rent vasculogenesis and cardiomyogenesis for functional regenerative recovery after myocardial infarction. Circulation 113: 1311–1325.
37. Timmermans F, Plum J, Yoder MC, Ingram DA, Vandekerckhove B, et al. (2009) Endothelial progenitor cells: identity defined? J Cell Mol Med 13: 87–102.
38. Tanaka R, Wada M, Kwon SM, Masuda H, Carr J, et al. (2008) The effects of flap ischemia on normal and diabetic progenitor cell function. Plast Reconstr Surg 121: 1929–1942.
39. Dimmeler S, Aicher A, Vasa M, Mildner-Rihm C, Adler K, et al. (2001) HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. J Clin Invest 108: 391–397.
40. Kalka C, Masuda H, Takahashi T, Kalka-Moll WM, Silver M, et al. (2000) Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci U S A 97: 3422–3427.
41. Vasa M, Fichtlscherer S, Aicher A, Adler K, Urbich C, et al. (2001) Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. Circ Res 89: E1–7.
42. De Palma M, Venneri MA, Roca C, Naldini L (2003) Targeting exogenous genes to tumor angiogenesis by transplantation of genetically modified hematopoietic stem cells. Nat Med 9: 789–795.
43. Gothert JR, Gustin SE, van Eekelen JA, Schmidt U, Hall MA, et al. (2004) Genetically tagging endothelial cells in vivo: bone marrow-derived cells do not contribute to tumor endothelium. Blood 104: 1769–1777.
44. Timmermans F, Van Hauwermeiren F, De Smedt M, Raedt R, Plasschaert F, et al. (2007) Endothelial outgrowth cells are not derived from CD133+ cells or CD45+ hematopoietic precursors. Arterioscler Thromb Vasc Biol 27: 1572–1579.
45. Case J, Mead LE, Bessler WK, Prater D, White HA, et al. (2007) Human CD34+AC133+VEGFR-2+ cells are not endothelial progenitor cells but distinct, primitive hematopoietic progenitors. Exp Hematol 35: 1109–1118.
46. Asai J, Takenaka H, Kusano KF, Ii M, Luedemann C, et al. (2006) Topical sonic hedgehog gene therapy accelerates wound healing in diabetes by enhancing endothelial progenitor cell-mediated microvascular remodeling. Circulation 113: 2413–2424.
47. Ii M, Nishimura H, Iwakura A, Wecker A, Eaton E, et al. (2005) Endothelial progenitor cells are rapidly recruited to myocardium and mediate protective effect of ischemic preconditioning via "imported" nitric oxide synthase activity. Circulation 111: 1114–1120.

Shape selection of twist-nematic-elastomer ribbons

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How microscopic chirality is reflected in macroscopic scale to form various chiral shapes, such as straight helicoids and spiral ribbons, and how the degree of macroscopic chirality can be controlled are a focus of studies on the shape formation of many biomaterials and supramolecular systems. This article investigates both experimentally and theoretically how the chiral arrangement of liquid crystal mesogens in twist-nematic-elastomer films induces the formation of helicoids and spiral ribbons because of the coupling between the liquid crystalline order and the elasticity. It is also shown that the pitch of the formed ribbons can be tuned by temperature variation. The results of this study will facilitate the understanding of physics for the shape formation of chiral materials and the designing of new structures on basis of microscopic chirality.

liquid crystal elastomers | chiral imprinting

Recent researches have revealed that chirality plays a critical role in controlling the shape of self-assembled supramolecular aggregates. A range of chiral shapes, including tubes with "barber-pole" markings, spiral ribbons (with cylindrical curvature and helical central line), and helicoids (with Gaussian saddle-like curvature and straight central line), have been observed in a rich variety of biological materials and their synthetic analogues. These materials include several amphiphiles (1–3), peptides (4–7), diacetylenic lipids (8, 9), gemini surfactants (10, 11), and multicomponent mixtures in bile (12, 13). Such aggregates often become bilayers, and the bilayer membranes form tubules, spiral ribbons, or helicoids in contrast to the normal expectation that the minimum energy state of the bilayers would be flat, or be large spherical vesicles with the minimum curvature. In addition, the correlation between material characteristics and the macroscopic shape of chiral aggregates is markedly complicated. For example, mixed bilayers of saturated and diacetylenic phospholipids change their shape between micron-scale cylindrical tubules, spiral ribbons, or nanometer-scale tubules, in response to temperature variation (14). Charged gemini surfactants with chiral counterions show a transition between spiral ribbons and helicoids as a function of molecular chain length (10). Many theoretical studies have been reported to explain what determines the size and shape of tubules, helicoids, and spiral ribbons (10, 15–18).

In this article, we will show, both experimentally and theoretically, how a flat twist-nematic-elastomer (TNE) film when subjected to temperature change can easily achieve the goal of shape selection between helicoids and spiral ribbons. Nematic elastomers (NEs) are a unique class of materials (19–23). Formed by cross-linking liquid crystalline polymers, NEs possess both the elastic properties of rubbers and the orientational properties of liquid crystals. The combination of these two properties makes the shape of NEs very sensitive to external stimuli. In this article, we will focus on NE films in which the nematic order orientation changes smoothly by 90° from the bottom surface to the top surface with the director at the midplane parallel to the long or short axis of the film as shown in Fig. 1. The director's change in orientation through the film's thickness leads to gradients in the induced strain when the film is heated or cooled, giving rise to complex changes in the sample's overall shape. Broer and coworkers (24, 25) reported that temperature variation or light irradiation can turn a flat ribbon of densely cross-linked stiff liquid crystal networks with a similar twist orientation into a ribbon of saddle-like shape or spiral ribbon. Godinho et al. (26) showed that the self-winding of helices in jets and electrospun fibers obtained from cellulosic mesophases results from an off-axis core line defect disclination. The NEs (i.e., loosely cross-linked elastomeric liquid crystal networks) possess considerably stronger coupling between mesogen orientation and network deformation than the materials in these studies (24–26). We will demonstrate that the NE films with the twist configuration mentioned above form helicoids or spiral ribbons in response to temperature variation. We will also show that these TNE films select the shape according to the value of their width-to-thickness ratio: the narrow TNE films twist around their central lines upon temperature change, forming helicoids; however, when the width-to-thickness ratio of the films becomes larger than a certain critical value, the central lines of the films curve into helices and the films themselves form spiral ribbons. In addition, we will also show how the helical/twist pitch and handedness change with temperature and the width-to-thickness ratio of the films.

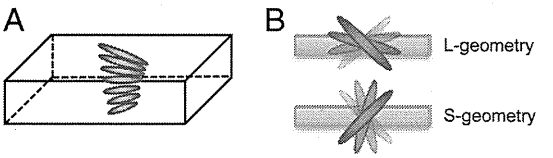

Fig. 1. Schematics of the director configuration of TNE ribbons: (*A*) side view, (*B*) top view of the L- and S-geometry. Nematic director twists left-handedly by 90° between the top and bottom surfaces with the director at the midplane parallel to the long or short axis of the ribbon.

In contrast to the chiral supramolecular aggregates of the order of nano- or micrometer scale, the shape selection and variation of the TNE films occur in the macroscopic scale of the order of milli- or centimeter, and the dimensional parameters of the TNE films can be experimentally varied as desired and the pitch of formed ribbons can thus be well controlled. These features facilitate to characterize the geometrical parameters of the shapes and to elucidate the dimensional effect on the shape selection. The results of the present study will provide an important basis of the understanding of the physics for the shape formation of chiral materials, and the designing of new structures on basis of microscopic chirality.

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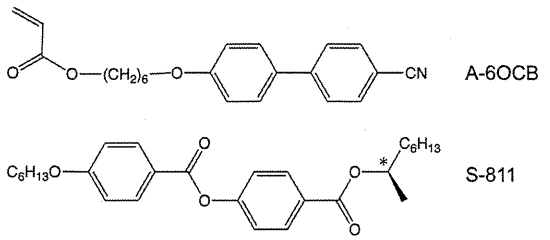

Fig. 2. Monoacrylate mesogenic monomer A-6OCB and chial dopant S-811.

Results

Experiment. Here we focus on the shape variation of TNE films with various widths driven by temperature change. The director in the TNE films left-handedly rotates by 90 ° between the upper and bottom surfaces. The twist nematic configuration was imprinted in the elastomer matrix by the cross-linking reaction in the presence of a nonreactive chiral dopant. This chiral imprinting was demonstrated in the preparations of cholesteric liquid crystal elastomers.(27–29) The side-chain-type TNEs were prepared by photopolymerization of the achiral mesogenic monoacrylate (A-6OCB in Fig. 2) and 1,6-hexanediol diacylate (cross linker) dissolved in a miscible nematic solvent with a controlled amount of the nonreactive chiral dopant (S-811 in Fig. 2) that induces a 90° left-handed rotation of director between the two glass substrates. The surfaces of the glass substrates were coated with uniaxially rubbed polyimide layer, and they were placed in such a manner that the rubbing direction could cross with each other. The polarized optical microscopy confirmed that the dried elastomeric films with a thickness of 35.2 μm possessed a 90° twist director configuration even after the removal of the chiral dopant and nematic solvent. The long ribbon specimens were cut out from the film sheet so that the director at the midplane is either along the *long* axis or along the *short* axis of the ribbons (designated as L- and S-geometry, respectively, see Fig. 1). The ribbons with various widths (*ca.* $0.2 \sim 0.8$ mm) were prepared, and the length of the ribbons ($5 \sim 10$ mm) was considerably longer than the widths. We observed the shape of the ribbons immersed in a temperature-controllable silicone oil bath by optical microscopy. The silicone oil is a nonsolvent for the TNEs, and the ribbons have no mechanical constraint in the oil bath.

We find that the TNE ribbons select a helicoid or spiral ribbon depending on the width. In the narrow case, the shape is a helicoid with Gaussian saddle-like curvature (Fig. 3), while the shape in the wide case is a spiral ribbon with cylindrical curvature (Fig. 4). In both cases, the temperature (T) variation greatly changes the structural parameters of the ribbons such as twist pitch (p_T) (of helicoids), helical pitch (p_H), and diameter (d) (of spiral ribbons), involving a reversal of handedness (Figs. 3 and 4). This shape change is thermally reversible (Fig. 3*C*). The strong T effect on the ribbon shape originates from a large change in local nematic order induced by T variation. In fact, in the nematic phase of $T < T_{NI}$ ($T_{NI} = 367$ K is the nematic-isotropic transition temperature) with T-dependent nematic order, the structural parameters strongly depend on T, while they are independent of T in the isotropic phase of $T > T_{NI}$ with no nematic order (Figs. 3*C* and 4*C*). The ribbons become almost flat at a certain temperature (T_{flat}) around 353 K, as shown in Fig. 3*A*. It should be noted that T_{flat} is different from the preparation temperature of the films ($T_0 = 313$ K). The preparation state involving *ca.* 50wt% solvent at T_0 corresponds to the initial flat state with twist alignment, but the subsequent volume reduction to the dry state causes a twist distortion due to a finite strain gradient driven by anisotropic shrinking. In general, a finite volume change in nematic gels results in a considerably anisotropic shape variation (30, 31). In fact, the ribbons at the temperatures slightly above T_0 show a considerable twist (Figs. 3*C* and 4*C*), although no structural data in the dry state at T_0 was obtained due to the glassy state: The glass transition temperature of the dry film was *ca.* 50 °C.

The direction of the director at the midplane relative to the long axis of the ribbons change the handedness of the helicoids and spiral ribbons: At the temperatures below T_{flat}, the helicoids and spiral ribbons with L-geometry are right-handed, while those with S-geometry are left-handed (Figs. 3 and 4). In other words, the cooling (that is, an increase in local nematic order) induces the right- and left-handed winding in L- and S-geometries, respectively.

The shape transition between helicoids and spiral ribbons driven by width variation is clearly observed in the high-temperature isotropic state where the structural parameters are substantially independent of T (Fig. 5). For both L- and S-geometries, the shape transition occurs, but the critical width of the transition for L-geometry ($w_c \approx 0.3$ mm) is smaller than that for S-geometry ($w_c \approx 0.4$ mm). We also notice that the spiral ribbons with L- and S-geometries are not symmetric, and the spiral ribbon with L-geometry is wound a little more tightly than that with S-geometry: The values of p_H and d with L-geometry are slightly smaller than those with S-geometry. This trend is also observed in Fig. 4. In contrast, the helicoids with L- and S-geometries are almost symmetric, which can be seen in Fig. 3.

