JCS/JCC/JACR/JATS 2024 guideline on cardiovascular practice with consideration for diversity, equity, and inclusion

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Guideline

JCS/JCC/JACR/JATS 2024 guideline on cardiovascular practice with consideration for diversity, equity, and inclusion☆

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Abbreviations: ABI, ankle–brachial index; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; AD, Alzheimer's disease; ADL, activities of daily living; AE, arrhythmic event; AF, atrial fibrillation; AMI, acute myocardial infarction; AR, aortic regurgitation; ARB, angiotensin-receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; AS, aortic stenosis; BK, background knowledge; BMI, body mass index; BP, blood pressure; BS, Brugada syndrome; CA, catheter ablation; CAD, coronary artery disease; CCS, chronic coronary syndrome; CI, confidence interval; CKD, chronic kidney disease; CLTI, chronic limb threatening ischemia; CQ, Clinical Question; CR, cardiac rehabilitation; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CS, cardiac sarcoidosis; CTEPH, chronic thromboembolic pulmonary hypertension; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DCB, drug-coated balloon; DD, D-dimer; DLCO, diffusing capacity for carbon monoxide; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EVAR, endovascular aneurysm repair; EVT, endovascular treatment; FRQ, future research question; HBR, high bleeding risk; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; IC, informed consent; ICD, implantable cardioverter defibrillator; ICD-11, International Classification of Diseases version 11; ICH, intracerebral hemorrhage; I/HPAH, idiopathic or heritable pulmonary arterial hypertension; LBBB, left bundle branch block; LDL, low-density lipoprotein; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac or cerebrovascular event; MACE, major adverse cardiac event; MC, mechanical complication; MI, myocardial infarction; MMSE, Mini-Mental State Examination; mPAP, mean pulmonary arterial pressure; MR, mitral regurgitation; MS, mitral stenosis; MT, mechanical thrombectomy; OR, odds ratio; OS, open surgery; PAD, peripheral artery disease; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; PTE, pulmonary thromboembolism; RCT, randomized controlled trial; rt-PA, recombinant tissue-type plasminogen activator; SDM, shared decision making; SDOH, social determinants of health; SPPB, short physical performance battery; SRT, septum reduction therapy; TAVI, transcatheter aortic valve implantation; TR, tricuspid regurgitation; TRI, transradial intervention; VHD, valvular heart disease; VF, ventricular fibrillation; VT, ventricular tachycardia; VTE, venous thromboembolism; WHO, World Health Organization.

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Refer to Appendix 2 for the details of members.

JCS Joint Working Groups: The Japanese Circulation Society; Japanese College of Cardiology; The Japanese Association of Cardiac Rehabilitation; The Japanese Association for Thoracic Surgery; The Japan Geriatrics Society; The Japanese Association for Gender-Specific Medicine; The Japan Stroke Society; Japan Atherosclerosis Society; Japanese College of Angiology; The Japanese Society of Psychiatry and Neurology; Japan Society of Obstetrics and Gynecology; Japanese Heart Rhythm Society; Japanese Society of Pediatric Cardiology and Cardiac Surgery; Japanese Society of Echocardiography; The Japanese Society for Cardiovascular Surgery; The Japanese Society for Vascular Surgery; Japanese Association of Cardiovascular Intervention and Therapeutics; The Japanese Heart Failure Society; Japanese Circulation Association; Japanese Society of Obstetric Medicine; Japanese Society of Gender Identity Disorder; Japanese Pulmonary Circulation and Pulmonary Hypertension Society.

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Clinical Question (CQ) List

CQ1. Should Sex/Gender Differences Be Considered in Comprehensive Cardiac Rehabilitation (CR) for Women With Heart Failure (HF)?

Recommendation

Comprehensive CR for women with HF can improve exercise tolerance and prognosis as well as or better than that in men. However, it is recommended that sex differences be considered when implementing CR because women have lower rates of participation in CR.

(Agreement rate: 91.3 %, Level of Evidence: B)

CQ2. Should Sex Differences Be Considered When Performing Transcatheter Aortic Valve Implantation (TAVI)?

Recommendation

The reduction in events (death, stroke, HF hospitalization) with TAVI is comparable in males and females. However, since women experience a higher incidence of bleeding complications, it is recommended that sex differences be carefully taken into account during postoperative care.

(Agreement rate: 87.0 %; Level of Evidence: B)

CQ3. Should Sex Differences Be Considered When Using Conventionally Established Ankle-Brachial Index (ABI) Cutoff Values?

Recommendation

When using the conventionally established ABI cutoff values, it is recommended to consider sex differences because females have lower values than males, and the diagnostic and prognostic power of ABI ≤0.9 is inferior in females compared with males.

(Agreement rate: 80 %; Level of Evidence: C)

CQ4. Should Revascularization for Peripheral Artery Disease (PAD) Be Aggressively Recommended in Female Patients?

Recommendation

Female patients with PAD have a higher prevalence of chronic limb threatening ischemia (CLTI) and more severe and diverse background diseases than male patients, and their outcomes after bypass and endovascular treatment (EVT) have been considered poor. However, with the improvements in EVT, including drug-coated balloon (DCB), there has been no difference in post-revascularization outcomes between the sexes, although the prevalence of CLTI cases are still more prevalent in females. Based on this background, we weakly recommend aggressive revascularization of PAD in females.

(Agreement rate: 91.3 %, Level of Evidence: C)

CQ5. When Diagnosing Female Patients With Deep Vein Thrombosis (DVT), Is It Recommended to Establish a Female-Specific Cutoff Value for D-Dimer (DD)?

Recommendation

Although DD values differ between male and female patients with and without pulmonary embolism (PE) and DVT, (respectively), it is difficult to find any clinical diagnostic benefit in setting a sex-specific cutoff value for the diagnosis of DVT patients. It is weakly recommended not to set female-specific cutoff values when diagnosing female patients with DVT.

(Agreement rate: 91.3 %; Level of Evidence: B)

CQ6. Should Endovascular Aneurysm Repair (EVAR) for Abdominal Aortic Aneurysm in Female Patients Be Aggressively Recommended?

Recommendation

Aggressively performing EVAR for female patients is weakly recommended, with consideration to improve outcomes, such as strictly discussing the anatomical factors, including the access routes and the aneurysm size threshold for surgery.

(Consensus rate: 87 %; Level of Evidence: C)

CQ7. Should Ablation Therapy for Asymptomatic Atrial Fibrillation (AF) in Young Patients Be Highly Recommended?

Recommendation

Performing ablation therapy for asymptomatic AF in young patients is recommended.

(Agreement rate: 95.7 %; Level of Evidence: C)

CQ8. When Should Antihypertensive Treatment Be Initiated for Pregnant Women With Chronic Hypertension?

Recommendation

It is strongly recommended that antihypertensive treatment be initiated for pregnant women with chronic hypertension if blood pressure is ≥140/90 mmHg.

(Agreement rate: 95.8 %; Level of Evidence: B)

CCQ9. Should Age Be Considered in the Treatment of Pulmonary Arterial Hypertension (PAH)?

Recommendation

It is recommended that age be considered in the treatment of PAH, as it has been reported that older patients may have less prognostic benefit and more side effects than younger patients.

(Expert Consensus)

CQ10. Which "Physical Frailty Assessment" Is Recommended as a Prognostic Indicator for Older HF Patients in Japan?

Recommendation

We strongly recommend the use of the J-CHS criteria, walking speed, grip strength, 6-minute walking distance, and short physical performance battery (SPPB) for "assessment of physical frailty" as prognostic indicators for older HF patients in Japan.

(Agreement rate: 91.3 %, Level of Evidence: B)

CQ11. Which "Assessment of Mental and Psychological Frailty" Is Recommended as a Prognostic Indicator for Older HF Patients in Japan?

Recommendation

The Mini-Mental State Examination (MMSE), Mini-Cog, and 5-item Geriatric Depression Scale (5-GDS) are strongly recommended for "assessment of mental and psychological frailty" as prognostic indicators for older HF patients in Japan.

(Agreement rate: 90 %, Level of Evidence: C)

CQ12. Should Age Be Considered in Determining the Indications and Procedures for Standby Abdominal Aortic Surgery (Including Endovascular Treatment)?

Recommendation

It is recommended that age and the patient's preoperative condition (e.g., frailty) be fully considered in determining the indication and procedure for standby abdominal aortic surgery (including endovascular treatment) for patients older than 80 years.

(Agreement rate: 90.4 %, Level of Evidence C)

CQ13. What Trends Among Healthcare Providers Contribute to Improving the Outcomes and Quality of Care for Cardiovascular Patients?

Recommendation

Facility size and proficiency in medical practice may affect the prognosis of patients with cardiovascular disease. It is also weakly recommended

that close communication between healthcare providers and patients, patient-centered medical services, and adherence whenever possible to practice guidelines be considered, as they improve the prognosis and quality of care for cardiovascular patients.

(Agreement rate: 86.3 %, Level of Evidence: B)

Introduction

On the Revision of the Guidelines

The original "Guideline for gender-specific cardiovascular disease (CVD)," published in 2010, served as Japan's pioneering document highlighting gender differences in cardiovascular practice [1]. Over the past decade, societal dynamics have grown increasingly complex and diverse, amplifying the need for guidelines that encompass a broader range of diversity considerations in cardiovascular care. In response, a thorough revision has been undertaken, resulting in the newly titled "Guidelines for cardiovascular practice with consideration for diversity, equity and inclusion".

The key updates are as follows.

Title and Structure: The guidelines have evolved to encompass 6 key chapters: "Decision Making", "Sex/Gender", "Life Stages: Youth, Pregnancy, Aging", "Race/Ethnicity", "Social Determinants of Health (SDOH)", and "Diversity in Medical Professionals".
Inclusion of SDOH: For the first time in Japanese guidelines, the SDOH are highlighted, acknowledging their critical impact on health outcomes.
Diversity of Medical Professionals: The revised guidelines explore how variety in healthcare providers' backgrounds and working styles can significantly affect medical performance and patient care.
Transgender People: A partnership with the Japanese Society of Gender Identity Disorder has led to the inclusion of a section on transgender individuals, backed by a review of cardiovascular disease within this population [2].
Guideline Methodology: Developed in accordance with the "Minds Clinical Practice Guideline Preparation Manual 2020 ver. 3.0" [3] of The Japan Council for Quality Health Care (JQ), these guidelines represent Japan's pioneering document to explicitly tackle "diversity".
Evidence Surveyed: The revision has highlighted a notable gap in domestic evidence concerning diversity, with most data still being derived internationally.

This guideline represents a cross-disciplinary effort, supported by numerous academic societies, including the Japan Cardio-Vascular Alliance, and incorporating, for the first time, a patient representative from the Japanese Circulation Association. Their invaluable insights have emphasized the need for treatments to account for differences in sex and/or age, and other demographic factors. We sincerely appreciate their cooperation. We received a comment from a member of the patient representative group that "even if the effectiveness of treatment differs depending on gender, age, or other factors, we would like the explanation to include these factors".

Finally, the guideline development team comprised many young professionals and women who are at the forefront of their respective fields. In particular, women accounted for 56 % (23 of 41 team members and 20 of 36 collaborators). However, only 5.6 % of the members of the guideline development team of the Society published in 2008–2010 were female [4]. In recent years, domestic and international public research grants have required that the organizations applying for funding be composed of a diverse group of members who can bring different perspectives [5,6]. Guidelines committee for practice on diverse populations should also include representatives of diverse groups. It should be emphasized that during the development of this guideline, senior members played a pivotal role in mentoring less experienced younger and/or female colleagues through a series of online workshops and discussions.

With the advent of the era of artificial intelligence, the implementation of personalized medical care that takes diversity into account is becoming more reliable. We anticipate that this guideline will contribute significantly to advancing of this field. However, there are numerous critical clinical issues that remain unaddressed within the guideline because diversity consideration in cardiovascular practice is a cross-disciplinary theme. Additionally, given the current limitations in overall evidence, this guideline should be viewed as a foundation for future clinical research and subsequent revisions.

Process of Creating the Clinical Practice Guidelines

These guideline recommendations were generated via formal systematic review of the available evidence based on methodology suggested by the Minds Medical Practice Guideline Development Manual ver. 3.02020 (Japan Council for Quality Health Care) [3]. The Minds Medical Practice Guideline Development Manual was based on the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach for Japanese guidelines [7].

1. Scope

The aim of this guideline is to improve the prognosis of patients with cardiovascular disease by identifying various factors relevant to the practice of both patients and healthcare professionals.

In recent years, the importance of sex- and/or gender-specific medical care has been highlighted. In cardiovascular medicine especially, postmenopausal female patients have clinical profiles that differ from premenopausal female patients. However, developing medical care that takes such diversity into account is still a work in progress. **Chapters II–IV** list sex/gender, age (life stage), and race/ethnicity as physiological and sociological diversities that should be considered in clinical cardiovascular practice (Fig. 1).

The background knowledges (BKs) are concise summaries of background knowledge, without overlapping previous guidelines of the JCS. In addition, regarding basic and specialized knowledge that can be obtained from other guidelines and publications, we have only listed the relevant guidelines and publications and provided them as references.

For clinical questions (CQs), we identified important clinical issues where differences in sex or age (life stage) affect clinical practice and conducted a systematic review. Because the targets of comparison were sex and age differences, there were no direct interventional studies. Thus, we examined differences not in effectiveness of tests and treatments but in rates of adverse events or prognosis. As a result of systematic reviews and panel voting, questions for which there was insufficient evidence to make recommendations were proposed as future research questions (FRQs).

The Good Practice Statement (GPS) was employed in medical practices deemed by the Guideline Development Group to be of high medical importance, possessing a clear rationale or substantial net benefit, even in the absence of new systematic reviews (SRs).

CQs were selected and approved by Working Group for the Guideline. Each CQ is expressed as PI (E) CO model. PI(E)CO stands for patient/population, intervention (or exposure), comparison and outcomes.

The present clinical practice guidelines target adult patients aged >14 ears. The definition of young adult was voted on and decided as 15–45 years old by Working Group for the Guideline and the JCS Guideline Committee. For some specific diseases, the age setting of the representative article is used as a standard. The definition of older adults follows the definition of the Japan Federation of Gerontological Societies (Table 1) [8].

2. Systematic review

For each CQ, 2 members performed a systematic review independent of a panel member of Working Group. Existing practice guidelines,

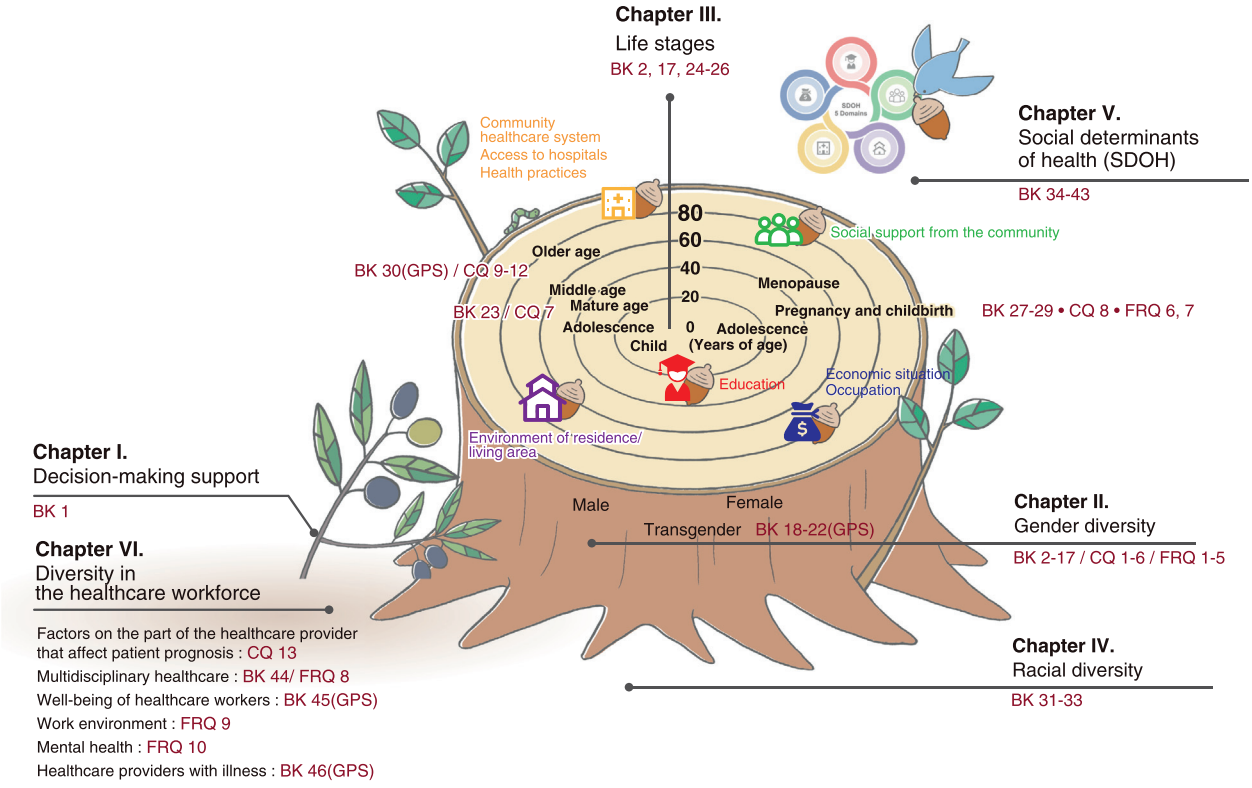


Fig. 1. Health and healthcare issues to be addressed with consideration for diversity, equity, and inclusion in the guideline.

systematic review (SR)/meta-analysis (MA) articles, and individual research articles were searched in this order of priority. Individual research articles were searched for randomized controlled trials (RCTs), non-randomized controlled trials (non-RCTs), and observational studies. If sufficient evidence was found for the highest priority evidence type, the search was terminated, and the evidence was evaluated and integrated. MEDLINE and Ichu-Shi Web (Japan Medical Abstracts Society) were searched for individual research articles and MEDLINE, Ichu-Shi Web, and The Cochrane Library for SR/MA articles. The search period for all databases was until the end of June 2022, and for The Cochrane Library until issue 5, 2022.

The Cochrane assessment tool was used to assess the risk of bias for individual studies, and the GRADE approach was used to assess the total body of evidence. Integration of effectiveness indicators was based on qualitative integration, with quantitative integration where appropriate.

3. Generation of recommendation

The recommendation was formulated in alignment with the modified Delphi method. The first draft of the recommendations was developed by the SR team and panel members, referencing the evaluation sheets and Summary of Finding (SoF) tables generated by SR. This process incorporated considerations such as the 'certainty of summative evidence across outcomes', the 'balance between desirable and undesirable effects', 'patient and public values and aspirations', and 'resource use (cost)'. The panel members subsequently voted on these recommendations. The final recommendations and their strength were then established based on the voting results, in accordance with the Evidence to Decisions (EtD) framework (Table 2). The recommendation and certainty of the evidence were expressed according to the GRADE system (Tables 3 [9], 4 [3]). The question "CQ9. Should age be considered in the treatment of pulmonary arterial hypertension?" received 69 % agreement, which is <80 %. But for consistency with guidelines to be published later, we decided it was a CQ and listed the recommendation as expert consensus.

4. Finalization

In addition to the external evaluators recommended by the CPGC Group, the guidelines were evaluated based on AGREE II by the chair of the guideline committee and the chair-designated evaluation committee members.

Table 1
Definitions of age in these guidelines.

Terminology	Age (years)
Young	15–45
Pre-old	65–74
Old	75–89
Super-old	≥90

For the definition of elderly, see "The Japanese Geriatrics Society and the Japan Geriatrics Society (eds.): Report of the Working Group on Definitions Concerning the Elderly" [8].

Table 2
EtD framework.

Criteria for determining the strength of recommendations by voting
(1) Consensus was reached when ≥75 % of the panel members voted and ≥ 80 % of them agreed
(2) If >80 % of the votes are concentrated on "Strong", then "Strong" is recommended
(3) If (2) conditions are not met, but >80 % of the votes are concentrated in a particular direction, one of the "conditional" recommendations will be made
(4) (3) If the criteria in (4) are not met, but >80 % of the votes are concentrated on "Conditionally recommended for either the intervention or the comparison subject", then the recommendation is "Conditionally recommended for either the intervention or the comparison subject"
(5) No recommendation for CQs that cannot be determined by a second ballot
(6) The recommendation "to consider" lacks clarity, so we have avoided the expression "strong" or "weak"

CQ, clinical question; EtD, evidence to decisions.

Table 3
Strength of recommendations according to the GRADE system.
(Adapted from Hiraoka E, et al. 2023 [9].)

Strength of recommendation	Expression	Criteria
1: Strong recommendation	We recommend… It is recommended to perform… It is recommended not to perform…	The certainty that desirable or undesirable effects Outweigh undesirable or desirable effects is high
2: Weak recommendation	We suggest… It is suggested to perform… It is suggested not to perform…	The certainty that desirable or undesirable effects Outweigh undesirable or desirable effects is low

The external evaluation committee members submitted their comments individually, and the guideline development group discussed the need to change the content of the guideline in response to each comment and decided on a response. The draft underwent external evaluation and pre-publication evaluation by Minds, the Japan Agency for Health Care Excellence. The final version was published after approval by the JCS Committee.

5. Revision procedures

To be decided by deliberation of the Guidelines Committee of the Japanese Circulation Society.

6. Sources of funding for guideline editing

The stipend was provided by the JCS in accordance with the regulations of the Guidelines Committee of the JCS.

7. List of conflicts of interest of members of the Guideline Research Group

Available on the following website.

I. Decision Making

BK1. Diversity-Health Conscious Decision Making

Today, more than ever healthcare providers are expected to be proactive in recognizing the diversity of their patients and in sharing options based on appropriate information. Consideration for diversity is crucial for delivering equitable medical care to patients from various backgrounds, including sex/gender, age, ethnicity, and social status. Understanding the unique situation (e.g., pregnancy, history of childbirth, childcare, menopause, being older and vulnerable with multiple illnesses, and language barriers living in Japan) is crucial in the decision-making process and cannot be ignored. It is also important to provide information on social resources, such as public support with the cooperation of social workers, etc., taking into consideration the socioeconomic status, including employment, of the patient.

Shared decision making (SDM) is the process by which patients and healthcare providers work together to make optimal healthcare decisions and has rapidly gained interest in recent years [10,11]. The key to SDM is the development of a collaborative relationship between healthcare providers and patients. Based on available evidence and clinical experience, healthcare providers provide the patient with clear information about the benefits and harms of multiple options, if available, and costs if possible, and patients provide healthcare providers with information about their lifestyle, beliefs, and values. As well as information sharing, the process of sharing treatment goals is also very important.

Informed consent (IC) and SDM are similar in terms of communication between healthcare providers and patients. IC is given when healthcare providers share their knowledge of best practices based on scientific evidence and clinical experience, and patients accept this information when it is appropriately provided. On the other hand, SDM can be described as a process of simultaneous decision-making and consensus-building through trial and error. This approach respects diverse patient preferences and values while acknowledging the limitations and uncertainties of evidence. In scenarios where multiple options exist and no single solution is clearly optimal, SDM facilitates a collaborative approach to determining the best course of action.

In the field of cardiology, the American Heart Association published a Scientific Statement in September 2023 [12] emphasizing that "patient participation in health care decisions, patient-clinician communication, and patient-centered models of care are SDM promotes health equity through evidence sharing and recognition of individual needs and values".

Recognition and consideration of diversity and the understanding and dissemination of SDM are among the key clues to the Japanese Circulation Society meeting society's expectations in the future.

Table 4
Grade of certainty for body of evidence according to the GRADE system.
(Adapted from Minds Manual Developing Committee. 2020 [3] with modification.)

	Certainty	Definition
A	High	Certainty for the estimate of the effect is high
B	Moderate	Certainty for the estimate of the effect is moderate
C	Low	Certainty for the estimate of the effect is low
D	Very low	Certainty for the estimate of the effect is very low

II. Sex and Gender Differences in Patients with Cardiovascular Disease (CVD)

1. Epidemiology by Sex and Age

BK2. Sex and Age Differences in the Prevalence in CVD in Japan

Heart disease, accounting for 14.8 % of fatalities, is the second leading cause of death in Japan, according to the 2022 Vital Statistics. Cerebrovascular disease follows as the fourth, at 6.8 % [13]. Together, they contribute to a mortality rate akin to malignant neoplasms (cancer), causing over 340,000 deaths annually. In Japan, where comprehensive data on cardiovascular patients is limited, and epidemiological information regarding the distribution of patients by sex and classification is notably scarce compared to other countries.

