (18.4)     143 (21.5)       Income quintile     1     100003 (19.0)     1728 (16.7)     245 (18.7)     1370 (17.3)     102 (15.3)       2     10 724 (20.4)     1959 (18.9)     257 (19.6)     1608 (20.3)     148 (22.3)       3     10 627 (20.2)     2117 (20.4)     249 (19.0)     1609 (20.3)     157 (23.6)       4     10 714 (20.4)     124 (14)     257 (19.6)     1707 (2.4)     129 (19.4)       Missing     294 (0.6)     40 (0.4)     9 (0.7)     27 (0.3)     \$5**       Hypertension     46 111 (87.8)     7954 (76.7)     1007 (76.9)     718 (30.5)     595 (89.5)	Age, yr, mean ± SD	65.9 ± 9.8	67.5 ± 11.2	68.3 ± 11.4	72.6 ± 9.0	72.5 ± 9.1		
65-74     18 626 (35.4)     3197 (30.6)     395 (30.2)     2795 (35.2)     216 (32.5)       75-84     10 220 (19.4)     2801 (270)     388 (29.6)     3128 (39.4)     269 (40.5)       ≥ 85     775 (1.5)     401 (3.9)     68 (5.2)     553 (70)     51 (77)       Fural residence     8204 (15.6)     1756 (16.9)     203 (15.5)     1457 (18.4)     143 (21.5)       Income quintlie     -     -     -     -     -     -       1 (lowest)     10 003 (19.0)     1728 (16.7)     245 (18.7)     1370 (17.3)     102 (15.3)       3     10 627 (20.2)     2117 (20.4)     249 (19.0)     1608 (20.3)     148 (22.3)       3     10 627 (20.2)     214 (21.4)     257 (19.6)     1705 (21.5)     127 (19.1)       5 (highest)     10 184 (19.4)     2310 (22.3)     282 (22.3)     1617 (20.4)     129 (19.4)       Missing     294 (0.6)     40 (0.4)     9 (0.7)     27 (0.3) $\leq$ 5**       Hypertension     46 111 (82.8)     794 (75.7)     1007 (76.9)     7185 (90.5)     155 (89.5) <td< td=""><td>40–64</td><td>22 925 (43.6)</td><td>3969 (38.3)</td><td>458 (35.0)</td><td>1460 (18.4)</td><td>129 (19.4)</td></td<>	40–64	22 925 (43.6)	3969 (38.3)	458 (35.0)	1460 (18.4)	129 (19.4)		
75-84     10 220 (19.4)     2801 (27.0)     388 (29.6)     3128 (39.4)     289 (40.5) $\geq$ 85     775 (15)     401 (3.9)     68 (5.2)     553 (7.0)     51 (7.7)       Rural residence     8204 (15.6)     1756 (15.9)     203 (15.5)     1457 (18.4)     143 (21.5)       Income quintile     1     10003 (19.0)     1728 (16.7)     245 (18.7)     1370 (17.3)     102 (15.3)       2     10724 (20.4)     1959 (18.9)     257 (19.6)     1608 (20.3)     148 (22.3)       3     10 627 (20.2)     2117 (20.4)     249 (19.6)     1705 (21.5)     127 (19.1)       5 (highest)     10 144 (19.4)     2214 (21.4)     257 (19.6)     1705 (21.5)     127 (19.1)       5 (highest)     10 141 (87.8)     7954 (75.7)     1007 (76.9)     7186 (90.5)     595 (69.5)       Atrial fibrillation     2373 (4.5)     1343 (13.0)     304 (23.2)     990 (12.5)     155 (23.3)       Recent MI     942 (17.9)     679 (6.5)     91 (7.0)     1285 (16.3)     108 (16.2)       Previous PCI     8773 (16.7)     617 (6.0)     70 (5.3)     1004	65-74	18 626 (35.4)	3197 (30.8)	395 (30.2)	2795 (35.2)	216 (32.5)		
2 85     775 (1.5)     401 (3.9)     68 (2.2)     553 (7.0)     51 (7.7)       Rural residence     8204 (15.6)     1756 (16.9)     203 (15.5)     1457 (18.4)     143 (21.5)       Income quintile     1     10 003 (19.0)     1728 (16.7)     245 (18.7)     1370 (17.3)     102 (15.3)       2     10 724 (20.4)     1959 (18.9)     257 (19.6)     1608 (20.3)     148 (22.3)       3     10 627 (20.2)     2117 (20.4)     249 (19.0)     1609 (20.3)     157 (23.6)       4     10 714 (20.4)     2214 (21.4)     257 (19.6)     1705 (21.5)     127 (19.1)       5 (highest)     10 184 (19.4)     2310 (22.3)     292 (22.3)     1617 (20.4)     129 (19.4)       Missing     234 (0.6)     40 (0.4)     9 (0.7)     27 (0.3)     s 5**       Hypertension     46 111 (87.8)     7954 (78.7)     1007 (76.9)     7185 (90.5)     595 (89.5)       Atrial fibrillation     2373 (4.5)     1343 (13.0)     304 (23.2)     990 (12.5)     155 (23.3)       Recent MI     20 643 (39.4)     422 (4.1)     55 (4.2)     1656 (20.9)	75–84	10 220 (19.4)	2801 (270)	388 (29.6)	3128 (39.4)	269 (40.5)		
Bural residence     B204 (15.6)     1756 (16.9)     200 (15.5)     1457 (18.4)     143 (21.5)       Income quintile	> 85	775 (15)	401 (3.9)	68 (5 2)	553 (70)	51 (77)		
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Bural residence	8204 (15.6)	1756 (16.9)	203 (15.5)	1457 (18.4)	143 (21.5)		