Theory. We develop a theoretic model to explain the experimental results. The two physical quantities we need are liquid crystal order tensor Q_{ij} and nonlinear strain tensor $\varepsilon_{ij} = \frac{1}{2}(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} + \frac{\partial u_k}{\partial x_i}\frac{\partial u_k}{\partial x_j})$, where the Einstein summation convention on repeated indices has been assumed. $\boldsymbol{x}$ and $\boldsymbol{u}$ represent, respectively, the position of a mass point before deformation and the corresponding displacement vector induced by the deformation. The elastic energy is assumed to take a simple form,

$$f = \mu(\varepsilon_{ij}\varepsilon_{ij} - \alpha\varepsilon_{ij}\delta Q_{ij}), \qquad [1]$$

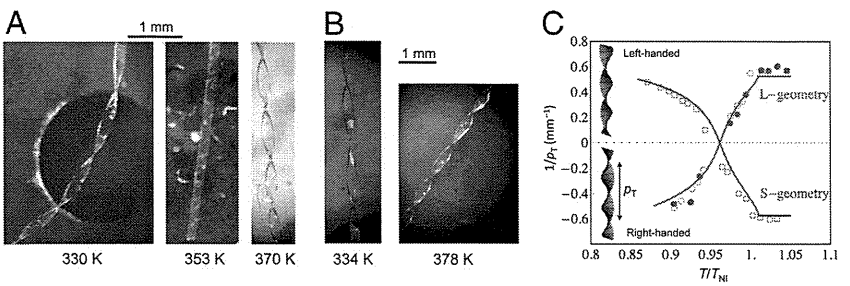

Fig. 3. Helicoids formed by the narrow TNE films with the thickness 35.2 μm. (*A*) Shape of the L-geometry ribbons: left-handed at 370 K; almost flat at 353 K; right-handed at 330 K. The ribbon width is 0.23 mm. (*B*) Shape of the S-geometry ribbons: right-handed at 378 K; left-handed at 334 K. The ribbon width is 0.22 mm. (*C*) Temperature dependence of the inverse of the twist pitch (p_T). The pitches of the left- and right-handed twist are defined to be positive and negative, respectively. The open and filled symbols represent the data obtained in the cooling and heating processes, respectively; and the (red) circles and the (blue) squares represent the data of the L-geometry and those of the S-geometry, respectively. The lines represent the theoretical predictions.

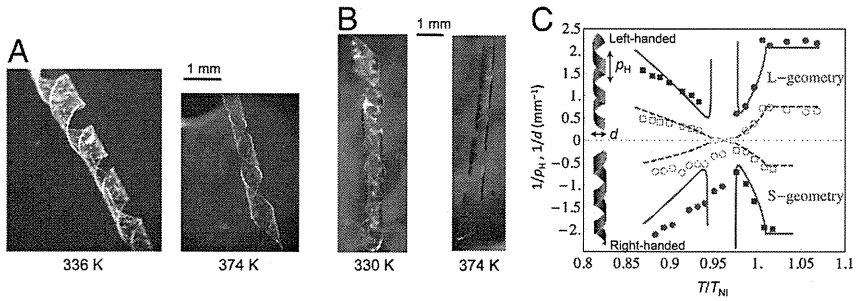

Fig. 4. Spiral ribbons formed by the wide TNE films with the thickness 35.2 μm. (*A*) Shape of the L-geometry ribbons: left-handed at 374 K; right-handed at 336 K. The ribbon width is 0.76 mm. (*B*) Shape of the S-geometry ribbons: right-handed at 374 K; left-handed at 330 K. The ribbon width is 0.83 mm. (*C*) Temperature dependence of the inverses of the helical pitch (p_H) and the diameter (d), where the lines represent the theoretical predictions. The pitches of the left- and right-handed twist are defined to be positive and negative, respectively. The inverse of the pitches is represented by the open symbols and the inverse of the diameters by the filled symbols. The (red) circles and (blue) squares represent, respectively, the data of the L-geometry and the data of the S-geometry. The thick (solid or dashed) lines represent the theoretical predictions for the structural parameters of spiral ribbons, and the thin dashed lines are the theoretic prediction of the pitch inverse of helicoids.

where μ is the shear modulus, α the coupling constant, and δQ_{ij} the change of liquid crystal order tensor induced by external stimuli. Given the incompressibility constraint $\epsilon_{ii} = 0$ for small deformations, this simple energy form is then good enough to capture the main feature of the problem we study here. Note that δQ_{ij} is now defined in the body frame to ensure rotational invariance (32). We further assume that when subjected to external stimuli the change of the body-frame order tensor is mainly caused by the order parameter change δS and that the principle axes of the order tensor keep fixed in the body frame although they do rotate with the film in the laboratory frame, namely, we assume $\delta Q_{ij} = \delta S(n_i n_j - \frac{1}{3}\delta_{ij})$, where $\boldsymbol{n}$ is the orientation of the nematic director at T_{flat}, twisting from the bottom surface to the top surface of the film. Integrating the above energy density along the direction perpendicular to the film plane and along the short axis of the film yields an effective 1D energy density (17) as a function of the curvature tensor C_{ij},

$$f_{1D} = \mu dw[a_K K^2 + bC_{xy} + a_X C_{xx}^2 + a_Y C_{yy}^2 + \sqrt{a_X a_Y}(2C_{xy}^2 + K)], \quad [2]$$

where d and w are respectively the thickness and width of the film, $K = C_{xx}C_{yy} - C_{xy}^2$ is the Gaussian curvature, and x and y represent, respectively, the directions parallel to the long and short axis of the film. The curvature tensor equals $C_{ij} = \partial^2 h/\partial x_i \partial x_j$, where h is the out-of-plane normal displacement. The linear term in C_{xy} is a chiral symmetry-breaking term, inducing the film to twist; the first term represents the in-plane stretch energy cost (33); and the other terms are the bending energy cost. The coefficients, which will be given in the *Methods* section, are determined by three parameters: the ratio between w and d, the product of the coupling constant α and the order parameter change δS, and the twist angle span θ_S.

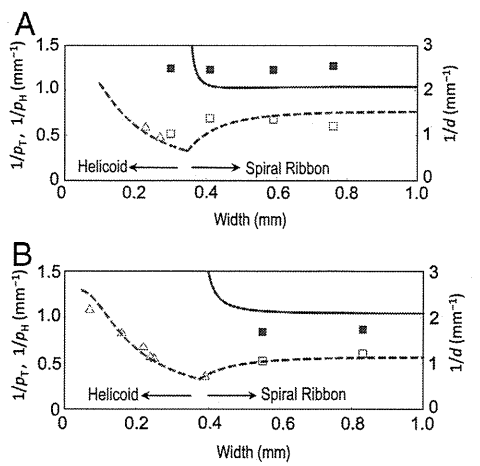

Fig. 5. Width effect on the shape selection of the TNE ribbons with (*A*) L-geometry and (*B*) S-geometry. The ribbon thickness is 35.2 μm. The shape is observed at 378 K in the isotropic state. The shape transition occurs at *ca.* 0.3 mm and *ca.* 0.5 mm for L- and S-geometries, respectively. The (red) triangles represent the pitch inverse of the helicoids, and the open and filled (blue) squares represent the pitch inverse and diameter inverse of the spiral ribbons, respectively. The lines are the theoretical predictions.

The theoretical results can be obtained by minimizing f_{1D} with respect to C_{ij}: for a given temperature change, narrow films form helicoids with the curvature of their central line C_{xx} being zero and the torsion of their central line C_{xy} determined by the equation $b + 2\sqrt{a_X a_Y}C_{xy} + 4a_K C_{xy}^3 = 0$; wide films form spiral ribbons with $C_{xx} = [b^2/(64a_X\sqrt{a_X a_Y}) - 3a_Y/(2a_K)]^{1/2}$ and $C_{xy} = -b/(8\sqrt{a_X a_Y})$. The Gaussian curvature is $K = -(\frac{1}{2}\sqrt{a_X a_Y}C_{xx}^2 + a_Y C_{xy}^2)/(a_K C_{xx}^2 + a_Y)$. Note that K is always negative; only in the limit $w/d \to \infty$, K tends to zero and the films form perfect spiral ribbons. (Ribbons of various curvatures are shown in Fig. S1). The critical width w_c that determines what type of ribbon to form is given by the condition $a_k b^2 = 96(a_X a_Y)^{3/2}$. In the case of $\theta_S = \pi/2$, this condition simplifies to

$$(w_c/d)^2 = \frac{4}{3}\pi^2\sqrt{\frac{40}{3}\left[(\alpha\cdot\delta S)^{-2} + (\alpha\cdot\delta S)^{-1}\left(\frac{1}{6} + \frac{1}{\pi}\right)\right]}. \quad [3]$$

To compare the theoretical predictions with the experimental observations, we proceed to connect the product of the coupling constant and the order parameter (αS) to temperature T. For this purpose, we examine how much a corresponding nematic elastomer with planar orientation extends as temperature is lowered. It is easy to deduce from Eq. **1** that the extension along the nematic director in this case is $\Lambda = \sqrt{1 + \frac{2}{3}\alpha S}$. By fitting the experimentally measured curve of $\Lambda(T)$ (see Fig. S2), we obtain $\alpha S = 3.3(1.01 - T/T_{\text{NI}})^{2/3}$ as the T dependence of αS.

Given the relation between T and αS, we can then determine how C_{xx}, C_{xy}, and the critical width w_c vary with temperature T. The pitch and the diameter of the helicoids and spiral ribbons can thus be determined accordingly. The theoretical predictions of their change with temperature are plotted in Fig. 3*C* and Fig. 4*C*. In Fig. 4*C*, the thin dashed lines represent the pitch of helicoids; outside the thin-dashed-line region, the helicoids become spiral ribbons whose diameter first increases rapidly and then decreases slowly with temperature change (see Fig. S1 for an illustration of the shape change). Fig. 5 shows how the pitch and diameter of the ribbons vary with the width. From these figures we can find that the theoretical results agree well with the experimental observa-

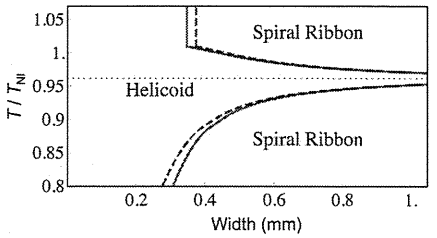

Fig. 6. Theoretical Phase diagram of TNE ribbons in the width-temperature space. The ribbon thickness is 35.2 μm. The phase boundary of the L-geometry and the S-geometry is represented, respectively, by the red solid line and the blue dashed line. The handedness of the formed ribbons changes as the dotted line at $T_{flat}/T_{NI} = 0.962$ is crossed.

tions. Shown in Fig. 6 is the phase diagram in the temperature-width space. This figure and Eq. **3** show clearly that w_c goes to infinity as T approaches T_{flat}. Alternatively speaking, a sample with the width larger than the minimum of w_c always first forms a helicoid and then becomes a spiral ribbon as the temperature is further tuned away from T_{flat}, as shown in Fig. 4*C*.

Discussion

In summary, TNE films can form helicoids or spiral ribbons upon temperature change. The optimal shape and curvature (34, 35) of the films depend on the competition between the bending energy cost and the in-plane elastic energy cost. Films with a small width-to-thickness ratio are easier to be stretched than to be bended and thus form helicoids, which have a large Gaussian curvature but no bending; while, on the contrary, those with a large width-to-thickness ratio are easier to be bended than to be stretched and thus form spiral ribbons, with a small Gaussian curvature but a large bending. The pitch and handedness of the formed ribbons are completely determined by only two parameters: the temperature and the width-to-thickness ratio.

To obtain helicoids/spiral ribbons, a chiral symmetry-breaking driving force is a must (otherwise temperature change would cause only a uniform stretch or shrink of the whole sample). In the systems we consider, the twist (chiral) arrangement of the achiral nematogens from the bottom to the top surface of the film was initially induced by the chiral dopants. After the removal of these dopants, this twist (chiral) arrangement is memorized by the polymer network; and it yields the required chiral driving force, when temperature change occurs and induces a tendency of local shape change (stretch or shrink along the nematic director). Therefore, the chiral symmetry breaking in TNE films is induced by the chiral arrangement of achiral molecules rather than by the chiral molecular-structure as in the case of supramolecular aggregates.

On the whole, the experimental results agree well with the theoretical results. However, in the experiments, the precise characterization of the shape at the temperatures near T_{flat} was difficult due to the saddle-like shape having no definite winding. Therefore, the data of the structural parameters near T_{flat} are lacking in Figs. 3*C* and 4*C*. This difficulty precluded the experimental assessment of the theoretical prediction of the transition from spiral ribbons to helicoids occurring at T close to T_{flat} for wide TNE films. The reasons causing the relatively large difference between the experimental results and the theoretical results for the low temperature part of the L-geometry in Fig. 4*C* are not clear to us.

We also investigated samples in which the nematic director on the midplane of the films does not align along the long or short ribbon axis. In this case, straight helicoids are not allowed because of the absence of the antisymmetry about the midplane. The dependence of the shape of the formed spiral ribbons on the width and temperature is similar to those of the L-geometry and S-geometry described above. Although the span angle θ_s is fixed to be 90° in the experiments, our theory is also able to predict how θ_s affects the ribbon shape: approximately speaking, for fixed width and temperature, when θ_s increases from zero, the pitch and diameter of the formed ribbons first decrease, reaching a minimum at somewhere between $\pi/2$ and π, and then show a decaying oscillation behavior afterwards. A detailed analysis of how the twist configuration along the normal direction of films changes the ribbon shape will be presented elsewhere.