By sex, cardiovascular diseases exhibit a greater prevalence in males, though the specific proportions vary by disease categories (Fig. 2A) [14–22]. As per the 2005–2020 emergency resuscitation statistics (Utstein data), more than two-thirds of out-of-hospital cardiopulmonary uncountable due to ventricular fibrillation (VF) or ventricular tachycardia (VT) are in males [14]. Currently, there are no national registry studies specifically for atrial fibrillation (AF). However, in large-scale national registry studies conducted since the J-RYTHM study, the proportion of female patients ranges between 23 and 41 %. When data from all these studies are aggregated, the overall proportion of female patients stands at 29 % [15–21]. Among the hereditary arrhythmias, Brugada syndrome is more prevalent in males [22–27], early repolarization syndrome tends to affect males more [28], but congenital and secondary QT prolongation syndrome is more common in females [29–31]. On the other hand, the renowned MONICA study (the World Health Organization MONItoring Trends and Determinants in CArdiovascular Disease Project) reported that the incidence of acute myocardial infarction (MI) is lower in Japanese women than in the rest of the world [32]. Sex differences analyzed in the 2012–2020 Japanese Registry Of All Cardiac and Vascular Diseases (JROAD) report (JROAD-Gender) [33] indicated that female patients with acute coronary syndrome (ACS: MI and unstable angina) accounted for 29 %, in line with previous epidemiological studies [34–37]. Female patients with acute heart failure (AHF) represented approximately 48 %, while in the same database-based registry study, JROADHF, 47 % were female, particularly among older patients with heart failure with preserved ejection fraction (HFpEF) [38]. (For

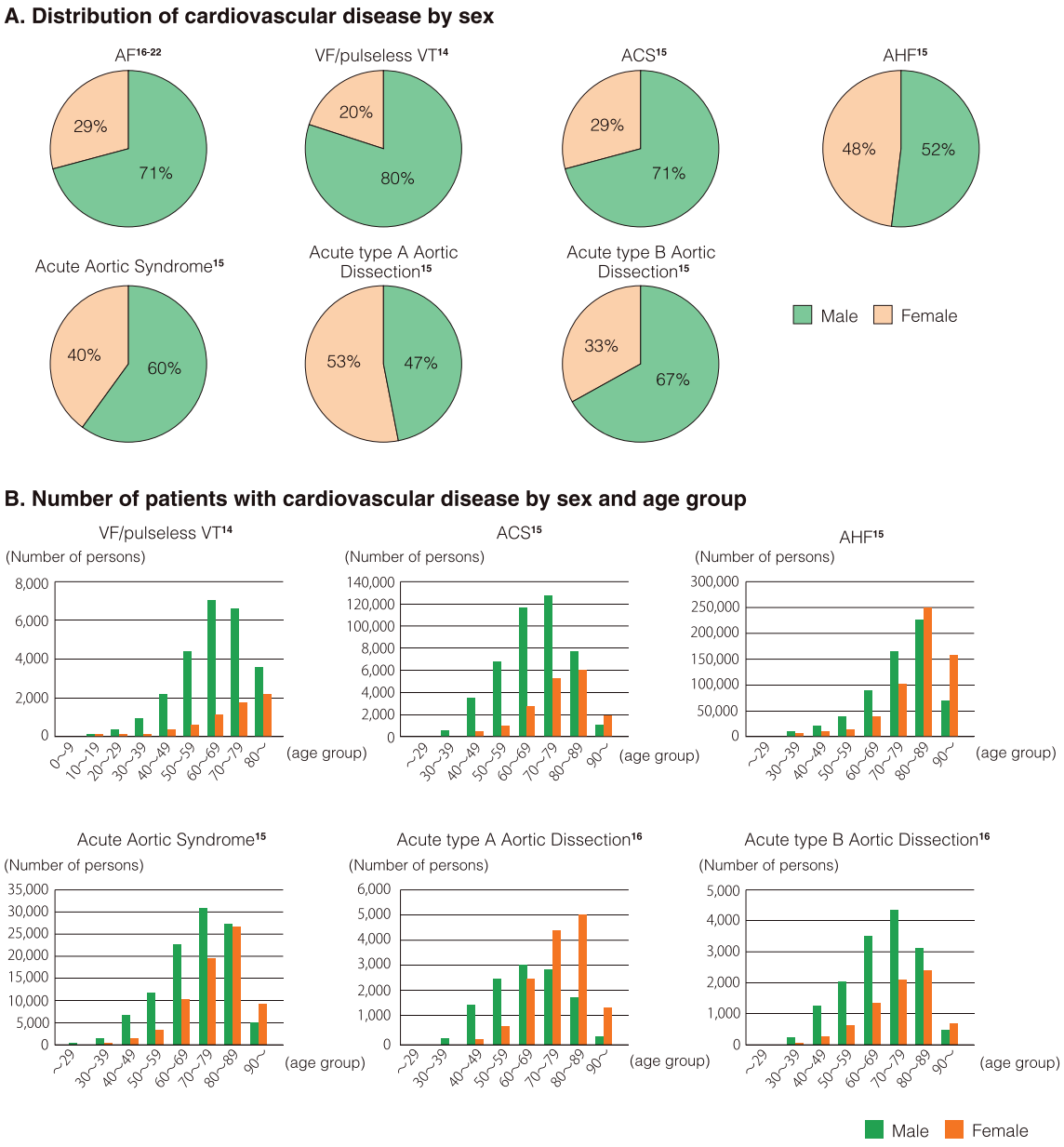


Fig. 2. (A,B) Number of patients with cardiovascular disease by sex and age group.
(Source: Prepared based on Ishii M, et al. 2023 [14], Kodani E, et al. 2016 [15], Akao M, et al. 2013 [16], Okumura Y, et al. 2017 [17], Hayashi K, et al. 2018 [18], Inoue H, et al. 2009 [19], Suzuki S, et al. 2011 [20], Miyazaki S, et al. 2018 [21], Brugada J, et al. 2002 [22].).

clinical features of HF in women, see BK7.) Acute aortic syndromes (ruptured aortic aneurysm, acute aortic dissection) constituted 40 % of cases, with 67 % of type B dissection cases occurring in males, and 53 % of type A cases were in females [36]. Previous reports from overseas put the proportion of female patients in type A aortic dissection at 31–44 %, compared with 35 % when the total number of cases is combined [39–49]. However, when restricted to reports based on domestic surgical cases, the incidence in female is 49 %, showing almost no sex difference [50,51]. When it comes to stroke, females account for 51 % of all stroke-related deaths, nearly mirroring the proportion in males. For more information, please refer to BK16.

In terms of age distribution, the prevalence of cardiovascular diseases rises with advancing age. VF/pulseless VT, more common in men, occurs in the 60s, while ACS and type B aortic dissection peak in the 70s. In contrast, AHF and type A aortic dissection, less common in males/females and more prevalent in males/females, have their peak incidence in the 80s. Type A and type B aortic dissection show different and unique distributions (Fig. 2B) [14–22]. Type A aortic dissection and heart failure have a peak at an older age, suggesting a strong aging effect on the onset of these conditions, and as a result, a high proportion of females are likely to be involved. Further detailed studies are expected to provide new insights into sex and age differences.

BK3. Health Status and Sex/Gender Issues in the Development of CVD in Japan

Japan is currently experiencing an unprecedented super-aging society. In 2020, the average life expectancy was 87.60 years for females and 81.49 years for male, reaching a new record high. In 2022, 29.0 % and 15.6 % of the total population were aged 65 or older and 75 or older, respectively, with 57 % and 61 % will be female [52]. According to the population projections for Japan (2023 Estimates) by the National Institute of Population and Social Security Research [53], the average life expectancy will increase to 85.89 years for men and 91.94 years for females in 2070. The total population will decline to 70 % of the current level

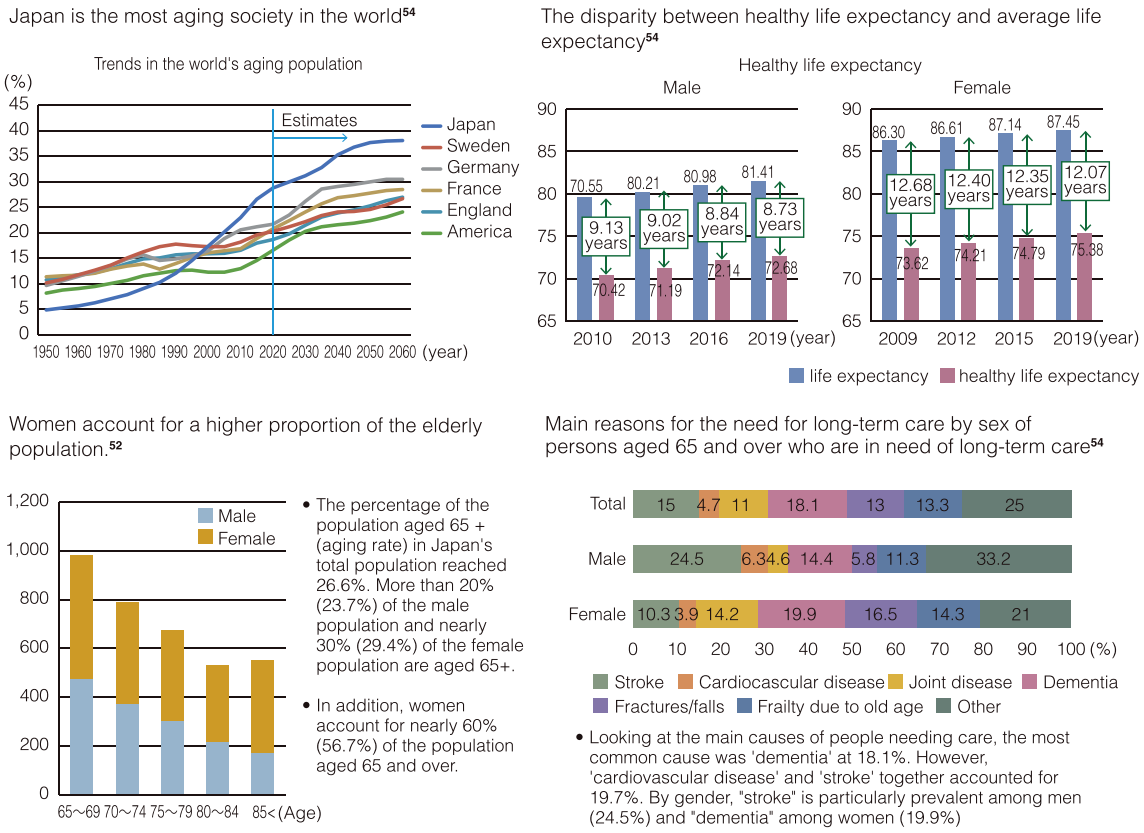


Fig. 3. Health status of older Japanese women.
(Source: Prepared based on Ministry of Health, Labour and Welfare [52], Cabinet Office [54].).

in 50 years. The aging of Japan's population will continue in the future, and the (aging rate) is estimated to increase from 28.6 % in 2020 to 38.7 % in 2070 [53].

As for healthy life expectancy (Fig. 3), which indicates life without limitations in daily living, it was 75.38 years for female and 72.68 years for male in 2019, an increase of 0.59 years for female and 0.54 years for male over the 3 years from 2016; however, the difference between average life expectancy and healthy life expectancy, or the period of time required for long-term care, in 2019 will be 12.06 years for female and 8.73 years for male [54]. Dementia and CVD (stroke and heart disease) are the main causes of the need for long-term care.

The number of births in Japan reached its peak in 1949 and shown a declining trend since 1975. In 2022, Japan's total fertility rate dropped to a historic low of 1.26, a decline influenced in part by the COVID-19 pandemic [55]. The average age of Japanese mothers at the birth of their first child has risen over time, reaching 30.9 years in 2021, a significant increase from the average age of 25.7 years in 1975. Over the past few decades, this age has remained relatively stable at around 30 years [56].

During Japan's post-war Showa period, female's roles were largely defined by traditional expectations: after completing high school, they typically either entered the workforce until marriage or engaged in domestic work, eventually assuming the role of housewives (Fig. 4). By 1960, it was common for almost 98 % of women to be married by the age of 50 years, reflecting the societal expectations and norms of that era. However, in recent years, as societal attitudes toward marriage and family have evolved, the life choices of Japanese women have become increasingly diverse. By 2020, the percentage of women married by age 50 dropped to 69.3 %, with a notable shift in marital status: 15.8 % never married, 10.2 % separated, and 1.4 % widowed. This change has led to a variety of household types, including women who remain unmarried and live alone, those living with parents, single parents or those living alone post-separation or bereavement, and women who remarry or marry after a separation or bereavement [57].

The percentage of women enrolled in higher education (undergraduate) has increased significantly since 1990 although it remains lower than that of men [58]. Similarly, while the employment rate among women has risen, a substantial proportion is employed in non-regular or irregular positions.

The proportion of older people aged ≥65 years living alone is higher for women than for men, at almost 70 % of the total. By age group, almost 60 % of men are in the first half of their lives, aged 65–74, while about 60 % of women are in the second half of their lives, aged ≥75. Approximately 20 % of women also live in households with a person aged ≥85 [59].

Relative poverty rates by gender and age group show that poverty tends to increase with age for both men and women, but the poverty rate is generally higher for women than for men, and the gap widens with age [60].

2. Understanding CVD in Relation to Sex/Gender Differences

2.1 Ischemic Heart Disease

BK4. Complications of Acute Myocardial Infarction in Female Patients. The incidence of mechanical complications (MC) associated with acute myocardial infarction (AMI), including left ventricular free wall rupture (LVFWR), ventricular septal rupture (VSR) or left ventricular septal perforation (VSP), and papillary muscles rupture (PMR), has decreased to <2 % since 2000 [61]. (For details on MCs, see "Guidelines for acute coronary syndrome, 2018 Revision" by the Japanese Circulation Society). Nevertheless, in-hospital mortality rates remain high, ranging from 30 % to 93 % including surgical repair cases [61–74]. Moreover, a higher frequency of MCs in female patients has been reported, approximately 1.5-fold that

Women's Lifestyle change from SHOWA-era to HEISEI and REIWA-era[57,58,60]

- Marriage and Family Diversification[57]

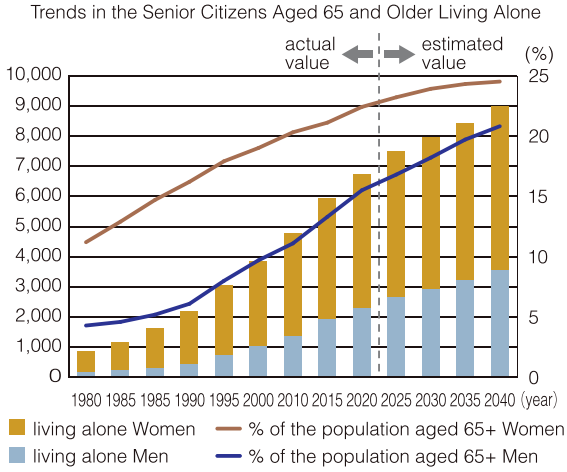
  In 1960, approximately 98% of women had married at age 50. 69.3% of women were married at age 50 in 2020. Women who live alone, women who live with their parents, women who become single parents or single-parent households due to separation or bereavement after marriage, women who remarry and become married after separation or bereavement, etc.

- Increase in the percentage of women entering college (12.7% in 1975 → 50.7% in 2018)[58]
- Poverty among elderly single women (Relative poverty rate for single women is 44.6% (twice that of the elderly population as a whole)[60]
- Increase in female employment rate (57% in FY2001 → 70.6% in 2020)[57]
- Gender disparity among non-regular workers (female 54.4%, male 22.2%)[57]

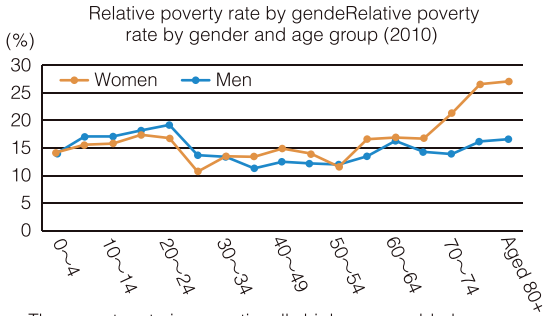
International Comparison on Births[55]

Nation	Total Fertility Rates		Out-of-Wedlock Birth Rates	
	year	(%)	year	(%)
Japan	2020	1.34	2019	2.3
Korea	2020	0.84		
Singapore	2020	1.10		
France	2019	1.86	2019	61.0
Germany	2019	1.54	2019	33.3
Italy	2019	1.27	2019	35.4
Sweden	2019	1.71	2019	54.5
England	2018	1.68	2017	48.2
U.S.	2020	1.64	2019	40.0

Number of people aged 65+ living alone is on the rise[54]



Older women living alone are in poor economic conditions.[60]



- The poverty rate is exceptionally high among elderly single-person women-headed households and single-mother households.

Fig. 4. Gender issues for Japanese women.
(Source: Prepared based on Cabinet Office [54], Ministry of Health, Labour and Welfare [55], Gender Equality Bureau, Cabinet Office [57], Ministry of Education, Culture, Sports, Science and Technology [58], Gender Equality Bureau, Cabinet Office [60].).

of male patients. Female sex have been identified as an important risk factor for MCs [64,66,73,75,76]. Recent large registry data from the USA showed no sex difference in in-hospital mortality rate for non-ST-segment elevation myocardial infarction (NSTEMI) group (17.5 % in females vs. 18.4 % in males; $P = 0.51$), but a significantly higher rate in female than in male patients for STEMI (47.9 % in women vs. 38.2 % in men; $P < 0.001$) [61]. Furthermore, a significantly higher mortality rate was also reported for female patients with cardiogenic shock (odds ratio [OR] 1.18; 95 % confidence interval [CI]: 1.03 to 1.35; $P = 0.016$). Therefore, MCs associated with AMI in female patients should be careful [61]. Of the several types of MCs, LVFWR and VSR (or VSP) are reported to be significantly higher in females, but no sex difference has been observed for PMR [61–63]. The reasons for the sex-based difference in frequency of occurrence remain unclear. Contributing factors to the higher incidence of VSR (or VSP) in females may include older age at presentation, greater number of comorbidities, frequency of atypical symptoms leading to delayed treatment, and possibility of prolonged survival post-diagnosis of VSR (or VSP). Additionally, the intraventricular septum is on average thinner in females than in males [77].

Another complication of AMI in female patients is perioperative bleeding complications. Although many reports showed no sex differences in rates of in-hospital mortality and major adverse cardiac or cerebrovascular events (MACCE) associated with AMI, the incidence of in-hospital bleeding complications is approximately 1.7 to 3-fold higher in female patients [78–84]. In particular, TIMI major/minor bleeding and access site bleeding tend to be more prevalent. The Japanese J-PCI registry data also reported no sex difference in in-hospital mortality rate in NSTEMI (OR 1.05; 95 % CI: 0.79 to 1.40; $P = 0.747$), but the incidence of in-hospital bleeding complications was significantly higher in females (OR 1.94; 95 % CI 1.35 to 2.79; $P < 0.001$) [82]. Therefore, among the in-hospital complications, special attention should be given to bleeding complications in female patients.

BK5. Bleeding Risk and Antiplatelet Therapy After PCI in Female Patients. The assessment of bleeding risk post-PCI under antiplatelet therapy considers both the acute and chronic phases, further differentiated into acute and chronic coronary syndromes (ACS and CCS). Studies from Europe and the USA have notably identified female sex as a significant risk factor for heightened in-hospital and short-term bleeding risks in the acute phase following percutaneous coronary intervention (PCI) among ACS patients (hazard ratio [HR] = 1.77–2.57) [83,85–88,88a]. Similar findings have been reported in Japan (OR = 1.94–3.84) [82,89–91]. This trend is consistent even in trials including CCS patients (HR = 2.22 and OR = 3.84) [92,93].

The primary contributor to the elevated rate of acute post-PCI bleeding in females, including both ACS and CCS patients, is bleeding at the vascular puncture site [92]. The bleeding rate varies depending on the puncture site, with transradial intervention reducing bleeding events by up to one-third compared with transfemoral intervention in both men and women [89,92,94–97]. However, in the chronic phase after PCI, female sex is not identified as a risk factor for bleeding complications in ACS and CCS patients in international trials, and

it is not included in the CREDO-Kyoto Bleeding Risk Score in Japan [97–102].

Determining the type and duration of antiplatelet therapy after PCI requires a balance between bleeding risk and thromboprophylaxis for each patient. The 2017 ESC guidelines do not provide convincing evidence of sex differences in efficacy and safety for dual antiplatelet therapy (DAPT) [98].

Regarding the type of DAPT, both clopidogrel and the novel P2Y12 inhibitors (ticagrelor, prasugrel, and cangrelor) demonstrate comparable safety and efficacy in both sexes [99–101], therefore sex is not a primary consideration when using these agents. Nevertheless, most trials have included ACS patients, and evidence supporting the use of novel P2Y12 inhibitors in CCS patients is limited. The GLOBAL LEADERS trial demonstrated that in female CCS patients, at 1 month after PCI, a ticagrelor monotherapy group had twice the bleeding rate than the 1-year DAPT group with ticagrelor alone vs. clopidogrel plus aspirin [102]. That result implies that potent P2Y12 inhibitors such as ticagrelor should be used cautiously in female CCS patients. However, the Japanese indication for ticagrelor is limited to specific cases.

For prasugrel, a reduced dose (loading/maintenance, 20/3.75 mg) has been approved in Japan, taking into consideration the bleeding risk in East Asians. The prasugrel postmarketing surveillance in Japan indicates that female sex is not a bleeding risk factor from day 31 to 12 months post-PCI, even in CCS patients and older patients [92]. Therefore, sex may not a significant consideration when using prasugrel, even in CCS patients.

Assessing bleeding risk for determining the duration of DAPT, the 2016 ACC/AHA guideline emphasizes qualitative bleeding risk factors and identifies female sex as a factor [103]. In contrast, the 2017 ESC guideline and the 2020 JCS Focused Update Guidelines recommend evaluating high bleeding risk (HBR) as the primary consideration [98,104]. To assess HBR, the 2020 ESC guidelines utilized the PRESICE-DAPT score and the ARC-HBR criteria as references [105]. The ARC-HBR criteria do not include sex [106]. However, it is noted that females are more likely to meet the ARC-HBR criteria and have higher ARC-HBR scores, primarily due to their higher prevalence of factors such as older age, chronic kidney disease (CKD), and anemia [92,96,107]. The 2020 JCS Focus Update Guidelines establish their own J-HBR criteria, which include Japanese-specific factors such as heart failure (HF), low body weight, peripheral arterial disease, and frailty, in addition to the ARC-HBR criteria [104]. The J-HBR criteria had been validated as more sensitive but less specific than the original ARC-HBR criteria [108].

In conclusion, sex-based differences do not strongly influence the type, dose, and duration of antiplatelet therapy after PCI. However, it is important to recognize that many patients with ischemic heart disease, especially Japanese female patients, often fall into the high bleeding risk category due to specific risk factors. Therefore, treatment should be individualized, considering those factors [108a].

BK6. Sex and Gender Differences in the Secondary Prevention and Prognosis of Ischemic Heart Disease. Patients with CVD need to focus on secondary prevention [109,110], but there are few reports in Japan that take sex differences into account. It has been reported that among smokers undergoing PCI, females have a higher incidence of cardiovascular events than males (13.6 % vs. 8.0 %; $P = 0.016$) [111]. Smoking cessation has been reported to reduce the risk of cardiovascular events in both sexes within 2 years, with a significantly reduced risk in females [112] and they may benefit more from guidance on smoking cessation.

For lipid metabolism ameliorators, a meta-analysis found that cardiovascular events were significantly reduced by HMG-CoA reductase inhibitors (statins) in both sexes, without any differences [113]. There was also no sex difference in the secondary prevention effect of non-statin lipid disorder medications (small intestinal cholesterol transporter inhibitors [ezetimibe] and PCSK-9 inhibitors) [114]. However, it has been noted that there are differences in the opportunity for statin administration between sexes. A smaller proportion of women receive statins after ACS (89.4 % vs. 85.2 %; $P = 0.004$) [115] and thus a lower proportion reach target low-density lipoprotein cholesterol levels (37.9 % vs. 29.7 %; $P = 0.02$) [116,117]. Females under the age of 65 years are more likely to discontinue statins because of side effects and low adherence [118]. Discontinuation of statins in females with no cardiovascular risks other than dyslipidemia may be due to low adherence because of fewer risk factors. An analysis of the PROMETHEUS registry showed that among patients with AMI undergoing PCI, the proportion of patients receiving guideline-recommended drugs at discharge was lower in females than in males (69.3 % vs. 30.7 %) [119]. Failure to take guideline-recommended drugs correlated with prognosis, with higher 30-day all-cause mortality rates in females who did not have coronary risk factors and did not take recommended drugs [120,121].

Weight management and comprehensive cardiac rehabilitation (CR) are also important in secondary prevention [122,123]. The large Swedish SWEDEHEART registry reported that exercise-based CR (exCR) after MI reduced all-cause mortality rates in both sexes, but more significantly in females (hazard ratio: 0.81 for males, 0.54 for females) [124]. On the other hand, the EuroCaReD registry of 12 European countries found that the recurrence rate with exCR participation was similar for males (9.0 %) and females (9.6 %) among patients with heart disease, including coronary artery disease (CAD) [125]. There are reports that exCR after MI affected women's more positive attitudes toward treatment [126]. However, participation in CR was lower among women (32 % vs. 23 %) [127–129], as they tend to be less likely to participate due to less importance given to their own health issues, low motivation, fear, and low health literacy [130,131]. Because they are more likely to respect opportunities for information exchange and emotional support from medical staff, encouragement from family, friends, and medical staff may be a solution to participation in CR by women patients [130–135]. In recent years, online managed CR in the home has been proposed and patients' satisfaction has increased [136] (see also CQ1).

Hypertension and diabetes are also important considerations in secondary prevention [137], and further study is needed in Japan to determine recommendations that take sex and gender into account in the management of secondary prevention.

FRQ1. Should Sex Differences Be Considered in Intervention Cutoff Values for Coronary Artery Calcification and Coronary Fractional Flow Reserve Ratio?.

Answer

Although sex differences in CT coronary calcification scores and the degree of coronary flow reserve fractional flow reserve are observed, sex differences in intervention cutoff values require further investigation.

Commentary

Coronary artery calcification (CAC) score as assessed by less invasive CT scanning is a direct marker of atherosclerosis in both sexes, although females tend to have lower CAC scores than males [138–142]. In a prospective cohort study of male and female patients with suspected CAD, almost 50 % of the females had a CAC score of 0 and <10 % had a score ≥400, whereas male patients had a higher proportion of CAC scores between 100 and 400 and 20 % had a score ≥400 [138]. The accuracy of predicting significant coronary artery stenosis is greatly improved in males by assessing CAC in addition to conventional risk factors, but not as accurately in females [138]. In predicting cardiovascular events, some reports suggest that a cutoff CAC score of ≥100 or ≥ 200 for males and ≥ 400 for females improves predictive ability [143]. Sex differences in intervention cutoff values require further investigation.

Fractional flow reserve (FFR) can assess function (presence or absence of ischemia) along individual coronary lesions and is an important indicator in determining treatment strategy. Angiographically, females reportedly have higher FFR values than males, despite similar coronary stenotic lesions and vessel diameters [144–146]. This sex difference is thought to be due to older age, smaller body surface area, smaller left ventricular volume, smaller vessel diameter, and smaller myocardial volume in females [145,147,148]. Currently, a cutoff value of 0.8 is used for FFR for both sexes, but this does not allow for sex differences

in short- and long-term prognoses [144,145,149,150]. Further study of sex differences in FFR are needed.

FRQ2. Do Females Have a Higher Incidence of MINOCA (Myocardial Infarction With Non-Obstructive Coronary Arteries)/INOCA (Ischemia With Non-Obstructive Coronary Arteries)? Is the Prognosis Poor?.

Answer

Although there are many reports of higher incidence in females, further studies are needed, including prognosis.

Commentary

Sex differences in the morbidity and prognosis of MINOCA and INOCA have been reported in a limited number of studies conducted outside of Japan.

Morbidity of MINOCA

Reports from the Turkish MINOCA-TR registry [151,152], a joint registry of Australia and Canada [153], and research in China [154] consistently indicate a higher proportion of females with MINOCA compared with myocardial infarction with obstructive coronary arteries (MIOCA) (MINOCA 45.0–46.9 % vs. MIOCA 22.8–28.2 %). The VIRGO study in Spain, which included male and female patients aged 18–55 years, revealed a 5-fold greater likelihood of females developing MINOCA [155].

Prognosis of MINOCA

The VIRGO study found no significant difference in mortality rates between the sexes at 1- and 12-month follow-up [155]. Similarly, the Australian and Canadian registry found no sex difference in in-hospital mortality rates [153]. However, in the study from China, female sex was identified as a risk factor for major adverse cardiac events (MACE) at 1 year after MINOCA [154]. This discrepancy may be attributed to variations in the underlying etiology of MINOCA [156]. MINOCA cases associated with cardiomyopathy, particularly prevalent among female patients, showed the worst outcomes, with a 19 % MACE rate at 1 year and a 27 % long-term mortality rate over 8 years.

Morbidity of INOCA

Among patients excluded from the ISCHEMIA trial due to INOCA, females had a higher odds ratio of 4.2 (95 % CI: 3.4–5.2) [157] for INOCA. Female patients with INOCA, as reported by the Heart Quest cohort, demonstrated a higher prevalence of microvascular angina, accounting for 60.8 % of cases [158].

Prognosis of INOCA

The international multicenter CONFIRM study did not find sex differences in MACE or overall mortality rates during a mean follow-up of 2.3 years in propensity-matched INOCA patients [159]. Regarding the rate of cardiac death and MI among the female patients with INOCA, the WISE study reported 12.8 % occurrence at 10 years' follow-up [160].

The incidence of both MINOCA and INOCA is suggested to be higher in females, and the prognosis of both MINOCA and INOCA appears to be influenced by the underlying disease. However, it is important to note that further research is needed to explore sex/gender, age, and racial differences in the incidence and prognosis of MINOCA and INOCA.

2.2 Heart Failure (HF)

BK7. Sex Differences in the Clinical Features, Pathogenesis, and Prognosis of HF.

1. Clinical Features

As the global population ages, understanding sex-based clinical differences among patients with HF becomes increasingly important. Studies comparing background factors and comorbidities have shown that female HF patients are older and have more hypertension, valvular disease, anemia, renal dysfunction, and less CAD than male patients [161–165]. Female patients need to be made aware of secondary cardiomyopathies such as those resulting from anthracycline-based breast cancer treatments [166] or related to peripartum and autoimmune conditions [167]. Additionally, sex differences have been reported in frailty, with a meta-analysis of 29 studies comprising 8854 HF patients revealing that females had a 26 % higher relative risk of frailty than males [168].

