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Long-Term Relative Survival after Stroke: The Dijon Stroke Registry

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Keywords

Stroke · Outcome · Survival analysis · Mortality · Relative survival · Ischemic stroke · Intracerebral hemorrhage · Population-based studies · Stroke registry

Abstract

Objective: The aim of this study was to assess long-term survival after stroke and to compare survival profiles of patients according to stroke subtypes, age, and sex, using relative survival (RS) method. ***Methods:*** All patients with a first-ever stroke were prospectively recorded in the population-based Dijon Stroke Registry from 1987 to 2016. RS is the survival that would be observed if stroke was the only cause of death. Ten-year RS was estimated using a flexible parametric model of the cumulative excess mortality rate, which was obtained by matching the observed all-cause mortality in the stroke cohort to the expected mortality in the general population. A separate model was fitted for each stroke subtypes, first fitted for each age and sex separately, and then adjusted for age and sex. ***Results:*** In total, 5,259 patients (mean age 74.9 ± 14.3 years, 53% women) were recorded including 4,469 ischemic strokes (IS), 655 intracerebral hemorrhages (ICH), and 135 undetermined strokes. In IS patients, unadjusted RS was 82% at 1 year and decreased to 62% at 10 years. Adjusted RS showed a lower survival in older age groups ($p < 0.001$), but no difference between men and women ($p = 0.119$). In ICH patients, unadjusted RS was 56 and 42% at 1 and 10 years, respectively, with a lower adjusted survival in older age groups ($p < 0.001$), but no sex differences ($p = 0.184$). ***Conclusion:*** This study showed that RS after stroke is lower in older than in younger patients but without significant sex differences, and survival profiles differ according to stroke subtypes. Since RS allows a better estimation of stroke-related death than observed survival does, especially in old patients, such a method is adapted to provide reliable information when considering long-term outcome.

Introduction

Despite major improvements in both prevention and acute management over the last decades, stroke remains a devastating disease. According to the Global Burden of Diseases estimates, stroke accounts for more than 5.5 million deaths each year worldwide, thus making it the sec-

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ond most common cause of mortality [1, 2]. Although many studies on poststroke survival have been published, only a few of them provided information about medium- or long-term survival, and data from population-based settings are scarce [3–10]. In addition, previous reports on this topic exclusively focused on observed survival, the main limitation of which is that it does not distinguish between deaths related to stroke and those related to all other causes. Hence, the use of such a method makes it difficult to interpret the findings since mortality after a stroke results not only from the event itself but also from natural mortality and other competing causes. This limitation is all the more pronounced in a context of an aging population and an increase in the number of elderly stroke patients [11].

Therefore, the aim of this study was to assess long-term survival after stroke in a large population-based registry using relative survival (RS) method to overcome the limitations of observed survival and to compare survival profile of patients according to stroke subtypes, age, and sex. RS is used to summarize the excess mortality the stroke patients have in comparison with a corresponding general population group and can be interpreted as the patients' survival if the mortality from other competing causes of death than the stroke of the patients were ruled out.

Methods

Study Population and Case-Ascertainment Procedures

This work was based on data obtained from the Dijon Stroke Registry [11, 12], an ongoing population-based registry that complies with the defined criteria for conducting "ideal" incidence stroke studies [13], and the guidelines for the reporting of incidence and prevalence studies in neuroepidemiology according to Standards of Reporting of Neurological Disorders [14]. Case collection and adjudication procedures have been previously described [11, 12]. Briefly, multiple overlapping sources of information were used to identify all hospitalized and not hospitalized cases of stroke among residents of the city of Dijon, France (156,000 inhabitants currently), between 1987 and 2016. Stroke was defined according to the WHO criteria (i.e., "rapidly developing clinical signs of focal, at time global, disturbance of cerebral function, lasting >24 h or leading to death with no apparent cause other than that of vascular origin") [15]. All suspected cases of stroke were adjudicated by a stroke-trained investigator of this study (M.G. and Y.B.). For this study, analyses were restricted to patients with first-ever stroke (first-time event in a patient's life), and the following stroke subtypes were considered: ischemic stroke (IS) and spontaneous intracerebral hemorrhage (ICH), based on neuroimaging reports, and stroke of undetermined type if neuroimaging was not available. Vital status was systematically recorded thanks to the use of death certificates and was followed over 10 years after stroke or up to January 1, 2018.