Methods

Materials. The monoacrylate mesogenic monomer A-6OCB (Fig. 1) was synthesized by the method described in literature (36). 4-n-Hexyloxy-4′-cyanobiphenyl 6OCB (Sigma-Aldrich) and 1,6-hexanediol diacrylate (Sigma-Aldrich) were employed as miscible nematic solvent and cross linker, respectively, and they were used as received. The chiral dopant S-811 (Fig. 2) and photoinitiator bis(cyclopentadienyl)bis[2, 6-difluoro-3-(1-pyrryl)phenyl]titanium (Irgacure 784®) were kindly supplied from Merck KGaA and Chiba Specialty Chemicals Co., respectively. The mixing of A-6OCB with the nematic solvent was required to broaden the temperature range of the nematic phase, because the nematic phase of A-6OCB is very narrow (only *ca.* 2 °C) due to the high crystallizability. The mixing ratio of A-6OCB and nematic solvent was 5:4 by weight. The cross-linker concentration was 7 mol%.

Sample Preparation. The chiral properties of the mixtures of A-6OCB, 6OCB, and S-811 were characterized by the pitch of the resultant helicoidal structure corresponding to the distance of a 2π screw rotation of the molecular packing. The pitch was evaluated by the Cano wedge method (37, 38). The inverse pitch almost linearly varies with the concentration of S-811, which is similar to the behaviors of conventional liquid crystal mixtures with chiral dopants. The total twist angle of the mesogens was defined as the angle between the bounding mesogenic molecules at the bottom and top glass substrates whose surfaces were coated with a uniaxially rubbed polyimide layer. S-811 induced a left-handed twist configuration of the mesogens. For the sample preparation, the top and bottom glass substrates were placed in such a manner that the rubbing direction could cross with each other. The concentration of S-811 (0.06 wt%) was adjusted such that the total twist angle could become 90°, the distance between the two substrates being 40 μm.

For cross-linking reaction, the glass cell was irradiated using a xenon lamp with emission at a wavelength 526 nm for 30 min. The cross-linking temperature was 40 °C which is *ca.* 8 °C lower than the transition temperature of the mixture. The cell was immersed in dichloromethane for several days until the resultant gel film detached from the glass substrates due to the swelling pressure. The films were allowed to swell fully in dichloromethane in order to wash out the unreacted materials and chiral dopants. The swollen gel films were gradually deswollen by stepwise addition of methanol to dichloromethane. The ribbon specimens with L- and S-geometries (Fig. 1*B*) were cut out from the dried film at a temperature where the film became flat ($T_{flat} \approx 353$ K), because the dried film at room temperature was considerably curled and twisted. We confirmed that the dried film possessed a 90° twist rotation of director by polarized optical microscopy.

Measurements. The length and width of the ribbon specimens were measured by optical microscope. The thickness of the ribbon was evaluated to be 35.2 μm using a laser displacement sensor LT-9500 and LT-9010M (Keyence) at T_{flat}.

The shape of the ribbons immersed in a custom-made temperature-controllable bath of a silicone oil was observed with an optical microscope with CCD camera. The silicone oil was a nonsolvent for the specimen. The ribbons in the oil bath were subjected to no mechanical constraint. The twist pitch, helical pitch, and diameter at each temperature were evaluated by video analysis. The temperature was varied stepwise after confirming the equilibration of the shape of the specimen at each temperature.

Derivation of the 1D Effective Energy. We use the energy given in Eq. **1**. The nematic director $\boldsymbol{n}$ remains parallel to the film plane (or the xy-plane), and therefore, $\delta Q_{xz} = \delta Q_{yz} = 0$. The angle θ between the director $\boldsymbol{n}$ and the long axis of the film (or the x-axis) changes linearly with the depth to the film surfaces: for the L-geometry, we have $\theta = -\theta_S z/d$, where z is the distance to the midplane of the film, and θ_S is the twist angle span, namely, the difference between the angle on the top surface ($z = d/2$) and the angle on the bottom surface ($z = -d/2$); for the S-geometry, $\theta = -\theta_S z/d + \pi/2$. The Frank energy has been ignored here because the typical length scale, i.e., the pitch of the ribbons, in these experiments is of the order millimeters. Given the traceless constraint and the condition that $\epsilon_{xz} = \epsilon_{yz} = 0$, the strain tensor has only three independent components, ϵ_{xx}, ϵ_{yy}, and ϵ_{xy}. To reduce the full

3D energy density to an effective 2D one, we then express the displacement vector $\boldsymbol{u}$ of points away from the midplane in terms of the displacement vector $\boldsymbol{u}^{\mathrm{m}}$ of points on the midplane (33). To the linear order of z, we have $u_x = u_x^m - z \cdot \partial u_z^m/\partial x$, $u_y = u_y^m - z \cdot \partial u_z^m/\partial y$, and $u_z = u_z^m - z \cdot (\partial u_x^m/\partial x + \partial u_y^m/\partial y)$. Substituting the expressions for $\boldsymbol{u}$ and expressions for θ into Eq. **1** and then integrating along the z-direction yield a 2D energy density including terms linear in ϵ_{xx} and ϵ_{yy}, whose reference space is the equilibrium state of T_{flat}. To eliminate these linear terms, we change the reference space of the strain tensor to a new state, the equilibrium state of the case that the out-of-plane normal displacement is suppressed, which is acquired by a deformation from the flat geometry with the stretch along the long ribbon axis to be $\Lambda_{xx} = [1 + \frac{1}{2}\alpha \cdot \delta S(\frac{1}{3} + \sin\theta_S/\theta_S)]^{1/2}$ and the stretch along the short axis to be $\Lambda_{yy} = [1 + \frac{1}{2}\alpha \cdot \delta S(\frac{1}{3} - \sin\theta_S/\theta_S)]^{1/2}$ for the L-geometry and $\Lambda_{xx} = [1 + \frac{1}{2}\alpha \cdot \delta S(\frac{1}{3} - \sin\theta_S/\theta_S)]^{1/2}$ and $\Lambda_{yy} = [1 + \frac{1}{2}\alpha \cdot \delta S(\frac{1}{3} + \sin\theta_S/\theta_S)]^{1/2}$ for the S-geometry. We then express the in-plane elastic energy as a function of the Gaussian curvature (33). Assuming the curvature is nearly constant on the ribbon surface (17) and integrating the 2D energy density along the short ribbon axis, we thus obtain Eq. **2**, in which the coefficients are $a_K = \frac{3}{640} w^4 \Lambda_{xx}^2 \Lambda_{yy}^5$, $a_X = \frac{1}{6} d^2 \Lambda_{xx}^4 \Lambda_{yy}$, $a_Y = \frac{1}{6} d^2 \Lambda_{yy}^5$, and $b = \pm\frac{1}{2}\alpha \cdot \delta S \cdot d \cdot \Lambda_{xx}\Lambda_{yy}^2 \cdot (\sin\theta_S - \theta_S \cos\theta_S)/\theta_S^2$ (+ for the L-geometry and − for the S-geometry). The L-geometry and S-geometry are not exactly symmetric to each other because the Λxx and Λ_{yy} of the L-geometry are different from those of the S-geometry.

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1. Nakashima N, Asakuma S, Kim JM, Kunitake T (1984) Helical superstructures are formed from chiral ammonium bilayers. *Chem Lett* 10:1709–1712.
2. Pfannemuller B, Welte W (1985) Amphiphilic properties of synthetic glycolipids based on amide linkages .1. Electron-microscopic studies on aqueous gels. *Chem Phys Lipids* 37:227–240.
3. Lee SJ, et al. (2008) Self-assembled helical ribbon and tubes of alanine-based amphiphiles induced by two different formation mechanisms. *Tetrahedron* 64:1301–1308.
4. Zhang SG, Holmes T, Lockshin C, Rich A (1993) Spontaneous assembly of a self-complementary oligopeptide to form a stable macroscopic membrane. *Proc Natl Acad Sci USA* 90:3334–3338.
5. Aggeli A, et al. (1997) Responsive gels formed by the spontaneous self-assembly of peptides into polymeric beta-sheet tapes. *Nature* 386:259–262.
6. Pashuck ET, Stupp SI (2010) Direct observation of morphological tranformation from twisted ribbons into helical ribbons. *J Am Chem Soc* 132:8819–8821.
7. Castelletto V, Hamley IW, Hule RA, Pochan D (2009) Helical-ribbon formation by a beta-amino acid modified amyloid beta-peptide fragment. *Angewante Chemie International Edition* 48:2317–2320.
8. Schnur JM (1993) Lipid tubules—a paradigm for molecularly engineered structures. *Science* 262:1669–1676.
9. Spector MS, Price RR, Schnur JM (1999) Chiral lipid tubules. *Adv Mater* 11:337–340.
10. Oda R, Huc I, Schmutz M, Candau SJ, MacKintosh FC (1999) Tuning bilayer twist using chiral counterions. *Nature* 399:566–569.
11. Oda R, Artzner F, Laguerre M, Huc I (2008) Molecular structure of self-assembled chiral nanoribbons and nanotubules revealed in the hydrated state. *J Am Chem Soc* 130:14705–14712.
12. Chung DS, Benedek GB, Konikoff FM, Donovan JM (1993) Elastic Free-energy of anisotropic helical ribbons as metastable intermediates in the crystallization of cholesterol. *Proc Natl Acad Sci USA* 90:11341–11345.
13. Zastavker YV, et al. (1999) Self-assembly of helical ribbons. *Proc Natl Acad Sci USA* 96:7883–7887.
14. Spector MS, Singh A, Messersmith PB, Schnur JM (2001) Chiral self-assembly of nanotubules and ribbons from phospholipid mixtures. *Nano Lett* 1:375–378.
15. Selinger JV, Spector MS, Schnur JM (2001) Theory of self-assembled tubules and helical ribbons. *J Phys Chem B* 105:7157–7169.
16. Selinger RLB, Selinger JV, Malanoski AP, Schnur JM (2004) Shape selection in chiral self-assembly. *Phys Rev Lett* 93:158103.
17. Ghafouri R, Bruinsma R (2005) Helicoid to spiral ribbon transition. *Phys Rev Lett* 94:138101.
18. Nyrkova IA, Semenov AN (2010) Twisted surfactant structures: an advanced theoretical model. *Soft Matter* 6:501–516.
19. de Gennes PG (1975) Réflexions sur un type de polymères nématiques. [Some reflexions about a type of nematic liquid crystal polymers]. *CR Acad Sci II B* 281:101–103 French.
20. Kupfer J, Finkelmann H (1991) Nematic liquid single-crystal elastomers. *Makromol Chem-Rapid* 12:717–726.
21. Warner M, Terentjev EM (2003) *Liquid Crystals Elastomers* (Clarendon Press, London).
22. Xie P, Zhang RJ (2005) Liquid crystal elastomers, networks and gels: advanced smart materials. *J Mater Chem* 15:2529–2550.
23. Urayama K (2007) Selected issues in liquid crystal elastomers and gels. *Macromolecules* 40:2277–2288.
24. Mol GN, Harris KD, Bastiaansen CWM, Broer DJ (2005) Thermo-mechanical responses of liquid-crystal networks with a splayed molecular organization. *Adv Funct Mater* 15:1155–1159.
25. Harris KD, et al. (2005) Large amplitude light-induced motion in high elastic modulus polymer actuators. *J Mater Chem* 15:5043–5048.
26. Godinho MH, Canejo JP, Feio G, Terentjev EM (2010) Self-winding of helices in plant tendrils and cellulose liquid crystal fibers. *Soft Matter* 6:5965–5970.
27. Hasson CD, Davis FJ, Mitchell GR (1998) Imprinting chiral structures on liquid crystalline elastomers. *Chem Commun* 2515–2516.
28. Courty S, Tajbakhsh AR, Terentjev EM (2003) Stereo-selective swelling of imprinted cholesteric networks. *Phys Rev Lett* 91:085503.
29. Marty JD, Gornitzka H, Mauzac M (2005) Chiral molecular imprinting in liquid-crystalline network. *Eur Phys J E* 17:515–520.
30. Urayama K, Arai YO, Takigawa T (2005) Volume phase transition of monodomain nematic polymer networks in isotropic solvents accompanied by anisotropic shape variation. *Macromolecules* 38:3469–3474.
31. Urayama K, Arai YO, Takigawa T (2005) Anisotropic swelling and phase behavior of monodomain nematic networks in nematogenic solvents. *Macromolecules* 38:5721–5728.
32. Stenull O, Lubensky TC (2006) Soft elasticity in biaxial smectic and smectic-C elastomers. *Phys Rev E* 74:051709.
33. Landau LD, Pitaevskii LP, Lifshitz EM, Kosevich AM (1986) *Theory of Elasticity, Third Edition* (Butterworth-Heinemann, Oxford).
34. Warner M, Modes CD, Corbett D (2010) Curvature in nematic elastica responding to light and heat. *P Roy Soc A* 466:2975–2989.
35. Warner M, Modes CD, Corbett D (2010) Suppresion of curvature in nematic elastica. *P R Soc A* 466:3561–3578.
36. Shibaev VP, Kostromin SG, Plate NA (1982) Thermotropic liquid-crystalline polymers .6. Comb-like liquid-crystalline polymers of the smectic and nematic types with cyanobiphenyl groups in the side-chains. *Eur Polym J* 18:651–659.
37. Cano R, Chatelain P (1961) Sur les variations de lequidistance des plans de grandjean avec le titre des melanges de P-Cyanobenzalaminocinnamate damyle actif et inactif. [About the variations of Grandjean plans equidistance as a function of the active and inactive species amounts in amyle-p-cyanobenzyl-cinnamate mixtures]. *CR Hebd Acad Sci* 253:1815–1817 French.
38. Oswald P, Pieranski P (2005) *Nematic and Cholesteric Liquid Crystals* (CRC Press, Boca Raton).