1 (lowest)   10 003 (19.0)   1728 (16.7)   245 (18.7)   1370 (17.3)   102 (15.3)     2   10 724 (20.4)   1959 (18.9)   257 (19.6)   1608 (20.3)   148 (22.3)     3   10 627 (20.2)   2117 (20.4)   249 (19.0)   1609 (20.3)   157 (23.6)     4   10 714 (20.4)   2214 (21.4)   257 (19.6)   1705 (21.5)   127 (19.1)     5 (highest)   10 184 (19.4)   2310 (22.3)   292 (22.3)   1617 (20.4)   129 (19.4)     Missing   294 (0.6)   40 (0.4)   9 (0.7)   27 (0.3)   ≤ 5**     Hypertension   46 111 (87.8)   7954 (76.7)   1007 (76.9)   7185 (90.5)   595 (89.5)     Atrial fibrillation   2373 (4.5)   1343 (13.0)   304 (23.2)   990 (12.5)   155 (23.3)     Recent MI   20.684 (39.4)   422 (4.1)   55 (4.2)   1659 (20.9)   132 (19.8)     Remote MI   9432 (17.9)   679 (6.5)   91 (70)   1285 (16.3)   1008 (16.2)     VEF, %      102 (15.3)   102 (14.8)   30 (64.7)     VEF, %     20   905 (1.7)   43		0201 (10.0)	1100 (10.0)	200 (10.0)		110 (210)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1 (lowest)	10 003 (19 0)	1728 (16.7)	245 (18 7)	1370 (173)	102 (15.3)		
2   167 L2 (c0.47)   230 (10.2)   1230 (10.2)   1600 (120.3)   167 (22.6)     3   10 627 (20.2)   2117 (20.4)   224 (14)   1609 (20.3)   157 (23.6)     4   10 714 (20.4)   2214 (21.4)   257 (19.6)   1705 (21.5)   127 (19.1)     5 (highest)   10 184 (19.4)   2310 (22.3)   292 (22.3)   1617 (20.4)   129 (19.4)     Missing   224 (0.6)   40 (0.4)   9 (0.7)   27 (0.3)   ≤ 5**     Hypertension   46 111 (87.8)   7954 (76.7)   1007 (76.9)   7185 (90.5)   595 (89.5)     Atrial fibrillation   2373 (4.5)   1343 (13.0)   304 (23.2)   990 (12.5)   155 (23.3)     Recent MI   20 684 (39.4)   422 (4.1)   55 (4.2)   1659 (20.9)   132 (19.8)     Remote MI   9432 (17.9)   679 (6.5)   91 (7.0)   1295 (16.3)   108 (16.2)     Previous PCI   8773 (16.7)   617 (6.0)   70 (5.3)   1004 (12.7)   68 (10.2)     LVEF, %   2   50   32 237 (61.4)   8843 (85.3)   1040 (79.4)   5630 (70.9)   435 (65.4)     35-50   12 762 (24.3)   967 (9	2	10 724 (20 4)	1959 (18.9)	257 (19.6)	1608 (20.3)	1/18 (22 3)		
5   10 GL (0L2)   2111 (GL3)   240 (130)   100 (E0.0)   101 (E0.0)     4   10 714 (20.4)   2214 (21.4)   2257 (19.6)   1705 (21.5)   127 (19.1)     5 (highest)   10 184 (19.4)   2310 (22.3)   292 (22.3)   1617 (20.4)   129 (19.4)     Missing   294 (0.6)   40 (0.4)   9 (0.7)   27 (0.3) $\leq$ 5**     Hypertension   46 111 (87.8)   7954 (76.7)   1007 (76.9)   7185 (90.5)   595 (89.5)     Atrial fibrillation   2373 (4.5)   1343 (13.0)   304 (23.2)   990 (12.5)   155 (23.3)     Recent MI   20 684 (39.4)   422 (4.1)   55 (4.2)   1659 (20.9)   132 (19.8)     Remote MI   9432 (17.9)   679 (6.5)   91 (7.0)   1295 (16.3)   108 (16.2)     Previous PCI   8773 (16.7)   617 (6.0)   70 (5.3)   1004 (12.7)   68 (10.2)     Heart failure   10 126 (19.3)   4729 (45.6)   848 (64.8)   3714 (46.8)   430 (64.7)     LVEF, %        5630 (70.9)   435 (65.4)     35-50   12 762 (24.3)   967 (9.3)   176 (13.4)	3	10 627 (20.2)	2117 (20 4)	2/9 (19.0)	1609 (20.3)	157 (23.6)		
4101014(2.14)(2.14)(2.14)(2.15)1103(2.15)127(13.1)5(highest)101014(19.4)2310(22.3)292(22.3)1617(20.4)129(19.4)Missing294(0.6)40(0.4)9(0.7)27(0.3) $\leq 5^{**}$ Hypertension46111(87.8)7954(76.7)1007(76.9)7185(90.5)595(89.5)Atrial fibrillation2373(4.5)1343(13.0)304(23.2)990(12.5)155(23.3)Recent MI20684(39.4)422(4.1)55(4.2)1659(20.9)132(19.8)Pervious PCI8773(16.7)617(6.0)70(5.3)1004(12.7)68(10.2)Heart failure10126(19.3)4729(45.6)848(64.8)3714(46.8)430(64.7)LVEF, %1292(13.4)1398(17.6)145(18.4)20-3512762(24.3)967(9.3)176(13.4)1398(17.6)132(20.8)<20-35		10 714 (20.2)	2014 (21.4)	257 (19.6)	1705 (21.5)	127 (10 1)		
S (injtrest)10 164 (15.4)2310 (22.3)232 (22.3)1017 (20.4)125 (15.4)Missing294 (0.6)40 (0.4)9 (0.7)27 (0.3) $\leq 5^{+*}$ Hypertension46 111 (87.8)7954 (76.7)1007 (76.9)7185 (90.5)595 (89.5)Atrial fibrillation2373 (4.5)1343 (13.0)304 (23.2)990 (12.5)155 (23.3)Recent MI20 684 (39.4)422 (4.1)55 (4.2)1659 (20.9)132 (19.8)Remote MI9432 (17.7)617 (6.0)70 (5.3)1004 (12.7)68 (10.2)Heart failure10 126 (19.3)4729 (45.6)848 (64.8)3714 (46.8)430 (64.7)LVEF, %25032 237 (61.4)8843 (85.3)1040 (79.4)5630 (70.9)435 (65.4)35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< < 20	E (highoat)	10 194 (20.4)	2214 (21.4)	207 (19.0)	1617 (20.4)	120 (10.4)		