2. Patient's Condition

When stratified by left ventricular ejection fraction (LVEF), female patients tend to have higher LVEF and a greater proportion of HFpEF (LVEF >50 %) than male patients [162,165,169–171], which is attributed to higher systolic and diastolic LV elastance in females, which increases more rapidly with age [172]. Females are more likely to have HFpEF due to concentric remodeling, which often results in diastolic dysfunction [173], whereas males are more likely to have HF with reduced EF (HFrEF; LVEF <40 %) due to eccentric remodeling [174]. Estrogen also has a protective effect on the cardiovascular system, but the loss of this effect at menopause may cause activation of the renin–angiotensin–aldosterone system and effects on the NO-cGMP pathway, contributing to the development of HFpEF [175].

3. Medical Treatment

For the treatment of HFrEF, β-blockers are more likely to decrease blood pressure (BP) and heart rate in females than in males at equivalent doses. Furthermore, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are associated with >2-fold the risk of angioedema and cough in females. Conversely, β-blockers and ACE inhibitors/ARBs can improve prognosis at higher doses in males, whereas efficacy can be expected from lower doses in females [176], possibly due to their lower glomerular filtration rate, lower hepatic blood flow and liver enzymes, and lower metabolic efficiency of fat-soluble drugs due to higher body fat percentage. Differences in side effects and efficacy of therapeutic agents by sex should be noted [167].

4. Prognosis

Sex-related disparities in HF prognosis are inconsistent across studies. Some international reports suggest that female patients had fewer all-cause deaths than males [164,171,177,178], while others find similar mortality rates after adjusting for background factors [163,179,180]. This discrepancy is probably due to social determinants of health, including fewer treatment and examinations performed, fewer prescriptions of guideline-recommended medications, and less social support for female patients [170,181,182]. In a Japanese report, a study examining sex differences with stage C/D HF patients enrolled in the CHART-2 study found that the mortality rate was lower among the female patients after adjustment for age and other background factors [165]. Their prognosis in Japan is generally considered better than that of male HF patients.

BK8. Considerations in the Nonpharmacologic Treatment of HF by Sex.

1. Cardiac Resynchronization Therapy (CRT)

Lower mortality rates and fewer HF hospitalizations are reported in female than in male patients [183]. In a subanalysis of the RAFT trial involving NYHA II–III patients [184], females who underwent CRT had significantly lower mortality and hospitalization rates compared with males, and additionally, female patients receiving CRT by defibrillator (CRT—D) for primary prevention experienced the lowest ventricular arrhythmia rates [184]. A meta-analysis of 3 randomized trials in NYHA II patients also found that in patients with left bundle branch block (LBBB) with a QRS width of 130–149 ms, there was a 76 % reduction in HF and death in females but no significant reduction in males [185]. A single-center report on the association between QRS width and CRT response rate in NYHA III–IV nonischemic cardiomyopathy patients with LBBB found that female patients had a

higher response rate to CRT, even with shorter QRS durations [186], potentially attributed to their smaller left ventricles and shorter QRS duration compared with males [187].

2. Implantable Cardioverter Defibrillator (ICD)

Although the SCD-HeFT trial found lower all-cause mortality rates in female patients for primary prevention of sudden death [188], a meta-analysis including 5 large clinical studies (MUSTT, MADIT-II, DEFINITE, SCD-HeFT, COMPANION) found no significant sex difference in all-cause deaths. Furthermore, the benefit from ICD is reported to be greater in male patients [189], with studies suggesting that ICD may be less appropriate for primary prevention in female patients [189–191]. An analysis of patients with ICD or CRT-D enrolled in the MADIT trial reported a significantly lower risk of ventricular arrhythmias in females with a background of nonischemic cardiomyopathy [192]. However, previous studies have not revealed sex differences in the usefulness of ICD for secondary prevention [193]. The low proportion of females enrolled in large clinical studies of ICD therapy to date (8–29 %) limits any mention of sex differences in ICD therapy.

3. Septum Reduction Therapy (SRT)

Worse outcomes have been reported in female patients with hypertrophic cardiomyopathy (HCM) than in males, because female patients with HCM are older and are often diagnosed with more severe symptoms [194,195]. A study examining sex differences in surgical myocardiectomy for patients with hypertrophic obstructive cardiomyopathy (HOCM) found that female patients had higher preoperative NYHA class and more severe mitral regurgitation. They also had lower postoperative survival rates, with a median survival of 3.9 years shorter than male patients [196]. However, no significant difference in survival after SRT by sex after adjusting for background factors has been reported. It should be noted that female patients have a higher rate of pacemaker implantation after percutaneous transluminal septal myocardial ablation (PTSMA) than males (10.5 % vs. 6.8 %; $P < 0.001$), warranting careful consideration [197].

4. Implantable Left Ventricular Assist Device (LVAD)

The HeartMate II registry reported a 1.6-fold higher risk of driveline infections associated with LVADs in male patients [198], but data from the J-MACS registry showed no sex difference in bleeding and thrombotic complications [199]. A single-center report noted a trend toward more gynecological bleeding in female patients [200]. Of the 837 patients in the J-MACS registry, no sex difference was found in the 3-year mortality rate of the 168 patients who underwent bridge-to-bridge LVAD implantation [201].

5. Heart Transplant

Recipient and donor sex combinations can influence survival after heart transplantation. Male recipients who receive hearts from female donors have lower survival rates [202–205], possibly due to factors such as heart size mismatch, immunological factors, and sex hormone effects [205,206]. However, an analysis of the International Society for Heart and Lung Transplantation registry for acute rejection and the appearance of post-transplant coronary artery lesions has shown no effect of sex combination [202].

CQ1. Should Sex/Gender Differences Be Considered in Comprehensive Cardiac Rehabilitation (CR) for Women With HF?.

Recommendation

Comprehensive CR for women with HF can improve exercise tolerance and prognosis as well as or better than that in men. However, it is recommended that sex differences be considered when implementing CR because women have lower rates of participation in CR.

(Agreement rate: 91.3 %; Level of Evidence: B)

Commentary

Comprehensive CR is “strongly recommended” in HF guidelines from stage A to D, and the evidence base has grown rapidly in recent years. However, there is a lack of evidence on the effectiveness of CR in patients with HFpEF, in older patients, especially in older women with HFpEF.

Outcomes to determine the effects of CR can be broadly categorized into exercise tolerance, such as the 6-minute walk and peak oxygen uptake, and prognosis, such as quality of life, cardiovascular events and death [207]. The RCT of CR (HF-ACTION), conducted in 2331 HF patients with LVEF <35 %, found that after 3 months of intervention, the improvement in peak oxygen uptake did not differ significantly by gender. Otherwise, there was a significant improvement in all-cause death in women (hazard ratio: 0.74 for women and 0.99 for men, $P = 0.027$). These results suggest that comprehensive CR is effective in women. A meta-analysis (ExTraMATCH II) of 3990 patients in an RCT showed that 1 year after CR intervention, women improved significantly more than men in the 6-minute walk test ($P = 0.034$) and in peak oxygen uptake ($P = 0.036$) [208]. However, the effect of CR on quality of life (Minnesota Living with HF Questionnaire) and prognosis (all-cause death, HF death, all-cause hospitalization, HF hospitalization) did not differ significantly by gender. Unfortunately, this meta-analysis was not age-adjusted for subgroup analysis, and the small proportion of women (25 %) was unlikely to provide sufficient power to detect gender differences. In Japan, a multicenter retrospective cohort [209] enrolled 3277 HF patients, 862 of whom participated in outpatient CR, 38 % of participants were women, and found no difference in the risk of all-cause mortality or HF hospitalization by gender. This study was a subgroup analysis, so no age-adjusted analysis was performed. In addition, a large retrospective study [210] using data from the Japanese Journal of Admission and Outcomes in Cardiovascular Disease (JROAD) enrolled 10,473 HF patients admitted for HF at 158 centers in 2013; 3210 patients received inpatient CR, 45 % of whom were women, and the study demonstrated significantly lower rates of rehospitalization for cardiovascular events with inpatient CR interventions. Notably, the study included a propensity score-matched subgroup analysis that showed no significant difference in the risk of cardiovascular death and rehospitalization for cardiovascular events by gender.

In conclusion, women with HF have equal or better exercise tolerance and prognostic benefit from CR than male patients, and participation in CR is strongly recommended for women. However, women have lower rates of referral from healthcare providers [211], participation [212] and continuation [213] in CR than men patients, which is problematic, and Canada has issued CR guidelines focused on women [214]. To improve participation rate of women in CR, the following suggestions have been made: disease education and counseling tailored to women, creating an environment conducive to participation such as women exercise class, psychosocial considerations, providing preferred forms of exercise (dance, yoga, Pilates, etc.), and promoting home-based CR.

BK9. Sex Differences in Takotsubo Cardiomyopathy. Takotsubo cardiomyopathy is characterized by a much higher incidence and greater frequency in postmenopausal females [215–219]. In addition, psychological stress is more often involved, whereas male patients tend to have more physical stress [216,217].

On the other hand, male patients with takotsubo cardiomyopathy have a higher frequency of in-hospital complications and a poorer prognosis. The Tokyo CCU Network and the International Takotsubo Registry reported that ventilator management was significantly more common in male patients (28.6 % vs. 12.7 %; $P < 0.05$, 29.5 % vs. 16.0 %; $P < 0.001$) [216,217]. The international multicenter GEIST Registry also reported more cardiogenic shock in male patients after propensity score

matching (16 % vs. 6 %; P < 0.05) [220], and significantly higher in-hospital deaths [217–220], indicating the need for more careful acute management in male patients.

In the International Takotsubo Registry, males were also reported to have higher all-cause mortality rates (12.9 % vs. 5.0 %; P < 0.001) and significant cardiac and cerebrovascular events (16.0 % vs. 8.7 %; $P = 0.002$) at long-term follow-up of patients with takotsubo cardiomyopathy [217]. Although the international multicenter GEIST registry found no sex-significant difference in mortality rates after propensity score matching, the mortality rate at long-term follow-up was higher in male patients [220]. Thus male patients with takotsubo cardiomyopathy are characterized by a distinct high-risk phenotype requiring close in-hospital monitoring and long-term follow-up.

The pathogenesis of the disease may differ between the sexes [221]. Takotsubo cardiomyopathy is caused by sympathetic-mediated microvascular ischemia. In postmenopausal females, the decrease in estrogen, a regulator of endothelial damage and vasomotor tone, increases vasoconstriction, making them more susceptible to stress-related microvascular ischemia [222]. Males have lower resting sympathetic tone and less microvascular ischemia, requiring greater noradrenergic stimulation to induce takotsubo cardiomyopathy, which may result in more myocardial injury and a higher incidence of acute complications and death [223].

BK10. Sex/Gender Differences in Secondary Cardiomyopathies.

1. Cardiomyopathy Secondary to Infiltrative Disease: Cardiac Amyloidosis

There are no sex differences in the prevalence or clinical course of cardiac amyloidosis associated with primary amyloid light-chain (AL) amyloidosis [224].

90 % of wild-type transthyretin cardiac amyloidosis (ATTRwt) patients are male [225,226]. Females with ATTRwt are older at diagnosis, presenting higher values of NT-proBNP and left ventricular intraventricular pressure than males, as well as more significant cardiac hypertrophy and right heart dysfunction [227].

Hereditary ATTR (ATTRv) also requires consideration of sex differences, with 80 % of Val30Met variant types and 60 % of non-Val30Met variant types being in males [228]. The latest Transthyretin Amyloidosis Outcomes Survey (THAOS) results show that the symptomatic Val30Met variant type has a more pronounced incidence of myocardial hypertrophy in males [229].

2. Cardiomyopathy Secondary to Accumulation Disease: Danon Disease, Fabry Disease

Danon disease and Fabry disease are X-linked. In male Danon disease, the 3 significant symptoms of cardiomyopathy, myopathy (muscle weakness and atrophy), and mental retardation appear in the teens. Females often present with cardiomyopathy only at age ≥ 30 years.

Fabry disease mainly affects vascular endothelial cells, autonomic ganglia, sweat glands, kidneys, myocardium, and cornea. Female carriers (heterozygotes) are also known to develop the disease [224]. The clinical features are diverse in female patients, ranging from asymptomatic to severe organ damage similar to males, and the age of onset is not constant [230].

3. Cardiomyopathy Secondary to Neuromuscular Disease: Associated With Duchenne or Becker Muscular Dystrophy

Patients with Duchenne and Becker muscular dystrophies can develop cardiomyopathy and the progressive muscle weakness is caused through X chromosome linkage [231]. Female carriers usually do not develop skeletal muscle abnormalities, but about 8 % of them develop cardiac dysfunction, including dilated cardiomyopathy, making long-term follow-up necessary [232].

4. Cardiomyopathy Secondary to Systemic Syndromes: Mitochondrial Cardiomyopathy

Mitochondrial cardiomyopathies are diagnosed as systemic mitochondrial cardiac lesions such as MELAS (mitochondrial encephalomyopathy, encephalopathy, lactic acidosis, and strokelike episodes associated with stroke-like symptoms) and MERRF (myoclonus epilepsy associated with ragged-red fibers). However, the diagnosis is often difficult in isolated cases of cardiomyopathy, and clinical evidence regarding prognosis and sex differences is insufficient.

5. Cardiomyopathy Secondary to Inflammatory Disease: Sarcoidosis

The incidence of cardiac sarcoidosis (CS) does not differ by sex in the West but is more common in middle-aged and older females in Japan [233].

In the ILLUMINATE-CS registry in Japan (age 61.6 ± 11.4 years, $n = 512$), males with cardiac sarcoidosis were significantly younger, had more history of VT/VF and AF and had lower LVEF than females. It has also been reported that being male is significantly associated with the risk of VT/VF and sudden cardiac death compared with being female, even after adjusting for prior VT/VF (hazard ratio: 1.73, $P = 0.008$) [234].

6. Cardiomyopathy Secondary to Inflammatory Disease: Myocarditis

The causes of myocarditis are diverse, including viral and autoimmune, but the clinical characteristics and effect of sex differences on treatment and prognosis remain unclear [235].

A retrospective cohort study of myocarditis using the JROAD-DPC showed a higher proportion of female patients with fulminant myocarditis compared with non-fulminant myocarditis but no sex differences in histology or life expectancy (death events at 90 days) [236].

7. Cardiomyopathy Secondary to Drugs: Drug-Induced Cardiomyopathy

Drug-induced cardiomyopathy caused by cardiotoxic drugs which are essential treatment for some cancer patients [237,238]. Specific risk factors for anthracycline-induced cardiotoxicity include cumulative dose, age (>65 years, <18 years), and underlying medical conditions such as hypertension and female sex [239].

8. Cardiomyopathy Secondary to Addiction: Alcoholic Cardiomyopathy

Sex differences in the prevalence of alcoholic cardiomyopathy have not been consistently reported, partly due to the influence of confounding factors (such as depression and frequency of alcohol consumption). Females metabolize alcohol differently than males, have a lower threshold for developing alcoholic cardiomyopathy, and are more likely to develop alcoholic cardiomyopathy in a shorter period [240–242].

9. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Ventricular tachycardia and sudden death occur more frequently in males than in females and they have a poorer prognosis, with sex hormones and exercise itself being suggested as possible etiologic factors [224].

10. Peripartum Cardiomyopathy

Peripartum cardiomyopathy can occur in females without a history of any cardiomyopathy during pregnancy or within 6 months after

delivery [243]. Although the incidence in Japan is not high, at approximately 1 in 15,000 deliveries, it is one of the main causes of maternal death [244]. Advanced maternal age, hypertensive disorders in pregnancy and multiple pregnancy are known as major risk factors of peripartum cardiomyopathy. In addition, it has been discovered that approximately 10–20 % of patients have genetic mutations associated with dilated cardiomyopathy [245]. Several basic research studies have suggested potential mechanisms, including cleaved prolactin [246], anti-angiogenesis [247], inflammation [248], and myocardial remodeling disorder [249]. Recently, trials have been made to develop disease-specific treatments, such as inhibiting prolactin secretion [250].

BK11. Sex Differences in the Etiology and Prevalence of Valvular Heart Disease.

1. Aortic Valve Disease

Aortic stenosis (AS) accounts for 47 % of all valvular heart diseases (VHD) and predominantly affects males. Sex chromosome aneuploidy (e.g., Turner syndrome) is an established risk factor for aortic bicuspid valves and AS, suggesting that X-linked genes play a role in normal aortic development [251]. However, age-related AS is more common in females, and 70 % of AS cases occur in those aged >80 years. It has been found that AS in females is characterized by less calcification of the aortic valve and greater fiber component. The Japanese Circulation Society Guidelines for the treatment of VHD also define a baseline value of ≥2000 for males and ≥ 1200 for females for the calcium score (Agatston Unit) by CT in assessing the severity of AS [252].

Aortic valve regurgitation (AR) accounts for 18 % of all VHD, and is more common in males of all ages, with a greater sex difference in incidence than AS, probably because males are more prone to endocarditis, which can cause bicuspid valves and VHD [253,254].

2. Mitral Valve Disease

Rheumatic heart disease is an important cause of mitral valve disease and is more common in females than in males in all age groups. Conversely, nonrheumatic patients are more often male than female for both mitral stenosis (MS) and mitral regurgitation (MR) [255]. Although the incidence of rheumatic MS has decreased significantly in developed countries, degenerative MS is increasing in older patients.

Although males are more likely to develop left ventricular remodeling due to ischemic heart disease, there is no difference between the sexes in the development of secondary MR. [256] As for mitral valve prolapse, females have thicker valve leaflets and less posterior deviation and flailing than males, so deviation itself is more frequent but less severe than in males [257].

3. Tricuspid Valve Disease

Tricuspid regurgitation (TR) of moderate or greater severity is found in 0.55 % of patients in the USA, and its prevalence is higher in females, even when corrected for age [253,258]. In addition, once mild TR occurs, it is more likely to progress from moderate to severe in female patients [259].

CQ2. Should Sex Differences Be Considered When Performing Transcatheter Aortic Valve Implantation (TAVI)?.

Recommendation

The reduction in events (death, stroke, HF hospitalization) with TAVI is comparable between the sexes. However, since women experience a higher incidence of bleeding complications, it is recommended that sex differences be carefully taken into account during postoperative care.

(Agreement rate: 87.0 %; Level of Evidence: B)

Commentary

We reaccessed 27 prospective/retrospective observational studies that took into account short- and mid-term outcomes and sex differences in TAVI cases with AS [260–286]. Certain clinical outcomes have been confirmed for the event-preventive effect of TAVI for severe AS. Short-term mortality rates (30-day mortality, in-hospital mortality) generally do not differ by sex, although higher mortality was reported in some female patients [261,265,267,268,275]. The reductions in stroke, and HF hospitalizations were also comparable between the sexes. On the other hand, bleeding requiring transfusion or intervention beyond invasive therapy (VARC-3 criteria type 2 or higher) [260,261,263,265,267,268,273–276,279,283,286] and vascular-related complications [261–263,265,267–269,272,273,275–278,282,284–286] were reported to occur significantly more frequently in female patients, requiring careful attention in postoperative care. However, there are a wide variety of other potential bleeding points, including vascular injury above the puncture site associated with device delivery, aortic dissection, peripheral vascular embolism, acute lower extremity artery occlusion at the puncture site, and cardiac rupture/cardiac tamponade in rare cases. It is more important to confirm a system to deal with perioperative events, especially in the case of female patients. In general, their higher preoperative frailty and smaller body size may increase the risk of access route injury, but Wang et al. [271] reported that female rather than male patients tend to have a narrower artery and smaller devices. Their report showed no sex difference in perioperative bleeding or vascular-related events, which could be interpreted as a favorable clinical outcome for small device selection [271].

Perioperative pacemaker implantation is reported to be performed significantly more commonly in men [260,263–265,267,270,276,286]. It can be assumed that this is a complication associated with the type and size of TAVI device and its implantation location, but this is an issue for which systematic analysis is needed.

There are also reports of no difference in long-term outcomes (survival ≥1 year) by sex or significantly better in females [263,264,266,268,270,273,275,276,281,286].

Finally, it should be added that this analysis was performed to evaluate the usefulness of sex-disaggregation of cases in which the indication for TAVI had already been established, and is not a comparison with surgical aortic valve replacement in terms of indications for treatment or perioperative management.

FRQ3. Should Sex/Gender Differences Be Considered in Determining the Indication for Surgical Treatment of Severe Mitral Regurgitation?.

Answer

There are reports of higher mortality rates and risk of reoperation in surgical treatment for MR in female than in male patients, possibly due to a bias in the selection of surgical technique for the former and unique preoperative conditions. Further study is needed.

Commentary

In recent years, focusing on sex differences in short- and mid-term mortality rates and MACCE incidence after mitral valve surgery, poorer outcomes for female patients than for male patients have been reported that [287–290]. On the other hand, sex differences do not necessarily affect postoperative outcomes [291–294], and some reports suggest that the poorer clinical outcomes in mitral valve surgery for female patients may be due to the influence of initial condition on the perioperative outcome [295]. Female patients have a higher risk background (i.e., older age, advanced HF), which may have a negative effect on postoperative outcomes [291,294]. It has also been reported that valve replacement is often the procedure of choice for female patients [292,293,296], which may affect surgical outcomes.

The left ventricular system, as measured by echocardiography [287,295] is significantly smaller in females, which may also affect postoperative outcomes. When treating female patients with MR, clinicians should explain that aging and the development of HF may affect surgical outcomes, and refer them to surgeons earlier.

The guideline group voted not to make a recommendation on this clinical question and decided that it would be desirable to conduct further studies. Invasive treatment of mitral valve disease has been

advancing in recent years, and it is hoped that more individualized treatment will be realized.

BK12. Sex/Gender Differences in the Etiology and Prevalence of Pulmonary Hypertension (PH). PH is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg measured by right heart catheterization at rest. Recently, however, the ESC/ERS modified the definition of PH as mPAP >20 mmHg [297]. This section summarizes sex differences in the etiology and the prevalence of PH, which are conformed to JCS2017 guidelines [298], and Table 5 indicates sex differences in PH and chronic thromboembolic pulmonary hypertension in various multicenter registries.

1. Group 1: Pulmonary Arterial Hypertension

Various multinational registries of pulmonary arterial hypertension (PAH) patients demonstrated that 64–80 % of those enrolled in the studies were female [299–302], and a Japanese multicenter study of PAH also showed 71–76 % female patients [303,304]. In particular, idiopathic/hereditary PAH (I/HPAH), PAH with connective tissue disease (CTD-PAH), and PAH with congenital heart disease (CHD-PAH) are more common in females. Conversely, PAH associated with human immunodeficiency virus infection and PAH associated with portal hypertension are slightly prevalent in males [305,306].

Although I/HPAH is more common in young people, recent reports indicate that older-onset I/HPAH is increasing worldwide, and the average age of the patients in each I/HPAH registry has increased. The prevalence of young-onset PAH is higher in females; however, sex differences become less pronounced with age [307]. In addition, female sex is a risk of PAH onset at a young age. On the other hand, several studies have reported that male sex is an independent risk factor of PAH survival, and that a similar trend is shown in male HPAH with *BMPR2* gene mutation.

2. Group 2: Pulmonary Hypertension Due to Left Heart Disease

PH due to left heart disease (LHD-PH) is the most common form of PH. Furthermore, 40–75 % of patients with HFrEF and 36–83 % of those with HFpEF are reported to have concomitant PH [308]. Although there are no large observational studies examining sex difference in LHD-PH with the same diagnostic criteria, a report from Japan indicates that 37 % of LHD-PH patients were female [303].

Table 5
Sex differences in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension in various multicenter registries.
(Source: Prepared based on Badesch DB, et al. 2010 [299], Tamura Y, et al. 2017 [304], Rådegran G, et al. 2016 [305], Hoeper MM, et al. 2022 [306], Barco S, et al. 2020 [317].)

Registry	Etiology of PH	Enrollment period	n	Females (%)
USA REVEAL [299]	PAH	2006–2007	2525	79.5
	I/HPAH		1166	80.3
	CTD-PAH		639	90.1
	CHD-PAH		250	73.6
	PoPH		136	50.0
SAPHER [305]	PAH	2008–2014	457	64.0
	I/HPAH		227	55.0
	CTD-PAH		140	78.0
	CHD-PAH		61	60.0
COMPERA [306]	PAH	2010–2019	2531	63.6
	I/HPAH		1698	59.5
	CTD-PAH		536	81.0
	CHD-PAH		128	65.6
	HIV-PAH		24	45.8
	PoPH		145	44.1
JAPHER [304]	PAH	2008–2013	180	76.0
SAPHER [304]	CTEPH	2008–2014	184	50.0
European CTEPH registry [317]	CTEPH	2007–2012	679	49.9

CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; I/HPAH, idiopathic/hereditary PAH; PAH, pulmonary arterial hypertension; PoPH, portopulmonary hypertension.

3. Group 3: Pulmonary Hypertension Due to Chronic Lung Disease

Chronic obstructive pulmonary disease and interstitial lung disease are the most common causes of PH due to chronic lung disease (CLD-PH). Many registries report that CLD-PH is more common in males [309,310].

4. Group 4: Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

CTEPH is considered to be a rare complication of pulmonary thromboembolism (PTE) and deep vein thrombosis. PTE occurs less frequently in Japan than in Europe and the USA [311]. The rate of progression from PTE to CTEPH varies among studies, but one has reported that 3.8 % of surviving cases of PTE become chronic and persistent [312]. Repeated venous thrombosis is a risk of chronic PTE, and there is no association with sex [313]. Although there is no sex difference in CTEPH worldwide [314,315], some reports from Japan indicated it is more common in females [316]. In addition, a European registry demonstrated that female CTEPH patients are diagnosed at older ages, and less frequently treated with pulmonary artery thromboendarterectomy compared with male patients [317] due to the high incidence of peripheral lesions. However, the long-term prognosis of CTEPH is better in female patients than in male patients [318].

FRQ4. Should Sex/Gender Differences Be Considered in the Treatment of Idiopathic/Hereditary Pulmonary Arterial Hypertension?.

Answer

A trend toward worse prognosis in males has been reported for the same treatment. Evidence on criteria for recommended treatment that account for gender differences is still lacking.

Commentary

Idiopathic or heritable pulmonary arterial hypertension (I/HPAH) is more common in females and several registries have reported a better prognosis for them compared with males [319–321]. Some reports suggest that sex is a prognostic predictor of clinical worsening of PH and death in I/HPAH [322–324], and some report that female patients with I/HPAH have better right heart function at the time of diagnosis and greater hemodynamic improvement after induction of pulmonary vasodilators than male patients [325], despite the higher incidence of the disease in females. The pathomechanism is thought to be influenced by sex hormones and comorbidities in male I/HPAH patients, but the detailed mechanism remains unclear.

The prognosis of PH has dramatically improved in Japan with the development of pulmonary vasodilators that act on 3 pathways: the prostacyclin pathway, the endothelin pathway, and the nitric oxide pathway [303,326,327]. Specifically, in patients diagnosed with I/HPAH, upfront combination therapy is recommended based on risk stratification, and lung transplantation is considered if the disease is refractory to optimized medical therapy including parenteral pulmonary vasodilators. Sudden death may occur in patients with severe I/HPAH during the course of the disease. Based on The Japan Society of Transplantation Fact Book 2022, approximately 37.5 % of patients registered for lung transplantation, including those with I/HPAH without associated pulmonary artery hypertension, die while on the waiting list. Therefore, early registration for lung transplantation is recommended for patients who are candidates for this procedure. Sex may also be considered as a reference criterion when considering lung transplantation, but existing evidence is insufficient.

BK13. Autoimmune Diseases and HF/CVD. Autoimmune diseases are prevalent among females and often lead to cardiovascular complications.