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Guidelines for Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery (JCS 2008)

– Digest Version –

JCS Joint Working Group

Table of Contents

(*Circ J* 2011; **75:** 989–1009)

Introduction to the Revised Guidelines

As the population ages, more elderly patients are undergoing surgery. An increasing number of patients with heart disease are undergoing noncardiac surgery, and guidelines for perioperative cardiovascular evaluation and management for patients undergoing noncardiac surgery have become necessary. The Committee on Preparation for "the Guidelines for Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery", which was established in 2001 at the request of the Scientific Committee of the Japanese Circulation Society, published the first edition of the guidelines in 2002.

While the ACC/AHA Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery highlighted the perioperative management of patients with ischemic heart disease, our guidelines were intended to comprehensively describe ischemic heart disease and other common heart diseases which physicians often encounter during noncardiac surgery, and include risk management during pregnancy and delivery. In the present guidelines, the evidence and general agreement on the efficacy of diagnostic and treatment procedures are classified into Class I to III to help practitioners use the guidelines efficiently.

Class I: Conditions for which there is evidence for and/or general agreement that the procedure/treatment is useful.
Class II: Conditions for which there is conflicting evidence regarding the usefulness of a procedure/treatment.
Class IIa: Weight of opinion is in favor of usefulness.
Class IIb: Usefulness is less well established by evidence.
Class III: Conditions for which there is evidence and general agreement that a procedure/treatment is not useful.

Five years have passed since the release of the first edition of the guidelines, during which time surgical treatment has become more common among elderly patients and the diagnostic and treatment techniques for heart disease have further advanced. The guidelines were thus revised to reflect these changes.

In the present edition, we added to and substantially revised the descriptions about the role of percutaneous coronary intervention (PCI), focusing on drug eluting stents (DES), and aortic stent grafts during the treatment of patients undergoing noncardiac surgery. The descriptions of other cardiovascular diseases were also revised to reflect new findings.

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This English language document is a revised digest version of Guidelines for Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery reported at the Japanese Circulation Society Joint Working Groups performed in 2007 (website: http://www.j-circ.or.jp/guideline/pdf/JCS2008_kyo_d.pdf).
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However, it is quite difficult to conduct prospective randomized clinical studies in patients undergoing surgery, who are often in critical condition, and the data from such studies are also limited in many countries. Please note that the data obtained in this area of study described in the present guidelines may include many biases, as in the case of the first edition.

I Outline

1. Outline of Diagnosis and Evaluation

In order to determine treatment strategies of noncardiac surgery and obtain information necessary to ensure safe surgery, history taking and physical examination should be performed to identify patients in whom the risk for cardiovascular complications is high, and diagnosis and evaluation should then be performed. Physicians should at this point also consider the long-term risk of cardiovascular disease as well. In general, the risk for cardiac complications is high among patients with a marked decrease in exercise capacity (≤ 4 metabolic equivalents [METs]), and careful evaluation of such patients is often necessary.

(1) Risk Classification

The risk factors for cardiac complications during the perioperative period are classified as shown in **Table 1**.[1–7] Patients with major risk factors require intensive care during the perioperative period. In some cases, non-urgent noncardiac surgery must be postponed or cancelled in patients with major risk factors. Systems to predict the incidence of cardiac complications by scoring of relevant factors such as the Cardiac Risk Index System (CRIS) in **Table 2** have been proposed.[8]

(2) Preoperative Evaluation

In principle, preoperative cardiovascular evaluation should be performed using noninvasive techniques. However, Holter ECG and echocardiography are not useful in evaluating the risk of perioperative myocardial infarction. Appropriate techniques must be used, even if they are invasive. In addition, there is little pathological significance to a slight increase in cardiothoracic ratio that results from horizontal position of the heart due to obesity or other causes, or a single supraventricular extrasystole, ectopic sinus rhythm, atrial fibrillation, a single unifocal ventricular extrasystole, or first degree atrioventricular block in patients with excellent exercise capacity. Unnecessary examinations should be avoided. Since the incidence of serious complications of invasive examinations such as cardiac catheterization and cervical angiography is about 1%,[9,10] such examinations must be reserved for patients in whom the results of examination will significantly contribute to the improvement of prognosis and results of noncardiac surgery. **Table 3** lists the criteria for indication of preopera-

Table 1. Risk Factors for Cardiac Complications During the Perioperative Period of Noncardiac Surgery

1) Major risk factors
- Unstable coronary artery disease
  Myocardial infarction occurring 7 to 30 days before surgery with clinical signs/symptoms and laboratory findings of myocardial ischemia detectable on noninvasive examinations, unstable angina, or severe angina (Canadian Class III or IV angina)
- Decompensated congestive heart failure
- Severe arrhythmias
  Advanced atrioventricular block
  Symptomatic ventricular arrhythmia
  Supraventricular arrhythmia associated with abnormal ventricular rates
- Severe valvular disease

2) Intermediate risk factors
- Mild angina (Canadian Class I or II angina)
- History of myocardial infarction with abnormal Q waves
- History of compensated congestive heart failure or congestive heart failure
- Diabetes mellitus
- Renal failure

3) Mild risk factors
- Advanced age
- Abnormal ECG (left ventricular hypertrophy, left bundle branch block, ST-T abnormalities)
- Rhythm other than sinus
- Decrease in cardiac functional capacity (decrease in exercise capacity)
- History of stroke
- Poorly-controlled hypertension

Table 2. Cardiac Risk Index System (CRIS)

		Points
History	Age >70 years	5
	Myocardial infarction in previous 6 months	10
	Aortic stenosis	3
Physical examination	S_3 gallop, jugular venous distention, or congestive heart failure	11
ECG	Rhythm other than sinus	7
	>5 PVC/min	7
General status and laboratory findings	PaO_2 <60 mmHg	3
	$PaCO_2$ >50 mmHg	3
	Potassium <3 mEq/L	3
	BUN >50 mg/dL	3
	Creatinine >3 mg/dL	3
	Bedridden	3
Surgery	Emergency	4
	Intrathoracic	3
	Intraabdominal	3
	Aortic	3

Incidence of cardiac complications
Class I (0 to 5 points): 1%, Class II (6 to 12 points): 5%,
Class III (13 to 25 points): 11%, Class IV (≥26 points): 22%

PVC, premature ventricular contraction; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; BUN, blood urea nitrogen.
Adapted from *N Engl J Med* 1977; **297**: 845–850,[8] with permission from Massachusetts Medical Society.

Table 3. Guidelines for Coronary Angiography

Class I

- Evidence for high risk of adverse outcome based on noninvasive test results
- Angina unresponsive to adequate medical therapy
- Unstable angina
- Equivocal noninvasive test results in patients at high clinical risk and undergoing high-risk surgery

Class III

- Low-risk noncardiac surgery with known coronary artery disease and no high-risk results on noninvasive testing
- For screening of patients not undergoing appropriate noninvasive testing*
- Asymptomatic after coronary revascularization with excellent exercise capacity
- Mild stable angina with good left ventricular function and no high-risk noninvasive test results
- Noncandidate for coronary revascularization owing to concomitant medical illness, or severe left ventricular dysfunction
- Undergoing adequate coronary angiography within 5 year*
- Refusal to consider coronary revascularization

Adapted from *J Am Coll Cardiol* 2002; **39**: 542–553,[11] with permission from Elsevier Inc. *Added to this table.

tive coronary angiography.[11] It is expected that innovative techniques such as multislice computed tomography (CT) will change diagnostic strategies in the near future.

It should be noted that stress ECG, stress myocardial perfusion imaging, and other techniques commonly considered noninvasive procedures may occasionally cause even death when significant stenosis of the left main coronary trunk or severe aortic valve stenosis is present.

(3) Perioperative Monitoring

Although it is important to promptly detect perioperative cardiac complications in patients undergoing noncardiac surgery, appropriate monitoring should be performed in selected patients in whom cardiac complications are likely to occur for appropriate period of time. Excessive use of invasive monitoring must be avoided. Esophageal stethoscopes, peripheral temperature and percutaneous oxygen saturation monitoring are not specific for cardiac complication.

i) ECG

ECG monitoring is best performed for patients with arrhythmia or coronary artery disease. Although postoperative myocardial ischemia is a strong predictive factor for perioperative cardiac complications, angina is missing in many cases. Once perioperative myocardial infarction occurs, 30 to 50% of patients will die, and long-term survival rate will be decreased. ST-segment monitoring is of diagnostic and therapeutic value.[6,12,13] It is preferable that ECG monitoring should be continued until preoperative drug regimens for cardiac complications have been completely resumed. ECG monitoring before, during, immediately after surgery, and succeeding 2 days is a cost-effective strategy.

Arrhythmias during the early postoperative period are often caused by factors other than problems of the heart. Since supraventricular arrhythmia often disappears spontaneously and heart rhythm returns to sinus rhythm after causal factors have been eliminated, cardioversion is not recommended as a routine procedure for patients with it.

Table 4. Recommendations Regarding PCI and Patient Management Prior to Noncardiac Surgery

1. Dual antiplatelet therapy using aspirin and thienopyridine (ticlopidine or clopidogrel) is the most beneficial regimen for preventing in-stent thrombosis. It is recommended that, following stenting, especially using DES, patients undergo dual antiplatelet therapy for 12 months. Early discontinuation of this regimen significantly increase the risks of in-stent thrombosis, myocardial infarction, and death.
2. Physicians should be aware that dual antiplatelet therapy is required after stenting, and consider avoidance of DES implantation in patients who cannot complete 12-months thienopyridine therapy. Physicians should well consider whether to use DES or not in patients who have or are suspected to have malignant disease.
3. For patients who are to undergo PCI and who may require invasive procedures or surgery within 12 months after PCI, physicians should consider use of bare metal stents or balloon angioplasty rather than DES implantation.
4. Physicians should fully explain to patients the importance of antiplatelet therapy with thienopyridine, and instruct them to consult a physician when they need to discontinue antiplatelet therapy.
5. When invasive procedures are performed in patients with stents on antiplatelet therapy, physicians should be aware that early discontinuation of antiplatelet therapy after stenting may have serious complications, and should carefully discuss with cardiologists over the optimal treatment strategy.
6. It is preferable that elective surgery with a high risk of bleeding during and after surgery be avoided during the 12-months period after implantation of DES and at least one month after implantation of bare metal stents.
7. When patients with DES must discontinue thienopyridine therapy for surgical procedures, they should continue aspirin therapy whenever possible, and should resume thienopyridine therapy promptly after surgery. When all antiplatelet agents must be discontinued, it is preferable that patients be treated with heparin. However, there is no evidence of prevention of in-stent thrombosis by heparin therapy in patients receiving DES or bare metal stents, and heparin therapy is empirically conducted in many institutions in Japan.

PCI, percutaneous coronary intervention; DES, drug eluting stents.

ii) Blood Pressure

Patients at risk for abrupt hemodynamic changes during noncardiac surgery should be continuously monitored for blood pressure using an arterial line.[14] Although blood pressure, when used as a single measure, does not accurately reflect hemodynamic condition and cardiovascular events,[15] continuous blood pressure monitoring during a limited period of time is indicated for certain types of patients such as those at high risk of perioperative myocardial infarction.

iii) Central Venous Line, Pulmonary Artery (Swan-Ganz) Catheter

A central venous line is inserted and placed in patients whom significant hemodynamic changes can occur during the perioperative period for inotropic support and rapid fluid administration. However, central venous pressure provides limited information about hemodynamic conditions. Monitoring using a pulmonary artery catheter may enable detailed evaluation of hemodynamics in high-risk patients, though there are problems associated with its insertion and placement.

iv) Transesophageal Echocardiography

Although transesophageal echocardiography gives important informations in patients whom monitoring of blood pressures and cardiac output is not sufficient, its usefulness in patients

Table 5. Guidelines for Use of β Blockers During the Perioperative Period of Noncardiac Surgery

Class I

1. β blockers should be continued in patients undergoing surgery who are receiving β blockers to treat angina, symptomatic arrhythmias, hypertension, or other indications.
2. β blockers should be given to patients undergoing vascular surgery at high cardiac risk owing to the finding of ischemia on preoperative testing.