Initiality $254$ (0.5) $40$ (0.4) $3$ (0.7) $27$ (0.3) $5.3$ Hypertension46 111 (878) $7954$ (76.7) $1007$ (76.9) $7185$ (90.5) $595$ (89.5)Atrial fibrillation $2373$ (4.5) $1343$ (13.0) $304$ (23.2) $990$ (12.5) $155$ (23.3)Recent MI $20.684$ (39.4) $422$ (4.1) $55$ (4.2) $1659$ (20.9) $132$ (19.8)Remote MI $9432$ (17.9) $679$ (6.5) $91$ (70) $1295$ (16.3) $108$ (16.2)Previous PCI $8773$ (16.7) $617$ (6.0) $70$ (5.3) $1004$ (12.7) $68$ (10.2)Heart failure $10$ 126 (19.3) $4729$ (45.6) $848$ (64.8) $3714$ (46.8) $430$ (64.7)LVEF, % $=$ $=$ $=$ $=$ $=$ $2 50$ $32$ 237 (61.4) $8843$ (85.3) $1040$ (79.4) $5630$ (70.9) $435$ (65.4) $35-50$ $12$ 762 (24.3) $967$ (9.3) $176$ (13.4) $1398$ (17.6) $145$ (21.8) $20-35$ $4911$ (9.3) $346$ (3.3) $67$ (5.1) $654$ (8.2) $66$ (9.9) $< 20$ $905$ (1.7) $43$ (0.4) $13$ (10) $115$ (1.4) $60.9$ Cerebrovascular disease $5132$ (9.8) $970$ (9.4) $133$ (10) $115$ (1.4) $60.9$ Cerebrovascular disease $6424$ (12.2) $1079$ (10.4) $139$ (10.6) $1389$ (17.5) $108$ (16.2)COP D or asthma $14$ 702 (28.0) $3301$ (31.8) $439$ (33.5) $2726$ (3.4) $251$ (37.7)Diabetes mellitus $25$ 267 (48.1) $3218$ (31.0)	S (highest)	204 (0.6)	2310 (22.3)	292 (22.3)		- 5**		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hyportonsion	46 111 (979)	7054 (76 7)	1007 (76.0)	7195 (00 5)	<u>505 (90 5)</u>		
Athan infinitation2.373 (4.3)1.343 (13.0)3.04 (23.2)9.99 (12.5)1.55 (3.3)Recent MI20.684 (39.4)422 (4.1)55 (4.2)1.659 (20.9)1.32 (19.8)Remote MI9.432 (17.9)6.79 (6.5)9.1 (7.0)1.295 (16.3)1.08 (16.2)Previous PCI8.773 (16.7)617 (6.0)70 (5.3)1.004 (12.7)6.8 (10.2)Heart failure10.126 (19.3)4.729 (45.6)8.48 (64.8)3.714 (46.8)4.30 (64.7)LVEF, % $>$ $>$ $>$ $>$ $>$ $>$ $>$ $>$ $>$ $>$ 2 5032 237 (61.4)8.843 (85.3)10.40 (79.4)5.630 (70.9)4.35 (65.4) $>$		40 111 (07.0)	1934 (76.7)	1007 (76.9)	/ 165 (90.5)	595 (69.5)		
Hebelin Mi20 684 (39.4)422 (4.1)55 (4.2)1659 (20.9)152 (19.3)Remote MI9432 (17.9)679 (6.5)91 (7.0)1295 (16.3)108 (16.2)Previous PCI8773 (16.7)617 (6.0)70 (5.3)1004 (12.7)68 (10.2)LVEF, %430 (64.7)≥ 5032 237 (61.4)8843 (85.3)1040 (79.4)5630 (70.9)435 (65.4)35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20		2373 (4.5)	1343 (13.0)	304 (23.2)	990 (12.5)	155 (23.3)		
Hermote MI94.32 (17.9)67.9 (6.5)91 (7.0)12.95 (16.3)108 (16.2)Previous PCI8773 (16.7)617 (6.0)70 (5.3)1004 (12.7)68 (10.2)Heart failure10 126 (19.3)4729 (45.6)848 (64.8)3714 (46.8)430 (64.7)LVEF, % </td <td></td> <td>20 684 (39.4)</td> <td>422 (4.1)</td> <td>55 (4.2)</td> <td>1659 (20.9)</td> <td>132 (19.8)</td>		20 684 (39.4)	422 (4.1)	55 (4.2)	1659 (20.9)	132 (19.8)		
Previous PCI87/3 (16.7)61/ (6.0)70 (5.3)1004 (12.7)68 (10.2)Heart failure10 126 (19.3)4729 (45.6)848 (64.8)3714 (46.8)430 (64.7)LVEF, %≥ 5032 237 (61.4)8843 (85.3)1040 (79.4)5630 (70.9)435 (65.4)35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20		9432 (17.9)	679 (6.5)	91 (7.0)	1295 (16.3)	108 (16.2)		
Hear tailure10 12b (19.3)4729 (45.6)848 (64.8)3714 (46.8)430 (64.7)LVEF, % $\geq 50$ 32 237 (61.4)8843 (85.3)1040 (79.4)5630 (70.9)435 (65.4)35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20	Previous PCI	8773 (16.7)	617 (6.0)	70 (5.3)	1004 (12.7)	68 (10.2)		
LVEF, %≥ 5032 237 (61.4)8843 (85.3)1040 (79.4)5630 (70.9)435 (65.4)35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20	Heart failure	10 126 (19.3)	4729 (45.6)	848 (64.8)	3714 (46.8)	430 (64.7)		
≥ 5032 237 (61.4)8843 (85.3)1040 (79.4)5630 (70.9)435 (65.4)35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20	LVEF, %							
35-5012 762 (24.3)967 (9.3)176 (13.4)1398 (17.6)145 (21.8)20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20	≥ 50	32 237 (61.4)	8843 (85.3)	1040 (79.4)	5630 (70.9)	435 (65.4)		
20-354911 (9.3)346 (3.3)67 (5.1)654 (8.2)66 (9.9)< 20	35–50	12 762 (24.3)	967 (9.3)	176 (13.4)	1398 (17.6)	145 (21.8)		
< 20905 (1.7)43 (0.4)13 (1.0)139 (1.8)13 (2.0)Missing1731 (3.3)169 (1.6)13 (1.0)115 (1.4)6 (0.9)Cerebrovascular disease5132 (9.8)970 (9.4)163 (12.5)1073 (13.5)82 (12.3)Peripheral arterial disease6424 (12.2)1079 (10.4)139 (10.6)1389 (17.5)108 (16.2)COPD or asthma14 702 (28.0)3301 (31.8)439 (33.5)2726 (34.3)251 (37.7)Diabetes mellitus25 267 (48.1)3218 (31.0)422 (32.2)3639 (45.9)266 (40.0)Severe obesity20 490 (39.0)3951 (38.1)563 (43.0)3106 (39.1)281 (42.3)Hypothyroidism969 (1.8)206 (2.0)40 (3.1)186 (2.3)18 (2.7)Liver disease351 (0.7)153 (1.5)37 (2.8)81 (1.0)111 (1.7)Anemia4918 (9.4)977 (9.4)203 (15.5)1113 (14.0)136 (20.5)Venous thromboembolism173 (0.3)57 (0.5)10 (0.8)46 (0.6)≤ 5**Dialysis1047 (2.0)195 (1.9)34 (2.6)233 (2.9)22 (3.3)Baseline creatinine, μmol/L1038 (79.3)6158 (77.6)522 (78.5)120-1794487 (8.5)855 (8.2)163 (12.5)1037 (13.1)93 (14.0)≥ 1801698 (3.2)261 (2.5)63 (4.8)381 (4.8)32 (4.8)	20–35	4911 (9.3)	346 (3.3)	67 (5.1)	654 (8.2)	66 (9.9)		
