The Association between Cardiovascular Disease Admission Rates and
The Coronavirus Disease 2019 Lockdown and Reopening of a Nation:
a Danish Nationwide Cohort Study

Running title: Impact of Covid-19 on cardiovascular admissions

Jawad H. Butt, MD;¹ Lauge Østergaard, MD;¹ Thomas A. Gerds, Dr.rer.nat;²,³
Marie D. Lauridsen, MD;¹ Kristian Kragholm, MD, PhD;⁴ Morten Schou, MD, DMSc;⁵
Matthew Phelps, PhD;² Gunnar H. Gislason, MD, PhD;²,⁵ Christian Torp-Pedersen, MD, DMSc;⁶
Lars Køber, MD, DMSc;¹ Emil L. Fosbøl, MD, PhD¹

¹Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
²The Danish Heart Foundation, Copenhagen, Denmark.
³Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark.
⁴Departments of Cardiology, North Denmark Regional Hospital and Aalborg University Hospital, Denmark.
⁵Department of Cardiology, Herlev-Gentofte University Hospital, Copenhagen, Denmark.
⁶Department of Clinical Research and Cardiology, Nordsjællands Hospital, Hillerød, Denmark.

Address for Correspondence:
Jawad Haider Butt, MD
Department of Cardiology
Rigshospitalet, Copenhagen University Hospital
Blegdamsvej 9, 2100 Copenhagen, Denmark
E-mail: jawad_butt91@hotmail.com
Abstract

Background: To investigate the admission rates of cardiovascular diseases, overall and according to subgroups, and subsequent mortality rates during the Covid-19 societal lockdown (March 12, 2020) and reopening phase (April 15, 2020) in Denmark.

Methods and Results: Using Danish nationwide registries, we identified patients with a first-time acute cardiovascular admission in two periods: 1) January 2-October 16, 2019 and 2) January 2-October 15, 2020. Weekly incidence rates of a first-time cardiovascular admission, overall and according to subtypes, in the two periods were calculated. The incidence rate of first-time cardiovascular admissions overall was significantly lower during the first weeks of lockdown in 2020 compared with a similar period in 2019 but increased after the gradual reopening of the Danish society. A similar trend was observed for all subgroups of cardiovascular diseases. The mortality rate among patients admitted after March 12 was not significantly different in 2020 compared with 2019 (mortality rate ratio 0.98 [95% CI, 0.91-1.06]).

Conclusions: In Denmark, we observed a substantial decrease in the rate of acute cardiovascular admissions, overall and according to subtypes, during the first weeks of lockdown. However, after the gradual reopening of the Danish society, the admission rates for acute cardiovascular diseases increased and returned to rates similar to those observed in 2019. The mortality rate in patients admitted with cardiovascular diseases during lockdown was similar to that of patients during the same period in 2019.
Introduction

The rapid global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an unprecedented threat to global health and confers a substantial burden on healthcare systems and providers worldwide. The primary strategy to alleviate the increasing burden on healthcare systems has been containment of SARS-CoV-2 and reorganizing, prioritizing, and allocating health and medical resources to the management of patients with the illness it causes, coronavirus disease 2019 (Covid-19). However, this strategy may impact optimal treatment delivery to patients with other acute, and perhaps more severe and fatal, conditions.