Class IIa

1. β blockers are probably recommended for patients undergoing vascular surgery in whom preoperative assessment identifies coronary heart disease.
2. β blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk as defined by the presence of multiple clinical risk factors.
3. β blockers are probably recommended for patients in whom preoperative assessment identifies coronary heart disease or high cardiac risk as defined by the presence of multiple clinical risk factors and who are undergoing intermediate- or high-risk procedures.

Class IIb

1. β blockers may be considered for patients who are undergoing intermediate- or high-risk procedures, including vascular surgery, in whom preoperative assessment identifies intermediate cardiac risk as defined by the presence of a single clinical risk factor.
2. β blockers may be considered in patients undergoing vascular surgery with low cardiac risk who are not currently on β blockers.

Class III

1. β blockers should not be given to patients undergoing surgery who have absolute contraindications to β blockade.

Adapted from *J Am Coll Cardiol* 2006; **47**: 2343–2355,[19] with permission from Elsevier Inc.

undergoing noncardiac surgery has not been established.[16,17] Transesophageal echocardiography is a somewhat invasive technique, and its use as a continuous monitoring method should be limited to during surgery.

2. Outline of General Management

(1) Preoperative Management

Although the most common strategy for improving cardiac condition before noncardiac surgery is drug treatment, preoperative intensive care or cardiac surgery may be performed before noncardiac surgery. Generally, preoperative medication for cardiovascular disease should be continued during and after surgery.

i) Cardiac Surgery Before Noncardiac Surgery

There is much debate concerning whether PCI and coronary artery bypass grafting (CABG) prior to noncardiac surgery can improve the short- and long-term prognosis of patients. It is preferable that such cardiac procedures be performed only in patients who meet the criteria provided in the ACC/AHA Guidelines. However, there is much confusion in the clinical setting regarding the indication of PCI, which have recently been advanced. We therefore provide guidelines for the indication of PCI in patients undergoing noncardiac surgery to ensure best practice in the current healthcare environment in Japan (**Table 4**).[18]

Since symptomatic valvular stenosis is often related to perioperative severe heart failure, patients with valvular stenosis often require balloon valvotomy or valve replacement prior to noncardiac surgery. Since patients with valvular regurgitation often maintain stable hemodynamics during the perioperative period, noncardiac surgery may be prioritized in this patient population. However, it is difficult to maintain hemo-

Table 6. Guidelines for the Prevention of Venous Thromboembolism During the Perioperative Period of Noncardiac Surgery

Patient condition and surgical techniques	Indications
Minor surgery in patients <40 years of age with no risk factors*	Early ambulation
Moderate-risk surgery in patients ≥40 years of age with no risk factors	ES, LDH (2 hours preoperatively and every 12 hours after), or IPC of the lower extremities
Major surgery in patients ≥40 years of age with risk factors	LDH (every 8 hours) or LMWH. IPC of the lower extremities if prone to wound bleeding.
Very high-risk surgery in patients ≥40 years of age with risk factors	LDH, LMWH, or dextran combined with IPC of the lower extremities. In selected patients, perioperative warfarin (INR 2.0 to 3.0) may be used.
Total hip replacement	LMWH (postoperative, subcutaneous, twice daily, fixed dose unmonitored) or warfarin (INR 2.0 to 3.0, started preoperatively or immediately after surgery), or adjusted dose unfractionated heparin (started preoperatively). ES or IPC may provide additional efficacy.
Total knee replacement	LMWH (postoperative, subcutaneous, twice daily, fixed dose unmonitored) or IPC of the lower extremities.
Hip fracture surgery	LMWH (preoperative, subcutaneous, fixed dose unmonitored) or warfarin (INR 2.0 to 3.0). IPC of the lower extremities may provide additional benefit.
Intracranial neurosurgery	IPC of the lower extremities with or without ES. Consider adition of LDH in high-risk patients.
Acute spinal cord injury with lower extremity paralysis	Adjusted dose heparin or LMWH for prophylaxis. Warfarin may also be effective. LDH, ES, and IPC of the lower extremities may have benefit when used together.
Patients with multiple trauma	IPC of the lower extremities, warfarin, or LMWH when feasible, serial surveillance with duplex ultrasonography may be useful. In selected very high-risk patients, consider prophylactic inferior vena cava filter.

*Risk factors for venous thromboembolism: Advanced age, prolonged bed rest or paralysis, history of venous thromboembolism, malignant tumor, major surgery of the abdomen, pelvis, or lower extremities, obesity, varicose veins, congestive heart failure, myocardial infarction, stroke, fractures in the abdomen, pelvis, or lower extremities, hypercoagulability, and high-dose estrogen therapy.
ES, graded compression elastic stockings; LDH, low-dose subcutaneous heparin; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; INR, international normalized ratio.
Adapted from *J Am Coll Cardiol* 1996; **27**: 910–948[21], with permission from Elsevier Inc.

dynamics in patients with left ventricular dysfunction.

ii) Hypertension
Untreated or poorly controlled hypertension (diastolic blood pressure ≥110 mmHg) should be controlled prior to noncardiac surgery, preferably with β blockers, which have been suggested to decrease the incidence of perioperative myocardial infarction. Perioperative treatment with β blockers may decrease the incidence of cardiovascular complications of noncardiac surgery not only in patients with hypertension but also in those with heart disease or at high risk of perioperative cardiac events (Table 5).[19] Patients with hypertension before surgery are prone to be hypotensive during surgery,[19,20] and should be carefully managed to avoid perioperative heart/renal complications.

iii) Heart Failure
The presence of dilated or hypertrophic cardiomyopathy is closely associated with perioperative heart failure. Such patients need close evaluation of hemodynamic condition before noncardiac surgery and medical therapy to be eligible for noncardiac surgery, and must undergo intensive care and close monitoring after surgery. Patients with chronic decompensated heart failure, in particular, may benefit from invasive monitoring and intensive care. When noncardiac surgery is indicated children with congenital heart disease and heart failure, they should be treated with digitalis, diuretics, and water restriction to control heart failure before surgery. Some children require treatment with catecholamines and vasodilators.

iv) Venous Thromboembolism
Table 6 shows the guidelines for prevention of venous thromboembolism during the perioperative period of noncardiac surgery.[21]

v) Patients After Cardiac Surgery
The risk of perioperative ischemia or reinfarction is expected to be low in patients following coronary revascularization when they are asymptomatic. However, patients with residual ischemia after coronary revascularization require careful management in a manner similar to that for patients with coronary disease.

It is important to adjust anticoagulation therapy in patients who have undergone mechanical valve replacement. Since the incidence of thrombosis is higher in mitral prosthesis than in aortic prosthesis, patients with mitral prosthesis should be managed more carefully.

The risk of perioperative cardiac complications is generally low among patients who have undergone corrective surgery for congenital heart disease. However, patients should be carefully evaluated for remaining defects. Since patients who have undergone palliative surgery only still have congenital heart disease, careful management is required.

Warfarin therapy should be discontinued one week prior to such surgery if possible, or 2 days prior to the surgery at the latest. Warfarin should be replaced with heparin in patients at high risk of thromboembolism. Vitamin K is sometimes used to antagonize the effects of warfarin prior to emergency surgery. Physicians should be aware that complete normalization of coagulation activity may occur in many cases. High-risk patients such as those with mechanical valves should resume anticoagulation therapy following noncardiac surgery as soon as the risk of bleeding has disappeared.

vi) Malignant Tumors and Cardiac Surgery
When cardiac surgery is performed in patients with malignant tumor, extracorporeal circulation during cardiac surgery may decrease immune function and disseminate cancer cells into the circulation. In patients with ischemic heart disease, such problems may be minimized by selecting off-pump coronary bypass surgery.

(2) Management of Anesthesia and Peri- and Postoperative Management

i) Selection of the Methods and Agents of Anesthesia
There are no particular anesthetic methods that yield significant myocardial protection during surgery. The most important prognostic factors are complications and surgical techniques. Although local anesthesia combined with intravenous anesthesia and/or analgesics was previously considered safe, a report pointed out that 30-day mortality was highest for it among the anesthetic methods evaluated.[22] Epidural anesthesia and spinal anesthesia are used in some cases, but may not be indicated for patients receiving anticoagulants and those with poor cardiac function. The effects of narcotics on the cardiovascular system are stable, but respiratory depression may occur. All volatile anesthetics may affect the cardiovascular system through a decrease in cardiac contractile force and decrease of afterload. When volatile anesthetics are administered to patients with heart diseases, hemodynamics should be monitored very carefully. Recently, intravenous anesthesia with propofol has been established as a standard method of anesthesia. Mask anesthesia, when performed by experienced anesthesiologists, is often safer than local anesthesia, during which respiratory and circulatory management is often difficult.

ii) Maintenance of Body Temperature During Surgery
Hypothermia during surgery is an obvious risk factor for perioperative cardiac events in patients at risk for heart disease. Active warming to maintain body temperature is recommended.[23]

iii) Perioperative Pain Control
Most cardiac events in patients undergoing noncardiac surgery occur during postoperative period. In facilitating early ambulation, normalizing blood coagulation, and preventing postoperative pulmonary embolism, adequate postoperative pain control is quite important. Patient-controlled analgesia (PCA) is a method with high patient satisfaction, and pain scores achieved with PCA are lower than with other analgesic methods. For example, epidural or spinal anesthesia with narcotics is beneficial in many respects, and physicians should consider use of this method when it is possible.

iv) Perioperative Nitroglycerin
Perioperative nitroglycerin therapy may be beneficial in high-risk patients with signs of myocardial ischemia without hypotension who have received nitroglycerin, but is contraindicated for patients with hypovolemia or signs of hypotension.

(3) Prevention of Cardiac Complications During Emergency Surgery

Patients who require emergency surgery often have conditions that may affect the heart such as anemia and hypovolemia. Physicians must often start emergency surgery without appropriate evaluation of the risk of surgery and obtaining information on previous treatment of heart disease. In this situation, patients are likely to develop complications including

Table 7. Pregnancy and Delivery in Patients With Uncorrected Congenital Heart Disease

Atrial septal defect	No problem in most cases
Ventricular septal defect	No problem in most cases
Patent ductus arteriosus	No problem in most cases
Congenital aortic stenosis	Pressure gradient of ≤50mmHg (No problem if ≤25mmHg)
Coarctation of the aorta	Pressure gradient of ≤20 to 30mmHg, asymptomatic
Pulmonary artery stenosis	Pressure gradient of ≤80mmHg
Tetralogy of Fallot	Pregnancy and delivery are dangerous if hematocrit is ≥60%; arterial oxygen saturation is ≤80%; or increased right ventricular pressure had developed or syncope has occurred.
Cyanotic complex cardiac anomalies	No consensus
Eisenmenger syndrome	Contraindicated
Marfan syndrome	No expansion of the ascending aorta

cardiac complications. Physicians must pay special attention to possible ischemic heart disease, since emergency surgery is often initiated without performing coronary angiography, namely, the only method for its definitive evaluation.

i) Preoperative Management

Especially in patients with trauma, it is often difficult to obtain sufficient information before emergency surgery. It is preferable that physicians be aware of the possibility of heart disease. Physicians should assess the presence/absence of known risk factors for heart disease whenever possible. When arteriosclerotic lesions or other findings known to be associated with heart disease are present, physicians should assume that the patient has heart disease and manage them as such. A history of "asthma" is a word of caution, and may in fact represent heart failure.

Physicians should carefully examine the ECG for findings suggestive of myocardial ischemia, and consider coronary artery disease a possible cause of ventricular extrasystole, bradycardia, and/or blocks. When left ventricular hypertrophy is present, the presence of aortic stenosis or cardiomyopathy should be suspected.

Chest X-ray should be carefully evaluated for cardiomegaly, pulmonary congestion, and aortic calcification.

It is quite important to improve general condition before surgery. Anemia, hypovolemia, poor oxygenation, and peripheral hypoperfusion must be treated to the extent possible.

ii) Intraoperative Management

The ECG is often the only continuous monitor available during surgery. Since bleeding and evaporation may exacerbate hypovolemia and anemia, patients should be carefully monitored for myocardial ischemia. When ST change, hypotension, or frequent arrhythmia occurs, hemodynamics and cardiac function should be evaluated using the ECG and transesophageal echocardiography, and appropriate treatment should be given. When heart failure or arrhythmia occurs, it is essential to control water balance, electrolyte balance, and anemia, if present. Since the incidence of ventricular fibrillation increases when the body temperature is 34°C or lower, hypothermia should be prevented.[24] Patients are especially prone to develop hypothermia during surgery with large-volume transfusion and/or rapid fluid administration and extensive surgery. It should be noted that rapid transfusion may cause hypocalcemia.

iii) Postoperative Management

Appropriate postoperative management including adjustment of fluid volume is important to prevent cardiac overload, especially in critically ill patients. Postoperative hyperglycemia may cause osmotic diuresis and consequent dehydration. Following emergency surgery, water and electrolyte balance are prone to be out of order. If hypokalemia is present, patients are more prone to develop atrial fibrillation and ventricular extrasystole.[25]

Prolonged bed rest after emergency surgery may induce venous thrombosis and pulmonary embolism. If a venous line was placed in femoral vein or leg vein before surgery, it should be changed to a new position in the upper extremities after the patient's condition has stabilized.

iv) Injuries to the Heart or Thoracic Great Vessels Associated With Multiple Trauma

Thoracic aorta injury account for many death after blunt trauma, althogh their frequency among total cases is not high.[26,27] Thoracic aorta injury often occur in the ascending aorta and the proximal descending aorta. Since patients with ascending aorta injury often fall into catastrophic condition rapidly, physicians treat patients mainly with injuries of the proximal descending aorta. When chest X-ray reveals a widened mediastinum and a large volume of pleural effusion or when echocardiography reveals pericardial effusion, CT and transesophageal echocardiography should be performed to exclude aortic injury prior to noncardiac surgery.