Missing1731 (3.3)169 (1.6)13 (1.0)115 (1.4)6 (0.9)Cerebrovascular disease5132 (9.8)970 (9.4)163 (12.5)1073 (13.5)82 (12.3)Peripheral arterial disease6424 (12.2)1079 (10.4)139 (10.6)1389 (17.5)108 (16.2)COPD or asthma14 702 (28.0)3301 (31.8)439 (33.5)2726 (34.3)251 (37.7)Diabetes mellitus25 267 (48.1)3218 (31.0)422 (32.2)3639 (45.9)266 (40.0)Severe obesity20 490 (39.0)3951 (38.1)563 (43.0)3106 (39.1)281 (42.3)Hypothyroidism969 (1.8)206 (2.0)40 (3.1)186 (2.3)18 (2.7)Liver disease351 (0.7)153 (1.5)37 (2.8)81 (1.0)11 (1.7)Anemia4918 (9.4)977 (9.4)203 (15.5)1113 (14.0)136 (20.5)Venous thromboembolism173 (0.3)57 (0.5)10 (0.8)46 (0.6)≤ 5**Dialysis1047 (2.0)195 (1.9)34 (2.6)233 (2.9)22 (3.3)Baseline creatinine, µmol/L1038 (79.3)6158 (77.6)522 (78.5)120-1794487 (8.5)855 (8.2)163 (12.5)1037 (13.1)93 (14.0)≥ 1801698 (3.2)261 (2.5)63 (4.8)381 (4.8)32 (4.8)	< 20	905 (1.7)	43 (0.4)	13 (1.0)	139 (1.8)	13 (2.0)		
Cerebrovascular disease5132 (9.8)970 (9.4)163 (12.5)1073 (13.5)82 (12.3)Peripheral arterial disease6424 (12.2)1079 (10.4)139 (10.6)1389 (17.5)108 (16.2)COPD or asthma14 702 (28.0)3301 (31.8)439 (33.5)2726 (34.3)251 (37.7)Diabetes mellitus25 267 (48.1)3218 (31.0)422 (32.2)3639 (45.9)266 (40.0)Severe obesity20 490 (39.0)3951 (38.1)563 (43.0)3106 (39.1)281 (42.3)Hypothyroidism969 (1.8)206 (2.0)40 (3.1)186 (2.3)18 (2.7)Liver disease351 (0.7)153 (1.5)37 (2.8)81 (1.0)11 (1.7)Anemia4918 (9.4)977 (9.4)203 (15.5)1113 (14.0)136 (20.5)Venous thromboembolism173 (0.3)57 (0.5)10 (0.8)46 (0.6)≤ 5**Dialysis1047 (2.0)195 (1.9)34 (2.6)233 (2.9)22 (3.3)Baseline creatinine, µmol/L1038 (79.3)6158 (77.6)522 (78.5)12043 934 (83.6)8538 (82.3)1038 (79.3)6158 (77.6)522 (78.5)1201698 (3.2)261 (2.5)63 (4.8)381 (4.8)32 (4.8)	Missing	1731 (3.3)	169 (1.6)	13 (1.0)	115 (1.4)	6 (0.9)		
Peripheral arterial disease $6424 (12.2)$ $1079 (10.4)$ $139 (10.6)$ $1389 (17.5)$ $108 (16.2)$ COPD or asthma $14 702 (28.0)$ $3301 (31.8)$ $439 (33.5)$ $2726 (34.3)$ $251 (37.7)$ Diabetes mellitus $25 267 (48.1)$ $3218 (31.0)$ $422 (32.2)$ $3639 (45.9)$ $266 (40.0)$ Severe obesity $20 490 (39.0)$ $3951 (38.1)$ $563 (43.0)$ $3106 (39.1)$ $281 (42.3)$ Hypothyroidism $969 (1.8)$ $206 (2.0)$ $40 (3.1)$ $186 (2.3)$ $18 (2.7)$ Liver disease $351 (0.7)$ $153 (1.5)$ $37 (2.8)$ $81 (1.0)$ $11 (1.7)$ Anemia $4918 (9.4)$ $977 (9.4)$ $203 (15.5)$ $1113 (14.0)$ $136 (20.5)$ Venous thromboembolism $173 (0.3)$ $57 (0.5)$ $10 (0.8)$ $46 (0.6)$ $≤ 5^{**}$ Dialysis $1047 (2.0)$ $195 (1.9)$ $34 (2.6)$ $233 (2.9)$ $22 (3.3)$ Baseline creatinine, µmol/L $<$ $1038 (79.3)$ $6158 (77.6)$ $522 (78.5)$ $120 - 179$ $4487 (8.5)$ $855 (8.2)$ $163 (12.5)$ $1037 (13.1)$ $93 (14.0)$ $≥ 180$ $1698 (3.2)$ $261 (2.5)$ $63 (4.8)$ $381 (4.8)$ $32 (4.8)$	Cerebrovascular disease	5132 (9.8)	970 (9.4)	163 (12.5)	1073 (13.5)	82 (12.3)		
COPD or asthma14 702 (28.0)3301 (31.8)439 (33.5)2726 (34.3)251 (37.7)Diabetes mellitus25 267 (48.1)3218 (31.0)422 (32.2)3639 (45.9)266 (40.0)Severe obesity20 490 (39.0)3951 (38.1)563 (43.0)3106 (39.1)281 (42.3)Hypothyroidism969 (1.8)206 (2.0)40 (3.1)186 (2.3)18 (2.7)Liver disease351 (0.7)153 (1.5)37 (2.8)81 (1.0)11 (1.7)Anemia4918 (9.4)977 (9.4)203 (15.5)1113 (14.0)136 (20.5)Venous thromboembolism173 (0.3)57 (0.5)10 (0.8)46 (0.6)≤ 5**Dialysis1047 (2.0)195 (1.9)34 (2.6)233 (2.9)22 (3.3)Baseline creatinine, µmol/L12043 934 (83.6)8538 (82.3)1038 (79.3)6158 (77.6)522 (78.5)1204487 (8.5)855 (8.2)163 (12.5)1037 (13.1)93 (14.0)23 (4.8)≥ 1801698 (3.2)261 (2.5)63 (4.8)381 (4.8)32 (4.8)	Peripheral arterial disease	6424 (12.2)	1079 (10.4)	139 (10.6)	1389 (17.5)	108 (16.2)		