Table 6
Autoimmune diseases and cardiovascular disease risk.
(Source: Prepared based on Drosos GC, et al. 2022 [329], Lindhardsen J, et al. 2011 [330], Symmons DP, et al. 2011 [331], Cervera R, et al. 2015 [343], Tanaka K, et al. 2016 [344], Liao KP. 2017 [345], Lu X, et al. 2021 [346], Kim CH, et al. 2017 [347], Butt SA, et al. 2019 [350], Bartoloni E, et al. 2015 [351].)

Disease	ASCVD	HF
Rheumatoid arthritis	1.5–3-fold [330,331,343–345]	1.5-fold [331]
Systemic lupus erythematosus	2–3-fold[a] [346]	2–3-fold [346,347]
Systemic scleroderma	1.4–3-fold [329,350]	2–3-fold [350]
Sjogren's syndrome	1.5–2.5-fold [329,351]	N/A
Mixed connective tissue disease	–2-fold [329]	N/A

ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; N/A, not applicable.
[a] A report from Sweden found that the rate of death from cardiovascular disease in systemic lupus erythematosus (SLE) patients was 3-fold that of the general population, but in female patients aged 20–39 years, the rate was 16-fold that of females of the same age group [345–348]. A report from the USA showed that the incidence of MI in females with SLE aged 35–44 years was >50-fold higher than in females of the same age group [349].

Conditions such as pericarditis in rheumatoid arthritis (RA), pericarditis and mitral valve disease in systemic lupus erythematosus (SLE), thromboembolism in antiphospholipid antibody syndrome, arrhythmias in scleroderma and mixed connective tissue disease are well documented (Table 6). HF and atherosclerotic cardiovascular disease (ASCVD) are more common in patients with autoimmune diseases, especially in younger females, when compared with the general population [328–330]. Acute HF in RA and SLE patients often presents atypical symptoms and carries a higher mortality rate [331].

The increased risk of ASCVD in autoimmune disease patients can be attributed to coronary risk factors: high-dose and long-term steroid therapy; microcirculatory dysfunction; elevated inflammatory cytokines and chronic inflammation leading to atherosclerosis [328,332]. Patients with autoimmune diseases and traditional coronary risk factors are at even greater risk of CAD, compared with the general population [333]. Aggressive interventions, such as smoking cessation and controlling blood glucose and lipid levels, are recommended for primary and secondary prevention [329,334].

Furthermore, specific ASCVD risk factors related to autoimmune diseases, such as disease activity and duration, must be considered, emphasizing the importance of managing the primary disease to prevent ASCVD [335,336]. Some biological disease-modifying antirheumatic drugs have shown effectiveness in reducing ASCVD incidence [337,338]. In the CANTOS study, the anti-interleukin-1β monoclonal antibody canakinumab was found to inhibit cardiovascular events among patients with a history of MI and elevated levels of high-sensitivity C-reactive protein [339]. However, the broader effects of anti-cytokine therapies on RA and their association with cardiovascular events requires further investigation [328,329].

Takayasu arteritis and giant cell arteritis, which are thought to be related to autoimmune mechanisms, also occur more frequently in females than in males (for details, see the Japanese Guideline [340]). Patients with Takayasu arteritis have a higher incidence of ASCVD and HF than the general cohort of the same age [341]. It has been reported that methotrexate suppressed cardiovascular complications in patients with Takayasu arteritis [342].

2.3 Arrhythmia

BK14. Female Patients With Atrial Fibrillation (AF) and Cognitive Dysfunction. It has been demonstrated that genetic factors and vascular risk factors such as aging, hypertension, diabetes, and dyslipidemia are risk factors for dementia; in addition, reports indicate that AF is also an independent risk factor for dementia [352,353].

A large-scale prospective cohort study from the USA targeted 37,035 patients from the database of Intermountain Heart Collaborative Study and found an increased incidence of dementia in patients with AF during a mean 5-year follow-up period [354]. The Joint Statement on Arrhythmias and Dementia by the European, North American, Asia-Pacific, and South American Arrhythmia Societies made reference to the role of AF in cognitive decline [355]. In that statement, 2 meta-analyses are presented to examine the incidence of cognitive decline in AF patients with a history of stroke, and both showed a higher risk of cognitive decline or dementia in the AF group than in the non-AF group, with OR of 2.43 (95%CI 1.70–3.46; $P < 0.001$) [356] and a relative risk of 2.70 (95%CI 1.82–4.00) [357].

On the other hand, it has been shown that dementia is also more common in AF patients without a history of stroke [352,358]. A meta-analysis of 8 prospective studies showed that AF is an independent risk factor for developing dementia in AF patients without a history of stroke (hazard ratio 1.42, 95%CI 1.17–1.72; $P < 0.001$) [359].

No consensus has been reached on sex differences in cognitive decline in AF. A cross-sectional study of dementia and AF in 6584 residents near Rotterdam reported a significant association between AF and dementia only in females (OR 3.0, 95%CI 1.5–5.9) [352]. In addition, 2685 participants of the SNAC-K study were followed for a mean of 5.8 years to examine the risk of developing dementia and Alzheimer's disease (AD) in AF patients. The results showed that females had a significantly higher risk of developing dementia and AD than males (hazard ratio 1.46, 95%CI: 1.10–2.94 vs. 1.59, 95%CI: 1.02–2.49) [360]. In a Taiwanese study, the incidence of dementia in AF patients aged ≥56 years was significantly higher in females than in males [361]. On the other hand, in the Framingham study with 3–6 years of follow-up, males with AF showed significant declines in several cognitive function test items compared with females [362]. A prospective cohort study in the USA examined the risk of cognitive decline in patients with AF found no sex differences [363,364].

Mechanisms of AF and the development of dementia include the involvement of elevated inflammatory markers such as C-reactive protein [365], asymptomatic cerebrovascular lesions caused by micro-cerebral emboli, and low cerebral capacity caused by chronic reduction in cerebral blood flow due to irregular contraction of the left atrium [366,367] and so on. Furthermore, amyloid deposition has been reported as one of the mechanisms of AD in female AF patients. As a mechanism of amyloid deposition, it is known that AF causes marked atrial enlargement in females [367], and that the elongation of the atria increases blood atrial natriuretic peptide concentration, which promotes amyloid formation via estrogen receptors [368,369].

Some papers have shown that anticoagulation with direct oral anticoagulants (DOACs) reduced the incidence of stroke and dementia compared with warfarin [370]. There is a report that patients who underwent catheter ablation (CA) for AF had less new onset of dementia, including AD and cerebrovascular dementia, than those did not [371]. It has been reported that female patients are less likely to receive CA than males in both Europe and the USA [372,373], and in Japan also, fewer female patients receive rhythm control therapy [374]. In the future, detailed studies should be conducted to prevent cognitive decline in female patients with AF, including the relationship between treatment, including CA, and improvement in cognitive function.

FRQ5. Should Sex/Gender Differences Be Considered When Treating AF?.

Answer

There are biological differences between male and female patients with respect to the risk of adverse outcomes from AF, and treatment of

female patients with AF should be tailored to their individual cases, taking into account their clinical characteristics and biological differences.

Commentary

Female patients with AF are characterized by a higher age at onset [375] than male patients, more comorbidities, a higher risk of stroke [376] and death [372], and more severe symptoms [377], leading to a lower quality of life [378]. A study using a European database also found that female patients with AF had worse outcomes than males, with higher mortality-to-incidence ratios. This suggests that there is a widening healthcare disparity between the sexes across Europe and that there are biological differences between them with respect to the risk of adverse outcomes from AF [379].

Female patients with symptomatic AF tend to prefer rate control over rhythm control and prefer pharmacologic therapy over electrical cardioversion [380]. The EAST-AF NET 4 trial reported consideration to improve outcomes with early rhythm control interventions, including CA for AF, and a subanalysis reported no sex difference in prognostic improvement with early rhythm control [381].

Although there is still no consensus on sex differences in the use of antiarrhythmic drugs for rhythm control, several studies have reported that female patients are more prone to develop torsades de pointes and sick sinus syndrome than male patients [382–384].

Regarding CA of AF, a meta-analysis of 19 observational studies showed that female patients have a shorter duration of maintenance of sinus rhythm after CA and more complications [384]. Female AF patients are often underdiagnosed, have delayed timing to see a doctor [385,386], and a longer period from diagnosis to CA compared with male patients, which may contribute to the risk of AF recurrence. Subsequent substudy of the CABANA study showed that the incidence of complications from CA was very low in both sexes, with no differences. It also showed that treatment with CA compared to pharmacotherapy significantly reduced the risk of recurrence in both sexes [387].

BK15. Sex/Gender Differences in the Risk of Sudden Death in Brugada Syndrome (BS). BS is a syndrome of sudden death (SD) from VF with a characteristic coved ST-segment elevation (type 1 ECG) in the right precordial leads. The prevalence of BS with spontaneous type 1 ECG is estimated to be 0.10 % in European countries and 0.94 % in Asian countries. Males account for 80–90 % of diagnosed patients [388,389].

Sex differences in prevalence have been explained by ion channels and right ventricular outflow tract conduction reserve, but the details remain unclear. It has been reported that the density of Ito in the right ventricular epicardium is higher in males and that the male hormone testosterone increases Ito, which in turn manifests as coved-type ECG [390–393]. In addition, the concept has recently been proposed that decreased right ventricular outflow tract conduction reserve, which has been reported to vary with age and sex as described above, is the final pathway in BS [388,394].

Whether sex is a risk for SD in BS is inconclusive; in a number of studies examining risk factors for arrhythmic events in BS, multivariate analysis showed that history of cardiopulmonary arrest, arrhythmogenic syncope, and spontaneous type 1 ECG were independent risk factors, with sex showing showed no significant differences [26,395,396]. In previous large cohort studies, sex was also not identified as an independent risk factor after adjustment for other risk factors [389]. On the other hand, a report focusing on sex differences found that arrhythmic event rates were significantly lower in females than in males [397–400]. In a meta-analysis of 4140 BS patients, including 918 female patients, the OR of event occurrence in males compared with females was 2.06 (95%CI 1.46–2.91, $P < 0.0001$). In addition, the reports showed sex differences in patient background/event risk factors, with females having less spontaneous type 1 ECGs than males (8–31 % vs. 23–55 %) [400]. Risk factors for events in female BS patients varied, but spontaneous type 1 ECG was not an independent risk factor in any report [398–400]. Female BS patients have a lower event rate than males, suggesting different patient backgrounds and risk factors.

2.4 Vascular Disease

CQ3. Should Sex Differences Be Considered When Using Conventionally Established Ankle-Brachial Index (ABI) Cutoff Values?.

Recommendation

When using the conventionally established ABI cutoff values, it is recommended to consider sex differences because females have lower values than males, and the diagnostic and prognostic power of ABI ≤0.9 is inferior in females compared with males.

(Consensus rate: 80 %; Level of Evidence: C)

Commentary

An ABI ≤0.9 is one definition used to detect PAD, and 0.91–0.99 is also considered a risk group for cardiovascular events [401,402]. However, female patients have lower ABI values than male patients, and the trend is similar for all races [401,403]. Therefore, there is still no clear answer as to the validity of the cutoff value of 0.9 for female patients.

One possible reason for low ABI values in female patients might be the effect of reflected pulse wave on limb BP due to height (distance between heart and limb) differences between the sexes [403,404]. However, Kapoor et al. showed that ABI values were lower in females even when adjusted for height and CVD risk factors and concluded that low ABI values in healthy females are not due to potential PAD risk but are influenced by being female independently of height [404]. The Okinawa Peripheral Artery Disease study in Japan also showed that ABI values in females were lower than those in males and were lowest in females younger than 40 years and highest in those aged 60–69 years. Among females under 60 years of age, there was no difference in atherosclerosis risk factors between those with ABI values <0.9 and those with higher values, indicating that ABI values <0.9 are not necessarily due to arterial stenosis [405].

There have been previous attempts to correct for sex differences by setting the cutoff value for females at 0.85 [402,403]. In a report of a cohort with disease by the Atherosclerosis Risk In Community, the incidence of CAD increased exponentially when using a threshold of 0.9 for males and 0.8 for females, although the sample size was small. The aforementioned value of 0.85 also seems reasonable [403]. However, Hiramoto et al. reported that the risk of stroke and PAD was higher in female patients with an ABI of 0.9–1.0 [406]. Taking all findings into consideration, it is unclear whether reducing the ABI cutoff value for females is appropriate. On the other hand, the diagnostic and prognostic power of an ABI ≤0.9 in females is inferior to that in males. Other risk factors, such as comorbidities, should be taken into account for evaluation [407].

CQ4. Should Revascularization for Peripheral Artery Disease (PAD) Be Aggressively Recommended in Female Patients?.

Recommendation

Female patients with PAD have a higher prevalence of chronic limb threatening ischemia (CLTI) and more severe and diverse background diseases than male patients, and their outcomes after bypass and endovascular treatment (EVT) have been considered poor. However, with the improvements in EVT, including drug-coated balloon (DCB), there has been no difference in post-revascularization outcomes between the sexes, although the prevalence of CLTI cases are still more prevalent in females. Based on this background, we weakly recommend aggressive revascularization of PAD in females.

(Agreement rate: 91.3 %, Level of Evidence: C)

Commentary

It has been reported the female patients have a higher prevalence of asymptomatic PAD, a higher proportion of CLTI in PAD, and poorer revascularization outcomes than male patients [408,409]. However, with the recent evolution of EVT devices such as DCB and dramatic changes in revascularization treatment strategies, there is no longer a clear sex difference in outcomes [410]. After 2015, the EVT era, 2 systematic reviews were published. In the one by Wang et al. for all post-

revascularization patients, females had a higher 30-day mortality rate, as well as major amputation, graft occlusion, and access problems, than the male patients, but there was no sex difference in long-term survival, patency, or limb salvage outcomes [408]. Lee et al. also found that female PAD patients had more CLTI and all-cause deaths than male patients, but lower rates of major amputation [409], possibly because female patients are less likely to receive treatment until the disease is more severe and may have more risk factors at the time of treatment. One study of open surgery (OS) found that socioeconomic factors such as race, income, and insurance did not play a role [411]. On the other hand, a sociodemographic study of EVT reported that female patients were older, presented more severely, had poorer outcomes, and were more likely to be socially isolated after discharge from the hospital [412]. In patients with intermittent claudication, inadequate preoperative medications and high incidence of repeat surgery have been reported [413].

The sex difference for death and other primary outcomes varies among reports. In a large Korean registry of EVT cases, the female patients had worse mortality rate, cardiac complications, and major amputation rates than the male patients [414]. Some reports from the USA showed that perioperative death after EVT was worse for female patients, but the major amputation rate was better [415,416]. On the other hand, there are some reports that the short- and long-term mortality rates after EVT were lower for female patients or equal to that for the male patients [417–419]. In large cohort analyses in Germany, mortality, cardiac complications, and major amputation rates were better in female patients after both OS and EVT [420,421]. Revascularization outcomes are thought to vary by region, race, and cohort selection.

In terms of patency, in the review by Wang et al., EVT but not OS showed a benefit for female patients [408]. The DURABILITY trial, which assessed bypass patency, also showed no difference in short-term outcomes between the sexes, but females had lower patency and walking function after 3 years [422].

In an analysis of the DCB cohort, the female patients were older and had smaller diameter of treated vessels, but there was no difference in outcome [423]. Major amputations and major complications were more common in male patients, even though there were more CLTI cases among the female patients [424]. DCB may increase the patency rate of EVT, which may be good news for female patients, who have been thought to have poor access routes. Future reports are awaited.

CQ5. When Diagnosing Female Patients With Deep Vein Thrombosis (DVT), Is It Recommended to Establish a Female-Specific Cutoff Value for D-Dimer (DD)?.

Recommendation

Although DD values differ between male and female patients with and without pulmonary embolism (PE) and DVT, respectively, it is difficult to find any clinical diagnostic benefit in setting a sex-specific cutoff value for the diagnosis of DVT patients. It is weakly recommended not to set female-specific cutoff values when diagnosing female patients with DVT.

(Agreement rate: 91.3 %; Level of Evidence: B)

Commentary

The risk of VTE in female patients cannot be discussed without the events of pregnancy and childbirth, which cause venous compression and blood over-coagulation. Four of the five articles remaining from the systematic review were cohorts of pregnant females.

In the only multicenter cohort study comparing DD values between the sexes, 1042 females and 710 males at low to moderate risk (Wells score ≤ 6 for PE and ≤ 2 for DVT) who presented to emergency departments were compared. The DD values were significantly higher in males than in females in the groups with PE and without DVT, and were significantly lower in males than in females in the group without PE. However, optimization of cutoff values by specificity and sensitivity showed no significant sex differences in PE or DVT, and it was concluded that there was no need to set cutoff values for each sex [425].

A systematic review and meta-analysis of DD threshold to exclude acute VTE in pregnant females was published in 2021 [426], including 4 studies and 1194 subjects; 0.32 % (1/312) of patients were diagnosed with untreated VTE after 3 months despite negative DD values. DD measurement was useful for VTE screening with a high sensitivity of 99.5 %, but the authors did not conclude that the cutoff should be increased for pregnant females [426]. Chan et al. included 228 pregnant females as controls and measured DD in 5 assays. The median DD increased significantly with gestational week, and pregnant females with DVT had higher DD values than those without DVT [427]. The prevalence of DVT was 6.6 %. For each assay, a higher specificity (62–72 %) was obtained for pregnant females while maintaining a high sensitivity (80–100 %) by increasing the cutoff value.

There are also Japanese reports examining DD value changes during pregnancy and number of fetuses [428,429]. An analysis of a single-center cohort examining 1026 pregnant females showed that DD levels increased with pregnancy week: to ≥3.2 μg/mL in 2 % at <20 weeks, 10 % at 30–34 weeks, and 16 % before delivery (20 % had 1–3.2 μg/mL). A total of 7 patients had DVT, 5 cases of which occurred at <20 weeks, suggesting that the risk of DVT does not correlate with the increase in DD over time. It was also shown that DD values were higher in twin and triplet pregnancy than with singletons [428]. The authors presented the assessment in the Japanese obstetric and gynecological practice guidelines that cesarean sections are considered more high-risk than vaginal deliveries [430], but did not assess those risks due to the small number of cases. Nishii et al. reported significantly higher DD values in the first and third trimesters of pregnancy than in the first trimester, consistent with the above results [429]. In the third trimester, DD values in the DVT-positive group was high (mean value of 2.6 μg/mL) but did not exceed the cutoff value of 3.2 μg/mL set in both of the Japanese studies. This indicated that DD levels in pregnancy are strongly influenced by factors other than thrombus in the search for accurate DVT screening, including higher DD values in twin pregnancies.

CQ6. Should Endovascular Aneurysm Repair (EVAR) for Abdominal Aortic Aneurysm in Female Patients Be Aggressively Recommended?.

Recommendation

Aggressively performing EVAR for female patients is weakly recommended, with consideration to improve outcomes, such as strictly discussing the anatomical factors, including the access routes and the aneurysm size threshold for surgery.

(Consensus rate: 87 %; Level of Evidence: C)

Commentary

Outcomes after EVAR are worse for female patients than males due to anatomical features of their arteries (smaller, more fragile, and more easily damaged) and socioeconomic factors such as less access to medical care. Three recent systematic reviews with meta-analysis note that females are morphologically less suited for EVAR than males and therefore have lower intervention rates and higher operative mortality rates [431–433]. These reviews also suggested that postoperative renal and cardiac complications and lower extremity ischemia are frequent in females, contributing to the high mortality rate, with a strong message that they be enrolled in strict surveillance of procedures and outcomes after EVAR [431–433]. However, these suggestions were made based on much data from before 2010. Nowadays, there are many advanced techniques and devices that can be selected according to the patient's anatomy. Thus, there may be more hopeful evidence for females.

In fact, many large cohort analyses have reported no sex differences in all-cause and aortic-related deaths since 2013 [434–439]. The mandatory nationwide registry of patients undergoing abdominal aortic aneurysm (AAA) repair in the Netherlands seems reflect real-world results and showed no significant sex differences in mortality rates [434]. However, female patients still showed higher incidence of perioperative and postoperative complications and reinterventions [435,436], as well as longer hospital stays [437], suggesting that there still remains a sex

disadvantage. In these studies, female patients were older [434–439] and included more smokers [438,439] compared with males. Other studies reported that females had shorter and more angulated infrarenal necks [440–442], less heart disease [443], and less diabetes [438]. In patients with 30-day survival after EVAR, long-term aortic-related mortality was significantly higher in females than in males [444], even though they had less preoperative cardiovascular risk. The high incidence of Type 1 endoleak in female patients is likely due to morphologic disadvantages [435,445]. Ovation, a recently developed device that contains a proximal sealing ring, showed no sex difference in endoleak or all-cause death despite the adverse neck characteristics of females [446]. Future device-specific analysis will be required.

In terms of factors that make outcomes worse for females after EAVR, Deery et al. found that they had higher rates for 30-day mortality and more major complications after EVAR for intact AAA. However, after adjusting for aortic size index (aortic diameter/body surface area), the sex difference reduced, although female patients were older, had smaller aneurysms, and had more obstructive pulmonary disease [447]. The EUROSTAR registry also found that the long-term mortality rate was higher in female patients but no longer significantly different when adjusted for age, American Society of Anesthesiologists risk classification, cardiovascular comorbidities, aneurysm morphology, and surgical factors [448]. Barbey et al. found that the difference in survival between the sexes disappeared when adjusted for the modified frailty index, a factor that is a measure of frailty [449]. In the propensity score match analysis by Behrendt et al., short- and long-term survival and even re-treatment rates were not significantly different between the sexes, suggesting the importance of background factors, especially those that can be controlled [450]. One study found that female sex was an independent risk factor for intestinal ischemia after EVAR with a low OR (1.6) [451]. Risk control may improve outcomes after EAVR for females. However, sex differences in postoperative outcomes are reported to vary depending on race and country [452,453]. The environment surrounding female patients can have a strong influence on the prognosis after EAVR.

After AAAs smaller than the aneurysmal diameter threshold for surgery (5.5 cm in males, 5.0 cm in females) were treated by EAVR, short-term morbidity, 30-day mortality, and reintervention rates were higher in the female patients than in males [454]. Thus, the diameter threshold may need to be discussed strictly with female patients. In addition, access complications, associated with long-term mortality and morbidity, are reported to be prevalent, particularly in females, due to the risks of skin incisions [450,455,456]. EVAR by percutaneous puncture may be more recommended for female patients.

2.5 Stroke

BK16. Stroke in Female Patients.

1. Epidemiology

Stroke is the second leading global cause of death, and also a significant contributor to the development of care-dependent conditions [457]. In Japan, stroke ranks as the 4th leading causes of death, accounting for 7.3 % of all fatalities in 2021. Notably, 50.7 % of stroke-related deaths are of female patients while males represent 49.3 % [458]. Globally, the lifetime risk of stroke is reported to be 25.1 % for women and 24.7 % for men. Furthermore, regional variations exist, with East Asia recording the highest risk levels for both sexes (40.6 % for males and 36.3 % for females) [459].

Age-adjusted incidence rates of stroke are generally higher in males [460], but there are age-specific patterns in the sex differences of stroke risk. Younger females face a greater risk than younger males [461–463]. In the middle-aged to <75 age group, males have a higher risk, whereas the trends diminish or even reverse in older age groups [461,464,465].

The incidence of stroke types varies depending on sex. Females have a higher risk of intracranial aneurysms and subarachnoid hemorrhage, whereas males have a higher incidence of ischemic stroke [464,465a] and intracerebral hemorrhage (ICH) [461,466]. The social context is also noteworthy. At stroke onset, female patients are more likely to be widowed, unmarried, or living alone, and they often face greater disabilities in their activities of daily living [467].

2. Risk Factors

Common stroke risks affect the sexes differently in terms of impact (Fig. 5) [376,468–472]. Among female-specific risks, oral contraceptives are associated with younger age groups [473]. Menopause-related hormone replacement therapy correlates with total and ischemic stroke risk. There are also reports that the small doses of transdermal estrogen replacement therapy do not significantly increase this risk [474].

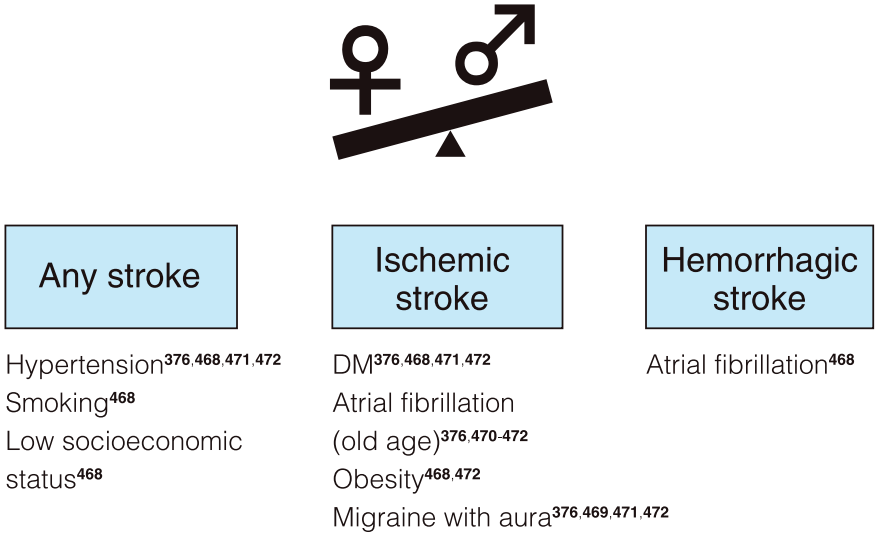


Fig. 5. Stroke risks associated with gender differences and more prevalent in women. DM, diabetes mellitus.
(Source: Prepared based on Bushnell C, et al. 2014 [376], Peter SAE, et al. 2020 [468], Schürks M, et al. 2009 [469], Mikkelsen AP, et al. 2012 [470], Madsen TE, et al. 2018 [471], Rexrode KM, et al. 2022 [472].).

3. Symptoms and Diagnosis

Early detection of stroke symptoms is crucial for prompt diagnosis and treatment. Research indicates that approximately 9 % of stroke cases are overlooked in emergency departments [475]. Moreover, female patients have a 25 % higher risk of misdiagnosis [476]; multiple studies highlight that they are more likely to present with atypical stroke symptoms [477,478], such as headaches, fatigue, cognitive changes, general malaise, weakness, coma, and urinary incontinence [478–480]. These atypical symptoms can result in delays in correct diagnosis and treatment [481], as well as receiving less standardized diagnostic testing or treatment [482–484]. Standardized diagnostic procedures that account for sex differences need to be established.

4. Treatment

Intravenous recombinant tissue-type plasminogen activator (rt-PA) for acute stroke is less likely to be administered to female patients. However, regional differences are reported, with no apparent sex differences in Asian countries. The efficacy of rt-PA appears unaffected by sex [485,486]. Symptomatic ICH following rt-PA is more common in males [487]. Conversely, mechanical thrombectomy (MT) is more frequently performed in female patients with acute stroke [488,489], possibly because of the higher prevalence of AF, coupled with insufficient stroke prevention, in females, which may contribute to the elevated incidence of large-vessel occlusion and the increased utilization of MT. [472] Meta-analysis suggests no sex differences in the efficacy or safety of MT. [490] Additionally, acute EVT may have a more significant effect on favorable outcomes in female patients [491].

For idiopathic ICH, no therapeutic intervention demonstrates clear efficacy to date. No sex differences have been observed in the efficacy and safety of aggressive BP control in the acute phase [492,493]. Recently, specific reversal agents for oral anticoagulants have been developed and used for anticoagulant-associated ICH; however, sex differences for these agents remain unknown.