Priority of treatment in patients with multiple trauma depends on individual cases. When the aorta is repaired first, blood loss during extracorporeal circulation will be a concern, while if noncardiac surgery is performed first, perioperative aortic rupture may develop. When aortic injury is managed conservatively, the patient should be carefully evaluated to find out conditions requiring aggressive surgical treatment. CT is the most useful method for objective evaluation in such circumstances.

3. Pregnancy/Delivery and Heart Disease

(1) Pregnancy and Delivery in Patients With Congenital Heart Disease

Pregnancy and delivery pose no serious threats in women who had undergone corrective surgery for simple heart malformation or tetralogy of Fallot and have New York Heart Association (NYHA) Class II or better cardiac function. However, women should be carefully evaluated for remaining defects, since heart failure and/or arrhythmia may develop and cyanosis may be exacerbated during pregnancy and delivery.[28,29] **Table 7** outlines the safety of pregnancy and delivery for women with uncorrected congenital heart disease.[29–32]

Although cases of pregnancy and delivery in women with cyanotic complex cardiac anomalies such as complete transposition of the great arteries, tricuspid atresia, and univentricular heart who have or have not undergone corrective surgeries have been reported, the risk of death and complications including fetus associated with pregnancy is quite high in this population. Live birth is rare among women with an arterial oxygen saturation ≤85%.[33] Among women with

Table 8. Recommendations for Anticoagulation Therapy During Pregnancy in Patients With Mechanical Prosthetic Valves

a) **Weeks 1 through 35**

Class I

1. The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner; if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.
2. High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose not to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the mid-interval (6 hours after dosing) aPTT to 2 to 3 times control. Transition to warfarin can occur thereafter.

Class IIa

In patients receiving warfarin, INR should be maintained between 2.0 and 3.0 with the lowest possible dose of warfarin, and low-dose aspirin should be added.

Class IIb

Women at low risk (no history of thromboembolism, newer low-profile prosthesis) may be managed with adjusted-dose subcutaneous heparin (17,500 to 20,000 U BID) to prolong the mid-interval (6 hours after dosing) aPTT to 2 to 3 times control.

b) **After the 36th week**

Class IIa

1. Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor.
2. If labor begins during treatment with warfarin, a Caesarian section should be performed.
3. In the absence of significant bleeding, heparin can be resumed 4 to 6 hours after delivery and warfarin begun orally.

aPTT, activated partial thromboplastin time; INR, international normalized ratio; U, unit; BID, twice a day.
Adapted from *J Am Coll Cardiol* 1998; **32**: 1486–1588[39], with permission from Elsevier Inc.

Table 9. Antibiotic Prophylaxis During Labor and Delivery

1. **Standard regimen (Ampicillin, gentamicin, and amoxicillin)**
   - Initial dose
     30 minutes before procedure: Ampicillin 2 g plus gentamicin 1.5 mg/kg (maximal dose 80 mg) IV or IM
   - Next dose
     6 hours after initial dose: Amoxicillin 1.5 g PO (if this is not possible, repeat the initial-dose regimen 8 hours after initial dose)
2. **Allergic to ampicillin, amoxicillin, or penicillin (Vancomycin and gentamicin)**
   - Initial dose
     1 hour before procedure: Vancomycin 1 g IV (over ≥1 hour) plus gentamicin 1.5 mg/kg (maximal dose 80 mg) IV or IM
   - Next dose (if necessary)
     8 hours after initial dose: Repeat the initial-dose regimen
3. **Low-risk patients (Amoxicillin)**
   - Initial dose
     1 hour before procedure: Amoxicillin 3 g PO
   - Next dose
     6 hours after initial dose: Amoxicillin 1.5 g PO

IV, intravenous injection; IM, intramuscular injection; PO, oral administration.
Adapted from Elkayam U, Pregnancy and cardiovascular disease. *In*: Braunwald E, editor. Heart disease. A textbook of cardiovascular medicine, 5th edn. W.B. Saunders Company, 1997; 1843–1864[30]; with permission from Elsevier Inc.

complete transposition of the great arteries who have undergone the atrial switch operation, special care should be taken for those with decrease in function of the anatomical right ventricle, those complicated with atrioventricular valve regurgitation, and those complicated with sinus dysfunction. Data are limited on pregnancy and delivery in women following the Fontan procedure.

In women with Ebstein's malformation, the type and incidence of complications such as right heart failure, paradoxical embolism, and infectious endocarditis depend on the severity of tricuspid insufficiency, presence/absence of existing right heart failure, and severity of cyanosis.[34] Although the presence of cyanosis increases the incidence of complications of pregnancy and delivery,[35] a number of successful pregnancies and deliveries in women with Ebstein's malformation have been reported.[36]

(2) Pregnancy and Delivery in Women With Valvular Disease

Pregnant women with mild or moderate mitral stenosis may receive diuretics and β blockers to prevent and treat congestive heart failure and tachycardia,[37] respectively. Diuretics should be used carefully, since excessive use of them may cause hypovolemia and result in suboptimal uteroplacental circulation.[30,38] Percutaneous mitral valvuloplasty may be indicated for severe mitral stenosis before pregnancy. When heart failure not responding to medical therapy develops during pregnancy, physicians should consider percutaneous mitral valvuloplasty.[30] Pregnancy and delivery in women with acquired aortic stenosis should be treated similarly to that in those with congenital aortic stenosis. Mitral insufficiency and aortic insufficiency may often be treated with medical therapy when patient's condition is not severe. Angiotensin converting enzyme (ACE) inhibitors must be avoided during pregnancy, since these drugs will affect the development of the fetus. Surgery before pregnancy should be considered when women with severe valvular disease wish to become pregnant.

(3) Pregnancy and Delivery in Patients With Mechanical Prosthetic Valves

Table 8 shows the recommendations for anticoagulation therapy in pregnant women with mechanical prosthetic valves.[39] Both warfarin and heparin may pose the risk of bleeding and thrombosis in the mother and the fetus. Warfarin, which passes through the placenta, increases the incidences of spontaneous abortion, premature birth, and stillbirth, and causes fetal malformation in 0 to 20% of mothers receiving warfarin (the average incidence in the four most recent reports is 1.6%). The risk of fetal malformation is especially high when warfarin is administered during weeks 6 to 12 of gestation.[38] Although heparin therapy is considered safe, since it does not pass through the placenta, long-term heparin therapy may cause such as noninfective abscess, osteoporosis, thrombocytopenia, and bleeding.[39] It has been reported that thromboembolism occurs in 4 to 14% of patients receiving adequate anticoagulation therapy with heparin.[40–42]

Bioprosthetic valves are believed to be a good option for women who wish to become pregnant, since anticoagulation

Table 10. Effects of Cardiovascular Drugs During Pregnancy

Drug	Potential fetal adverse effects	Safety
Warfarin	Fetal bleeding in utero, embryopathy, CNS abnormalities	Unsafe
Heparin	None reported	Probably safe
Digoxin	Low birth weight	Safe
Quinidine	Toxic dose may induce premature labor and cause damage to fetal eighth cranial nerve	Safe
Procainamide	None reported	Not established
Disopyramide	May initiate uterine contractions	Not established
Lidocaine	In high blood levels and fetal acidosis may cause CNS depression	Safe
Mexiletine	Fetal bradycardia, intraurine growth retardation, low Apgar score, neonatal hypoglycemia, neonatal bradycardia, neonatal hypothyroidism	Not established
Flecainide	One reported fetal death	Not established
Amiodarone	Intraurine growth retardation, prematurity, hypothyroidism	Unsafe
Calcium blockers	Fetal distress due to maternal hypotension	Not established
β blockers	Intraurine growth retardation, apnea at birth, bradycardia, hypoglycemia, hyperbilirubinemia β_2 blockers may initiate uterine contractions	Safe
Hydralazine	None reported	Safe
Sodium nitroprusside	Potential thiocyanate toxicity with high dose, fetal mortality with nitroprusside in animal studies	Potentially unsafe
Organic nitrates	Fetal bradycardia	Not established
ACE inhibitors	Skull ossification defect, intraurine growth retardation, premature deliveries, low birth weight, oligohydramnios, neonatal renal failure, anemia and death, limb contractures, patent ductus arteriosus	Unsafe
Diuretics	Impairment of uterine blood flow, thrombocytopenia, jaundice, hyponatremia, bradycardia	Potentially unsafe

CNS, central nervous system; ACE, angiotensin converting enzyme.
Adapted from *J Am Coll Cardiol* 1998; **32**: 1486–1588[39], with permission from Elsevier Inc.

therapy is not necessary in patients with such valves unless they have a history of atrial fibrillation or thromboembolism. However, it is known that bioprosthetic valves deteriorate more rapidly in young patients, and reports have noted that deterioration of bioprosthetic valves is further promoted during pregnancy.[38,42,43] Physicians should adequately explain to patients the fact that they may have to undergo reoperation earlier as a result of pregnancy.

(4) Prevention of Infection During Pregnancy and Delivery in Patients With Heart Disease

The incidence of infective endocarditis after uncomplicated vaginal delivery in women with heart disease is believed to be low, and it is not generally recommended that patients in this population receive antibiotic prophylaxis. However, antibiotic prophylaxis during delivery is performed in patients with prosthetic valves, those with a history of endocarditis, those following corrective surgery of congenital heart malformation (depending on condition), those following shunt surgery, and those with mitral prolapse or insufficiency.[30] **Table 9** shows common methods of antibiotic prophylaxis.[30]

(5) Effects of Cardiovascular Drugs During Pregnancy

Table 10 presents the current findings on cardiovascular drugs commonly used during pregnancy.[30,39,44]

II Descriptions

1. Ischemic Heart Disease

(1) Diagnosis

Physicians should interview patients for subjective symptoms, personal and family history of ischemic heart disease, and the presence/absence of coronary risk factors and conditions frequently associated with ischemic heart disease. It should be noted that patients with diabetes and elderly patients often do not complain of significant symptoms of angina. It is important to check for exertional angina as well as atypical angina due to coronary spasm. It is common for the chest X-ray to reveal few findings typical of ischemic heart disease, and ECG at rest in the absence of anginal attacks is normal. Definitive diagnosis of ischemic heart disease can be made with coronary angiography. **Figure 1** shows a flow chart for considering indications for coronary angiography according to risk of noncardiac surgery.[21]

(2) Severity Evaluation and Risk

The severity of myocardial ischemia is correlated with angiographic findings such as the number of affected vessels, level of stenosis, and presence/absence of stenosis in the left main trunk, as well as the severity of angina. Evaluation of cardiac function and degree of mitral regurgitation is quite important for appropriate perioperative management of patients undergoing noncardiac surgery.

(3) Special Management

The indications for coronary revascularization as a part of management of patients undergoing noncardiac surgery are basically identical to those in patients in general. However, transcatheter intervention on PCI is especially preferred to bypass surgery in patients whose noncardiac disease has a poor prognosis and those in poor general condition including bleeding tendency.