Cardiovascular diseases are prevalent and a leading cause of death and acquired disability worldwide. Given that time from symptom onset to treatment is paramount to prevent excess morbidity and mortality in these patients, minimizing prehospital delay requires prompt recognition of symptoms and immediate contact to emergency medical services. However, the implementation of other preventive measures to mitigate the onward spread of the Covid-19 pandemic, for example a comprehensive societal lockdown strategy, may increase the reluctance of patients with symptoms suggestive of acute cardiovascular diseases to contact emergency medical services. Although emerging data suggest that admission rates of acute cardiovascular diseases, including acute coronary syndrome, heart failure, and stroke, have declined initially during the Covid-19 pandemic, the impact of a lockdown strategy and health care system reorganization on cardiovascular disease admission rates, overall and according to subgroups of cardiovascular diseases, on a nationwide scale have been sparsely investigated. More importantly, as societies worldwide are gradually reopening, data on admission rates of cardiovascular diseases during the reopening phase are lacking. In the event of a new pandemic or a new Covid-19 wave, such knowledge will be of great importance as it will shed light on the possible collateral effects of a societal lockdown strategy and reorganization of the healthcare system.
To address these gaps in knowledge, we performed a nationwide cohort study to investigate the admission rates of cardiovascular diseases, overall and according to subgroups of cardiovascular diseases, and subsequent prognosis, during the Covid-19 societal lockdown and reopening phase in Denmark.

Methods

Lockdown and reopening of the Danish society

As of March 12, 2020, the Danish authorities imposed extensive nationwide lockdown measures to prevent the spread of Covid-19 including closure of Danish borders, sending home all employees working in non-essential functions in the public sector, and closure of schools and daycare facilities.\(^{16}\) On March 18, 2020, these measures were further extended to include a ban of gatherings of more than 10 people.\(^{16}\) Further, the Danish healthcare system was reorganized, outpatient visits were converted to telemedicine or cancelled, whenever possible, and elective, nonvital procedures were cancelled or postponed. On April 6, the Danish authorities announced that the government would commence a gradual and controlled reopening of the Danish society. The first phase of reopening of the Danish society included reopening of schools for younger pupils (April 15) and liberal professions (April 20).\(^{16}\) The second phase included reopening of restaurants and cafes (May 18), schools for older pupils (May 18), cultural and recreational activities (i.e. museums, theaters, and outdoor parks) and research institutions (May 27).\(^{16}\) The third phase included an ease of the ban of gatherings to 50 people (June 8) and allowed all public sector employees to return to work in person (June 15).\(^{16}\)

Data sources
All citizens in Denmark are assigned a unique and personal identification number, which allows accurate linkage of nationwide administrative registries at an individual level for research purposes. For this study, data from several nationwide administrative registries were obtained. The Danish National Patient Registry holds information on all hospital admissions and outpatient contacts according to the International Classification of Diseases (ICD-8 until 1994 and ICD-10 from 1994). All patients are given one primary and, if appropriate, one or more secondary diagnoses at every hospital admission and outpatient contact in Denmark. The Danish National Prescription Registry comprises detailed information on dispensing date, strength, and quantity on all claimed drug prescriptions in Denmark. The Danish Civil Registration System contains data on birth date, sex, and vital status. The Danish registries are validated, of high quality, and have been described in detail previously.

Study population

The study population comprised every Danish citizen in two periods: 1) January 2- October 16, 2019 and 2) January 2- October 15, 2020. Patients were excluded if they were younger than 18 years or had a history of the outcome of interest (defined as any primary of secondary in-hospital or out-patient hospital diagnosis) prior to the date of inclusion (i.e. January 2, 2019 and 2020 for the 2019 and 2020 period, respectively). 2020 is a leap year and to ensure a similar potential follow-up period in both groups, patients in the 2019 and 2020 period were followed until October 16, 2019 and October 15, 2020, respectively. Patients in the 2020 period were included from January 2, 2020 to assess the rate of outcomes before and during lockdown. The 2019 period was included to compare the rate of cardiovascular disease admissions during the first 41 weeks of 2020 with a similar period in 2019 in order to account for temporal variability in hospital admissions.
We also assessed the total number of cardiovascular admissions (and not only the first during the study period) in the entire Danish population (i.e. both those with and without a history of cardiovascular disease).