Statistical Analysis

Analyses were based on the RS method. Although net survival (or specific survival) is defined as the survival that would be observed if stroke was the only cause of death [16, 17], in large cohorts, causes of death are not reliable, or not available. Therefore, net survival is preferably estimated from the RS method which uses the excess mortality rate [18]. The excess mortality rate is the mortality due to stroke defined as the difference between the observed mortality rate in the study population and the expected mortality rate in the general population (sharing the same sociodemographic characteristics: patients were matched with the general population on year of age, sex, calendar year, and place of residence). In this study, the observed mortality rate was derived from the Dijon Stroke Registry data, and the expected mortality rate was derived from life tables (provided by the INSEE: French "Institut National de la Statistique et des Etudes Economiques") according to age and year of death. For RS analyses, strokes of unknown origin were excluded because of small numbers ($n = 135$). Age at stroke onset was considered as a categorical variable: <65, 65–80, 80–85, and ≥85 years. Ten-year RS was estimated using a flexible parametric model of the cumulative excess mortality rate [19, 20]. A separate model was fitted for each stroke subtypes. A model was first fitted for each age and sex separately. Then, a multivariate model was generated after adjustment for age and sex. Time-dependent effects of age and sex were assessed using likehood-ratio test with $p < 0.05$ for significance level. The stpm2 command in STATA™ release 15 (STATA corp., College Station, TX, USA) was used to fit flexible parametric RS models [21].

Results

From January 1, 1987 to December 31, 2016, 5,259 stroke cases were recorded (mean age 74.9 ± 14.3 years, 53% women), including 4,469 IS, 655 ICH, and 135 undetermined strokes whose distribution by age and sex are reported in Table 1. Mean age at stroke onset was greater in women than in men whatever the stroke subtype.

In IS patients, the overall unadjusted RS, which can be regarded as patients' survival if the mortality from other competing causes of death than the stroke of the patients were ruled out, was 82, 79, 77, 72, and 62% at 1, 2, 3, 5, and 10 years, respectively (Table 2). As shown in Figure 1a, observed survival rates were lower than RS rates (at 10 years, they were 33 vs. 62%, respectively). At each time points, unadjusted RS was lower in women than in men, although the gap was less pronounced after 5 years following stroke onset. In addition, unadjusted RS dramatically decreased with increasing age, especially in patients ≥85 years old. Adjusted RS for age and sex with corresponding time-dependent effect showed a lower survival in older age groups ($p < 0.001$), but no dif-

Table 1. Distribution of stroke cases according to age, sex, and stroke subtypes

	Overall	IS	ICH	Unknown stroke
Men				
Age, years, mean (SD)§	71.9 (13.6)	74.8 (13.5)	71.3 (14.9)	77.9 (8.6)
Age, years, median (Q1–Q3)	74.1 (63.7–81.9)	74.1 (63.6–81.9)	74.0 (63.0–81.9)	78.0 (70.8–83.1)
Age groups, years, *n* (%)				
<65	669 (27)	577 (28)	90 (28)	2 (4)
65–80	973 (40)	828 (40)	119 (37)	26 (53)
80–85	415 (17)	349 (17)	55 (17)	11 (22)
≥85	406 (16)	342 (16)	54 (17)	10 (20)
Women				
Age, years, mean (SD)§	77.6 (14.4)	77.7 (14.3)	76.2 (15.3)	82.2 (12.3)
Age, years, median (Q1–Q3)	81.2 (72.8–87.0)	81.2 (73.0–86.9)	80.5 (71.2–87.1)	84.7 (79.2–97.6)
Age groups, years, *n* (%)				
<65	413 (15)	345 (15)	60 (18)	8 (9)
65–80	801 (29)	689 (29)	98 (29)	14 (16)
80–85	575 (20)	490 (21)	65 (19)	20 (23)
≥85	1,007 (36)	849 (36)	114 (34)	44 (51)

§ $p < 0.001$ for comparison between men and women each stroke subtypes.
IS, ischemic stroke; ICH, intracerebral hemorrhage.