There are several issues for patients whom CABG is indicated. Off-pump CABG and minimally invasive direct coro-

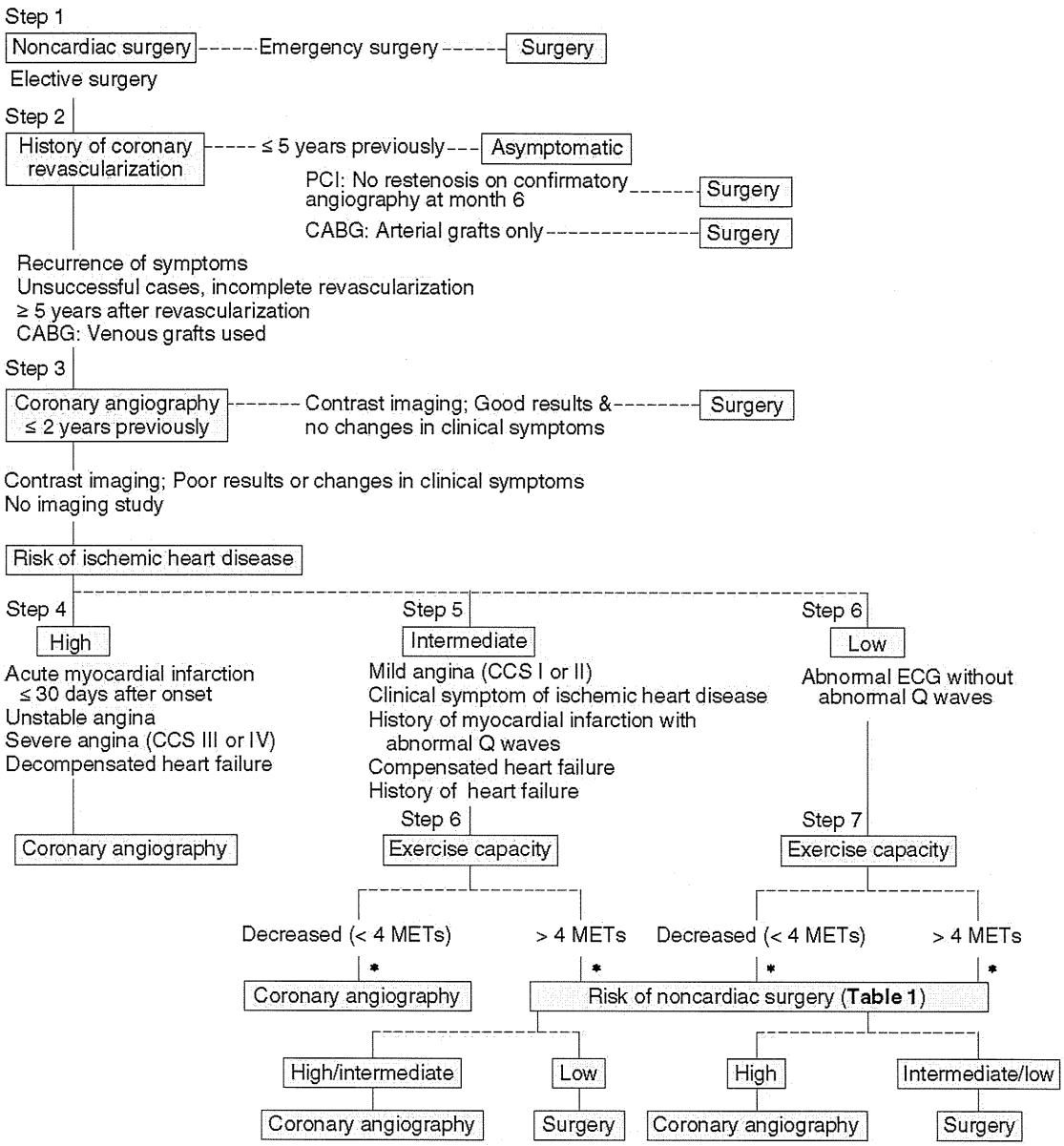

Figure 1. Flow chart of preoperative cardiac evaluation including coronary angiography. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; METs, metabolic equivalents. *Evaluation may include echocardiography, myocardial imaging, exercise stress testing, other than exercise stress testing, and Holter ECG. Consider cost-effectiveness of each testing.

nary artery bypass (MIDCAB) have been gaining popularity[45] although no consensus exists about the effects of extracorporeal circulation on malignant tumors. It is also important whether coronary revascularization and noncardiac surgery should be performed simultaneously or as two-stage surgery. Physicians should determine the schedule of surgeries carefully considering surgical invasiveness, posture during surgery, risk of surgical site contamination, and urgency of noncardiac surgery. If two-stage surgery is a choice, patency of bypass grafts and perioperative drug treatment will be major concerns in patients undergoing CABG first, while prevention of perioperative myocardial infarction will be important in patients undergoing noncardiac surgery first.

In patients undergoing PCI prior to noncardiac surgery, it has been recommended that conventional PCI without stenting be performed about 1 to 2 weeks prior to noncardiac surgery. However, PCI using stents, especially DES, requires potent anticoagulation therapy for a longer period of time, which may pose risks during noncardiac surgery and significantly affect the timing of noncardiac surgery. The use of DES should be considered only in selected cases (**Table 4**).[18]

(4) Intraaortic Balloon Pumping

Although intraaortic balloon pumping (IABP) may increase coronary blood flow, support cardiac function, and decrease afterload, the efficacy of perioperative IABP use in patients

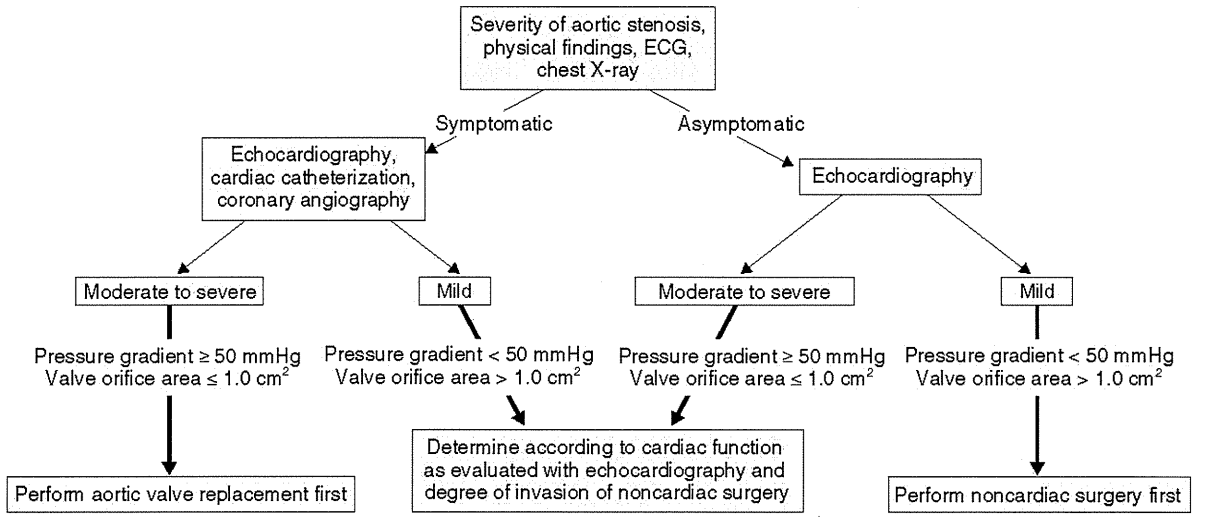

Figure 2. Treatment strategies for noncardiac surgery in patients with aortic stenosis.

undergoing noncardiac surgery has not been established. IABP support may be continued before and throughout surgery. A trocar may be placed in the femoral artery before surgery to ensure prompt insertion of IABP, or emergency IABP may be initiated during or after surgery. It should be noted that certain body positions hinder the use of IABP.

(5) Precautions Regarding Anesthesia and Perioperative Management in Patients Undergoing Noncardiac Surgery

Anesthesia should be induced with fentanyl, which causes fewer hypotension, and benzodiazepines such as midazolam and diazepam, and should be maintained with neuroleptanalgesia (NLA). Combined use with epidural anesthesia has been reported to be useful. When coronary vasodilators are used, physicians should be aware of the characteristics of drugs, i.e. low incidence of hypotension (Nitrol and nicorandil), short duration of action after withdrawal (nitroglycerin), and inhibition of spasm and slowing of heart rate (diltiazem), and should select appropriate drugs according to patient's condition. Small doses of dopamine may be useful to treat hypotension during surgery. Patients with severe coronary spasm should be treated with adequate doses of calcium blockers, undergo measures to prevent hypothermia and respiratory alkalosis, and have their blood pressure adequately controlled. During noncardiac surgery in patients with frequent ventricular extrasystoles, physicians should infuse lidocaine continuously, monitor and maintain serum potassium level, and keep an external defibrillator ready for use. "Precautions for anesthesia in cardiac surgery" should be followed.

2. Valvular Heart Disease

When cardiac murmur is heard prior to noncardiac surgery, physicians must identify the cause of the murmur, consider whether the murmur reflects a serious condition or not, whether further assessment is needed to investigate its severity, and whether prevention of infectious endocarditis is required. Diastolic murmurs are almost always pathologically significant, and diagnosis and investigation of them are required. It is quite rare for functional murmurs with a grade ≥III to IV on the Levine scale to be heard, but the loudness of murmurs depends on body size and does not accurately reflect the severity of valvular disease.

(1) Valvular Diseases and Noncardiac Surgery

i) Aortic Stenosis

Severe aortic stenosis is one of the most important risk factors for cardiac complications during noncardiac surgery.[46] It is preferable that noncardiac surgery be avoided or aortic valve replacement be performed prior to noncardiac surgery in patients with symptomatic aortic stenosis with a left ventricular-aortic pressure gradient of ≥50 mmHg, syncope, anginal pain, and/or left heart failure (**Figure 2**).[47]

ii) Mitral Insufficiency

No specific measures are required during noncardiac surgery in patients with mild or moderate mitral regurgitation and without signs/symptoms of heart failure. However, antibiotic prophylaxis is needed to prevent infectious endocarditis. Mitral valve surgery such as valvuloplasty and prosthetic valve replacement should be performed first in patients with grade ≥III mitral regurgitation and signs/symptoms of heart failure. It should be noted that mitral insufficiency often cause a seemingly favorable left ventricular ejection fraction. Perioperative antibiotic therapy is required to prevent infections not only in patients with clinically significant mitral valve prolapse but also in asymptomatic patients in whom echocardiography reveals findings of mitral regurgitation or thickened valve leaflets.[48]

iii) Tricuspid Insufficiency

Since patients with severe tricuspid insufficiency may exhibit significant hepatic congestion possibly resulting in hepatic disorders such as hepatic cirrhosis, modification of treatment strategies is often required if high-risk noncardiac surgery is to be performed.

iv) Aortic Insufficiency

In patients with aortic regurgitation of grade II or less, noncar-

diac surgery may be performed before cardiac surgery when appropriate measures including the prevention of infectious endocarditis are taken. In patients with aortic regurgitation of grade III or higher and those with clinical symptoms, physicians should be aware that the risk of noncardiac surgery is, depending on the type of surgery performed, often significantly high when performed prior to surgical treatment of aortic regurgitation. Fatal arrhythmia may occur in this patient population, and perioperative management is difficult. Although the risk of noncardiac surgery varies according to the type of procedure, it is preferable that surgical treatment of aortic valves be performed first before left heart function has significantly exacerbated.[49–51]

v) Mitral Stenosis

Most noncardiac surgical procedures may be performed in patients with mitral stenosis with a valve orifice area of ≥1.5 cm^2. However, heart rate should be controlled during the perioperative period, since tachycardia may induce serious pulmonary congestion. It is preferable that patients with severe mitral stenosis undergo percutaneous transcatheter balloon mitral commissurotomy, or surgical commissurotomy or mitral valve replacement before undergoing high-risk noncardiac surgery.[47]

vi) Prosthetic Valves

In order to prevent infectious endocarditis during the perioperative period, antibiotics should be administered to patients with prosthetic valves from the day before noncardiac surgery until laboratory data, such as leukocyte count and C-reactive protein (CRP), normalize, for example, 7 days after surgery. Anticoagulation therapy should be adjusted according to individual patient condition, considering the effects of anticoagulants that have been decreased in dose and the effects of heparin initiated during the perioperative period. Although patients with prosthetic valves used do discontinue anticoagulation therapy for about 3 days prior to less invasive procedures (such as dental treatment and surface biopsy), it is becoming a common practice that anticoagulation therapy is continued for less invasive procedures such as dental treatment. Perioperative heparin therapy is recommended for patients in whom the risk of bleeding is high when receiving oral anticoagulants and the risk of thromboembolism is also high in the absence of anticoagulant (e.g., patients with a mitral valve prosthesis are to undergo major surgery). Whenever possible, anticoagulation therapy should be discontinued one week before surgery, and heparin therapy should be initiated when prothrombin time and international normalized ratio (PT-INR) decreases below the therapeutic range. Although the optimal dose differs among individuals, heparin should be administered by continuous intravenous infusion at a dose of about 5,000 to 15,000 units/day until the day of surgery. Following surgery, the absence of postoperative bleeding must be confirmed, and administration of anticoagulants at regular doses should be resumed when patients can take drugs orally. When that is impossible, heparin should be administered as mentioned above until treatment with oral anticoagulants can be resumed.

(2) Treatment of Valvular Disease Before Noncardiac Surgery

Cardiac surgery is the only option available for patients with severe valve insufficiency. When patients with severe mitral stenosis need emergency noncardiac surgery such as repair for serious gastrointestinal bleeding, catheter balloon valvuloplasty is believed to reduce the risks of such surgery, and therefore to be beneficial.[52] However, mitral valve replacement is required in patients with atrial fibrillation, those with left atrial thrombus, and patients with very severe valve lesions.[53] Balloon valvuloplasty for aortic stenosis is not recommended. Since only limited data are available to this procedure, and the risk in elderly patients is quite high.