Diabetes mellitus $25\ 267\ (48.1)$ $3218\ (31.0)$ $422\ (32.2)$ $3639\ (45.9)$ $266\ (40.0)$ Severe obesity $20\ 490\ (39.0)$ $3951\ (38.1)$ $563\ (43.0)$ $3106\ (39.1)$ $281\ (42.3)$ Hypothyroidism $969\ (1.8)$ $206\ (2.0)$ $40\ (3.1)$ $186\ (2.3)$ $18\ (2.7)$ Liver disease $351\ (0.7)$ $153\ (1.5)$ $37\ (2.8)$ $81\ (1.0)$ $11\ (1.7)$ Anemia $4918\ (9.4)$ $977\ (9.4)$ $203\ (15.5)$ $1113\ (14.0)$ $136\ (20.5)$ Venous thromboembolism $173\ (0.3)$ $57\ (0.5)$ $10\ (0.8)$ $46\ (0.6)$ $\leq\ 5^{**}$ Dialysis $1047\ (2.0)$ $195\ (1.9)$ $34\ (2.6)$ $233\ (2.9)$ $22\ (3.3)$ Baseline creatinine, µmol/L $<$ $1038\ (79.3)$ $6158\ (77.6)$ $522\ (78.5)$ $120-179$ $4487\ (8.5)$ $855\ (8.2)$ $163\ (12.5)$ $1037\ (13.1)$ $93\ (14.0)$ ≥ 180 $1698\ (3.2)$ $261\ (2.5)$ $63\ (4.8)$ $381\ (4.8)$ $32\ (4.8)$	COPD or asthma	14 702 (28.0)	3301 (31.8)	439 (33.5)	2726 (34.3)	251 (37.7)		
Severe obesity20 490 (39.0)3951 (38.1)563 (43.0)3106 (39.1)281 (42.3)Hypothyroidism969 (1.8)206 (2.0)40 (3.1)186 (2.3)18 (2.7)Liver disease351 (0.7)153 (1.5)37 (2.8)81 (1.0)11 (1.7)Anemia4918 (9.4)977 (9.4)203 (15.5)1113 (14.0)136 (20.5)Venous thromboembolism173 (0.3)57 (0.5)10 (0.8)46 (0.6)≤ 5**Dialysis1047 (2.0)195 (1.9)34 (2.6)233 (2.9)22 (3.3)Baseline creatinine, µmol/L< 120	Diabetes mellitus	25 267 (48.1)	3218 (31.0)	422 (32.2)	3639 (45.9)	266 (40.0)		
Hypothyroidism969 (1.8)206 (2.0)40 (3.1)186 (2.3)18 (2.7)Liver disease $351 (0.7)$ $153 (1.5)$ $37 (2.8)$ $81 (1.0)$ $11 (1.7)$ Anemia4918 (9.4)977 (9.4)203 (15.5) $1113 (14.0)$ $136 (20.5)$ Venous thromboembolism $173 (0.3)$ $57 (0.5)$ $10 (0.8)$ $46 (0.6)$ $\leq 5^{**}$ Dialysis1047 (2.0)195 (1.9) $34 (2.6)$ $233 (2.9)$ $22 (3.3)$ Baseline creatinine, µmol/L $< 120$ $43 934 (83.6)$ $8538 (82.3)$ $1038 (79.3)$ $6158 (77.6)$ $522 (78.5)$ $120-179$ $4487 (8.5)$ $855 (8.2)$ $163 (12.5)$ $1037 (13.1)$ $93 (14.0)$ ≥ 1801698 (3.2) $261 (2.5)$ $63 (4.8)$ $381 (4.8)$ $32 (4.8)$	Severe obesity	20 490 (39.0)	3951 (38.1)	563 (43.0)	3106 (39.1)	281 (42.3)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Hypothyroidism	969 (1.8)	206 (2.0)	40 (3.1)	186 (2.3)	18 (2.7)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Liver disease	351 (0.7)	153 (1.5)	37 (2.8)	81 (1.0)	11 (1.7)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Anemia	4918 (9.4)	977 (9.4)	203 (15.5)	1113 (14.0)	136 (20.5)		
Dialysis     1047 (2.0)     195 (1.9)     34 (2.6)     233 (2.9)     22 (3.3)       Baseline creatinine, μmol/L     -	Venous thromboembolism	173 (0.3)	57 (0.5)	10 (0.8)	46 (0.6)	≤ 5**		
Baseline creatinine, μmol/L       < 120	Dialysis	1047 (2.0)	195 (1.9)	34 (2.6)	233 (2.9)	22 (3.3)		
< 120     43 934 (83.6)     8538 (82.3)     1038 (79.3)     6158 (77.6)     522 (78.5)       120-179     4487 (8.5)     855 (8.2)     163 (12.5)     1037 (13.1)     93 (14.0)       ≥ 180     1698 (3.2)     261 (2.5)     63 (4.8)     381 (4.8)     32 (4.8)	Baseline creatinine, µmol/L							
120-179     4487 (8.5)     855 (8.2)     163 (12.5)     1037 (13.1)     93 (14.0)       ≥ 180     1698 (3.2)     261 (2.5)     63 (4.8)     381 (4.8)     32 (4.8)	< 120	43 934 (83.6)	8538 (82.3)	1038 (79.3)	6158 (77.6)	522 (78.5)		
≥ 180 1698 (3.2) 261 (2.5) 63 (4.8) 381 (4.8) 32 (4.8)	120–179	4487 (8.5)	855 (8.2)	163 (12.5)	1037 (13.1)	93 (14.0)		
	≥ 180	1698 (3.2)	261 (2.5)	63 (4.8)	381 (4.8)	32 (4.8)		
Missing 2427 (4.6) 714 (6.9) 45 (3.4) 360 (4.5) 18 (2.7)	Missing	2427 (4.6)	714 (6.9)	45 (3.4)	360 (4.5)	18 (2.7)		
Chronic renal disease 2109 (4.0) 399 (3.8) 66 (5.0) 516 (6.5) 43 (6.5)	Chronic renal disease	2109 (4.0)	399 (3.8)	66 (5.0)	516 (6.5)	43 (6.5)		
Dementia 98 (0.2) 27 (0.3) $\leq 5^{**}$ 41 (0.5) 6 (0.9)	Dementia	98 (0.2)	27 (0.3)	≤ 5**	41 (0.5)	6 (0.9)		
Depression 733 (1.4) 157 (1.5) 37 (2.8) 149 (1.9) 13 (2.0)	Depression	733 (1.4)	157 (1.5)	37 (2.8)	149 (1.9)	13 (2.0)		
Psychosis 102 (0.2) 33 (0.3) 6 (0.5) 17 (0.2) ≤ 5**	Psychosis	102 (0.2)	33 (0.3)	6 (0.5)	17 (0.2)	≤ 5**		
Primary tumour 2486 (4.7) 601 (5.8) 96 (7.3) 539 (6.8) 48 (7.2)	Primary tumour	2486 (4.7)	601 (5.8)	96 (7.3)	539 (6.8)	48 (7.2)		
Metastatic cancer 248 (0.5) 72 (0.7) 10 (0.8) 40 (0.5) ≤ 5**	Metastatic cancer	248 (0.5)	72 (0.7)	10 (0.8)	40 (0.5)	≤ 5 <sup>**</sup>		
Charlson score, median (IQR) 2 (0–3) 1 (0–2) 2 (0–3) 2 (1–3)	Charlson score, median (IQR)	2 (0–3)	1 (0–2)	1 (0–2)	2 (0–3)	2 (1–3)		
Frailty¶ 8623 (16.4) 1204 (11.6) 213 (16.3) 1491 (18.8) 154 (23.2)	Frailty¶	8623 (16.4)	1204 (11.6)	213 (16.3)	1491 (18.8)	154 (23.2)		
No. of CABG grafts, median (IQR)     3 (3-4)     -     -     2 (1-3)     2 (1-3)	No. of CABG grafts, median (IQR)	3 (3–4)	_	_	2 (1–3)	2 (1–3)		