5. Clinical Outcomes

Female patients typically experience worse clinical outcomes after stroke [493a], in terms of death, quality of life, post-stroke depression, and limitation in activities. Contributing factors may include poorer health status at stroke onset, older age, and stroke severity [472,494]. Limited access to qualified clinical care, pre-stroke mobility, mental health, social isolation, lack of support systems, and poor socioeconomic status are also significant factors influencing worse outcomes [482,494–496]. Further research is warranted to understand the underlying mechanisms of these disparities.

2.6 Hypertension

BK17. Gender and Age Differences in the Achievement of Antihypertensive Targets. Achieving antihypertensive goals is an important part of hypertension treatment.

Hypertension treatment rates in Japan continue to rise, with 50 % of those in their 60s and > 60 % of those in their 70s; according to data from NIPPON DATA 2010, 30 % of males and 40 % of females reached the goal (BP <140/90 mmHg with oral antihypertensive medication). Differences by age are slightly lower for those in their 70s than for those in their 50s and 60s [497]. In 2016, the achievement rate increased year by year: 50s (33.3 % males, 45.1 % females), 60s (40.6 % males, 48.0 % females), and 70s (44.2 % males, 43.4 % females) (Fig. 6) [498], but only males in their 50s achieved the 2016 rate remained unchanged from 2010 [499].

On the other hand, in the USA, the rates of hypertension awareness, being treated, and achieving goals are, respectively, 83.8 %, 75.7 %, and 58.0 % for patients aged 40–59 years, and 85.4 %, 81.7 %, and 54.1 % for those aged ≥60 and older. The achievement rate of the goal is about 50 %, which is better than in Japan. The sex and racial differences are as follows: Caucasian male vs. Caucasian female 54.0 % vs. white females 58.7 %; African American male vs. African American female 41.4 % vs. black females 55.9 %; Hispanic males 38.1 % vs. Hispanic females 50.4 %; females also have a higher rate of achieving goals than males in the USA [500].

In the National Health and Nutrition Examination Survey, the rate of achievement of antihypertensive goals has improved for both sexes [501]. The recent improvement in medication adherence through the use of fixed-dose combination products, single-package medications, home nursing care, and drug management by visiting pharmacists may also contribute to achieving antihypertensive goals.

2.7 Transgender People

BK18. Exogenous Female Hormone Action on an Anatomical Male. The International Classification of Diseases (ICD)-11 renamed the traditional gender identity disorder as gender incongruence, and defined it as a condition in which the assigned sex at birth does not match the experienced gender. Hormone therapy for transgender women whose assigned sex at birth is male and experienced gender is female (AMAB: assigned male at birth) uses female hormones (estrogens) [502] to feminize body shape, including suppression of penile erection

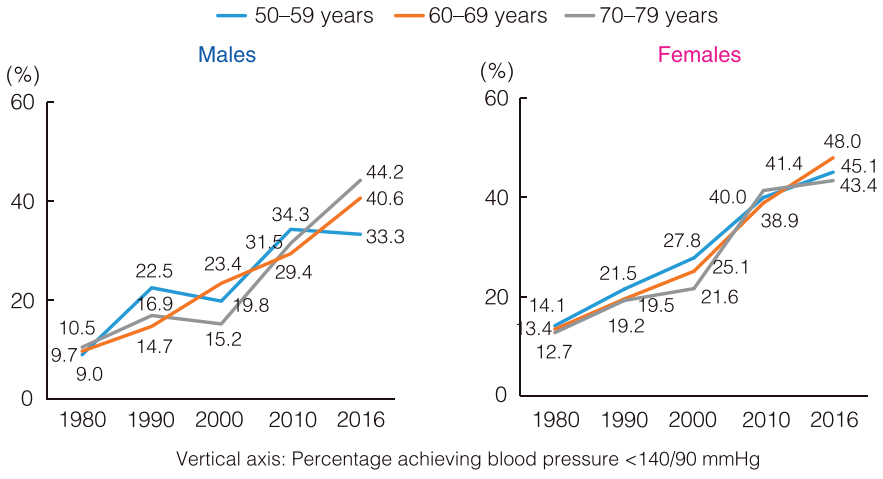


Fig. 6. Annual changes in the percentage of each sex achieving antihypertensive targets by age group in Japan (1980–2016). (Adapted from Miura K, chief investigator. Health, Labour and Welfare Policy Research Grants, 2019 [498].).

and breast enlargement. However, they are not effective enough in reduction of beard growth and feminization of the voice [503,504]. Decreased libido, irreversible testicular atrophy and loss of spermatogenesis may occur. Medical evidence for the benefit of concomitant use of anti-androgens is insufficient. Concomitant use of progestin (luteinizing hormone) preparations is also known to have adverse effects on lipids and blood vessels, and should not be used in principle [505].

Natural estrogen (17-β estradiol) 2.0–6.0 mg/day (oral), 17-β estradiol patch 100–400 μg (transdermal, replaced every 2 days), 17-β estradiol gel 1.0 g/day (transdermal), estradiol valerate (intramuscular, 10 mg every 2–3 weeks or 20 mg every 2–4 weeks), etc. are recommended [502]. However, there is currently no medical insurance coverage for hormone therapy for gender incongruence in Japan.

BK19. Epidemiology of CVD in Transgender Women. Hormone therapy for transgender women has been reported to have positive, negative, and no effects on lipid metabolism [506,507], possibly related to the variety of types, doses, and routes of administration of estrogen preparations, as well as the concomitant use of anti-androgens and progestins, depending on the study. The incidence of VTE in transgender women is reported to be higher than that in cisgender men and cisgender women whose sex at birth is consistent with their assigned sex [508], or in the general population [509]. However, there is no significant difference between transgender women and cisgender men or cisgender women with regard to cerebral infarction and MI [508].

Mortality rates for transgender women are higher than those for men and women in the general population, with higher rates by cause in CVD, lung cancer, diseases related to human immunodeficiency virus (HIV), and suicide [510]. Minority stress theory states that social prejudice, discrimination, and inadequate laws and systems lead to smoking, drinking, and drug abuse, which in turn lead to higher rates of depression and anxiety, cardiovascular events, suicide, and unexplained death [511].

Although there are currently no studies with high evidence, estrogen should be used without anti-androgens and progestin [2]. The occurrence of thrombosis should be taken into account; smoking and obesity should be eliminated. In the presence of advanced age, hypertension, or atherosclerosis, natural estrogen (17-β estradiol) preparations and routes other than oral administration should be considered [512]. Mental health during hormone therapy should also be taken into consideration.

BK20. Exogenous Male Hormone Action on an Anatomical Female. Gender incongruence is the name given to the condition in which there is an incongruence between the assigned sex at birth (assigned sex) and experienced gender [513]. Hormonal therapy using male hormones is used as a physical treatment for transgender men whose assigned sex at birth is female (AFAB: assigned female at birth). In Japan, testosterone enanthate 250 mg intramuscularly every 2–4 weeks is commonly administered, and administration is continued over a long period of time, even years. Administration of male hormones causes masculinization of physical characteristics, such as cessation of menstruation, a low-pitched voice, increased beard and body hair, increased muscle mass and strength, and an increased size of the clitoris [503,514,515].

BK21. Epidemiology of CVD in Transgender Men. There is concern about an increase in VTE, stroke, and MI, as male hormone administration has been reported to exacerbate risk factors for cardiovascular events, including exacerbation of atherogenic lipid profile [507,516], decreased vascular endothelial function [517], and accelerated atherosclerosis [518]. However, in a large cohort study, the hazard ratios for VTE, stroke, and MI in transgender men receiving male hormones adjusted for body mass index (BMI), smoking status, BP, and total blood cholesterol levels were not significantly higher in cisgender men (sex assigned at birth and experienced gender were matched male) or cisgender women (assigned sex at birth and experienced gender were matched female) [508]. In contrast, another large cohort study found a 3.69-fold higher risk of MI in transgender men who received male hormones compared with cisgender women, but no increased risk of stroke or VTE was observed compared with cisgender women or cisgender men [509]. In a prospective study that calculated cardiovascular risk based on the Framingham 30-year cardiovascular risk estimates in transgender men receiving male hormones, the hard cardiovascular risk calculated on a lipid basis was significantly increased from 2.79 % at baseline, to 3.46 % at 12 months, and 4.16 % at 24 months [516]. As discussed above, there are no consistent results suggesting a causal relationship between exogenous male hormone administration and subsequent cardiovascular events in transgender men.

At present, there is insufficient conclusive evidence based on high-quality, large-scale studies to assure the long-term cardiovascular safety of male hormone administration to transgender men [2].

BK22/GPS. Special Consideрations for Transgender Patients. According to a survey of transgender people [519], about a half of the respondents said that they hesitated to visit a medical institution or had had an unpleasant experience there. It should be noted that the degree of gender dysphoria among transgender people varies; not all of them are undergoing hormone therapy or gender reassignment surgery, and there are various stages of physical treatment (Table 7). Not all patients come out to their healthcare providers about their sexuality. Unless they report that they have undergone gender transition, they may not be identified as patients themselves. It is necessary to create an environment in which

Table 7
Key considerations and recommendations for transgender patients.

Recognition of variability in gender dysphoria
It should be noted that the degree of gender dysphoria among transgender people varies, as not all of them are undergoing hormone therapy or gender reassignment surgery, and there are various stages of physical treatment
Insurance card and name discrepancies
The gender and name on the insurance card (in the family register) may not match the gender that is imagined from appearance [520]
When confirming the identity of a patient, care should be taken in the location and manner of speaking to the patient
Respect for preferred names
Some patients may feel distress at being called by their birth names, so we should confirm the patient's wishes regarding their name, and consider using only the first name or a common name, as well as introducing a numbering system for anonymization
Inclusive medical questionnaires
Many patients are troubled when required to select their gender on medical questionnaires, etc. [519,521–523] It is recommended to add “other” to the options, or to provide a column for free entry
Gender-neutral facilities
It is beneficial to provide hospital gowns, changing spaces, and restrooms that can be used regardless of gender
Gender-neutral language
When asking about sexuality among background factors, avoid closed questions as much as possible and use gender-neutral expressions such as “partner” and “supporter”
Privacy and information sharing
When information is shared among healthcare providers, it is advisable to discuss in advance what should be written in the medical record and the range of people with whom the information should be shared, to avoid unexpected outing (disclosure of the patient's sexual orientation or gender identity to a third party without consent)
Flexible gender of medical examiners and caregivers
Some patients may be uncomfortable with being seen or touched during medical examinations. The gender of the examiner and caregivers should be flexible to accommodate their needs
Individualized hospitalization
If hospitalization is necessary, the best room for the patient is determined on a case-by-case basis, but it is not always possible to meet the patient's wishes
Education and awareness for medical personnel
Medical personnel's lack of understanding and inconsiderate treatment are also cited as factors that may prevent access to medical care [523,524]. It is desirable to educate medical personnel to disseminate accurate knowledge and correct prejudice in the future

all patients can receive medical care equally and comfortably, taking into consideration the diversity of sexuality.

III. Life Stages

1. Young Age and All Life Stages

BK23. Risk Factors to Intervene for Primary Prevention of Myocardial Infarction (MI) in Young Patients

Similar to older MI patients, 90.3–98 % of younger MI patients have ≥1 coronary risk factor [525,526]. Despite the high prevalence of coronary risk factors, the proportion of patients who are aware that they are at risk for MI and receive treatment such as statins, antihypertensive drugs, etc. before their first MI is low [527]. Risk factors may be missed or therapeutic interventions are insufficient in younger patients.

Smoking is a known risk factor for MI, but it is a particularly strong risk factor in young people [528–531], with smoking rates as high as 37.5–90 % in young MI patients compared with older MI patients [528–540], and smoking is reported to increase the incidence of MI 2.5–5.8-fold in younger patients compared with healthy nonsmokers [541,542]. A dose–effect response has been observed between the number of cigarettes smoked per day and MI, with smokers younger than 45 years old who smoked ≥25 cigarettes/day being 8-fold more likely to have a MI than nonsmokers [543]. Although smokeless tobacco has recently been introduced, its consumption has not yet been established as a cardiovascular risk factor [537]. Although there is no direct evidence that passive smoking increases acute myocardial infarction in young people, there is a report that it increases ischemic heart disease in middle-aged females in Japan [538]. Future studies are warranted.

Modifiable risk factors other than smoking that are more prevalent in younger MI patients are dyslipidemia and obesity. In a meta-analysis of patients with acute coronary syndromes (ACS) in Japan and other countries, the prevalence of familial hypercholesterolemia was 7.3 % [95 % confidence interval (CI), 5.3–10.0] in patients <60 years of age, whereas when age was restricted to <45 years, the prevalence increased to 13.7 % [8.2–22.1] [544]. To begin with, younger MI patients have a higher incidence of dyslipidemia [28.3–86 %] [525,526,530–532,537–539,545], compared with older MI patients [0.3–32.7 %] [526,532,536–539]. In a study of young Korean adults, persistently elevated low-density lipoprotein (LDL) cholesterol and triglyceride levels increased the incidence of MI [LDL cholesterol hazard ratio 1.204, 95%CI 0.756–1.916; triglyceride 1.152, 1.014–1.310] [546]. Regarding obesity, 0.3–32.7 % of older MI patients were obese [526,536,538–540], while 30–64.2 % of young MI patients were obese [531,536–539], and the risk of MI is 4.5-fold higher in obese patients than in non-obese patients among young patients [547].

There are sex differences in the coronary risk factors of young MI patients, with males more likely to smoke (58.1–90 %), have dyslipidemia (18.2–65 %), and obesity (48–56 %), while females are more likely to have diabetes (27–83 %) and hypertension (35–64 %) [526,548–552] Gender/sex differences should be taken into account when these risk factors are present. Although there are few reports in Japan on coronary risk factors in young myocardial infarction patients, a report from the J-PCI registry of first-time PCI patients indicates that coronary risk factors differ by sex and age group [553]. For primary prevention in young myocardial infarction patients, education and therapeutic intervention targeting each coronary risk factor, taking sex and age into consideration, are important, and further study is needed.

BK24. Age-Related Differences in Prognosis of Asymptomatic Atrial Fibrillation (AF)

Nearly half of all cases of AF are asymptomatic and AF is diagnosed incidentally through screening tests or implantable cardiac devices. Recently, it becomes possible to detect AF using portable ECGs, long-term ECGs, and smartwatches. In clinical practice, asymptomatic AF is often newly detected during stroke treatment. Therefore, early detection, clinical course, treatment and prognosis of asymptomatic AF have received increasing attention in recent years. Although there have been no previous studies investigating the effect of age on the prognosis of asymptomatic AF, we draw on the results of previous studies as described below.

Multiple studies have elucidated that the cardiovascular risk of AF patients increases with age. A study comparing the prognosis of younger (aged 65–74 years) and older (≥75 years) AF patients showed that the risk of all-cause death and major adverse cardiac events were 2.9- and 2.2-fold higher in the older group [554]. Another study of patients with isolated AF reported a 1.7-fold increase in all-cause death, a 2.1-fold increase in heart failure (HF), and a 2.4-fold increase in stroke for each 10-year increase in age at diagnosis [555].

In asymptomatic AF patients, the proportion of older patients (≥66 years) was reported to be 70 % [556]. The Fushimi AF Registry revealed that the mean age of patients with asymptomatic paroxysmal AF was older than that of those with symptomatic paroxysmal AF, and the risk of stroke and all-cause mortality was higher with asymptomatic AF [557]. There exist many studies comparing the prognosis of symptomatic and asymptomatic AF, and the results have been conflicting (worse in asymptomatic AF [558,559], comparable [556,560] and better [561]). Two meta-analyses examined the prognosis of symptomatic and asymptomatic AF, and found no difference in all-cause or cardiovascular death, and stroke embolism [562,563]. In the 10 studies included in these meta-analyses, the age distributions of asymptomatic and symptomatic AF were similar (asymptomatic: 53–76 years, symptomatic: 53–74 years).

According to these results, asymptomatic AF has a similar age distribution and clinical outcomes as symptomatic AF, and age seems to be a prognostic factor in patients with asymptomatic AF.

CQ7. Should Ablation Therapy for Asymptomatic AF in Young Patients Be Highly Recommended?

Recommendation

Performing ablation therapy for asymptomatic AF in young patients is recommended.

(Agreement rate: 95.7 %; Level of Evidence: C)

Commentary

It has been reported that the prognosis of patients with asymptomatic AF is worse than that of patients with symptomatic AF [558,559]. On the other hand, meta-analyses have shown no difference in prognosis [563].

Previously, AF ablation therapy was indicated for improving patients' quality of life, and so the indication for AF catheter ablation (CA) has been limited to symptomatic AF patients [564]. Since then, evidence has accumulated that AF ablation improves prognosis with or without symptoms [565].

Several studies have reported on the efficacy and safety of CA for asymptomatic AF. Some have reported that ablation therapy for asymptomatic cases was as safe and effective as for symptomatic cases, while others reported that it was less effective than for symptomatic cases [566,567]. A subanalysis of the CABANA trial reported in 2020 found that ablation prevented recurrence of AF as well as medical therapy, with or without symptoms [568].

Furthermore, a subanalysis of the EAST-AF NET 4 trial in 2021, which reported improved outcome with early rhythm control interventions including AF ablation, showed no difference in the clinical benefit of early rhythm control between asymptomatic and symptomatic patients [569].

There are also several reports that ablation for asymptomatic AF improves quality of life and exercise capacity [570,571]. Therefore, it is important to evaluate symptoms more carefully, as patients may find themselves symptomatic after ablation even if they themselves think they are asymptomatic.

The Arrhythmia Non-pharmacologic treatment guidelines (revised 2018) [572] includes a section on CA therapy for asymptomatic AF

and classifies this procedure as Class IIb because there are no randomized controlled trials (RCTs) that have examined the risks and benefits of CA for asymptomatic AF.

A recent systematic review of AF ablation for patients with juvenile AF classified the 1548 patients who underwent AF ablation into 4 age groups (232 patients <45 years, 438 patients 45–54 years, 570 patients 55–64 years, and 308 patients ≥65 years) for comparison of the efficacy of pulmonary vein isolation. A higher rate of maintenance of sinus rhythm without antiarrhythmic drugs was reported in patients <45 years with no major complications [573]. A German ablation registry compared 593 patients under the age of 45 years with 6650 patients older than 45 years, and found that the younger patients had fewer complications, shorter hospital stays, and less recurrent AF and use of antiarrhythmic drugs after 12 months [574]. A recent report also showed that among 6336 AF patients, 82 patients younger than 30 years were more likely to be maintain sinus rhythm with fewer ablations and had no long-term adverse outcomes [575]. They report that structural heart disease is the only independent predictor of AF recurrence in HF cases [576].

The EAST-AFNET 4 trial showed that early rhythm control improves the prognosis of AF [577], and a JACC review published in 2022 also ranked rhythm control in AF as a top priority [578]. It has also been shown that the transition from paroxysmal to persistent AF is less common with ablation therapy than with oral antiarrhythmic drugs [579].

The increased morbidity and mortality associated with AF is no less in asymptomatic cases than in symptomatic cases, and the effectiveness of ablation is comparable. Additionally, ablation is reported to be more effective and safer in younger patients [580]. On the other hand, it is certainly difficult to determine the efficacy of antiarrhythmic therapy or ablation in asymptomatic patients. Considering the prevention of future adverse events in young patients, we weakly recommend aggressive ablation therapy for asymptomatic AF in young patients.

BK25. Age-Related Differences in the Risk of Sudden Death in Brugada Syndrome (BS)

About 80 % of BS patients are aged between 17 and 59 years, with few children or older patients [581]. The age distribution of first arrhythmic events (AEs) among the 678 BS surveys was: 4.3 % were <16 years, 94.2 % were 16–70 years, and 1.5 % were > 70 years [582]. This age distribution of first AEs has not been completely explained. Recently, the concept that decreased right ventricular outflow tract conduction reserve, which reportedly varies with age and sex, has been proposed as the final pathway in BS [388,394].

Whether age is a risk for sudden death in BS is inconclusive; in a number of papers evaluating risk factors for AEs in BS, multivariate analysis showed that history of cardiopulmonary arrest, syncope, and spontaneous type 1 ECG were independent risk factors, while age showed no significant difference [26,395,396]. Previous large cohort studies have not confirmed that age is an independent risk factor after adjustment for other risk factors [389].

Elderly BS patients report a lower rate of fatal AEs among those aged >60 years compared with those <60 years old [388,583,584]. Also, in an observational study of 120 BS patients, those with an implantable cardioverter defibrillator (ICD) for >8 years, the incidence of VF peaked between 30 and 39 years and decreased with age, even in high-risk patients, with no first-ever cases over 70 years of age and only 2 recurrent cases over 70 years of age complicated by ischemic heart disease [585]. BS in older patients is characterized by a higher proportion of females, less spontaneous type 1 ECGs, and a lower rate of induction of ventricular arrhythmias on electrophysiologic testing, but the risk factors for fatal arrhythmic events are unknown. In conclusion, we assume that the risk of AE occurrence decreases with age.

BK26. Considerations for Female Patients With Hypertension at Different Life Stages

1. Sex Differences in Hypertension

The prevalence of hypertension in Japan is estimated to be 43 million, with 58.1 % of males and 38.1 % of females aged 40–74 years, and 71.5 % of males and 74.5 % of females aged ≥75 years, according to the 2020 National Health and Nutrition Survey [501]. Female hypertension includes pregnancy-induced hypertension and menopausal hypertension. The prevalence of male hypertension increases with age, starting in the 30s and peaking around age 70, whereas that of young female hypertension is low and female hypertension increases rapidly in the 50s and reaches the same level as in males in the 70s [586,587].

2. Perimenopausal and Postmenopausal Hypertension

Adrenal disease and sleep apnea are more frequent in perimenopausal and postmenopausal hypertension. Increased reactivity to stress and mental instability in menopause can cause elevated blood pressure (BP) and increased BP variability [588–593]. Increased activity of both the renin–angiotensin system and sympathetic nervous system from the effects of sex hormones and increased salt sensitivity form the basis of menopausal hypertension, and sometimes of treatment-resistant hypertension.

3. Premenopausal Hypertension

Pregnancy-related gestational hypertension and hypertension not related to pregnancy are broadly classified as premenopausal hypertension. Pregnancy-related hypertension will be described in a separate section, and please refer to the Japanese Society of Gestational Hypertension Clinical Practice Guidelines 2021 [594] and the JSH 2019 hypertension guidelines [595].

In the female life cycle, hypertension usually develops after menopause, and secondary hypertension should be checked in premenopausal hypertension [596]. In premenopausal women, renal vascular hypertension, aortic stenosis, and fibromuscular dysplasia should be especially differentiated [597].

4. Medical Treatment

Drug therapy should be prescribed based on the etiology and pathophysiology of the disease. During fertile period, teratogenicity and fetotoxicity to the fetus should be considered. Although there is no consensus regarding the effect of hormone replacement therapy on BP in perimenopausal females, β-blockers are effective in relieving symptoms of sympathetic tone, such as palpitations. Calcium-channel blockers are often used, but their vasodilating effects may aggravate menopausal symptoms such as lightheadedness and headache. In the ALLHAT trial, there was no difference in stroke prevention between angiotensin-converting enzyme (ACE) inhibitors and diuretics in males, but diuretics had a greater stroke prevention effect in females [588,598,599].

2. Pregnancy

FRQ6. What Is the Recommended Prepregnancy Antihypertensive Target for Female Patients With Hypertension Who Wish to Become Pregnant?

Answer

BP control in the normal range before conception may improve maternal and neonatal outcomes, but specific targets for lowering BP are not known.

Commentary

The BP targets before pregnancy to improve maternal and infant outcomes in hypertensive female patients are not yet clear. Controlling BP to <140/90 mmHg during pregnancy was shown to improve maternal and infant outcomes without impairing infant development [600], and a subanalysis of the same study reported that antihypertensive

treatment before pregnancy may be associated with improved maternal and infant outcomes [600].

In a prospective observational study, maternal and infant outcomes were better in the group who were diagnosed with hypertension before pregnancy but did not require antihypertensive medication (<140/90 mmHg) in early pregnancy than in the group that did require antihypertensive medication, and among those who required antihypertensive medication in early pregnancy, the group with BP <140/90 mmHg in early pregnancy had better maternal and infant outcomes then the group with BP >140/90 mmHg [601]. There is a report that the risk of developing superimposed preeclampsia was higher if the patient had hypertension for >4 years prior to pregnancy [602], and it is difficult to predict when pregnancy will occur. Therefore, it is recommended that hypertensive females who wish to have a baby should be treated with antihypertensive therapy to maintain BP <140/90 mmHg before pregnancy. However, there is a lack of evidence regarding prepregnancy antihypertensive goals and future research is needed.

BK27. Recommendations for Antihypertensive Drug Use in Female Patients With Hypertension Planning Pregnancy or Currently Pregnant

Renin–angiotensin system inhibitors are contraindicated for use during pregnancy. Fetal toxicity has occurred [603], particularly with use in the second trimester and beyond, and may result in fetal renal failure, fetal lung hypoplasia, limb contractures, and cranial and facial deformities. Previous reports suggested that the teratogenic risk of these drugs is not significant; however, it cannot be completely ruled out [604]. It should be noted again that the use of these drugs is contraindicated in all trimesters of pregnancy. Also note that the β-blocker atenolol has been associated with fetal growth retardation when used during pregnancy [605].

Based on the evidence to date, the following are the major antihypertensive drugs recommended in Japan and other countries.

1. Methyldopa (CNS Depressant)

Recommended for use in all trimesters [594,595,606–608]. No increased teratogenicity has been observed with use in the first trimester [609]. In addition, follow-up of infants born to mothers who used methyldopa during pregnancy showed no apparent abnormalities [610]. Caution should be exercised with regard to drowsiness and liver dysfunction in both mother and child.

2. Nifedipine Extended-Release and Amlodipine (Calcium Antagonists)

Nifedipine extended-release agents are safe to use during pregnancy [611,612]. Some guidelines [606–608] consider nifedipine extended-release agents, as well as methyldopa and labetalol, to be among the first-line agents for pregnancies complicated by hypertension. Previous reports suggest that there is no increased teratogenicity with the use of amlodipine [613].

3. Labetalol (α1 β-Blocker)

Recommended for use in guidelines [594,595,606–608], and can be used safely throughout the entire pregnancy [614].

4. Hydralazine (Vasodilator)

The antihypertensive effect of oral drugs is not strong [615], placing this drug in the second line for long-term administration.

CQ8. When Should Antihypertensive Treatment Be Initiated for Pregnant Women With Chronic Hypertension?

Recommendation

It is strongly recommended that antihypertensive treatment be initiated for pregnant women with chronic hypertension if BP is ≥140/90 mmHg.

(Agreement rate: 95.8 %; Level of Evidence: B)

Commentary

Emerging evidence revealed that in pregnant women with mild (140/90–160/110 mmHg) chronic hypertension, targeting BP <140/90 mmHg was associated with better pregnancy outcomes than as treatment only for severe hypertension (>160/110 mmHg), with no increase in the risk of small-for-gestational-age of the children. Four RCTs [600,616–618] and 1 observational study [619] from 32 studies were re-accessed. As a benefit to the mother, antihypertensive treatment reduced the incidence of superimposed preeclampsia [600,616,618]. As for safety to the child, a higher quality study [600,617] found no difference in the incidence of small-for-gestational-age and neonatal ICU admission within 48 h of birth. In light of this, it is strongly recommended that antihypertensive treatment be initiated for pregnant women with chronic hypertension if BP is ≥140/90 mmHg. However, because of the BP reduction from early to mid-pregnancy, the patient should be carefully monitored. Excessive BP reduction may decrease uteroplacental blood flow and cause fetal dysfunction, so the dose of antihypertensive drugs should be reduced depending on BP. There is still insufficient evidence regarding for the reduction of antihypertensive agents. The main antihypertensive drugs used in the studies were methyldopa, nifedipine, and labetalol.