Table 2. Unadjusted RS in IS patients according to age and sex

	1-year RS		2-year RS		3-year RS		5-year RS		10-year RS		*p* value
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Overall	81.8	80.5–83.0	79.2	77.8–80.6	76.8	75.2–78.2	72.1	70.3–73.8	62.4	59.8–64.8	
Age groups, years											<0.001
<65	93.7	91.9–95.0	91.6	89.6–93.3	90.1	87.8–92.0	87.7	85.1–89.9	82.8	79.1–85.9	
65–80	86.0	84.1–87.7	83.4	81.3–85.3	80.7	78.3–82.8	74.6	71.9–77.1	58.2	54.2–62.0	
80–85	78.8	75.6–81.6	75.3	71.7–78.5	71.8	68.0–75.3	64.6	60.2–68.6	46.8	39.6–53.7	
≥85	64.0	60.8–67.1	60.2	56.7–63.6	56.7	53.0–60.4	49.8	45.2–54.2	34.2	26.3–42.3	
Gender											<0.001
Men	84.3	82.5–86.0	81.6	79.6–83.4	78.9	76.7–81.0	73.9	71.3–76.2	62.9	59.1–66.4	
Women	79.5	77.6–81.2	77.2	75.2–79.0	74.9	72.8–76.9	70.7	68.3–72.9	62.0	58.4–65.3	

RS, relative survival; IS, ischemic stroke.

ference between men and women ($p = 0.119$; Table 3, Fig. 2).

In patients with ICH, the overall unadjusted RS was lower than that observed in IS patients, namely, 56, 54, 51, 48, and 42% at 1, 2, 3, 5, and 10 years, respectively (Table 4). Observed survival rates were lower than RS rates (24 vs. 42% at 10 years; (Fig. 1b). Unadjusted RS decreased with increasing age, although no difference was observed between age groups 80–85 years and age group ≥85 years beyond 5 years of follow-up. No difference in unadjusted RS was observed between men and women. Adjusted RS for age and sex confirmed a lower survival in older age groups ($p < 0.001$), without any sex differences ($p = 0.184$; Table 5, Fig. 3).

Discussion

To the best of our knowledge, this is the first population-based study reporting long-term survival of IS and ICH patients using RS method. RS is a very useful estimator of stroke-related death. Indeed, unlike ob-

Table 3. RS of IS predicted from multivariate model§

	1-year RS		2-year RS		3-year RS		5-year RS		10-year RS	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Men, years										
<65	93.5	91.7–95.0	91.3	89.2–93.1	89.7	87.2–91.7	86.9	84.2–89.3	81.2	77.0–84.7
65–80	85.7	83.5–87.6	82.8	80.4–85.0	79.7	77.0–82.2	72.9	69.7–75.9	54.4	49.4–59.2
80–85	78.3	74.5–81.6	74.3	69.9–78.1	70.3	65.6–74.5	61.9	56.6–66.8	41.4	33.1–49.5
≥85 years	63.3	58.7–67.5	58.7	53.6–63.3	54.5	49.2–59.4	46.2	40.3–51.8	28.4	19.8–37.5
Women, years										
<65	93.8	91.9–95.2	91.9	89.7–93.6	90.6	88.2–92.5	88.6	86.0–90.7	84.6	80.9–87.7
65–80	86.2	84.0–88.2	83.9	81.4–86.0	81.4	78.7–83.8	76.0	73.0–78.8	61.4	56.7–65.8
80–85	79.0	75.7–82.0	75.8	72.1–79.1	72.6	68.7–76.2	66.0	61.5–70.1	49.3	41.9–56.3
≥85	64.4	60.9–67.6	60.8	57.0–64.4	57.6	53.6–61.4	51.2	46.4–55.7	36.4	28.2–44.7

§ Multivariate RS model including time-dependent effects of sex ($p = 0.119$) and age ($p < 0.001$).
RS, relative survival; IS, ischemic stroke.