Note: CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease, IQR = interquartile range, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, SD = standard deviation.

\*Comparisons between surgery type yielded p < 0.001 for most variables, with the exception of severe obesity (p = 0.004), psychosis (p = 0.025) and metastatic cancer (p = 0.03). †Unless otherwise stated.

‡Mitral, aortic or tricuspid valve surgery.

§Mitral, aortic or tricuspid valve surgery.

According to the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnoses indicator.<sup>29–33</sup> \*\*Small cells with values ≤ 5 were not reported as per ICES policy, where back calculation may occur.

#### Research

Table 2: Cumulative incidence of events within 1 year after cardiac surgery, stratified by type of surgery**								
	Cumulative incidence of events % (95% confidence interval)							
Event	CABG n = 52 546	Single valve <i>n</i> = 10 368	Multiple valves n = 1309	CABG + single valve n = 7936	CABG + multiple valves n = 665			
Disability	4.6 (4.4–4.8)	6.5 (6.1–7.0)	9.0 (7.5–10.7)	9.0 (8.4–9.7)	13.1 (10.6–15.8)			
Death	3.5 (3.3–3.7)	5.2 (4.8–5.6)	10.7 (9.1–12.5)	9.2 (8.6–9.9)	14.1 (11.6–16.9)			
Disability or death	7.3 (7.1–7.6)	10.4 (9.8–11.0)	17.4 (15.4–19.5)	16.4 (15.6–17.2)	23.8 (20.6–27.1)			
Stroke	1.5 (1.4–1.6)	2.5 (2.2–2.8)	3.7 (2.7–4.8)	3.5 (3.1–4.0)	5.7 (4.1–7.7)			
≥ 3 nonelective hospital admissions	2.8 (2.6–2.9)	3.5 (3.2–3.9)	4.4 (3.3–5.6)	4.7 (4.3–5.2)	6.2 (4.5–8.2)			
Long-term care admission	0.7 (0.6–0.7)	1 (0.8–1.2)	1.5 (1.0–2.3)	1.5 (1.3–1.8)	1.8 (1.0–3.0)			
Note: CABG = coronary artery bypass grafting.								

\*Comparisons between surgery type yielded p < 0.001 for all variables.



Figure 1: Cumulative incidence of disability within 1 year after cardiac surgery. Note: CABG = coronary artery bypass grafting.

outcomes such as postoperative nausea, vomiting, pain and somnolence in order of unpleasantness,<sup>37–39</sup> but similar research has not been conducted in the realm of cardiac surgery. "Patient-centred" cardiac surgery research has instead employed standard, clinician-derived instruments (e.g., Seattle Angina Questionnaire, Rose Dyspnea Scale and Patient Health Questionnaire) that were based on expert consensus alone, without active input from patients.<sup>40</sup> These standard instruments may not be meaningful to all patients as they do not capture all relevant aspects of outcomes after treatment.<sup>41</sup> Outcomes are an important determinant of treatment satisfaction, and the use of patient-defined outcomes has the unique advantage of improving both patient satisfaction and adherence to treatment.

There is no universal agreement on the definition of disability in cardiovascular research.<sup>11</sup> Prospective studies using clinician-derived instruments are often limited by small sample size and short follow-up durations, within a single centre

### Research

**E**Mai



Figure 2: Cumulative incidence of death within 1 year after cardiac surgery. Note: CABG = coronary artery bypass grafting.

setting. In the present study, we used a new and versatile definition of disability based on patient preferences,<sup>16</sup> which is adaptable to both prospective trials and large retrospective cohorts. Knowledge generated from this broad epidemiologic study will inform areas of focus for practice-changing research in the future.

CABG is an advancing field in which operative mortality has steadily declined over the years.<sup>42</sup> This, together with the younger age of presentation for CABG, could explain the lower observed rates of disability after this procedure as compared with complex CABG and multiple valve procedures, which are often performed on older and frailer patients. Complex surgery is associated with greater physiologic stresses such as fluid and electrolyte shifts, prolonged bypass durations, and a higher likelihood of exposure to low cardiac output, hypotension, end organ injury and death.<sup>43</sup>

Single valve surgery, which constitutes mostly operations on the aortic and mitral valves, was associated with a higher incidence of disability than CABG. This observation could be explained by the fact that although patients requiring aortic valve surgery are a mixed population of younger, healthier (e.g., congenital bicuspid aortic valve) and older, sicker candidates (e.g., degenerative aortic valve disease), patients who undergo isolated mitral valve surgery are generally younger, with fewer comorbidities. In contrast, patients who undergo CABG often have other substantial comorbidities that coexist with coronary artery disease to affect their outcomes adversely.

To date, disability after cardiac surgery has been reported in the form of health-related quality of life, using instruments such as the Medical Outcomes Study 36-item Short Form (SF-36),<sup>44</sup> in several small observational studies. In a singlecentre study of 112 patients, patients reported higher than normative scores in subscales of social functioning, role physical and role emotional; and lower scores in physical function, bodily pain, general health, vitality social function and mental health at 1 year after CABG.<sup>45</sup> In a study of 534 consecutive patients aged 75 years and older who had undergone cardiac surgery, mean reported quality of life improved at 6 months postoperatively as compared with that at baseline.<sup>46</sup> In a study of 154 nonagenarians who underwent CABG or valve procedures, 83% of the survivors reported an improvement in quality of life and 4% a decline in quality of life 1 year after surgerv.47

Our findings show that the incidence of patient-defined disability may be greater than that previously described by traditional instruments. Moreover, we were able to describe the population-based incidence of disability by type of surgery and across a wider patient age range. We found that the burden of disability was higher than death after routine procedures such as isolated CABG and single valve surgery, and these findings were driven mostly by recurrent hospital admissions, followed by stroke, especially in those with heart failure, renal dysfunction, alcohol use disorder, dementia and depression. As patients' ability to make informed decisions is often influenced by the emotional and logistical repercussions of their disease

Research



Figure 3: Cumulative incidence of disability, death and the combination of these outcomes at 1 year after cardiac surgery.

diagnosis and limitations in health literacy, patients with these high-risk features should be the focus of informed perioperative counselling and undergo formal heart-team evaluation regarding the risks and benefits of alternative treatment strategies.

#### Limitations

Although it is possible that we attributed outcomes to the index surgery that may be a consequence of repeat surgery, having a repeat procedure within 1 year of index cardiac surgery is rare. In the present study, of a total of 4031 patients who developed disability during the year after surgery, only 145 (3.6%) had a repeat cardiac procedure before the onset of disability. Repeat procedures may be viewed as a moderator of disability, as patients who are prone to developing disability are also prone to procedure failure.