BK28. Secondary Prevention for Pregnant Women With Ischemic Heart Disease

In pregnancy, LDL-C, triglycerides, high-density lipoprotein-C, and lipoprotein (a) levels are higher than usual by 36 %, 170 %, 25 %, and 90 %, respectively [620], which is similar to familial hypercholesterolemia (FH) [621]. Pregnant women with a history of ischemic heart disease are at high risk, and FH patients in particular are at extremely high risk.

The use of statins in pregnancy has long been contraindicated, with the 2018 AHA/ACC guidelines [622]. The ESC 2019 guidelines [623], and the 2018 revision of the joint Japanese Cardiovascular Society/Japan Society of Obstetrics and Gynecology guidelines [624], stating that statins should be discontinued during pregnancy. However, recent reports have ruled out the teratogenicity of statins. In 2021, the FDA recommended that the maximum warning against statin use during pregnancy be removed and that statin use be avoided for normal pregnancies. Therefore, statin use during pregnancy should only be targeted to patients at very high risk, such as patients with FH homozygotes, and as secondary prevention, under the advice of an expert. Among lipid-lowering agents, anion-exchange resins can be used safely during pregnancy and lactation. Secondary prevention for severe hypercholesterolemia, such as FH, is lipoprotein apheresis, which can be safely performed during pregnancy [137].

ACE inhibitors and angiotensin-receptor blockers (ARBs) are also contraindicated in pregnancy. Aspirin can be safely administered [625].

BK29. Stroke Associated With Pregnancy and Delivery

The incidence of maternal stroke is roughly 3-fold higher in young individuals compared with general stroke rates [626]. In Japan, it affects 10.2 per 100,000 live births, primarily as hemorrhagic stroke (73.5 %), followed by ischemic (24.5 %) and mixed types (2 %). Hemorrhagic strokes are often linked to cerebral aneurysms (19.8 %), cerebral arteriovenous malformations (17.1 %), and pregnancy-related risks such gestational hypertension (11.7 %) and HELLP syndrome (8.1 %). In contrast, in ischemic strokes, specific pregnancy-related background diseases are associated, primarily including reversible cerebral vasoconstriction syndrome (24.3 %), venous infarction (24.3 %), and blood coagulation abnormalities (16.3 %) [627]. Migraine headaches also contribute to maternal stroke risk [628]. Approximately 50.5 % of cases occur during pregnancy [628], 14.4 % during delivery, and 35.1 % postpartum [627]. Poor prognosis (mRS3 or higher) is 39.6 % hemorrhagic, 16.2 % ischemic, with worse outcomes in hemorrhagic strokes, especially with pregnancy-induced hypertension and HELLP [627]. Treatment lacks

robust evidence due to exclusion of pregnant females from clinical trials [629], necessitating personalized risk–benefit assessments. National and international guidelines, as well as expert opinions, sporadically recommend considering thrombectomy on a case-by-case basis [629,630].

FRQ7. Is Cardiovascular Follow-up Recommended for Female Patients Who Develop Obstetric Complications?

Answer

Obstetric complications, such as hypertensive disorders in pregnancy (HDP) or gestational diabetes, are one of the predictors of future CVD. It is important to explain that and to provide lifestyle health guidance and a close examination of lifestyle-related factors within 1 year after delivery. Although the effect of primary prevention of CVD by continuous follow-up by cardiologists after 1 year postpartum is not known, continuous home BP monitoring and lifestyle guidance by health workers are useful for early diagnosis of lifestyle-related diseases.

Commentary

Pregnant females with complicated HDP face higher risks of cardiovascular complications, such as perinatal stroke, MI, cardiomyopathy, and aortic dissection. Moreover, they have increased susceptibility to long-term lifestyle-related and cardiovascular diseases [594]. The incidence of hypertension is 2–5-fold higher, coronary artery disease (CAD) 1.5–2.5-fold higher, stroke 1.5–2-fold higher, HF 1.5–4-fold higher and cardiomyopathy twice as high in females with HDP compared with those without this complication [631,632]. Gestational diabetes also elevates the risk of type 2 diabetes and CVD, with or without type 2 diabetes development [633]. Even within the first 10 years postpartum, females with gestational diabetes have about twice the rate of CVD than those without complications. Other obstetric complications, such as placental abruption [631,634], preterm delivery [631,634,635], stillbirth [634] and fetal growth retardation [631,635,636], increase the risk of subsequent CVD, especially ischemic heart disease and stroke, when compared with uncomplicated pregnancies.

To prevent future cardiovascular events, postpartum female patients with obstetric complications should be informed about the predictive nature of these complications and receive guidance on smoking cessation, adopting a healthy lifestyle, maintaining a proper weight and undergoing cardiovascular risk assessments [637]. It is advisable to visit a medical institution between 13 weeks and 1 year postpartum for an evaluation of lifestyle-related factors such as BMI, BP and lipid glucose metabolism [638]. Small studies have shown that such guidance and consultations can improve lifestyle and weight control [639].

The effectiveness of ongoing cardiovascular care beyond the first year postpartum in the primary prevention of CVD among females with obstetric complications remains uncertain. Recent RCT results indicate that home BP monitoring in women over 40 years of age with a history of preeclampsia or HELLP syndrome can improve the diagnosis and management of hypertension [640]. Hence, maintaining health management, including home BP monitoring and regular checkups, is recommended even after the first year postpartum.

Postpartum, female patients often have limited access to medical visits due to childcare responsibilities [641]. Therefore, RCTs focusing on online guidance interventions have been conducted among those with a history of obstetric complications within 4–5 years, as they may be effective in improving lifestyle and overall well-being [642,643].

3. Old Age

CQ9. Should Age Be Considered in the Treatment of Pulmonary Arterial Hypertension (PAH)?

Recommendation

It is recommended that age should be considered in the treatment of PAH, as it has been reported that older patients may have less prognostic benefit and more side effects than younger patients.

(Expert Consensus)

Commentary

An important evidence for the treatment of PAH in the older was presented on the COMPERA registry study, which enrolled European patients with pulmonary hypertension. PAH patients enrolled in the COMPERA registry were analyzed in clusters: Cluster 1: middle age (median 45 years) non-smokers with diffusing capacity for carbon monoxide (DLCO) ≥45 %; Cluster 2: older (median age 75 years) female with nonsmoking, DLCO ≥45 %, hypertension, CAD, diabetes, and body mass index (BMI) ≥30 (left heart phenotype); and Cluster 3: older male with history of smoking, low DLCO, and hypertension. Clusters 2 and 3 were classified as having a poorer response to pulmonary vasodilator therapy than Cluster 1, and were mainly treated with monotherapy, indicating a poor prognosis [644]. Cluster 1 is consistent with the clinical picture of classic idiopathic PAH, whereas clusters 2 and 3 are different from classic idiopathic PAH, with a high proportion of older patients. Analyses of the COMPERA registry and the ASPIRE registry for the UK Pulmonary Hypertension Study showed that the group of idiopathic PAH with a predicted DLCO <45 % (lung phenotype) had a poor response to treatment with pulmonary vasodilators, similar to patients with group 3 pulmonary hypertension [645]. Patients with a predicted DLCO <45 %, which is more common in older patients than in younger patients, should be considered for monotherapy, especially if they also have pulmonary veno-occlusive disease and ventilation-perfusion mismatch, and there are concerns about pulmonary edema complications and side effects such as hypoxemia caused by pulmonary vasodilators.

Based on the evidence from these registry studies, the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, revised and published in 2022, proposed a treatment algorithm that determines whether to choose monotherapy or combination therapy in the initial treatment of PAH, based on an assessment of whether the patient has cardiopulmonary comorbidities [297], defined as hypertension, obesity, diabetes, CAD, and mild pulmonary parenchymal impairment (a predicted DLCO <45 %) (recommended Class IIb). Although age is not included in the definition of cardiopulmonary comorbidities in these European guidelines, evidence from registry studies indicates that older patients with PAH often have cardiopulmonary comorbidities. Thus, the consideration of age in the treatment of PAH in the older patient is recommended, as it requires an accurate assessment of the patient's general condition with respect to the presence of cardiopulmonary comorbidities.

CQ10. Which "Physical Frailty Assessment" Is Recommended as a Prognostic Indicator for Older HF Patients in Japan?

Recommendation

We strongly recommend the use of the J-CHS criteria, walking speed, grip strength, 6-minute walking distance, and short physical performance battery (SPPB) for "assessment of physical frailty" as prognostic indicators for older HF patients in Japan.

(Agreement rate: 91.3 %; Level of Evidence: B)

Commentary

Frailty is a state of reduced physical reserve and susceptibility to physical dysfunction and is considered to be a condition that falls between independence and the need for nursing care [646].

a. J-CHS Standards

The phenotypic model of physical frailty widely used internationally is the Cardiovascular Health Study (CHS) criteria [647]. The Japanese translation is the J-CHS criteria, which are evaluated by 5 items: (1) weight loss, (2) muscle weakness, (3) fatigue, (4) slow walking speed, and (5) decreased physical activity [648]. In Japanese older HF patients, the 1-year all-cause mortality rate is significantly higher in the physical frailty group assessed by the J-CHS criteria at the time of hospital discharge [649–651].

b. Walking Speed (Normal Walking Speed)

A normal walking speed of <0.8 m/s is defined as a slow walking speed. In Japanese older HF patients, particularly those with preserved ejection fraction (HFpEF), 1-year and long-term mortality rates are associated with a slow walking speed [652,653]. Furthermore, slow walking speed also predicts low performance of activities of daily living (ADL) at hospital discharge [654]. There is no consistent view on the relationship between gait speed and death or rehospitalization in patients with HF with reduced ejection fraction (HFrEF), and further research is needed.

c. Hand Grip

Hand grip strength is a simple indicator of muscle strength that can be easily measured and is an estimate of whole-body muscle strength [655]. The reference values for grip strength used to determine sarcopenia in Asia are <28 kg for males and < 18 kg for females [656]. Low hand grip strength has been associated with 1-year mortality rates in elderly older Japanese HF patients [8].

d. 6-Minute Walk Test

This test measures the total distance walked in 6 min on a 30-m walking path and positively correlates with maximal oxygen uptake in HF patients [657]. In Japanese elderly older HF patients, the 1-year all-cause mortality and HF rehospitalization rates are higher in the group with a short 6-minute walk (<242 m) than in the group with a long walk (≥242 m) [658,659].

e. Short Physical Performance Battery

The SPPB consists of 3 items (0–4 points each) in the balance test, walk test, and rise test, with a total score ranging from a minimum of 0 to a maximum of 12, with higher scores indicating higher performance [660]. The 1-year all-cause mortality and HF rehospitalization rates are higher in the low SPPB group (0–6 points) than in the high SPPB group (7–12 points) [658].

CQ11. Which "Assessment of Mental and Psychological Frailty" Is Recommended as a Prognostic Indicator for Older HF Patients in Japan?

Recommendation

The Mini-Mental State Examination (MMSE), Mini-Cog, and 5-item Geriatric Depression Scale (5-GDS) are strongly recommended for "assessment of mental and psychological frailty" as prognostic indicators for older HF patients in Japan.

(Consensus rate: 90 %, Level of Evidence: C)

Commentary

Frailty includes physical frailty, psychiatric/psychological frailty, and social frailty. Psychiatric/psychological frailty refers to the mental and psychological aspects of frailty, such as cognitive dysfunction, depression, and anxiety. Cognitive function tests and psychological tests are used to evaluate psychiatric and psychological frailty.

a. Mini-Mental State Examination

The MMSE is a 30-point cognitive function test consisting of 11 items: time registration (5 points), place registration (5 points), immediate recall (3 points), calculation (5 points), delayed playback (3 points), item name (2 points), sentence recitation (1 point), verbal instructions (3 points), writing instructions (1 point), spontaneous writing (1 point) and graphic imitation (1 point). The higher the total score, the better the cognitive function [661]. In a multicenter study of elderly older HF patients aged ≥75 years in Japan, it was reported that MMSE ≤23 points was significantly associated with all-cause death [662].

b. Mini-Cog

The Mini-Cog is a simple 5-point cognitive function test that combines immediate recall, delayed recall (3 points), and clock drawing (2 points) [663]. It has been reported that Mini-Cog ≤2 points is significantly associated with all-cause death [662], and that the addition of mental and psychological frailty assessed by Mini-Cog to physical frailty is associated with significantly higher rates of all-cause death and readmission due to worsening HF at 1 year after hospital discharge [651].

c. 5-Item Geriatric Depression Scale

The 5-GDS is a 5-point scale for assessing geriatric depression consisting of 5 questions about depressed mood (but not including items about physical symptoms [664]. In a national multicenter prospective cohort study, coexistence of physical frailty and psychiatric/psychological frailty assessed by MMSE <26 points or 5-GDS >2 points was associated with increased rehospitalization and all-cause death due to worsening HF within 2 years of onset [665].

CQ12. Should Age Be Considered in Determining the Indications and Procedures for Standby Abdominal Aortic Surgery (Including Endovascular Treatment)?

Recommendation

It is recommended that age and the patient's preoperative condition (e.g., frailty) be fully considered in determining the indication and procedure for standby abdominal aortic surgery (including endovascular treatment) for patients older than 80 years.

(Consensus rate: 90.4 %, Level of Evidence C)

Commentary

Because most patients with aortic aneurysms are asymptomatic, the goal of aortic aneurysm surgery is to prevent rupture and improve life expectancy. The introduction of endovascular aortic aneurysm repair (EVAR) has contributed to the expansion of indications to high-risk patients who were previously considered off-limits to artificial vessel replacement, but its significance in older patients, whose life expectancy is limited, is debatable. In this CQ, we examined the evidence to determine whether age should contribute to patient stratification in determining the indications and procedures for standby abdominal aortic surgery in the older patient.

Although the goal of treatment of asymptomatic aortic aneurysms is to prevent rupture and prolong life expectancy, the maintenance of patient quality of life cannot be overlooked. In the systematic review, we evaluated the outcomes of survival, length of hospital stay, complication rate, maintenance of ADL, and maintenance of cognitive function.

A 5-year registry study of EVAR cases found that although 30-day mortality (1.4 % vs. 1.2 %, $P = 0.85$) and major adverse event rates (5.2 % vs. 3.6 %, $P = 0.23$) did not differ significantly between those over and under 80 years of age, age ≥ 80 was significantly associated with all-cause death on multivariate analysis [666]. A meta-analysis of 9 observational studies of EVAR for patients aged ≥80 years found significantly higher 30-day mortality (2.7 % vs. 1.5 %, $P < 0.001$) and mid-term mortality rates [667]. Also, in a review of 124,869 cases from the US Nationwide database, EVAR-related death, length of hospital stay, and discharge to a nursing facility increased with each decade of age [668]. Although not many studies have examined patients in their 90s, a systematic review of 6 observational studies found a 5 % 30-day mortality rate, complication rate of 22 %, and survival rates at 1, 3, and 5 years of 82 %, 56 %, and 17 %, respectively [669]. Although surgical outcomes in these older patients are poorer than in younger patients, many reports consider them acceptable (if not outweighed by the benefit of avoiding ruptured aneurysms), suggesting that careful stratification based on individual patient prognosis is more important in older patients.

For example, in an observational study of EVAR in patients aged ≥80 years stratified by ASA-PS score (American Society of Anesthesiologists-Physical Status: a preoperative physical status score by the American

Society of Anesthesiologists) [670], the perioperative mortality rate was significantly higher in patients with an ASA score ≥ 4 and peripheral arterial occlusive disease. However in other patients without these factors, EVAR was justified in terms of both perioperative and 5-year survival, even in the age range of 80 years.

With regard to procedure selection, given that several observational studies showed no difference in 30-day mortality rates between EVAR and open replacement in older patients in their 80s and a high reintervention rate in the EVAR group [671], advanced age is not an immediate contraindication to open surgery. However, considering the complication rate and postoperative hospital stay, as well as ADL maintenance, age may be a rationale for prioritizing EVAR in surgical selection [672]. Although there are no RCTs restricted to older patients, it is clear that EVAR is useful in reducing perioperative risk, especially in high-risk cases, as already reported in a large RCT of all ages [673]. It is important to fully evaluate anatomical compatibility and preoperative risk before making a case-specific surgical choice.

In the older cohort, even if perioperative risks can be avoided, it will take time for ADL that have declined during surgery to return to preoperative levels [672]. It is necessary to consider how this decline in ADL will affect life expectancy. The patient's and family's views on life and consensus-building are essential in determining whether the primary goal of avoiding the imminent risk of rupture is justified at the expense of ADL deterioration.

Although the appropriateness of standby abdominal aortic surgery in older patients should be judged on the basis of the potential short-term survival benefit, advanced age should not be the sole basis for excluding appropriate candidates for surgical intervention. However, patient stratification is even more important, and the choice of procedure should fully take into account the patient's preoperative condition, including frailty, maintenance of quality of life, and the patient's wishes and outlook on life.

BK30/GPS. How to Implement Advance Care Planning (ACP) for Patients With Cognitive Impairment and CVD

ACP is a process in which patients, their families, and healthcare professionals have discussions in advance to prepare for future changes, with the goal of supporting patient decision-making and consolidating future medical treatment and care in line with the patient's views and wishes [674,675]. Although ACP is recommended as Class I in the Guidelines for the treatment of acute and chronic HF by the Japanese Society of Cardiology/Japan Heart Failure Society [676], it is not yet sufficiently widespread in its implementation. Especially for end-of-life care of older patients, it is important to conduct multidisciplinary conferences and ACP before loss of cognition. On the other hand, superficial acquisition of DNAR (do not attempt resuscitation) instructions should never lead to the abandonment of essential life-saving procedures.

Cognitive dysfunction includes dementia, mild cognitive impairment (MCI), delirium, and depression, and these are caused by various pathological conditions. In particular, patients with CVD often suffer from cognitive decline against a background of stroke, HF, etc.

In a previous report, 25–75 % of patients with HF have cognitive dysfunction, which is related to (1) the effects of complications such as hypertension, diabetes mellitus, electrolyte and metabolic abnormalities, and infectious diseases, and (2) hemodynamic stress caused by HF and decreased cerebral blood flow due to decreased cardiac output and bradycardia [677]. Some of these factors improve with treatment of the underlying disease, and it is necessary to support decision making while knowing that cognitive decline is not necessarily irreversible [678].

The more severe the HF, the higher complication rate of cognitive dysfunction, so ACP should be started as early as possible so the patient can fully discuss treatment options with family members and healthcare providers. It may be necessary to provide encouragement to help the patient understand, depending on the degree of cognitive impairment. In the case of severe cognitive dysfunction, the patient's will should be inferred through discussion with family members and their giving of consent should be supported on behalf of the patient [679–681].

IV. Race and Ethnicity

BK31. Differences in the Development of Cardiovascular Disease (CVD) by Race

Racial differences in the development of CVD were examined for ischemic heart disease and cerebrovascular disease, respectively.

1. Ischemic Heart Disease

Ischemic heart disease (myocardial infarction (MI) and angina pectoris) is one of the leading causes of death worldwide. Therefore, much knowledge has been accumulated on its treatment and prevention. However, its prevalence is known to vary by race. In Japan, though the prevalence of this disease has been increasing due to the westernization of lifestyles, it is still low compared to the prevalence in Europe and the USA. One reason for this difference is considered to be genetic factors. A genome-wide association study (GWAS) published in 2020 [682] identified 18 disease susceptibility loci, including 1 newly identified region, based on analysis of data from approximately 50,000 individuals in the Japanese population. Furthermore, a meta-analysis integrating these data with GWAS analyses of a Western population of approximately 340,000 people in the USA and Europe identified 76 disease susceptibility loci, including 3 new regions. The effects of these 76 regions on the development of MI showed racial differences in some regions, suggesting the possibility of racial differences in genetic factors in the development of ischemic heart disease.

2. Cerebrovascular Disease

Cerebrovascular disease is the 4th leading cause of death in Japan. Although the number of deaths from cerebrovascular disease is decreasing, the rate of cerebrovascular disease has more than doubled from 118 deaths per 100,000 population in 1970 to 279 in 2005. In contrast to many Western countries, the mortality rate from stroke in Japan is higher than that from ischemic heart disease. Cerebral infarction, which accounts for 70–80 % of cerebrovascular disease, is classified as cardiogenic cerebral embolism, lacunar infarction, and atherothrombotic cerebral infarction. In general, atherothrombotic cerebral infarction and lacunar infarction are suggested to be associated with lifestyle-related diseases including hypertension, while cardiogenic cerebral embolism is associated with arrhythmia such as atrial fibrillation (AF). A genetic factor is suspected to be responsible for the high incidence of cerebral infarction in Japan. Moyamoya disease, which is recognized in East Asians, including Japanese, is a disease that causes severe stenosis or occlusion of the bilateral internal carotid arteries due to occlusion of the arterial rings of Willis and is designated as an intractable disease. The cause of the disease is unknown, but a genetic predisposition is suspected due to the familial nature of the disease, and a polymorphism of the ring finger protein 213 (RNF213) gene, Arg4810Lys, has been reported as a disease susceptibility gene [683]. In addition, this polymorphism was recently reported to increase the odds ratio of atherothrombotic stroke to 3.58 [684]. A European study did not identify this polymorphism in stroke victims, suggesting that it is a stroke subtype unique to East Asians, including Japanese. In addition, a recently reported GWAS analysis of “cardiogenic cerebral emboli” and “lacunar infarction” identified 35 new disease-susceptibility regions associated with AF [685].

BK32. Differences in Standard Values for Cardiovascular Tests by Race

For electrocardiography and echocardiography, studies including Japanese individuals provide evidence that racial differences are

present. For other tests, sufficient epidemiological data on Japanese subjects are not available as of this writing.

1. 12-Lead ECG

It was reported in 1946 that biphasic or negative T waves in precordial leads were more common in African American people [686], and in 1954, 22 % of healthy African people was reported to have ECG findings that were considered abnormal [687]. Mansi et al. analyzed ECG recordings from Saudi Arabian, Indian, Jordanian, Sri Lankan, Filipino, and Caucasian populations and found differences between groups, specifically in Sokolow-Lyon potentials and early transition patterns in males [688,689]. On the other hand, they found no differences in PR interval, QRS duration QT interval, P-axis, and QRS axis in males, and differences in QRS duration, P-axis, and QRS axis in female, but concluded that there was no clinical utility in these findings [688,689]. A cohort study in Hawaii (the Kohara Health Research Project) analyzed 1415 resting 12-lead ECGs and found that Japanese and Hawaiian people had significantly longer QTc interval than Caucasian subjects [690].

2. Standard Values for Echocardiography

It is evident that there are differences in physical attributes such as average height and weight between by Race. Ventricular size is among them [691,692], therefore it is imperative to derive standard values for Japanese patients from measurements obtained from the Japanese population [693].

BK33. Differences in Drug Metabolizing Enzyme Activities by Race

Individual differences in drug metabolism are not simply due to genetic differences in drug-metabolizing enzymes, but can be influenced by various factors such as age, sex, and diversity among populations (environmental factors, diet, lifestyle, etc.). Underlying diseases and interactions with other medications can further influence these pharmacokinetic changes. Because of individual differences in drug efficacy and adverse drug reactions, this issue is gaining attention in the realm of "personalized medicine", or "tailor-made medicine". In particular, hepatic metabolizing drugs are affected by individual differences in drug metabolizing enzyme activities (e.g., cytochrome P450 (CYP)). Among the CYP enzymes that metabolize cardiovascular drugs, CYP2C19, CYP2C9, and CYP2D6 have diminished or flawed activity due to genetic mutations. For example, clopidogrel is primarily metabolized by CYP2C19, which possesses the *2 and *3 polymorphisms known for lacking enzyme activity. These polymorphisms are prevalent in Asians, with almost 50 % of Japanese individuals reporting them, whereas 80 % of Caucasian exhibit the normal form [694]. This suggests potential racial differences in the efficacy of clopidogrel.

Warfarin and angiotensin II receptor blockers are metabolized by CYP2C9. CYP2C9*2 and CYP2C9*3 gene mutations decrease CYP2C9 activity and Vitamin K epoxide reductase (VKOR) activity, and the VKORC1-1639G>A gene polymorphism affects the optimal dosage of warfarin and may contribute to individual differences in its effectiveness [695]. Many direct factor Xa inhibitors are metabolized by CYP3A, and significant individual differences exist in CYP3A4 activity, a key enzyme in the metabolism of numerous drugs, especially those for CVD. Although some studies have highlighted racial differences in CYP3A4 activity [696], the evidence regarding racial disparities in responses to direct factor Xa inhibitors remains inconclusive.

Drugs metabolized by CYP2D6 include hepatic metabolic blocking agents and antiarrhythmic drugs. Approximately 10 % of Westerners have a CYP2D6 deficiency, a rate notably higher than in Japanese and Chinese populations where it is <1 %. This deficiency can affect the pharmacokinetics of metoprolol, propafenone, flecainide, mexiletine, and others [697].

V. Diversity in Social Determinants of Health and Well-Being

1. Overview of Social Determinants of Health

1.1 Introduction

Social determinants of health (SDOH) play a crucial role in the onset and prognosis of cardiovascular disease (CVD), alongside genetic and lifestyle factors. The "Health Japan 21" initiative emphasizes reducing health disparities by enhancing the social environment. Local efforts, such as creating communities that inherently support health, are gaining traction. However, the importance of the SDOH is often overlooked in the clinical setting. This guideline aims to enhance understanding of SDOH regarding CVD, urging healthcare professionals to be informed and proactive, ultimately improving healthcare quality.

This chapter consists of a general overview and individual sections. The overview shares the following information:

- Definition of SDOH
- Importance of SDOH in the cardiovascular field
- Approaches to interventions regarding SDOH.

The 5 major domains of the SDOH, as indicated in Healthy People 2020/2030 in the USA are (1) economic stability, (2) education access and quality, (3) social and community context, (4) Health Care Access and, (5) neighborhood and built environment (Fig. 7) [698]. The individual sections will cover a list of 10 BK (BK34–43) that are considered important concerning these 5 major domains of the SDOH.

SDOH factors correlate with the onset of CVD and the prognosis of patients with CVD. Although integrated community-level approaches, such as tobacco tax schemes and social prescribing, are starting to show evidence as intervention methods, we believe there is insufficient evidence to recommend them to physicians in actual clinical practice.

Note: The NI-HON-SAN study showed that Japanese-Americans in Hawaii and San Francisco have higher cardiovascular mortality rates than those in Japan, suggesting lifestyle and environmental factors, not just genetics, play a significant role in cardiovascular health [698].

1.2 Definitions of Social Determinants of Health

SDOH is a relatively new term, but the relationship between social stratification, particularly poverty, and ill health, has been long debated. The Black Report" [699] and the "Whitehall II Study" released in the UK in the 1980s [700] revealed that occupational status influences mortality rates even within non-poverty employment hierarchies. This highlighted that social stratification is not only a concern for the impoverished; it affects everyone in society. Recent global studies have underscored the attention needed for "health disparities" arising from non-medical and social determinants. These factors, leading to health disparities, are called the SDOH. The social factors are significant, and medical aspects are estimated to have minimal involvement in preventable deaths [701,702].

The World Health Organization (WHO) defines the SDOH as "The conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life." [703–705] Although this guideline provides commentary based on this definition, there is no uniform definition of SDOH [706,707]. The term itself is an abstract concept that does not represent independent discrete elements but comprehensively expresses interrelated and multilayered environmental factors.

The SDOH can be categorized into more specific domains or topics, and this guideline will adhere to the five domains outlined in Healthy People 2020/2030. It is important to emphasize the interconnectedness and layered relationships within these classifications.