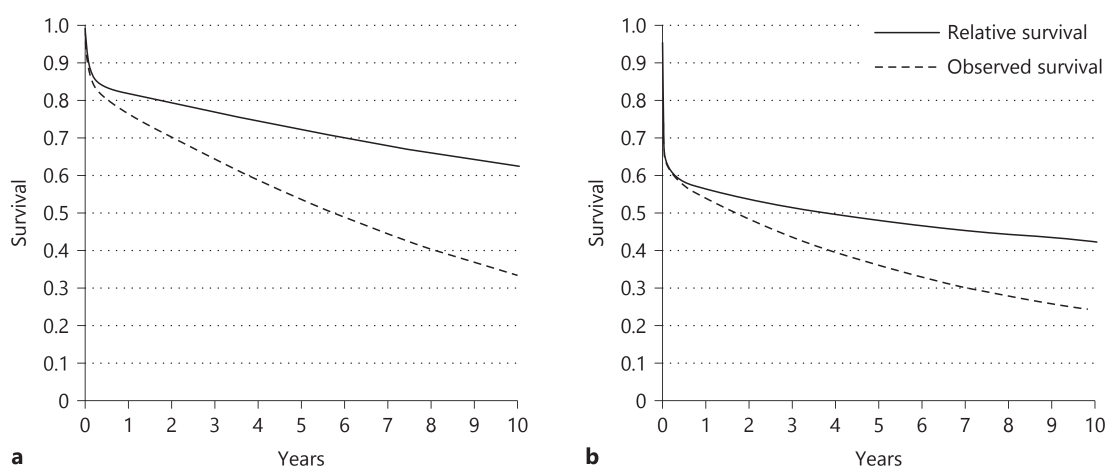

Fig. 1. Comparison between observed survival and RS in patients with IS (**a**) and ICH (**b**). RS, relative survival; IS, ischemic stroke; ICH, intracerebral hemorrhage.

served survival, RS offers the opportunity to rule out the risk of death from other causes. Since individual information on all comorbidities was not available, the advantage of RS is that being based on mortality in excess compared to the general population, it includes all causes of death related to the stroke, direct or indirect. As such, death due to comorbidities are included if the prevalence of the given comorbidity is higher in the population of stroke survivors than in the general population. As a result, in IS patients, after a follow-up of 10 years, we noted a probability of surviving of about 33% (observed survival), while the RS was over 62%. Similarly, in hemorrhagic stroke patients, 10-year observed survival was only 24%, whereas RS was 42%.

Previous studies reported data on observed survival but not on RS, and only a few of them provided medium- or long-term data [3–10]. Not surprising, and as noted in our study, observed survival was inversely associated with age and ICH subtype. Thanks to the RS approach,

Table 4. Unadjusted RS in patients with ICH according to age and sex

	1-year RS		2-year RS		3-year RS		5-year RS		10-year RS		*p* value
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	
Overall	56.3	52.3–60.1	53.6	49.5–57.5	51.4	47.3–55.3	47.9	43.5–52.1	42.3	36.9–47.6	
Age groups, years											<0.001
<65	73.8	66.0–80.1	72.1	64.2–78.5	70.7	62.7–77.2	68.2	59.9–75.2	64.0	54.4–72.1	
65–80	60.1	53.2–66.3	56.3	49.5–62.5	53.0	46.2–59.3	47.6	40.5–54.3	38.6	30.1–46.9	
80–85	47.0	37.9–55.6	42.8	33.8–51.5	39.4	30.2–48.3	33.9	24.2–43.8	25.5	14.7–37.8	
≥85	40.3	32.5–47.9	37.2	29.1–45.3	34.9	26.1–43.8	31.2	21.0–41.9	25.4	13.1–39.8	
Gender											0.314
Men	58.5	52.8–63.8	55.7	50.0–61.1	53.3	47.4–58.8	49.2	43.0–55.1	42.4	34.7–49.9	
Women	54.1	48.5–59.4	51.6	45.9–57.0	49.7	43.9–55.2	46.6	40.4–52.5	41.6	34.2–48.8	

RS, relative survival; ICH, intracerebral hemorrhage.