**Follow-up and outcomes**

Patients in both cohorts were followed from the date of inclusion until occurrence of the outcome of interest, death, or 41 weeks, whichever came first. The primary outcome was first-time admission for any cardiovascular cause (defined as any primary of secondary in-hospital diagnosis code of diseases of the circulatory system [ICD-10 code category I]). Secondary outcomes were first-time admission for each the following cardiovascular diseases (defined as any primary of secondary in-hospital diagnosis code): Cardiac arrest, arrhythmia, or atrioventricular block (ICD-10 codes I44-49), cerebrovascular disease (ICD-10 codes I60-69), heart failure, cardiomyopathy, or myocarditis, cardiomyopathy (ICD-10 codes I50, I40-43), ischemic heart disease (ICD-10 codes I20-25), hypertension (ICD-10 codes I10-15), deep vein thrombosis or pulmonary embolism (ICD-10 codes I801-803, I808-809, I821-823, I828-829, I26), and valvular heart disease, including infective endocarditis (ICD-10 codes I33-39). All diagnosis codes for outcomes have been validated with high positive predictive values in the Danish National Patient Registry.20,21

We also investigated the incidence rate of the primary outcome according to sex and age (above/below 60 years of age). In addition, we examined all-cause mortality among patients with a cardiovascular admission, overall and according to subgroups. In this analysis, all patients were followed from the date of admission until death, emigration, or end of follow-up (October 16, 2019 and October 15, 2020 for the 2019 and 2020 cohort, respectively).

**Patient characteristics**
Comorbidity was obtained using in-hospital and outpatient diagnosis codes any time prior to admission (eTable 1 for ICD-10 codes). Patients with hypertension were identified using claimed drug prescriptions as described previously.\textsuperscript{22,23} Pharmacotherapy at baseline was defined as claimed prescriptions within 180 days prior to admission (eTable 2 for Anatomical Therapeutic Chemical codes).

Statistics
Baseline characteristics were reported as frequencies with percentages or medians with 25\textsuperscript{th}-75\textsuperscript{th} percentiles. Baseline characteristics among patients with a cardiovascular disease admission before and after March 12 in 2019 and 2020, respectively, at the time of admission were reported. Incidence rates of outcomes per 1,000 person-years were calculated for each of the 41 weeks in 2019 and 2020, respectively, and reported with 95\% exact Poisson confidence intervals (CI). Incidence rate ratios with 95\% CI were calculated using unadjusted Poisson regression for each of the 41 weeks, with the corresponding week in 2019 as reference. Further, mortality rate ratios with 95\% CI among patients with a cardiovascular admission before and after March 12, respectively, were calculated using unadjusted Cox regression, with 2019 as reference. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, North Carolina, USA) and R (version 3.6.1, The R Foundation).\textsuperscript{24} The level of statistical significance was set at 5\%.

Ethics
In Denmark registry-based studies that are conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. However, the study is approved by the data responsible institute (the Capital Region of Denmark [approval number: P-2019-191]) in accordance with the General Data Protection Regulation.
Results

Total number of cardiovascular hospitalizations

The total number of cardiovascular admissions in Denmark during the first 4 weeks after March 12 was 6,561 and 4,761 in 2019 and 2020, respectively, corresponding to a 27.4% decline in 2020 (Figure 1). After the gradual reopening, the total number of cardiovascular admissions increased and returned to numbers similar to those observed in 2019.

First-time cardiovascular hospitalizations

In total, 3,492,404 and 3,494,706 Danish citizens who were 18 years of age or older, without a history of a cardiovascular disease and alive on January 2 in 2019 and 2020, respectively. Baseline characteristics of these cohorts are shown in eTable 3. The groups were comparable with respect to age, proportion of men, and comorbidity burden.

In 2019, 18,062 had a first-time cardiovascular hospital admission during the 41-week period in 2019 compared with 17,361 patients in 2020. After March 12, 13,290 patients had a cardiovascular admission in 2019 compared with 12,774 patients in 2020. Baseline characteristics of patients admitted with cardiovascular disease before and after March 12 in 2019 and 2020, respectively, at the time of admission are shown in Table 1. Overall, patients admitted after March 12 in 2019 and 2020 were comparable with respect to age, proportion of men, and comorbidities.