This study has several limitations. Data pertaining to stroke severity are unavailable in the databases used. As some patients who have a stroke experience full functional recovery, our findings may have overestimated the burden of strokerelated disability. Our definition of disability was based solely on patient perceptions and values. Further studies could aim to elicit feedback from family members and caregivers as well to codefine outcomes, with input and guidance from clinicians. We were unable to incorporate or validate our disability outcome with commonly used clinical disability assessment tools, as our definition of disability is limited by what is available in administrative data. Finally, cohort studies are by nature subject to residual confounding.

#### Conclusion

We studied the procedure-specific incidence of a patientdefined disability outcome in a large cohort of cardiac surgical patients. We found disability to be a more frequent complication than death in the year after isolated CABG and single valve surgeries. In addition, patients who undergo combined CABG and multiple valve surgery, and those who have a history of heart failure, baseline creatinine 180 µmol/L or greater, alcohol use disorder, dementia and depression are at the greatest risk for developing disability. Future research should

Table 3: Multivariable predictors of disability at 1-year after major cardiac surgery				
Variable	Subdistribution HR (95% CI)			
Age	1.03 (1.02–1.03)			
Female	1.38 (1.28–1.48)			
Surgery type (Ref.: Isolated CABG)				
Single valve	1.34 (1.21–1.48)			
Multiple valves	1.43 (1.18–1.75)			
CABG + single valve	1.38 (1.26–1.51)			
CABG + multiple valves	1.78 (1.43–2.23)			
Emergent procedure	1.40 (1.26–1.57)			
Rural residence	1.03 (0.94–1.12)			
Income quintile (Ref.: 5 [highest])				
1 (lowest)	1.33 (1.20–1.47)			
2	1.16 (1.05–1.29)			
3	1.11 (1.00–1.23)			
4	0.99 (0.89–1.10)			
Hypertension	1.16 (1.03–1.31)			
Atrial fibrillation	1.25 (1.14–1.37)			
Heart failure	1.66 (1.53–1.79)			
MI within 30 days	1.26 (1.17–1.36)			
Remote MI	1.13 (1.04–1.23)			
Previous PCI	0.94 (0.85–1.03)			
LVEF, % (Ref.: ≥ 50)				
< 20	1.10 (0.89–1.36)			
20–34	1.07 (0.99–1.16)			
35–49	1.00 (0.89–1.11)			
Cerebrovascular disease	1.40 (1.29–1.53)			
Peripheral arterial disease	1.23 (1.14–1.34)			
Smoker (Ref.: Never)				
Current	1.19 (1.09–1.30)			
Former	1.07 (0.99–1.15)			
COPD or asthma	1.32 (1.24–1.41)			
Pulmonary circulatory disorder	1.07 (0.91–1.24)			
Severe obesity	0.97 (0.91–1.03)			
Diabetes	1.38 (1.29–1.47)			
Hypothyroidism	1.10 (0.93–1.31)			
Anemia	1.39 (1.28–1.51)			
Baseline creatinine (µmol/L; Ref.: < 120)				
120–179	1.32 (1.21–1.45)			
≥ 180	1.81 (1.57–2.08)			
Dialysis	1.40 (1.19–1.64)			
Liver disease	1.33 (1.06–1.68)			
Alcohol use disorder	1.68 (1.39–2 03)			
Dementia	1.59 (1.13–2.24)			
Depression	1.66 (1.41–1.97)			
Psychosis	1.05 (0.62–1.76)			
Primary cancer	119 (106–134)			
Metastatic cancer	147 (108–199)			
	1.47 (1.00-1.33)			

Note: CABG = coronary artery bypass grafting, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, Ref. = Reference.

**CMAJ**OPEN

be dedicated to personalized disability risk prediction to inform better the joint therapeutic decision-making process and, in doing so, to improve the efficiency and effectiveness of health care delivery as well as patient satisfaction.

#### References

Research

**CMA**OPEN

- Hu J, Chen R, Liu S, et al. Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: a systematic review and metaanalysis. *J Cardiothorac Vasc Anesth* 2016;30:82-9.
- Favaloro RG. Critical analysis of coronary artery bypass graft surgery: a 30-year journey. J Am Coll Cardiol 1998;31:1B-63B.
- Karim MN, Reid CM, Huq M, et al. Predicting long-term survival after coronary artery bypass graft surgery. *Interact Cardiovasc Thorac Surg* 2018;26:257-63.
- Baillot RG, Joanisse DR, Stevens LM, et al. Recent evolution in demographic and clinical characteristics and in-hospital morbidity in patients undergoing coronary surgery. *Can J Surg* 2009;52:394-400.
- Myles PS. Meaningful outcome measures in cardiac surgery. J Extra Corpor Technol 2014;46:23-7.
- Chalmers I, Clarke M. Outcomes that matter to patients in tombstone trials. Lancet 2001;358:1649.
- Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. *JAMA* 2012;307:1583-4.
- Rahimi K, Malhotra A, Banning AP, et al. Outcome selection and role of patient reported outcomes in contemporary cardiovascular trials: systematic review. *BMJ* 2010;341:c5707. doi: 10.1136/bmj.c5707.
- Mulley AG. Inconvenient truths about supplier induced demand and unwarranted variation in medical practice. *BMJ* 2009;339:b4073. doi: 10.1136/bmj.b4073.
- Caine N, Harrison SC, Sharples LD, et al. Prospective study of quality of life before and after coronary artery bypass grafting. *BMJ* 1991;302:511-6.
- Wenger NK, Froelicher ES, Smith LK, et al. Cardiac rehabilitation as secondary prevention. Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute. *Clin Pract Guidel Quick Ref Guide Clin* 1995;Oct:1-23.
- Chocron S, Etievent JP, Viel JF, et al. Prospective study of quality of life before and after open heart operations. *Ann Thorac Surg* 1996;61:153-7.
- Siminoff LA. Incorporating patient and family preferences into evidencebased medicine. BMC Med Inform Decis Mak 2013;13(Suppl 3):S6.
- 14. Bensing J. Bridging the gap. The separate worlds of evidence-based medicine and patient-centered medicine. *Patient Educ Couns* 2000;39:17-25.
- Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? *BMJ* 1998;316:360.
- Sun LY, Tu JV, Lee DS, et al. Disability-free survival after coronary artery bypass grafting in women and men with heart failure. Open Heart 2018;5:e000911.
- Tu JV, Ko DT, Guo H, et al; Cardiac Care Network of Ontario's Variations in Revascularization Practice in Ontario Working G. Determinants of variations in coronary revascularization practices. *CMAJ* 2012;184:179-86.
- Tu K, Campbell NRC, Chen ZL, et al. Accuracy of administrative databases in identifying patients with hypertension. *Open Med* 2007;1:e18-26.
- Juurlink D, Preya C, Croxford R, et al. Canadian Institute for Health Information Discharge Abstract Database: a validation study. ICES investigative report. Toronto: Institute for Clinical Evaluative Sciences; 2006.
- Hux JE, Ivis F, Flintoft V, et al. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25:512-6.
- Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart* J 2002;144:290-6.
- Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9.
- Gershon AS, Wang C, Guan J, et al. Identifying individuals with physician diagnosed COPD in health administrative databases. COPD 2009;6:388-94.
- Schultz SE, Rothwell DM, Chen Z, et al. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can* 2013;33:160-6.
- Johnston A, Mesana TG, Lee DS, et al. Sex differences in long-term survival after major cardiac surgery: a population-based cohort study. *J Am Heart* Assoc 2019;8:e013260.
- 26. du Plessis V, Beshiri R, Bollman RD, et al. Definitions of "rural." Agriculture and rural working paper series, No. 61. Ottawa: Statistics Canada; 2002.
- Sun LY, Tu JV, Bader Eddeen A, et al. Prevalence and long-term survival after coronary artery bypass grafting in men and women with heart failure and preserved vs reduced ejection fraction. *J Am Heart Assoc* 2018;7:e008902.
  Tran DTT, Tu JV, Dupuis JY, et al. Association of frailty and long-term sur-
- Tran DTT, Tu JV, Dupuis JY, et al. Association of frailty and long-term survival in patients undergoing coronary artery bypass grafting. *J Am Heart Assoc* 2018;7:e009882.
- Lieberman AC, Weiner JP. Development and evaluation of the Johns Hopkins University risk adjustment models for Medicare+ Choice plan payment. Baltimore: Johns Hopkins University; 2003.