Interpreting the term "determinant" must be approached with caution, as SDOH are probabilistic and do not guarantee a direct cause-and-effect relationship [708]. Recognizing the role of SDOH highlights the need for healthcare professionals to avoid solely blaming patients for

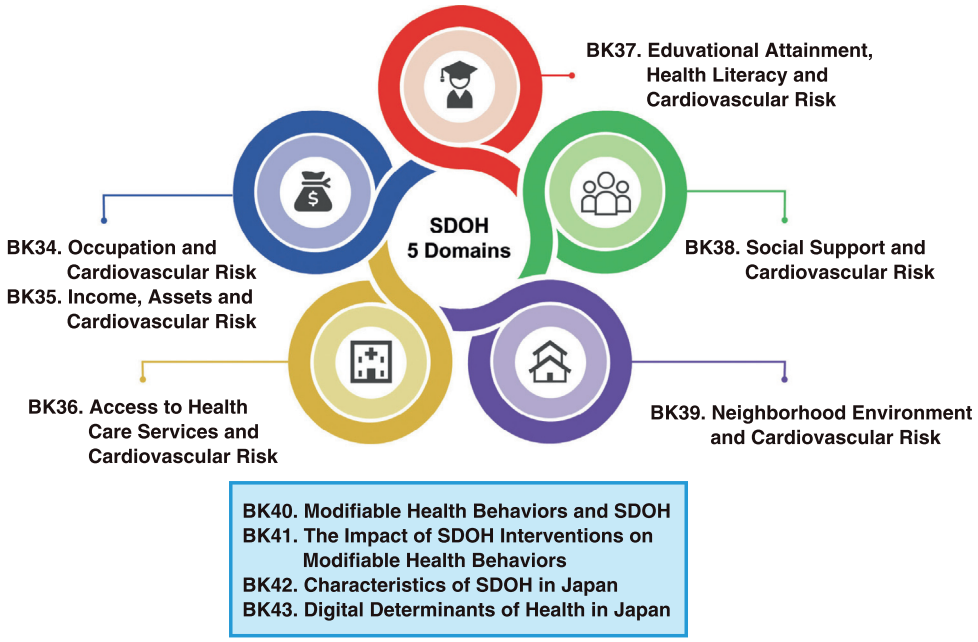


Fig. 7. Five domains of the social determinants of health and the BK (Background Knowledge) in this guideline. (Source: Prepared based on Healthy People 2010 [710].).

CVD. Instead, providing appropriate support and tailored interventions based on each patient's specific SDOH context is critical. For instance, rather than experience poor health, it is more accurate to understand that they have a higher likelihood of facing health challenges.

1.3 WHO Framework and Conceptual Models

As discussed, SDOH is a comprehensive concept. Each factor or determinant does not operate in isolation, but it is assumed that multiple determinants interact with each other to influence the risk of CVD. The WHO's framework offers an alternative categorization that is believed to be useful for understanding this concept (Fig. 8) [709]. Within this framework, SDOH is divided into structural determinants (social determinants of health inequalities) and intermediary determinants (social determinants of health). For example, income and education are structural determinants, whereas behaviors, biological factors, physical environments, and modifiable health behaviors (e.g., smoking, drinking, diet, and sleep) are some of the intermediary determinants. In the clinical setting, intermediary determinants are relatively easy to visualize and sometimes intervened upon. Furthermore, the framework indicates that macro-level decisions, such as policies addressing structural determinants, can influence CVD itself and are potentially important when considering health disparities.

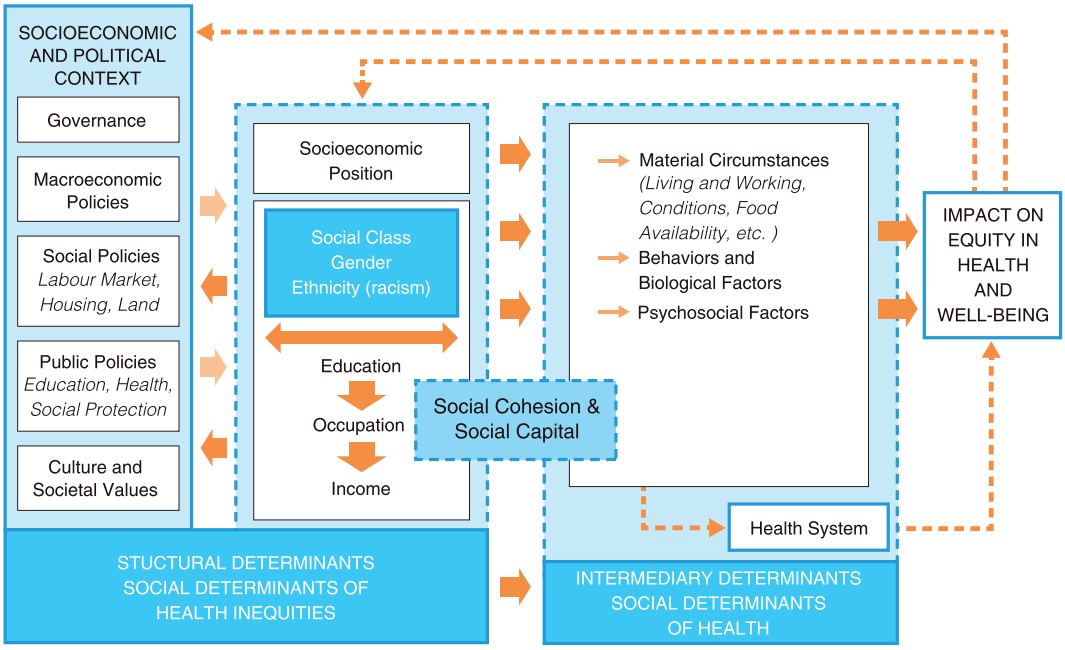


Fig. 8. WHO framework for the social determinants of health. (Adapted from WHO. 2010 [709].).

1.4 Practical Approach in Assessment and Intervention

The SDOH are multifaceted and their interplay is complex. Therefore, when screening and addressing SDOH, it is essential to consider available social systems, community resources, and welfare services. There is insufficient evidence to broadly recommend interventions for SDOH across diverse clinical settings. Similarly, there is not a consistent opinion on how to conduct SDOH screenings. Even within the United States Preventive Services Task Force (USPSTF), there is no uniform view on when and whether screenings should be performed. As a result, this guideline refrains from providing a definitive recommendation. Nonetheless, it is crucial to have a thorough understanding of (1) the various screening methods, and (2) the diversity of possible intervention strategies.

Therefore, these topics are now discussed in detail.

Screening Methods

The U.S. Centers for Disease Control and Prevention recommends assessing SDOH to achieve equitable health outcomes [710]. However, according to the systematic review, there is no standardized, one-size-fits-all screening tool [711]. Tools such as the "Health-Related Social Needs Screening Tool" and "PRAPARE Implementation and Action Toolkit" exist for SDOH assessment. In Japan, few institutions comprehensively evaluate SDOH, and there is insufficient evidence and infrastructure to advocate its broad implementation [712]. The importance of SDOH screening regarding CVD will be considered in future guidelines.

Diversity of Intervention Methods

There is also no standard approach for intervening in SDOH-related health disparities. Solutions require broader community and societal involvements beyond just healthcare institutions. Interventions range from macro-level policies such as tobacco and sugar taxes and social prescriptions, which connect individuals to community resources, to micro-level personal health strategies, with meso-level community-focused initiatives in between.

Additionally, educating healthcare professionals on SDOH is essential. Some examples are introduced in BK41. Interventions on SDOH. Resources, such as the one from the College of Family Physicians of Canada, are expanding. In Japan, SDOH is incorporated into the core medical education curriculum, with an increasing expectation for professionals and researchers to enhance their understanding and research of SDOH to improve the quality of cardiovascular care.

2. Parameters in Individual Life

BK34. Occupation and Cardiovascular Risk

Various aspects of occupation, such as job type [724,725], employment grade [726] and status [727–732], working hours [733,734], and shift work [735–738] have been reported as associated with risk factors for CVD. The mechanism of this association may involve work-related stress. Work stress is defined by the WHO as "the response people may have when presented with work demands and pressures that are not matched to their knowledge and abilities and which challenge their ability to cope" [739]. Work stress is considered a form of psychosocial stress and has been shown to influence the onset and exacerbation of CVD and the prognosis of CVD patients.

Neuroendocrine responses are involved in the mechanisms by which work stress can lead to CVD (Fig. 9) [740–749]. However, assessing work stress is challenging because of its subjectivity and the difficulty associated with synthesizing its significant components into comparable metrics. Therefore, simplified frameworks have been developed that can evaluate this abstract concept objectively; for example, the Job Strain model [750,751], the Effort-Reward Imbalance model [752,753] and the Organizational Justice model [754–756]. Of these, many studies using the Job Strain model have been reported because it evaluates job stress in terms of job demand and discretion (job control).

Collectively, no consensus has been reached on the association between occupational aspects and risk factors for and development of CVD, as negative associations have also been obtained depending on the subject, time period, and research method.

BK35. Income, Assets and Cardiovascular Risk

Income affects health by enabling consumption of health-promoting environments (work, housing), food, and exercise, as well as facilitating

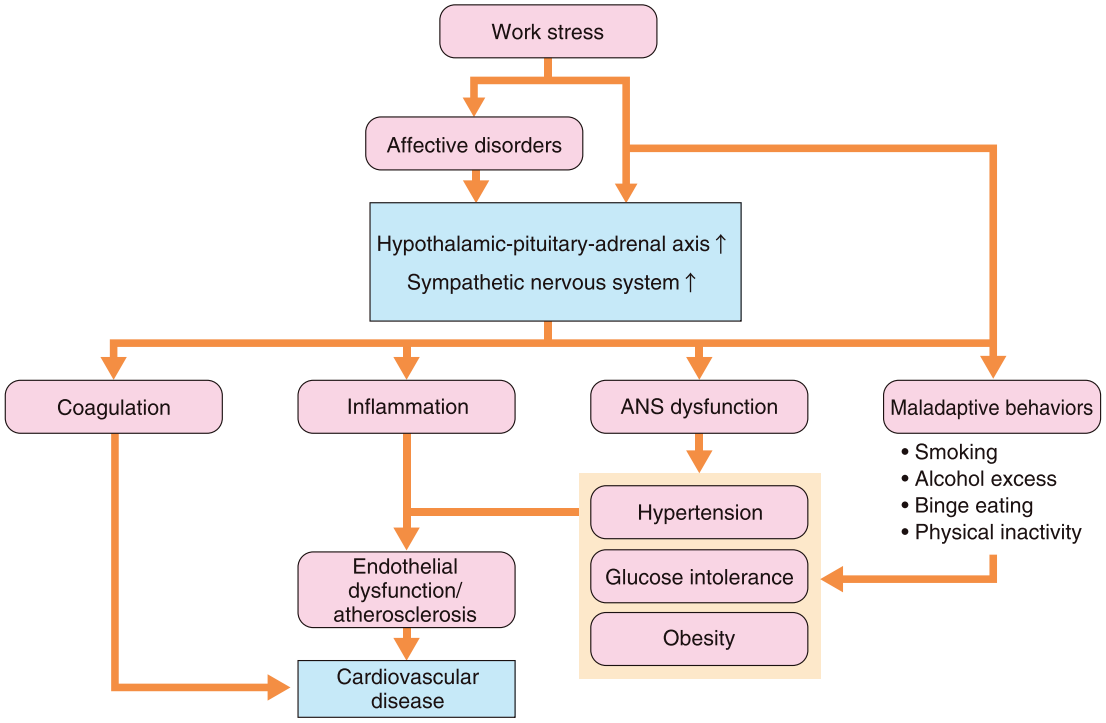


Fig. 9. Mechanism underlying the relationship between work stress and cardiovascular disease. ANS, autonomic nervous system. (Source: Prepared based on Rozanski A, et al. 2005 [740], Sara JD, et al. 2018 [741].).

access to healthcare services. Conversely, poor health may lead to reduced or lost income. Previous studies have shown that low-income individuals had a higher risk for CVD and death than high-income individuals [713,714], one reason being that low-income individuals lack adequate access to standard medical care. For example, low-income individuals are less likely to receive coronary intervention at the onset of acute myocardial infarction [715]. Low-income individuals were also less likely to receive cardiac rehabilitation after acute myocardial infarction [716] or to be prescribed guideline-recommended medications such as statins [717,718]. In addition, the prevalence of cardiovascular risks, such as obesity, hypertension, and diabetes, are higher among low-income than among high-income individuals [719,720]. Thus, many studies suggest an association between income and the risk and development of CVD.

"An individual's economic situation should be assessed not only by income but also by considering wealth, which include financial and physical assets such as housing, cars, investments, inheritances, and pension rights" [721]. Income captures the resources available during a particular period, whereas wealth reflects the accumulation of these resources. The relative importance of wealth to income changes over the life course. Changes in wealth result in changes in mental health and healthy behaviors and the amount of time spent on those behaviors. That is, they result in increased stress, smoking and drinking, and decreased leisure time physical activity, all of which are associated with increased CVD risk [722]. Thus, as with income, the main effect of wealth on health is likely to be indirect through consumption [723].

BK36. Access to Health Care Services and Cardiovascular Risk

Access to healthcare is a multifaceted concept, extending beyond mere proximity to a hospital. Levesque et al. define it as the opportunity to recognize health needs, seek and reach healthcare services, utilize them, and have those needs met [757]. This concept comprises 5 dimensions: Approachability, Acceptability, Availability and accommodation, Affordability, and Appropriateness, each corresponding to people's abilities to Perceive, Seek, Reach, Pay, and Engage with healthcare services (Fig. 10) [757].

Enhancing healthcare access holds the potential to reduce the risk of CVD and death at a population level [758]. In the acute treatment of ischemic heart disease, proximity to medical facilities with specialized care significantly affects life expectancy [759]. However, challenges such as distance, medical resources, and other factors can hinder immediate access to specialized care in certain areas. Income and health insurance coverage are also linked to healthcare access [760], although insurance alone may not uniformly affect all CVD risk factors.

In the context of Japan, the healthcare system is characterized by universal coverage and free access, making it one of the most accessible countries globally. The OECD highlights Japan's healthcare system for its 100 % insurance coverage and high patient satisfaction at 73 %, surpassing the OECD average of 71 %. Japan also boasts a high number of hospital beds per 1000 population at 12.8, significantly exceeding the OECD's average of 4.4 [761]. However, this exceptional accessibility can sometimes lead to consultations for minor ailments and inappropriate medical visits, which may encourage labor-saving practices and strain medical resources.

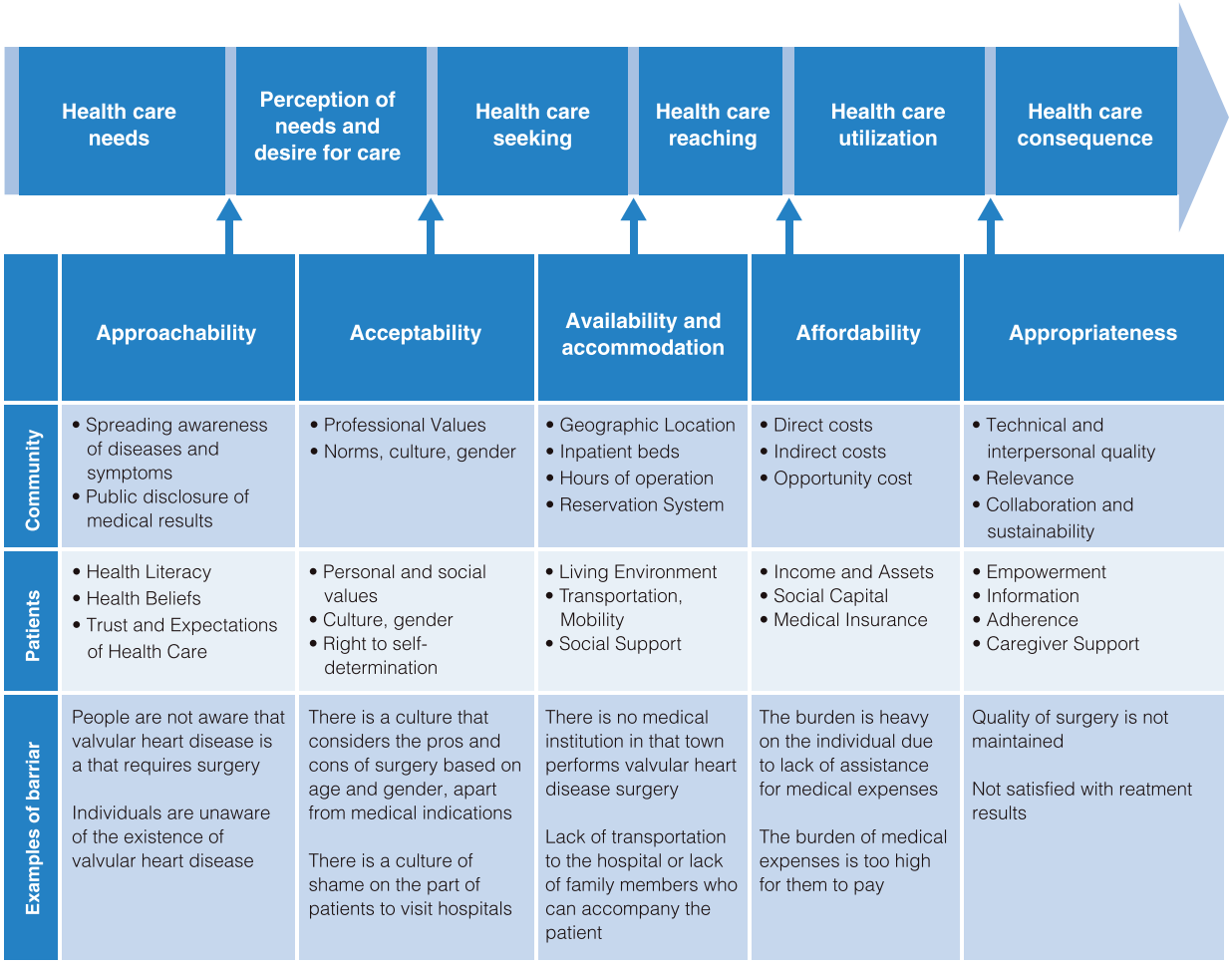


Fig. 10. Factors related to access to healthcare services using the example of valvular disease.
(Source: Prepared based on Levesque JF, et al. 2013 [757].).

BK37. Educational Attainment, Health Literacy and Cardiovascular Risk

Individuals with <10 years of education in Japan have higher mortality rates from all causes (hazard ratio 1.22, 95 % confidence interval (CI): 1.05–1.42) and CVD (hazard ratio: 1.44, 95%CI: 1.01–2.06) compared with those with >12 years of education [762]. Additionally, research indicates that less education diminishes the effectiveness of disease education interventions. Several factors contribute to the link between limited education and CVD risk. Firstly, less education is associated with reduced access to health care. Secondly, studies have shown that shorter education periods are linked to higher smoking rates, a well-established risk factor for CVD [763–766].

There is a concept of health literacy in relation to education. Sorensen et al. define health literacy that is linked to literacy and entails a person's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning health care, disease prevention and health promotion to maintain or improve quality of life during the life course [767].

Inadequate health literacy is strongly tied to patient morbidity, mortality, healthcare utilization, and costs. The American Heart Association has recognized the need for improving health literacy. Research by Peterson et al. demonstrated that among HF patients, health literacy is associated with all-cause death (adjusted hazard ratio 1.97 [95%CI 1.3–2.97]) [768]. Some studies suggest that interventions enhancing health literacy, such as patient education or telephone follow-up, can reduce hospitalizations and deaths, but others have not shown significant improvements [769–772].

In summary, although the combination of limited education and inadequate health literacy is associated with a higher risk of CVD incidence and death, it is imperative to avoid stereotypical assumptions that individuals with less education invariably possess insufficient health literacy. These findings underscore the critical need to simultaneously address both education and health literacy in efforts to alleviate the burden of CVD.

BK38. Social Support and Cardiovascular Risk

Social support is the support and assistance provided and perceived within a social network such as families and friends to help cope with biological, psychological, and social stressors [773]. Social support can be assessed in terms of both structural and functional aspects. Structural social support refers to the size and quality of a person's social network, such as marital status and number of friends, and its absence is typically characterized as social isolation. On the other hand, regardless of the presence of a structural network, the subjective perception of lacking necessary instrumental, informational, and emotional support is considered a functional aspect and is identified as feelings of loneliness [114,774–776].

Observational studies have reported the association between social support and the incidence of ischemic heart disease and stroke [777–789,956]. However, a study with 480,000 participants from the UK Biobank found no significant association between social support and the incidence of ischemic heart disease and stroke, after adjustment for multiple characteristics [790]. Lack of social support might contribute to incident ischemic heart disease and stroke via other cardiovascular risk factors as mediators, rather than having a direct effect, which might account for the observed discrepancies.

Social support is associated with both survival and functional outcomes in patients with ischemic heart disease and stroke, which is consistent among multiple studies [495,789,791–808]. Two large cohort studies demonstrated that social isolation, rather than perceived loneliness, was associated with death, underscoring the importance of a support person for such patients [790,809]. For patient with HF, several observational studies and their meta-analysis have also reported that lack of social support was associated with rehospitalization [810].

Randomized controlled trials (RCTs) on social support and CVD are scarce. Representative is the ENRICHD trial, which showed that cognitive behavioral therapy over 6 months in patients with ischemic heart disease improved depressive symptoms and perceived social support but not survival [811]. Future trials investigating the effect of interventions on social support with appropriate intervention periods and more specific intervention means are awaited.

BK39. Neighborhood Environment and Cardiovascular Risk

Neighborhood socioeconomic status (nSES), including income, education, employment, and housing status of the neighborhood, has been shown associated with the incidence and mortality rate of CVD [812]. Studies have demonstrated that lower nSES was associated with higher incidence and deaths of ischemic heart disease and stroke [813–824], as well as more rehospitalization in patients with HF [825,826]. Higher prevalence of cardiovascular risk factors such as hypertension and obesity in low nSES areas underlies these associations [827–830], which may be attributed to poor lifestyles such as smoking and physical inactivity [831,832]. In an RCT enrolling public housing residents in lower nSES areas in the US, the opportunity to move to higher nSES areas was associated with reduced prevalence of obesity and diabetes after 10 years, indicating that nSES may be a modifiable risk [833].

Food insecurity increases the risk of CVD [834]. In Japan, where food insecurity is not prominent, accessibility to heathy foods becomes more important. Easier access to fresh food stores is associated with less hypertension, obesity, and atherosclerosis [835–837], and higher density of fast-food restaurants is associated with more hypertension, obesity, and diabetes, as well as higher cardiovascular mortality rates [836–842].

Housing is critical in health, but both having a house to live in and the quality of that house matters [812]. Housing characteristics such as thermal quality and distance from major roads have been reported associated with incident CVD. Improvement in housing insulation lowers blood pressure in winter [843,844], and reduces ischemic heart disease hospitalizations [845]. In addition, proximity to major roads is associated with higher prevalence of hypertension and atherosclerosis [846–848], and higher incidence of ischemic heart disease and stroke [849–851], which is hypothesized to be attributed to noise and air pollution [846,847,852,853], such as ozone and PM2.5 [854–859].

Most studies on neighborhood environments have been conducted outside Japan. Given its unique cultural background and social structure, more evidence from Japan is keenly awaited.

BK40. Modifiable Health Behaviors and SDOH

Typical modifiable health behaviors include inappropriate diet, lack of physical activity, smoking, excess alcohol consumption, and irregular sleep habits. Overall, these are associated with the SDOH, including economic and occupational status, duration of education, social support, and other social circumstances.

Health behaviors, alongside genetic and environmental factors, significantly influence CVD [860–866]. Ultraprocessed foods [867–869], excessive salt intake [870–872], and high-caloric intake [873–875] are considered inappropriate diet, whereas the Mediterranean diets [876–878], fruit and vegetables [879–881], and fish [882–885] are beneficial. Lack of exercise [886–888], obesity [889,890], smoking [891,892], and excessive alcohol consumption [893,894] escalate tissue inflammation and oxidative stress, heightening the CVD risk. Other guidelines published by the Japanese Society of Cardiology also highlight the importance of these factors, especially physical activity [894a,894b,991].

Insufficient (<7 h) or excessive (>9 h) sleep and irregular sleep patterns have been linked to CVD through effects on blood pressure, inflammation, and glucose metabolism [895–899].

The American Heart Association introduced “Life's Essential 8”, a scoring system combining these five health behaviors with laboratory data on blood sugar, cholesterol, and blood pressure [900]. This quantitative approach facilitates individual health score assessment and monitoring over time. Stress and mental health are also introduced as factors influencing CVD.

These health behaviors are also related to the SDOH. Associations have been observed between income and reduced fast-food consumption, higher exercise, and non-smoking rates [901–904], higher education level and decreased obesity with increased exercise habits [905,906], and the proximity of fresh food stores to residences and vegetable and fruit intake [907,908]. Additionally, people residing in safe, walkable areas with amenities tend to exercise more [909–911]. Sleep quality has also been connected to social environment [912].

BK41. The Impact of SDOH Interventions on Modifiable Health Behaviors

Whereas individual-level interventions may lead to temporary improvements in health behaviors, SDOH interventions targeting structural and environmental factors can lead to sustainable changes that effectively reduce the risk of CVD.

Numerous studies have proven the effectiveness of multidisciplinary team-guided diet and lifestyle interventions in mitigating CVD risk [913–915]. However, these improvements often diminish once support ends, as health education focused solely on imparting knowledge does not guarantee long-term behavior change [916,917]. This highlights the importance of the SDOH and social environment-based interventions.

For instance, the UK's introduction of a sugar tax resulted in a 6500-cal reduction per person per year [918]. Additionally, individual efforts accounted for a mere 2 % salt reduction, while, processed food manufacturing changes resulted in a 15–20 % reduction [919]. In the USA, providing housing to homeless adults with chronic illnesses reduced hospitalizations, hospital days, emergency room visits, and healthcare costs [920–922]. Similarly, social prescribing that connects patients to community organizations fosters social support and improves health behaviors, subsequently reducing CVD risk [923,924]. Alternative salt usage in facility kitchens, as opposed to individual salt reduction education, resulted in lowered blood pressure and cardiovascular deaths [917,925]. School-based interventions promoting fruits, vegetables, and physical activity successfully reduced obesity and CVD risk [926–928]. Furthermore, providing nutritionally balanced meals to low-income insurance recipients decreased medical costs and hospitalizations [929,930].

SDOH interventions present numerous opportunities for health behavior improvement and CVD risk reduction. Although healthcare providers may find it challenging to address housing, occupation, and income-related SDOH on an individual basis, collaboration with professionals such as social workers, who can tackle these issues by considering their effect on modifiable health behaviors, is crucial.

BK42. Characteristics of SDOH in Japan. Japan has a favorable environment concerning the SDOH. However, it is not without its unique challenges, particularly pertaining to recent economic shifts and a growing aging population.

SDOH in Japan is considered favorable with a relatively low unemployment rate compared with Western countries, coupled with rich social capital characterized by cooperative behavior and trust within communities [931–933]. Air pollution levels in Japan are comparatively low on a global scale, ranking 144th out of 194 countries according to WHO statistics [934]. Furthermore, the incidence of homelessness in Japan is less than in the USA [935,936].

While some high-income countries grapple with the issue of uninsured individuals, Japan stands out with its universal health insurance coverage and high-cost medical care reimbursement system, ensuring affordable healthcare for the majority of its citizens [937]. In Japan, there is no gatekeeping to medical care, and the country also has a conspicuously large number of diagnostic medical equipment such as computer tomographies compared to other high-income countries [761]. This might be one of the reasons why Japan has comparatively lower CVD mortality and hospitalization rates than Western countries [938–940].