Compared with 2019, the incidence rate of cardiovascular admissions during the weeks 1-9 (apart from week 5) was not significantly different in 2020 (Figure 2). However, the incidence rate of cardiovascular admissions was significantly lower during the first weeks of lockdown in 2020 but increased after the gradual reopening of the Danish society and returned to rates similar to those observed in 2019.
The median follow-up from cardiovascular admission until end of follow-up was 135 days (25th-75th percentile, 54-212 days) and 128 days (25th-75th percentile 52-210 days) for patients admitted in 2019 and 2020, respectively. Among patients with a cardiovascular admission on March 12 or before, 613 (12.8%) patients died during follow-up in 2019 compared with 562 (12.3%) in 2020. Among those with a cardiovascular admission after March 12, 1,233 (9.3%) patients died during follow-up in 2019 compared with 1,151 (9.0%) in 2020. The mortality rate among patients admitted before and after March 12 was not statistically significantly different in 2020 compared with 2019 (mortality rate ratio 0.95 [0.85-1.07] and 0.98 [95% CI 0.91-1.06], respectively).

First-time cause-specific cardiovascular hospitalizations

Overall, the incidence rates of subgroups of cardiovascular admissions were significantly lower during the first weeks of lockdown in 2020 before increasing after the gradual reopening of the Danish society and returning to rates similar to those observed in 2019 (Figure 3 and Figure 4).

The mortality rates among patients with a cardiovascular admission in all subgroups admitted before and after March 12 were not statistically significantly different in 2020 compared with 2019 (Figure 5).

Sex and age

In both men and women, the incidence rate of cardiovascular admissions was significantly lower during the first weeks of lockdown in 2020 before increasing after the gradual reopening of the Danish society (eFigure 1). Likewise, the incidence rate of cardiovascular admissions was significantly lower during the weeks of lockdown in 2020 in both citizens aged below and above 60 years before increasing after the gradual reopening of the Danish society and returning to rates similar to those observed in 2019 (eFigure 2).
Discussion

In this nationwide study, we examined the admission rates of cardiovascular diseases, overall and according to subgroups of cardiovascular diseases, and subsequent prognosis, during the Covid-19 societal lockdown and reopening phase in Denmark. This study yielded the following major findings: First, there was a substantial decrease in the incidence rate of first-time (and any) cardiovascular admissions, overall and according to subgroups, during the weeks following the lockdown compared with the same period in the preceding year. Second, after the gradual reopening of the Danish society, the admission rates for cardiovascular diseases increased and returned to rates similar to those observed in the preceding year. Third, the all-cause mortality rate in patients admitted with cardiovascular diseases, overall and according to subtypes, during the lockdown was not significantly higher than that of patients during the same period in the preceding year.

Emerging data suggest that admissions for acute coronary syndrome, heart failure, and stroke have declined initially during the Covid-19 pandemic.⁴⁻¹² In addition, reports on acute cardiovascular admissions overall during the initial phase of Covid-19 pandemic are emerging.¹³⁻¹⁵ Recently, Toniolo et al. demonstrated a substantial decline in severe emergent cardiovascular hospitalizations, including acute coronary syndrome and severe brady-arrhythmia, in a single large tertiary center in Northern Italy.¹⁵ In addition, Bhatt et al. reported a marked decline in acute cardiovascular hospitalizations, including acute coronary syndrome, heart failure, and stroke, and shorter length of stay among those who were admitted across the tertiary care Mass General Brigham health system between January 1, 2019 and March 31, 2020.¹⁴ However, comprehensive, nationwide data on the rate of cardiovascular admissions and subsequent mortality, overall and according to subgroups, have not been published to date. To our knowledge, our study is among the first to investigate the impact of the Covid-19 pandemic on the incidence rate of admissions for a
broad range of cardiovascular diseases on a nationwide scale. Our study demonstrated a substantial decline in the incidence rate of first-time cardiovascular disease admissions during the weeks following the lockdown compared with the same period in the preceding year. Interestingly, the admission rates increased towards the end of the study period, when reopening of the Danish society was initiated.