- Sternberg SA, Bentur N, Abrams C, et al. Identifying frail older people using predictive modeling. Am J Manag Care 2012;18:e392-7.
- The Johns Hopkins Adjusted Clinical Groups Technical Reference Guide, version 9.0. Baltimore: Johns Hopkins University; 2009.
- 32. Bronskill S CM, Costa A, et al. Aging in Ontario: an ICES chartbook of health services use by older adults a technical report. Toronto: ICES; 2010.
- Bronskill S CX, Gruneir A, Ho M. Health system use by frail Ontario seniors: an in-depth examination of four vulnerable cohorts. Toronto: ICES; 2011.
- 34. Tu K, Wang M, Young J, et al. Validity of administrative data for identifying patients who have had a stroke or transient ischemic attack using EMRALD as a reference standard. *Can J Cardiol* 2013;29:1388-94.
- Victor JC, Monto AS, Surdina TY, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. N Engl J Med 2007;357:1685-94.
- Frank L, Basch E, Selby JV; Patient-Centered Outcomes Research Institute. The PCORI perspective on patient-centered outcomes research. *JAMA* 2014;312:1513-4.
- Macario A, Weinger M, Carney S, et al. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999;89:652-8.
- Eberhart LH, Morin AM, Wulf H, et al. Patient preferences for immediate postoperative recovery. Br 7 Anaesth 2002;89:760-1.
- Rashiq S, Bray P. Relative value to surgical patients and anesthesia providers of selected anesthesia related outcomes. BMC Med Inform Decis Mak 2003;3:3.
- McNamara RL, Spatz ES, Kelley TA, et al. Standardized outcome measurement for patients with coronary artery disease: consensus from the International Consortium for Health Outcomes Measurement (ICHOM). J Am Heart Assoc 2015;4:e001767.
- Revicki DA. Patient assessment of treatment satisfaction: methods and practical issues. *Gut* 2004;53(Suppl 4):iv40-4.
- 42. Ferguson TB Jr, Hammill BG, Peterson ED, et al. A decade of change–risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990-1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons. Ann Thorac Surg 2002;73:480-9, discussion 489-90.
- Sun LY, Chung AM, Farkouh M, et al. Defining a perioperative hypotension threshold in association with stroke in cardiac surgery. [published erratum in *Anesthesiology* 2019;130:360]. *Anesthesiology* 2018;129:440-7.
- Ware JE, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- Taghipour HR, Naseri MH, Safiarian R, et al. Quality of life one year after coronary artery bypass graft surgery. *Iran Red Crescent Med* J 2011;13:171-7.
- Gjeilo KH, Wahba A, Klepstad P, et al. Survival and quality of life in an elderly cardiac surgery population: 5-year follow-up. *Eur J Cardiothorac Surg* 2013;44:e182-8.
- Caceres M, Cheng W, De Robertis M, et al. Survival and quality of life for nonagenarians after cardiac surgery. *Ann Thorac Surg* 2013;95:1598-602.

Affiliations: The Division of Cardiac Anesthesiology, Department of Anesthesiology and Pain Medicine (Sun), University of Ottawa Heart Institute; the School of Epidemiology and Public Health (Sun), University of Ottawa; the Institute for Clinical Evaluative Sciences (Sun, Bader Eddeen); the Division of Cardiac Surgery, Department of Surgery (Mesana), University of Ottawa Heart Institute, Ottawa, Ont.

**Contributors:** Louise Sun contributed to conception and design of the study. Louise Sun and Anan Bader Eddeen contributed to data acquisition and analysis. Louise Sun, Anan Bader Eddeen and Thierry Mesana contributed to interpretation of data. Louise Sun drafted the work and Louise Sun, Anan Bader Eddeen and Thierry Mesana revised it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

**Funding:** The authors acknowledge support from an operating grant from the Canadian Institutes of Health Research (Grant #4752). Louise Sun was named Heart and Stroke Foundation of Canada National New Investigator and is supported by the University of Ottawa Tier 2 Clinical Research Chair in Big Data and Cardiovascular Outcomes and the Ottawa Heart Institute Research Corporation.

**Content licence:** This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BYNCND 4.0) licence, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is noncommercial (i.e., research or educational use), and no modifications or adaptations are made. See: https://creativecommons.org/ licenses/by-nc-nd/4.0/

**Data sharing:** The data set from this study is held securely in coded form at ICES. Although data sharing agreements prohibit ICES from making

#### Research

the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices. on.ca/DAS.

Acknowledgement: This study is supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The authors acknowledge that the clinical registry data used in this analysis is from participating hospitals through CorHealth Ontario, which serves as an advisory body to the MOHLTC, is funded by the MOHLTC, and is dedicated to improving the quality, efficiency, access and equity in the delivery of the continuum of adult cardiac and stroke care in Ontario, Canada. The authors also acknowledge the usage of data compiled and provided by the Canadian Institute for Health Information. These data sets were linked using unique encoded identifiers and analyzed at ICES.

**Supplemental information:** For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/9/2/E384/suppl/DC1.

**Disclaimer:** This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.