However, Japan faces a unique set of challenges. Employment-related challenges include a more significant wage and social status gap in non-regular employment [941–944], coupled with the prevalence of unreported unpaid overtime [945]. Contrary to trends in other countries, Japan sees a rise in mortality rates among managers [945a–945c]. Additionally, Tokyo has significantly less area of parkland per capita than cities such as New York and London, with fewer people engaging in exercise [946–948]. Housing insulation standards are markedly low in Japan, potentially contributing to CVD risk [949,950]. The aging population and increasing relative poverty rate further compound these health challenges, with approximately one in seven children living in relative poverty due to economic stagnation and the rise in part-time employment and single-parent or older households.

BK43. Digital Determinants of Health in Japan. Digital technology has the potential to transform not only the SDOH, but also the association between the SDOH and CVD. However, the growing “digital divide” could potentially exacerbate existing disparities.

Digital technology, particularly the internet and smartphones, has revolutionized access to information and resources [951]. The potential benefits for addressing SDOH include improved job and housing opportunities, access to educational resources, and more diverse options for food and clothing through online shopping. Social networks and online communities can also provide new forms of social support, potentially alleviating geographic disparities related to SDOH [952,953]. Additionally, the internet facilitates direct access to medical care, medication counseling, and health consultations, with online rehabilitation showing promise in this domain. Personal health records and online health portals can empower individuals to manage their health more effectively [954,955].

Moreover, digital technology may transform the traditional association between SDOH and CVD. For instance, with the internet and smartphones, regardless of availability in the immediate vicinity, fresh food can be accessed online, and individuals may choose to engage in physical activities by choosing safer neighborhoods using the internet. Wearable devices and smartphones can further facilitate the monitoring and intervention of CVD, aiding in addressing social isolation and loneliness, which are known risk factors for the condition [956–958]. However, digital technology may also have adverse effects on health, including eye health issues, sleep disorders, and negative mental health impacts due to digital addiction.

Thus, digital technology can have significant effect on both SDOH and CVD, and there is a proposed concept of the digital environment, including digital access, internet environment, and digital literacy, as new determinants of health that interact with SDOH, referred to as digital determinants of health (DDOH) [959]. However, the “digital divide” poses a significant challenge, particularly for older individuals and those with low incomes who may lack the necessary resources or skills to fully engage with digital technology [960]. In Japan, although smartphone penetration rates are among the highest globally, a sharp decline is observed in the older population [961].

VI. Diversity of Medical Professionals

CQ/BK/FRQ List

Numerous reports highlight how healthcare providers' actions and decisions can significantly influence patient outcomes. First, the diversity of medical providers encompasses variations in their expertise and disease management. Although it is difficult for patients and their families to choose their own providers, the characteristics of the provider's medical practice, such as proficiency, patient-centeredness, close communication, and adherence to guidelines, are factors that can improve patient outcomes. Characteristics of medical facilities may also affect patient outcomes. Furthermore, with the increase in the number of HF patients and the complexity of treatment and management, multidisciplinary cooperation, heart teams, and palliative care teams have come to play important roles.

Well-being, work environment, mental health, and support for balancing work and family life of the medical staff are newly included in this guideline as part of the scope of diversity in medical care. The primary purpose of medical care is to treat patients, but, on the other hand, there are cases in which medical personnel themselves suffer from excessive stress, which can lead to burnout and ultimately death due to overwork. Healthcare providers must be familiar with the high number of working hours and the management of mental stress among medical staff. There have been few reports on how to support medical staff in balancing work and family life when they become ill, but we believe that this is an important issue and have proposed what can be done at present by including this issue in the guideline.

CQ13. What Trends Among Healthcare Providers Contribute to Improving the Outcomes and Quality of Care for Cardiovascular Patients?

Recommendation

Facility size and proficiency in medical practice may affect the prognosis of patients with cardiovascular disease. It is also weakly recommended that close communication between healthcare providers and patients, patient-centered medical services, and adherence whenever possible to practice guidelines be considered, as they improve the prognosis and quality of care for cardiovascular patients.

(Agreement rate: 86.3 %; Level of Evidence: B)

Commentary

The effect of facility scale on patient's prognosis has been reported. First, the quality of CVD care was unrelated to the number of cases or scale of each facility in the UK [962]. In the USA, complication rates after cardiac surgery were similar in facilities with high and low numbers of procedures. However, when complications did occur, the mortality rate was lower at facilities with a higher number of cases [963]. In Japan, in-hospital mortality rates are lower in patients with myocardial infarction (MI) and HF in facilities with larger scales [938].

Proficiency in medical practice may affect patient outcomes. A narrative review found that percutaneous coronary intervention to the left main artery performed by skilled operators had a lower all-cause mortality rate at 30 days compared with unskilled operators but a similar all-cause mortality rate [964]. A systematic review of cardiac surgery also reported that off-pump coronary artery bypass surgery was not associated with significant differences in postoperative mortality or complication rates between skilled and unskilled practitioners [965]. Otherwise, for open aortic aneurysm repair, the number of cases per year performed by the practitioner was reported to be more significantly associated with outcome than cumulative years of experience [966]. In addition, CVD in older patients involves complex factors that require well-considered medical decision-making, physician skill training, and patient-centered care [967].

In recent years, observational studies [968–971] and a systematic review [972] have been published in which female physicians showed improved patient outcomes more than male physicians. However, due to the difficulty of performing randomized controlled trial (RCTs), a detailed examination of trends in medical practice by physicians is needed. In a study of older patients, treatment of HF hospitalizations by female physicians did not affect the 30-day mortality rate compared with male physicians, but readmission rates were significantly lower [968]. A study of patients with acute MI reported that management by female physicians improved prognosis, especially in female patients [969]. In Japan, a single-center study reported that the 30-day readmission rate was lower in patients treated by female cardiologists than that by male cardiologists [970], and cost-effectiveness was superior when female cardiologists were in charge [971]. The impact of sex differences of physicians on patient outcomes can be attributed to modifiable factors, including effective provider communication, patient-centered care, and adherence to clinical practice guidelines [973], patient-centered care [974,975], and a tendency to adhere to practice guidelines [976,977] have been identified as factors that improve prognosis.

BK44. Multidisciplinary Care and Cardiovascular Patient Outcomes

The prognosis of CVD patients is expected to be improved by multidisciplinary professionals utilizing their respective high expertise, sharing goals and information, and fulfilling their roles in collaboration and complementarity with each other.

Team medicine can be defined as “medical care in which a wide variety of medical staff engaged in medical care share goals and information on the premise of their high level of expertise, cooperate and complement each other while sharing the workload, and provide medical care that accurately responds to the patient's situation” [978–980]. Multidisciplinary medicine is patient-centered, and the composition of the interdisciplinary team and its program is flexible, depending on the disease stage, insurance system, available resources, and patient/family needs [981].

In the acute setting, multidisciplinary care has been reported to improve inpatient mortality rates [982–984], and transitional support for HF patients was effective in reducing the mortality rate and improving quality of life [985]. Systematic reviews have demonstrated that multidisciplinary care reduces overall mortality and hospitalization rates [986–990]. The Guidelines for HF or cardiac rehabilitation recommend multidisciplinary team care as Class I, Level of Evidence A [981,991,992].

Most of this evidence regards the effect of multidisciplinary care for hospitalized patients, but there are reports that multidisciplinary home visits by outpatient clinic physicians, nurses, physical therapists, dietitians, licensed psychologists, and others also reduce all-cause deaths after HF hospitalization [987]. On the other hand, a clinic-based studies meta-analysis showed little effect on all-cause deaths [986], and multidisciplinary disease management programs recruited in the community reported no effect on mortality or rehospitalization rates [993], so the role/effect of multidisciplinary care in community health care requires further investigation.

Multidisciplinary disease management programs for HF patients involving pharmacists were reported to improve prognosis [994,995]. In addition, specialized palliative care provided by hospital palliative care teams has been reported to benefit patient quality of life, symptom burden, and patient satisfaction [996].

Although collective decision-making in multidisciplinary care can have some negative effects, such as reducing individual responsibility, encouraging riskier treatment [997] and more meetings [998], overall it has the effect of improving the prognosis of CVD patients.

BK45/GPS. Multidisciplinary Team Care and Health Professional Wellbeing

Multidisciplinary team medicine may enhance the well-being of the healthcare providers themselves, and the well-being of the healthcare providers may facilitate cooperation.

In general, healthcare workers are under high stress, which has led to issues such as burnout [999]. However, there is growing interest in positive directions such as work engagement and well-being [1000]. Well-being is a concept that means being in a good physical, mental, and social state, with individual rights and self-actualization guaranteed. Multidisciplinary collaboration and well-being are related, and professionals with higher subjective well-being tend to build good relationships and cooperate in multidisciplinary collaborative settings [1001]. Multidisciplinary team care also improves satisfaction and teamwork among healthcare professionals, and as an example, getting together daily in a huddle meeting to share values is effective for this purpose [1002]. In addition, good multidisciplinary collaboration is considered essential to achieve the goal of safe, high-quality patient care [1003]. For example, it is widely known that multidisciplinary team care in the management of HF improves prognosis and prevents rehospitalizations [1004,1005].

Improvement of the well-being of the healthcare professionals themselves may be obtained by introducing programs to enhance their sense of well-being (e.g., meditation and mindfulness [1006]), in addition to conducting annual stress checks [1007] and regular mental health monitoring, which may contribute to effective teamwork.

FRQ8. Should Family Members Participate and Be Involved in the Treatment of Cardiovascular Patients?

Answer

In patients with ischemic heart disease and HF, family involvement in treatment can help improve prognosis and quality of life.

Commentary

Disease management programs are important for reducing mortality and rehospitalization rates in HF patients [987,1004]. However, it has been suggested that diverse individual problems are not fully being addressed by population-based disease management programs [1008–1010]. Because older patients with HF may have difficulty recognizing subjective symptoms and family members and healthcare providers may recognize symptoms on behalf of the patient. Family members in the multidisciplinary team are effective for both self-care and self-monitoring by the patient [1011,1012]. Family support plays an important role in helping female patients after acute coronary syndromes to participate in secondary prevention cardiac rehabilitation (CR) [134]. Furthermore, family involvement in discussions and decision-making about treatment and care would better reflect patient preferences in treatment and care and improve the quality of life of both the patient and family. On the other hand, it is important to consider that the time and financial burden on the family becomes excessive as the need for proactive family care for their patient [1013].

FRQ9. How Should the Work Environment Be Optimized to Accommodate Diversity on the Medical Side?

Answer

To enhance the working environment effectively, consider adopting the following strategies: (1) Work Quantity and Quality: Establish clear performance standards and provide resources and training to help employees meet these expectations, ensuring a balance between workload and the workforce. (2) Employee Autonomy: Empower employees with the discretion to make decisions about their work processes, fostering a sense of owner ship and responsibility. (3) Diverse Working Conditions: Create a flexible and inclusive workplace that caters to the needs of employees with varying work styles and personal commitments. (4) Work-Life Harmony: Promote policies and initiatives that support employees in achieving a healthy balance between their professionals' responsibilities and personal life. (5) Effective Communication: Foster an environment where open and transparent communication is encouraged at all levels, enhancing collaboration and mutual understanding. (6) Prevention of Verbal Abuse Violence, and Harassment: Implement a zero-tolerance policy and provide training to prevent and address all forms of workplace abuse, ensuring a safe and respectful environment. (7) Support for Healthcare Workers: offer targeted support and resources to healthcare professionals, recognizing the unique stresses and challenges of their field. (8) Patient and Community Engagement: Encourage cooperation and collaboration with patients and the community to improve service outcomes and satisfaction. (9) Addressing Physician Supply, Demant. and Maldistribution: Develop strategies to ensure an equitable distribution of medical professionals to meet the healthcare needs of various regions and populations. By focusing on these key areas, organizations can create a more productive, equitable, and supportive workplace for all employees.

Intervention targets include individuals, medical teams, medical institutions, governments and communities, and health service beneficiaries including patients, and mutual understanding and cooperation are important.

The most important factors are the leadership of the top management of the medical institution and the creation of an organization that can continue to improve.

Commentary

The well-being of healthcare professionals is closely linked to their working environment with enhancements in this setting crucial for individuals across various roles such as physicians [1014–1018], nurses [1018], and other healthcare professionals [1019–1021]. Notably, female physicians face a heightened risk of suicide [1015], underscoring the importance of addressing their needs, particularly during pregnancy. A study conducted among female physicians in Japan revealed that working long hours (>51 h/week) posed a significant risk factor for both imminent miscarriage and premature delivery, irrespective of age or physician's specialization [1022].

In Japan, the number of physicians per capita is lower than in other countries [1023], and the regional and departmental maldistribution of physicians has become a problem. As a result, the workload per physician is high, causing overwork and long working hours.

In Japan, the risk of CVD is increased among those who work long hours (>55 h/week, or approximately >60 h/month) [734,1024]. A significantly increased risk of developing depressive disorders is also observed among those who worked long hours, and the risk is stronger in Asian countries than in Western countries [1025]. In Germany, France, and the UK, aged 25–54 years, male physicians work <55 h/week and female physicians work <50 h/week [1026]. In Japan, the physician's working hours were 59 h/week in males and 51 h/week in females, for all age groups [1027]. In the USA, where physicians are evaluated for their performance rather than their working hours through the “White Collar Exemption”, physicians work 51.7 h/week for males and 44.4 h/week for females [1028].

Although a few countries permit extended working hours through an exception system called “opt-out,” many other countries enforce a mandatory 11-hour daily rest period, effectively establishing a weekly upper limit of 78 h. Cultural backgrounds and industrial health policies may influence working hours, and careful discussion is needed before applying Western standards to Japan.

Various perspectives can be considered to enhance the working environment [1029]. Specific interventions to achieve this may include: (1) Enhancing the quality and quantity of work by adjusting working hours, securing days off, managing on-call responsibilities, improving work efficiency, and promoting task shifting and sharing [1030,1031]. (2) Increasing flexibility and autonomy in work-related decisions [1016,1032]. (3) Providing diverse working conditions such as shorter work hours and access to social security benefits [1016,1021]. (4) Offering social support for healthcare workers and enhancing communication within the workplace [1016]. (5) Implementing measures to prevent verbal abuse, violence, and harassment [1033]. (6) Providing proper care and support for healthcare workers [1014,1016]. (7) Consolidating hospital functions, implementing group practice systems, and considering shift work arrangements [1028]. The 2024 work-style reform of doctors in Japan is expected to improve the working environment for doctors by (1) promoting appropriate labor management, (2) promoting task shifting/sharing, and (3) starting to regulate overtime limits and health security measures. To improve the working environment it is important for facility leaders such as directors and improvement teams to communicate information and show leadership [1034].

FRQ10. Does Solving the Mental Health Problems of Healthcare Professionals Improve the Quality of Medical Care for Patients?

Answer

Solving the mental health problems of healthcare professionals could improve the quality of medical care for patients.

Commentary

The rate of burnout among cardiologists is higher than in other medical professions, and is more prevalent among females [1029,1035]. Prolonged working hours, insufficient sleep and days off, the proliferation of electronic medical records, and an escalating regular workload are believed to affect physicians' health and work–life balance, leading to burnout [1029,1036]. Physician burnout is associated with alcohol and drug abuse, relationship disorders, depression, and suicide, leading to personal and professional problems such as high rates of medical errors, decreased quality and safety of care, decreased patient satisfaction, and worsened patient outcomes [1029,1030,1036,1037].

Regarding work–life balance, one of the positive concepts is work–family enrichment [1038]. Enriched roles at work have been reported to have a positive effect on health and are associated with lower rates of depression [1039] and burnout [1040], and higher life satisfaction [1041]. Positive home-to-work influences are associated with fewer chronic illnesses and improved mental health and well-being [1042,1043]. On the other hand, over-commitment and a certain temperament are considered to be factors that increase stress and have been linked to burnout [1044,1045]. Based on these findings, it is possible that solving the mental health problems of healthcare professionals will reduce burnout and improve the quality of medical care for patients.

Considering social aspects, the quality of life of healthcare professionals declined during the epidemic of the 2019 novel coronavirus infection (COVID-19) [1046], and female physicians, especially mothers, experienced work–family conflict, and depression and anxiety [1047,1048]. This may reduce the ability and opportunities for advancement of young female physicians up to mid-career [1047–1049]. Although burnout among medical personnel is likely to occur during disasters such as major earthquakes and epidemics such as COVID-19, organizations should predictably respond to burnout by monitoring individual stress levels, time management, work–life balance, and other factors [1050].

BK46/GPS. Employment Support for Health Professionals With Illness

For healthcare workers who are ill, the establishment of support systems and structures, making decisions on whether or not to work or return to work, and formulating and following up on support plans are required.

Mental and physical disabilities can affect anyone, and if healthcare professionals have difficulty performing their duties due to illness, they are eligible for employment support [1051]. It is desirable to view healthcare professionals working with illnesses as a form of diversity in the workplace and to provide support and systems that enable them to continue working.

The factors required for supporting the work–life balance of healthcare professionals include the following. (1) As each profession is specialized, it is difficult to transfer or support staff across job boundaries and departments. (2) It is not easy to make workload adjustments because hospitals serve as regional infrastructure. (3) The work burden on remaining staff is great. Especially in CVD medicine, a sudden increase in work burden can occur when dealing with highly urgent diseases.

As a specific way to promote support, it is recommended that when a staff member needs to take a leave of absence, a pamphlet should be provided that provides this information as well as leave of absence rules, regular notification, and procedures for sickness benefits. When the staff member is able to return to work, a support plan is prepared that takes the person's condition into consideration.

Privacy is extremely important throughout the entire process. It is also important that the staff member should be regularly and appropriately evaluated to avoid excessive work burden and unfairness falling on colleagues.

Appendix 1. Correspondence table between background questions in the Japanese guidelines and background knowledge in the English guidelines

BQ No.	Japanese	BK No.	English
BQ1	多様性に配慮した健康に関する意思決定支援とは何か?	BK1	Diversity-Health Conscious Decision Making
BQ2	生物学的性はどのように分化するか?	–	(Japanese only)
BQ3	性ホルモンの動態はどのようなものか?心血管系に影響するか?	–	(Japanese only)
BQ4	心血管系や代謝系において，性による特徴・経年変化の差はあるか?	–	(Japanese only)
BQ5	心血管疾患の発症に，性差および年齢差はあるか?	BK2	Sex and Age Differences in the Prevalence in CVD in Japan
–	(英語版のみ)	BK3	Health Status and Sex/Gender Issues in the Development of CVD in Japan
BQ6	急性心筋梗塞において，女性で注意すべき合併症は何か?	BK4	Complications of Acute Myocardial Infarction in Female Patients
BQ7	PCI後の抗血小板療法において性差を考慮すべきか?	BK5	Bleeding Risk and Antiplatelet Therapy After PCI in Female Patients
BQ8	虚血性心疾患の二次予防において，どのように性差を考慮すべきか? 予後に差はあるか?	BK6	Sex and Gender Differences in the Secondary Prevention and Prognosis of Ischemic Heart Disease
BQ9	心不全の臨床的特徴・病態・予後に性差はあるか?	BK7	Sex Differences in the Clinical Features, Pathogenesis, and Prognosis of HF
BQ10	心不全の非薬物療法において性差を考慮すべきか?	BK8	Considerations in the Nonpharmacologic Treatment of HF by Sex
BQ11	たこつぼ型心筋症発症後の急性期管理において，性差を考慮すべき点は何か?	BK9	Sex Differences in Takotsubo Cardiomyopathy
BQ12	二次性心筋症(たこつぼ心筋症以外)の診療において，どのように性差を考慮すべきか?	BK10	Sex/Gender Differences in Secondary Cardiomyopathies
BQ13	弁膜症の病因と有病率に性差はあるか?	BK11	Sex Differences in the Etiology and Prevalence of Valvular Heart Disease
BQ14	肺高血圧症の原因疾患に性差はあるか?	BK12	Sex/Gender Differences in the Etiology and Prevalence of Pulmonary Hypertension
BQ15	自己免疫疾患や炎症性血管疾患患者の心不全・心血管疾患の発症に性差はどのように関連するか?	BK13	Autoimmune Diseases and HF/CVD
BQ16	心房細動患者において，認知機能障害の発症に性差はあるか?	BK14	Female Patients With AF and Cognitive Dysfunction
BQ17	Brugada症候群の突然死リスクに性差はあるか?	BK15	Sex/Gender Differences in the Risk of Sudden Death in Brugada Syndrome
BQ18	脳卒中において，性差を考慮すべきか?	BK16	Stroke in Female Patients
BQ19	降圧目標達成率に性差・年齢差はあるか?	BK17	Gender and Age Differences in the Achievement of Antihypertensive Targets
BQ20	解剖学的男性に対して，外因性女性ホルモンはどのように作用するか?	BK18	Exogenous Female Hormone Action on an Anatomical Male
BQ21	トランスジェンダー女性の循環器病は，疫学的にどのように報告されているか?	BK19	Epidemiology of CVD in Transgender Women
BQ22	解剖学的女性に対して，外因性男性ホルモンはどのように作用するか?	BK20	Exogenous Male Hormone Action on an Anatomical Female
BQ23	トランスジェンダー男性の循環器病は，疫学的にどのように報告されているか?	BK21	Epidemiology of CVD in Transgender Men
BQ24/GPS	トランスジェンダーの患者に対して，診療上どのような配慮が必要か?	BK22/GPS	Special Considerations for Transgender Patients
BQ25	若年心筋梗塞の一次予防のために介入すべきリスク因子は何か?	BK23	Risk Factors to Intervene for Primary Prevention of Myocardial Infarction in Young Patients
BQ26	無症候性心房細動の予後に年齢差はあるか?	BK24	Age-Related Differences in Prognosis of Asymptomatic Atrial Fibrillation
BQ27	Brugada症候群の突然死リスクに年齢差はあるか?	BK25	Age-Related Differences in the Risk of Sudden Death in Brugada Syndrome
BQ28	女性のライフステージにおける高血圧の管理で考慮する点は何か?	BK26	Considerations for Female Patients With Hypertension at Different Life Stages

(*continued*)

BQ No.	Japanese	BK No.	English
BQ29	挙児希望のある女性や，妊娠中の高血圧患者が使用できる降圧薬は何か?	BK27	Recommendations for Antihypertensive Drug Use in Female Patients With Hypertension Planning Pregnancy or Currently Pregnant
BQ30	虚血性心疾患のある妊婦への二次予防は，どのようにするか?	BK28	Secondary Prevention for Pregnant Women With Ischemic Heart Disease
BQ31	妊娠・分娩に伴う脳卒中とはどのようなものか?	BK29	Stroke Associated With Pregnancy and Delivery
BQ32/GPS	高齢者の循環器診療において配慮すべき生理学的要因は何か?	–	(Japanese only)
BQ33/GPS	認知機能が低下した循環器病患者に対し，ACPはどのように行うべきか?	BK30/GPS	How to Implement Advance Care Planning for Patients With Cognitive Impairment and CVD
BQ34	心血管疾患の発症に人種差はあるか?	BK31	Differences in the Development of CVD by Race
BQ35	循環器系検査の基準値に人種差はあるか?	BK32	Differences in Standard Values for Cardiovascular Tests by Race
BQ36	薬剤代謝酵素活性に人種差はあるか?	BK33	Differences in Drug Metabolizing Enzyme Activities by Race
BQ37	循環器病のリスクについて，職業による差はあるか?	BK34	Occupation and Cardiovascular Risk
BQ38	循環器病のリスクについて，経済状況による差はあるか?	BK35	Income, Assets and Cardiovascular Risk
BQ39	循環器病のリスクについて，医療サービスへのアクセス状況による差はあるか?	BK36	Access to Health Care Services and Cardiovascular Risk
BQ40	循環器病のリスクについて，教育期間による差はあるか?	BK37	Educational Attainment, Health Literacy and Cardiovascular Risk
BQ41	循環器病のリスクについて，ソーシャルサポートによる差はあるか?	BK38	Social Support and Cardiovascular Risk
BQ42	循環器病のリスクについて，社会的環境(**BQ37–41**以外)による差はあるか?	BK39	Neighborhood Environment and Cardiovascular Risk
BQ43	健康行動はSDOHの影響を受けるか?	BK40	Modifiable Health Behaviors and SDOH
BQ44	SDOHへの介入は，健康行動の変容を通じて循環器病のリスクを改善するか?	BK41	The Impact of SDOH Interventions on Modifiable Health Behaviors
BQ45	わが国と諸外国との間で，SDOHに特徴の違いがあるか?	BK42	Characteristics of SDOH in Japan
BQ46	デジタルテクノロジーは，SDOHと循環器病にどのような影響を与えるか?	BK43	Digital Determinants of Health in Japan
BQ47	多職種によるチーム医療は心血管疾患患者の予後を改善させるか?	BK44	Multidisciplinary Care and Cardiovascular Patient Outcomes
BQ48/GPS	多職種によるチーム医療と医療者自身のwell-being は相互に影響するか?	BK45/GPS	Multidisciplinary Team Care and Health Professional Wellbeing
BQ49/GPS	さまざまな疾病を抱える医療者の就労支援をどう進めるべきか?	BK46/GPS	Employment Support for Health Professionals With Illness

BK, background knowledge; BQ, background question; GPS, good practice statement; SDOH, social determinants of health.

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(Listed in alphabetical order; affiliations as of March 2024)

Appendix 3. Disclosure of potential Conflicts of Interest (COI): JCS/JCC/JACR/JATS 2024 guideline on cardiovascular practice with consideration for diversity, equity, and inclusion (2021/1/1–2023/12/31)

Author	Member's own declaration items									COI of the marital partner, first-degree family members, or those who share income and property			COI of the head of the organization/department to which the member belongs (if the member is in a position to collaborate with the head of the organization/department)	
	Employer/ leadership position (private company)	Stakeholder	Patent royalty	Honorarium	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards	Employer/ leadership position (private company)	Stakeholder	Patent royalty	Research grant	Scholarship (educational) grant
Members: Yasuko K. Bando				MSD Nippon Boehringer Ingelheim Co., Ltd. Eli Lilly Japan K.K. Pfizer Japan Inc. Daiichi Sankyo Company, Limited. Novo Nordisk Pharma Ltd.										
Members: Mariko Harada-Shiba		Liid Pharmaceuticals, Inc.		Amgen K.K. Recordati Rare Diseases Japan K.K. Medpace Japan KK Kowa Company, Ltd. BML, INC. Protosera Inc. Novartis Pharma K.K.										
Members: Katsuyuki Hoshina						Japan Lifeline Co.,Ltd. Otsuka Medical Devices Co., Ltd								
Members: Tomomi Ide*				Nippon Boehringer Ingelheim Co., Ltd. Bayer Yakuhin, Ltd.		MEDINET Co., Ltd. Johnson & Johnson K. K. Pfizer Japan Inc.		MEDINET Co., Ltd.						
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Members: Yukiko Nakano*				Daiichi Sankyo Company, Limited. Otsuka Pharmaceutical Co., Ltd. Bristol-Myers Squibb TOA EIYO LTD. Nippon Boehringer Ingelheim Co.,			Takeda Pharmaceutical Company Limited THE CHUGOKU ELECTRIC POWER CO.,INC. Otsuka Pharmaceutical Co., Ltd. Nippon Boehringer							

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Collaborators:				Janssen										

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	Employer/ leadership position (private company)	Stakeholder	Patent royalty	Honorarium	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards	Employer/ leadership position (private company)	Stakeholder	Patent royalty	Research grant	Scholarship (educational) grant
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Notation of corporation is omitted.
The following persons have no conflict of interest to declare:
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Members: Junko Honye
Members: Toshimi Ikegame
Members: Miyuki Makaya
Members: Naoya Masumori
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Members: Yuko Wada
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In accordance with “The JAMS COI Management Guidance on Eligibility Criteria for Clinical Practice Guideline Formulation 2023”, all members have submitted their COIs for the past 3 years.
Some members (*) reported under the category of “Amount Category 3” or “Endowed departments established through donations by a company” and therefore do not have a vote in the guideline formulation process, to ensure fairness and transparency of the guidelines.

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