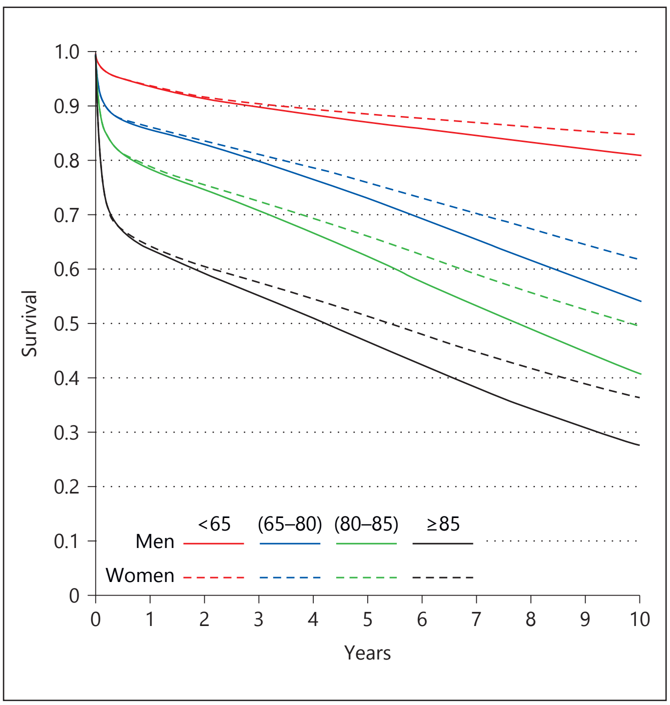

Fig. 2. RS after IS according to age and sex. IS, ischemic stroke; RS, relative survival.

our present study provides new findings about long-term specific survival profiles of patients according to stroke subtypes and age. Hence, patterns of RS differed between IS and ICH patients. RS after IS was 82% after 1 year and continued to gradually decrease over time to reach 62% after 10 years of follow-up. This result could be explained in part by deaths complicating stroke recurrences in IS patients in whom the prevalence of vascular risk factors is greater than that observed in the general population. In addition, in these patients, the underlying pathophysiological condition including atheroma and atrial fibrillation may contribute to new events, affecting both the cerebrovascular system, and other vascular beds, namely, coronary or limb arteries [22]. Analysis of RS by age groups revealed that the progressive decreasing survival over time following IS was not as pronounced in younger as in older patients. This result reflects that IS causes in the young substantially differ from those observed in older patients, with a greater proportion of cervical artery dissection, and patent foramen ovale, both of them conferring a lower risk of stroke recurrence and other vascular events than atheroma or atrial fibrillation do [23–25]. Another explanation for the differences observed according to age could be that poststroke functional outcome is better in younger than in older patients [26], thus reducing the risk of further complications including infections or trauma due to falls.

Profile of RS in ICH patients was different from that observed after IS. Actually, a high proportion of ICH patients died during the first year, and RS slightly gradually decreased thereafter. The greater initial clinical severity [27], together with the absence of very effective acute therapeutic strategies in ICH patients compared to IS patients, contributed to this observed high early mortality. Finally, risk of recurrent ICH or IS after a first ICH has been shown to be similar [28] and could contribute to further decreasing survival in our study.

Gender differences have been observed in several stroke survival studies that suggested a poorer outcome in women than in men [29]. Although unadjusted RS

Table 5. RS of patients with ICH predicted from multivariate model§

	1-year RS		2-year RS		3-year RS		5-year RS		10-year RS	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Men, years										
<65	73.6	65.4–80.2	71.8	63.4–78.5	70.1	61.7–77.1	67.2	58.3–74.7	62.1	51.4–71.0
65–80	60.3	52.5–67.1	56.3	48.6–63.3	52.6	44.9–59.7	46.2	38.1–54.0	35.5	25.9–45.3
80–85	47.4	36.9–57.1	43.0	32.8–52.9	39.0	28.7–49.2	32.4	21.6–43.6	22.1	10.9–35.8
≥85	40.4	30.5–50.0	37.0	27.0–47.0	33.9	23.5–44.7	29.0	17.5–41.5	21.3	8.7–37.5
Women, years										
<65	73.6	64.7–80.5	72.1	63.3–79.1	71.1	62.2–78.2	69.3	60.1–76.7	66.2	55.7–74.8
65–80	60.2	52.1–67.5	56.8	48.6–64.1	53.8	45.7–61.3	49.0	40.4–57.1	40.9	30.8–50.8
80–85	47.4	37.5–56.6	43.5	33.8–52.9	40.4	30.5–50.0	35.3	24.8–45.9	27.2	15.5–40.2
≥85	40.3	32.0–48.4	37.5	28.9–46.0	35.3	26.1–44.6	31.8	21.3–42.8	26.3	13.6–40.9

§ Multivariate RS model including time-dependent effects of sex ($p = 0.184$) and age ($p < 0.001$).
RS, relative survival; ICH, intracerebral hemorrhage.