It is possible that patients without established cardiovascular disease may have a different healthcare seeking behavior than those with established cardiovascular disease. In the present study, we assessed not only cardiovascular admissions in patients without a history of cardiovascular disease, but also the total number of cardiovascular admissions in the entire Danish population (i.e. both those with and without a history of cardiovascular disease). We found that the total number of cardiovascular admissions declined during the first four weeks of lockdown but increased and returned to numbers similar to those observed in 2019 after the gradual reopening.

The reasons for the significant decline in cardiovascular admissions in the weeks following the lockdown are unclear. It is possible that some individuals experiencing symptoms suggestive of acute cardiovascular disease may be more likely to stay at home, and perhaps seek alternative care, rather than attending emergency departments due to fear of acquiring or being exposed to Covid-19. Another possible explanation is that some patients may hesitate to seek medical care in order to avoid adding to an overburdened healthcare system. The decline in outpatient cardiovascular visits and postponement of elective procedures may also have contributed to the decline in cardiovascular admissions, because these often may serve as points of referral for inpatient hospitalization.\textsuperscript{14} Interestingly, a decline in influenza rates have been reported during societal lockdown.\textsuperscript{25,26} Although speculative, it is possible that the decline in rates of influenza and other infections – a risk factor for several acute cardiovascular diseases – to a lesser extent may have contributed to the decrease in cardiovascular admission rates. Another proposed explanation
for the observed decline in cardiovascular admissions has been a reduction in acute stressors – a risk factor for many acute cardiovascular conditions. However, this appears to be less likely given that several surveys suggest that adults report more symptoms of anxiety and stress during the COVID-19 pandemic than previously due to the direct or indirect consequences of the pandemic. Consequently, this would cause an increase – not a decrease – in acute cardiovascular conditions.

Whatever the reason, these findings have important implications for public health. The significant decline in cardiovascular admissions suggest that the Covid-19 pandemic may have a detrimental effect on medical care, and other downstream consequences are likely. For example, failure to diagnose and treat patients with minor ischemic stroke or transient ischemic attack portends a considerable increase in the risk of recurrent stroke. Likewise, sub-optimally treated or untreated acute myocardial infarction may increase the risk of developing heart failure. These findings also suggest that the message from governments worldwide to stay at home should be more nuanced and reinforce the necessity of a clear public health message to patients experiencing symptoms suggestive of acute cardiovascular disease to still seek emergency medical services rather than to stay at home or seek alternative care. Professional medical societies are aware of the potential collateral damage of the Covid-19 pandemic and societal lockdown and have issued statements and developed tools to increase recognition of symptoms of acute cardiovascular diseases, including stroke and acute coronary syndrome, in the general population and to underline the importance of immediate contact to emergency medical services should such symptoms occur. Although the cardiovascular admission rate increased after the gradual reopening of the Danish society and returned to a rate similar to that observed in 2019, these findings may be useful for policy makers and health care planners if a new pandemic or a new Covid-19 wave should occur. Thus, further efforts and initiatives to raise public awareness of symptoms suggestive of
acute cardiovascular diseases and other serious conditions are needed in case of a new pandemic or a new Covid-19 wave.