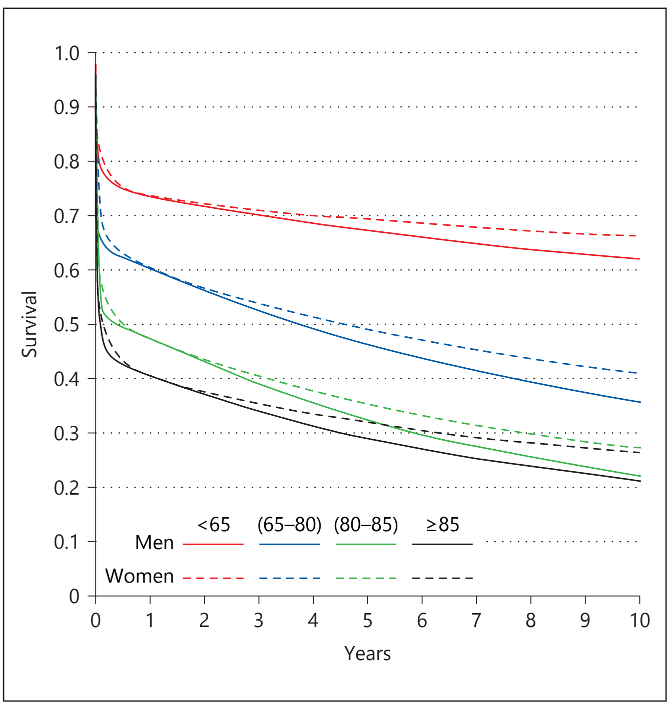

Fig. 3. RS after ICH according to age and sex. RS, relative survival; ICH, intracerebral hemorrhage.

tended to the apparent same assumption in our study, multivariable analyses concluded to an artefactual effect that was no longer significant after adjusting for age, thus reflecting that the older age at stroke onset in women than men accounts for the major part of sex differences in poststroke survival. This result is consistent with findings of the collaborative INSTRUCT study that gathered data from 13 population-based incidence studies including the Dijon Stroke Registry and that concluded that the 24% higher crude pooled 5-year mortality observed in women reversed after adjustment for confounding variable, thus suggesting that advanced age, more severe strokes, worse prestroke function, and atrial fibrillation contributed to their greater risk of death [30].

Our study has several strengths. Thanks to the population-based design of the Dijon Stroke Registry that complies with the quality criteria for incidence stroke studies [13], this work provides real life and exhaustive information about both IS and ICH. The use of a continuous validated hot- and cold-pursuit procedure allowed nearly complete data about vital status at 10 years, as information was missing in only 45 patients (0.9%). A limitation of this study is that we did not consider time period as a covariate. However, the flexible models used in the data analyses require large number of events and the numbers would have been low for some subgroups. The sample size, despite being collected over 20 years, was still quite small when there was a breakdown into age- and sex groups. Another potential limitation of our study is the absence of causes of death recording. However, RS methods were developed to address this issue that is common to large population-based studies, by estimating specific survival ruling out other causes of mortality by using general population life tables. It has been shown that these methods provide as good or even better results than methods relying on cause of death recording [31, 32]. Cause of death is indeed often multifactorial, and its attribution to stroke may be challenging in real life. Finally, we did not include subarachnoid hemorrhage in our analyses because this stroke subtype differs from IS and ICH regarding pathophysiological mechanisms and risk factors, and number of cases is low.

To conclude, this multidecade population-based study showed that RS after stroke is lower in older than in younger patients but without sex differences, and its profile differs between IS and ICH. The major differences between RS and observed survival at 10 years highlights the importance of using such a method, especially in a context of aging population, to deliver useful and comparable information in order to conduct public health policy adapted to the burden of chronic diseases.

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Disclosure Statement

M.G., V.J., G.R., A.-S.M., and C.Q. have no disclosure. Y.B. received honoraria for consulting fees from AstraZeneca, Bayer, BMS, Pfizer, Medtronic, MSD France, Amgen, Boehringer-Ingelheim, and Servier.

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