As the rapid spread of Covid-19 continues, healthcare systems worldwide are preparing for a surge of hospitalized Covid-19 patients by reorganizing, prioritizing, and allocating health and medical resources to the management of these patients. Although prevention and control of Covid-19 is very important, patients with other acute conditions should not be neglected and management of these patients must adhere to guidelines to the extent possible. However, the ability to deliver timely and efficacious care must be balanced with the risk of infectious exposure to the clinical team. On the other hand, the possible reluctance of patients to contact emergency medical services promptly may result in more severe disease presentation at the time of hospital arrival and thus worse outcomes. In our study, we demonstrated that mortality among patients with a cardiovascular admission, overall and according to subtypes, was not significantly higher after the implementation of the lockdown compared with a similar period in the preceding year. These data do not indicate that patients present with more severe cardiovascular disease or that reorganization of national healthcare systems, which may have influenced in-hospital treatment delay, including effective triage and rapid identification of treatment options, have had an impact on short-term mortality. However, the low number of events, limited follow-up, and lack of data on disease severity in this analysis does not allow for a long-term evaluation of the impact of the Covid-19 pandemic on acute cardiovascular disease care. More studies are, therefore, warranted in order to establish the impact of the Covid-19 pandemic on quality of care in acute cardiovascular diseases.

**Strengths and limitations**

We used data from complete and unselected nationwide administrative registries, which enables us to examine trends in hospital admissions on a nationwide scale. However, the observational nature
precludes the assessment of cause-effect relationships. Further, data on general practitioner visits were not available for this study, though the Danish Health Authority observed a substantial decline in general practitioner visits for any cause and fewer hospital referrals for e.g. suspicion of cancer during the Covid-19 lockdown.\textsuperscript{37} Thus, this observation further supports the notion that patients may be reluctant to contact the health care system. In addition, data on cause of death were not available, and we were therefore not able to examine out-of-hospital deaths attributed to cardiovascular diseases. Finally, given the low incidence of laboratory-confirmed Covid-19 cases and subsequent case-fatality in Denmark as compared with other countries, our findings may not be generalizable to countries with a greater burden of Covid-19 cases.

**Conclusions**

In this Danish nationwide study, we observed a substantial decrease in the rate of first-time acute cardiovascular admissions, overall and according to subtypes, during the weeks following the lockdown for the Covid-19 pandemic. However, after the gradual reopening of the Danish society, the admission rates for acute cardiovascular diseases increased and returned to rates similar to those observed in 2019. The all-cause mortality rate in patients admitted with cardiovascular diseases following the lockdown was not significantly higher compared with patients during the same period in the preceding year. These findings have important implications and reinforce the necessity of a clear public health message to patients experiencing symptoms suggestive of acute cardiovascular diseases to still seek emergency medical services, should a new pandemic or a new Covid-19 wave occur.

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Data availability

Data for this study are derived from Statistics Denmark. By law, these data are not allowed to be shared. Therefore, data cannot be made available to other researchers.

Disclosures

None.
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Figure legends

Figure 1. Total number of cardiovascular admissions from January 2 in 2019 and 2020

This figure shows the total numbers of all cardiovascular admissions from January 2-June 19, 2019 (blue line) and January 2-June 18, 2020 (red line).

Figure 2. Weekly incidence rates and incidence rate ratios of cardiovascular admissions from January 2 in 2019 and 2020

a) Weekly incidence rates of cardiovascular admissions per 1,000 person-years

b) Weekly incidence rate ratios of cardiovascular admissions in 2020 compared with 2019

This figure displays the weekly incidence rates per 1,000 person-years and incidence rate ratios of first-time cardiovascular admissions from January 2-June 19, 2019 and January 2-June 18, 2020. The incidence rates per 1,000 person-years and incidence rate ratios are displayed for all cardiovascular admissions.

Figure 3. Weekly incidence rates per 1,000 person-years and incidence rate ratios of subgroups of cardiovascular admissions from January 2 in 2019 and 2020

This figure displays the weekly incidence rates per 1,000 person-years and incidence rate ratios of first-time cardiovascular admissions from January 2-June 19, 2019 and January 2-June 18, 2020. The incidence rates per 1,000 person-years and incidence rate ratios are displayed for subtypes of cardiovascular admissions.

Figure 4. Weekly incidence rates per 1,000 person-years and incidence rate ratios of subgroups of cardiovascular admissions from January 2 in 2019 and 2020

This figure displays the weekly incidence rates per 1,000 person-years and incidence rate ratios of first-time cardiovascular admissions from January 2-June 19, 2019 and January 2-June 18, 2020. The incidence rates per 1,000 person-years and incidence rate ratios are displayed for subtypes of cardiovascular admissions.

Figure 5. Mortality rate ratios among patients with a cardiovascular admission, overall and according to subtypes, in 2020 compared with 2019
This figure shows the mortality rate ratios among patients with a cardiovascular admission before (January 2-March 12) and during lockdown (March 13-June 18) in 2020 compared with a similar period in 2019. The mortality rate ratios are displayed for patients with any cardiovascular admissions and subtypes of cardiovascular admissions.
Table 1. Characteristics of patients at their first-time cardiovascular admission before and after March 12 at the time of admission

| Characteristics                                      | January 2-Mar 12 | Mar 13-June 19/18 |
|------------------------------------------------------|------------------|-------------------|
|                                                      | 2019 N=4,772     | 2020 N=4,587      |
|                                                      | 2019 N=13,290    | 2020 N=12,774     |
| Demographics                                         |                  |                   |
| Age, median (25th-75th percentile)                   | 68 (56-77)       | 67 (55-77)        |
|                                                      | 66 (54-76)       | 67 (55-76)        |
| Male, N (%)                                          | 2,665 (55.8)     | 2,553 (55.7)      |
|                                                      | 7,430 (55.9)     | 7,718 (56.2)      |
| Comorbidities, N (%)                                  |                  |                   |
| Hypertension                                         | 1,100 (23.1)     | 937 (20.4)        |
|                                                      | 2,870 (21.6)     | 2,658 (20.8)      |
| Diabetes                                             | 261 (5.5)        | 261 (5.7)         |
|                                                      | 710 (5.3)        | 636 (5.0)         |
| Malignancy                                           | 705 (14.8)       | 631 (13.8)        |
|                                                      | 1,870 (14.1)     | 1,789 (14.0)      |
| Chronic kidney disease                               | 108 (2.3)        | 108 (2.4)         |
|                                                      | 335 (2.5)        | 287 (2.2)         |
| Chronic obstructive pulmonary disease                | 291 (6.1)        | 279 (6.1)         |
|                                                      | 751 (5.7)        | 664 (5.2)         |
| Liver disease                                         | 146 (3.1)        | 122 (2.7)         |
|                                                      | 395 (3.0)        | 336 (2.6)         |
| Dementia                                             | 35 (0.7)         | 21 (0.5)          |
|                                                      | 79 (0.6)         | 82 (0.6)          |
| Rheumatic disease                                     | 194 (4.1)        | 196 (4.3)         |
|                                                      | 540 (4.1)        | 526 (4.1)         |
| Concomitant medical treatment, N (%)                  |                  |                   |
| Lipid-lowering drugs                                  | 819 (17.2)       | 761 (16.6)        |
|                                                      | 2,148 (16.2)     | 2,089 (16.4)      |
| Aspirin                                              | 341 (7.1)        | 302 (6.6)         |
|                                                      | 895 (6.7)        | 718 (5.6)         |
| Beta-blockers                                         | 447 (9.4)        | 407 (8.9)         |
|                                                      | 1,179 (8.9)      | 1,072 (8.4)       |
| Calcium channel blockers                              | 744 (15.6)       | 667 (14.5)        |
|                                                      | 1,985 (14.9)     | 1,903 (14.9)      |
| RAS inhibitors                                        | 1,307 (27.4)     | 1,197 (26.1)      |
|                                                      | 3,577 (26.9)     | 3,395 (26.6)      |

*RAS, renin-angiotensin-aldosterone system*
a) Cardiac arrest, arrhythmia, and atrioventricular block

b) Cerebrovascular disease

c) Heart failure, cardiomyopathy, or myocarditis

d) Ischemic heart disease
Figure 4

a) Arterial hypertension

b) Deep vein thrombosis or pulmonary embolism

c) Valvular heart disease