(3) Management of Patients With Valvular Disease During Noncardiac Surgery

In patients with valve regurgitation, low peripheral vascular resistance is important. Hypertension is harmful, vasodilators should be used if necessary. On the other hand, patients with severe valve stenosis are often unable to accommodate hemodynamic changes due to fluid overload. Volume overload induces congestive heart failure, while excessive dehydration may cause circulatory collapse. Water balance should be managed strictly, especially in patients with aortic and mitral stenoses regardless of the severity of valve lesions. Since arrhythmia often occurs in patients with valvular diseases, appropriate antiarrhythmic therapy and heart rate control play key roles during the perioperative period.

3. Treatment of Congenital Heart Disease Before Corrective Surgery

The mortality after noncardiac surgery in neonates and infants with congenital heart disease is about twice that in those without it, and it has been reported that the presence of congenital heart disease significantly increases the risk of mortality even after minor noncardiac surgery.[54]

(1) Neonates and Infants

The prevalence of heart disease in neonates is 13.2 to 43% among those with esophageal atresia, 9 to 12.1% among those with anal atresia, 13.9 to 45.5% in those with exomphalos, 17.9 to 33% in those with duodenal atresia, and 10.5 to 12.5% in those with diaphragmatic hernia.[55–63] Children born with conditions requiring surgical treatment immediately after birth should be evaluated with echocardiography.

Although the methods of surgical correction of anal atresia and intestinal atresia/stenosis are well established, the mortality rates of neonates and infants with large exomphalos and diaphragmatic hernia are still high. In such infants, it is quite difficult to perform surgical correction of heart disease during early infancy. In children with esophageal atresia and heart disease, correction of esophageal atresia is often performed first. However, no consensus has been reached regarding the timing of heart surgery (before or after correction of esophageal atresia) or the strategy of treatment for esophageal atresia (one- or two-stage corrective surgery).

In neonates with congenital heart diseases that increase pulmonary blood flow, surgical correction of noncardiac disease may be performed during the first several days of life, during the period when pulmonary vascular resistance remains high, while in neonates with congenital heart diseases that decrease pulmonary blood flow, noncardiac surgery may be performed when cyanosis has improved by treatment with prostaglandin (PG) E_1 (0.05 to 0.1 μg/kg/min) to a stable hemodynamic condition.[55] No consensus exists regarding treatment strategy or the order of cardiac and noncardiac surgeries in patients with complex heart disease who exhibit cyanosis and increased pulmonary blood flow.

Many types of congenital heart diseases can be diagnosed

Table 11. Cardiac Risk Factors in Adult Patients With Congenital Heart Disease

1) **Major risk factors: Fatal cardiac complications may occur. Cardiac repair may be indicated first in some conditions.**
   * Eisenmenger syndrome
   * Significant persistent lesions/complications following reparative surgery
   * Decompensated heart failure
   * Severe hypoxemia (untreated cyanotic heart disease, following palliative surgery)
   * Severe arrhythmia

   Recommended management: Patients should be admitted to the intensive care unit (ICU) for perioperative management by specialists. Discontinuation or postponement of non-urgent noncardiac surgery is preferable. If corrective treatment (including catheter techniques, and/or pacemaker placement) is indicated for heart disease, it should be treated first.
2) **Intermediate risk factors: Factors that increase the risk of perioperative cardiac complications. Patient's condition should be carefully evaluated.**
   * Moderate persistent lesions/complications following reparative surgery
   * Compensated heart failure
   * Following palliative surgery (hypoxemia is present)

   Recommended management: Patients should be evaluated using necessary and sufficient intraoperative monitoring, and should be considered for treatment in the ICU during perioperative period whenever necessary.
3) **Mild risk factors: Cardiovascular abnormalities that have not themselves been demonstrated to increase the risk of perioperative cardiac complications.**
   * Congenital heart disease not requiring repair
   * Patients after cardiac repair in whom continued treatment is not required

Table 12. Severity of Residual Problems Following Corrective Surgery

Pulmonary hypertension (pulmonary arterial systolic pressure)		
Mild	30 to 50mmHg	
Moderate	50 to 70mmHg	
Severe	≥70mmHg	
Pulmonary artery stenosis or extracardiac conduit stenosis		
	Right ventricular pressure (pulmonary artery stenosis)	**Pressure gradient (extracardiac conduit stenosis)**
Mild	50 to 70mmHg	30 to 60mmHg
Moderate	70 to 100mmHg	60 to 90mmHg
Severe	≥100mmHg	≥90mmHg
Persistent left-to-right shunt		
	Pulmonary to systemic flow ratio (Qp/Qs)	
Mild	<1.5	
Moderate	1.5 to 2.0	
Severe	≥2.0	

with echocardiography, and cardiac catheterization and/or angiography is rarely required.

(2) Young Children

Baum et al reported that, in children ≥1 year of age, the mortality after noncardiac surgery was slightly higher in those with cardiac disease,[54] though the difference was not significant. Pulmonary hypertension (PH) and severe cyanosis and so on are considered as risk factors for mortality after noncardiac surgery, though no evidence has been obtained for this. Clinical experience has suggested that children following palliative surgeries such as shunt surgery and the Glenn procedure can tolerate noncardiac surgery well. When anesthetic procedures requiring mechanical ventilation are performed, prompt extubation may be preferable for ensuring favorable hemodynamics.

4. Adults With Congenital Heart Disease

(1) Cardiovascular Evaluation Prior to Noncardiac Surgery

Patients with congenital heart disease planned to undergo noncardiac surgery should be evaluated for history of cardiac surgery and the procedures used, presence/absence and type of persistent heart lesions, complications and sequelae of heart disease, clinical course after heart surgery, and current condition.

In patients planned to undergo low-risk noncardiac surgery as defined in the ACC/AHA Guidelines,[21] routine preoperative evaluation is sufficient. When high- or intermediate-risk noncardiac surgery is planned, patients should be evaluated for cardiovascular abnormality in detail. If the results are poor, cardiac surgery or catheter intervention prior to noncardiac surgery may be considered.

(2) Cardiac Risk Factors During the Perioperative Period

Table 11 lists common risk factors in adult patients with congenital heart disease.[21]

(3) Examinations Used in Preoperative Evaluation of Risk Factors

All patients with congenital heart disease require preoperative evaluation with 12-lead ECG, chest X-ray, and echocardiography. While arterial blood gas analysis, pulmonary ventilation/perfusion scintigraphy, and Holter ECG may be necessary in some cases, exercise stress testing and cardiac catheterization are indicated for only a small number of patients.

(4) Criteria for Severity of Persistent Heart Lesions

Table 12 presents the criteria for severity of heart lesions remaining after corrective surgery for congenital heart disease.[64]

(5) Problems Following Corrective Surgery

Following corrective surgery for acyanotic congenital heart disease, patients may experience embolism secondary to atrial arrhythmia/fibrillation; congestive heart failure due to a residual shunt; severe PH; mitral insufficiency/stenosis or left ventricular outflow obstruction following correction of atrioventricular septal defect; and restenosis of repaired aortic coarctation, among other conditions.

Patients born with cyanotic complex cardiac anomaly may often require reoperation at a later age even if they are treated with corrective surgery. Depending on the procedure of the corrective surgery, patients may exhibit characteristic hemodynamic changes for which special management may be needed during noncardiac surgery. Patients with the conditions listed in Table 12,[64] valvular regurgitation, or serious arrhythmia must be treated especially carefully. Patients with following conditions need special care: for patients after atrial switch operation, vena cava obstruction, pulmonary venous stenosis, right ventricular dysfunction which acts as systemic ventricle. For patients after atrial switch operation, pulmonary

Table 13. AHA Recommendations on Prophylactic Regimens for the Prevention of Infectious Endocarditis

1. Dental/upper respiratory tract procedures

(1) Standard
Amoxicillin 3g PO (1 hour before procedure)+amoxicillin 1.5g PO (6 hours after)

(2) High-risk patients
Ampicillin 2g+gentamicin 1.5mg/kg IV or IM (30 minutes before procedure)+amoxicillin 1.5g PO (6 hours after)

(3) Allergic to amoxicillin/penicillin
Erythromycin 1g PO (2 hours before procedure)+erythromycin 0.5g PO (6 hours after)
or
Clindamycin 300mg PO (1 hour before procedure)+clindamycin 150mg PO (6 hours after)

2. Gastrointestinal/genitourinary procedures

(1) Standard
Ampicillin 2g+gentamicin 1.5mg/kg IV or IM (30 minutes before procedure), amoxicillin 1.5g PO (6 hours after)

(2) Allergic to ampicillin/amoxicillin/penicillin
Vancomycin 1g IV+gentamicin 1.5mg/kg IV or IM (1 hour before procedure); may be repeated 8 hours after.

(3) Low-risk patients
Amoxicillin 3g PO (1 hour before procedure)+amoxicillin 1.5g PO (6 hours after)

PO, oral administration; IV, intravenous injection; IM, intramuscular injection.
Adapted from *JAMA* 1990; **264**: 2919–2922[48], with permission from American Medical Association.

artery stenosis. Patients who had undergone Fontan operation are prone to heart failure. About 10 years after the Fontan operation, patients are prone to develop supraventricular arrhythmias, thromboembolism, protein-losing gastroenteropathy, hepatic congestion, hepatic dysfunction, decrease in cardiac function, or other abnormal conditions, and thus require careful management.

(6) Problems With Uncorrected Congenital Heart Disease

No special perioperative management is required for noncardiac surgery in patients with congenital heart disease not indicated for surgery such as small atrial or ventricular septal defect and acyanotic tetralogy of Fallot. Many patients with large uncorrected left-to-right shunt exhibit Eisenmenger syndrome, and the risk of noncardiac surgery is quite high in these patients. Patients with cyanosis must be carefully managed for hypoxemia, polycythemia, prevention of visceral disorder, brain abscess, and infectious endocarditis.

(7) Important Aspects of Perioperative Management

Perioperative management of patients with a history of congenital heart disease who are undergoing noncardiac surgery is performed mainly to prevent heart failure, hypoxemia, and arrhythmias. Selective pulmonary vasorelaxants are effective in patients with right ventricular failure. It is important to prevent infectious endocarditis, air embolism, and brain abscess in patients with cyanotic heart disease. Table 13 lists the AHA's recommendations on antibiotic treatment for the prevention of infectious endocarditis.[48]

5. Aortic Diseases

(1) Diagnosis and Evaluation of Thoracic Aortic Aneurysm During Noncardiac Surgery

Table 14 lists the indications for surgical treatment of thoracic aortic aneurysm (TAA).

Table 14. Indications for Surgical Treatment (Including Interventions) of Aortic Aneurysms

Indications for surgical treatment of true aortic aneurysm

Class I:
- Ruptured aortic aneurysm
- Ascending aortic aneurysm associated with severe complications (aortic insufficiency associated with heart failure, or cardiac tamponade)
- Sinus of Valsalva aneurysm associated with intracardiac shunt (ruptured sinus of Valsalva aneurysm)
- True TAA ≥6cm of maximal diameter

Class IIa:
- True TAA ≥5cm in diameter in patients with Marfan syndrome
- True TAA 5 to 6cm in diameter
- Saccular aortic aneurysm
- True TAA associated with rapid expansion in diameter (>5mm/6 months)

Class IIb:
- True TAA 4 to 5cm in diameter

Indications for surgical treatment of false aortic aneurysm

Class I: All diagnosed false aortic aneurysms not associated with other organ injuries

Class IIb: False aortic aneurysm associated with other organ injuries

Indications for surgical treatment of dissecting aortic aneurysm

Class I:
- Type A acute dissection with patent false lumen (type I, II dissecting, type III retrograde)
- Aortic dissection with severe complications which surgery may improve or prevent progression of ruptured false lumen, redissection, cardiac tamponade, circulatory disorder associated with loss of consciousness and paralysis, aortic insufficiency associated with heart failure, myocardial infarction, blood flow disturbance in the visceral organs or the extremities
- Aortic dissection associated with aortic expansion (>6cm of maximal diameter)
- Chronic dissection associated with rapid aortic expansion in diameter (>5mm/6 months)

Class IIa:
- Aortic dissection not responding to blood pressure control and pain drug control
- Aortic dissection associated with Marfan syndrome

Class IIb:
- Type A acute dissection with occluded false lumen
- Aortic dissection 5 to 6cm of maximal diameter

TAA, thoracic aortic aneurysm.

Most patients with true aortic aneurysm, other than those with ruptured aortic aneurysm or impending aneurysm rupture, are asymptomatic.[65,66] When aortic aneurysm is suspected on chest X-ray or other examinations, contrast CT or magnetic resonance imaging (MRI) should be performed to confirm the diagnosis.[67,68] Avoidance of angiography is increasingly common now.

False aortic aneurysm developes mainly after injury, but is often overlooked during the period immediately after its development. Since the risk of rupture is high, patients diagnosed with false aortic aneurysm should be transferred as soon as possible to institutions where appropriate treatment is available.

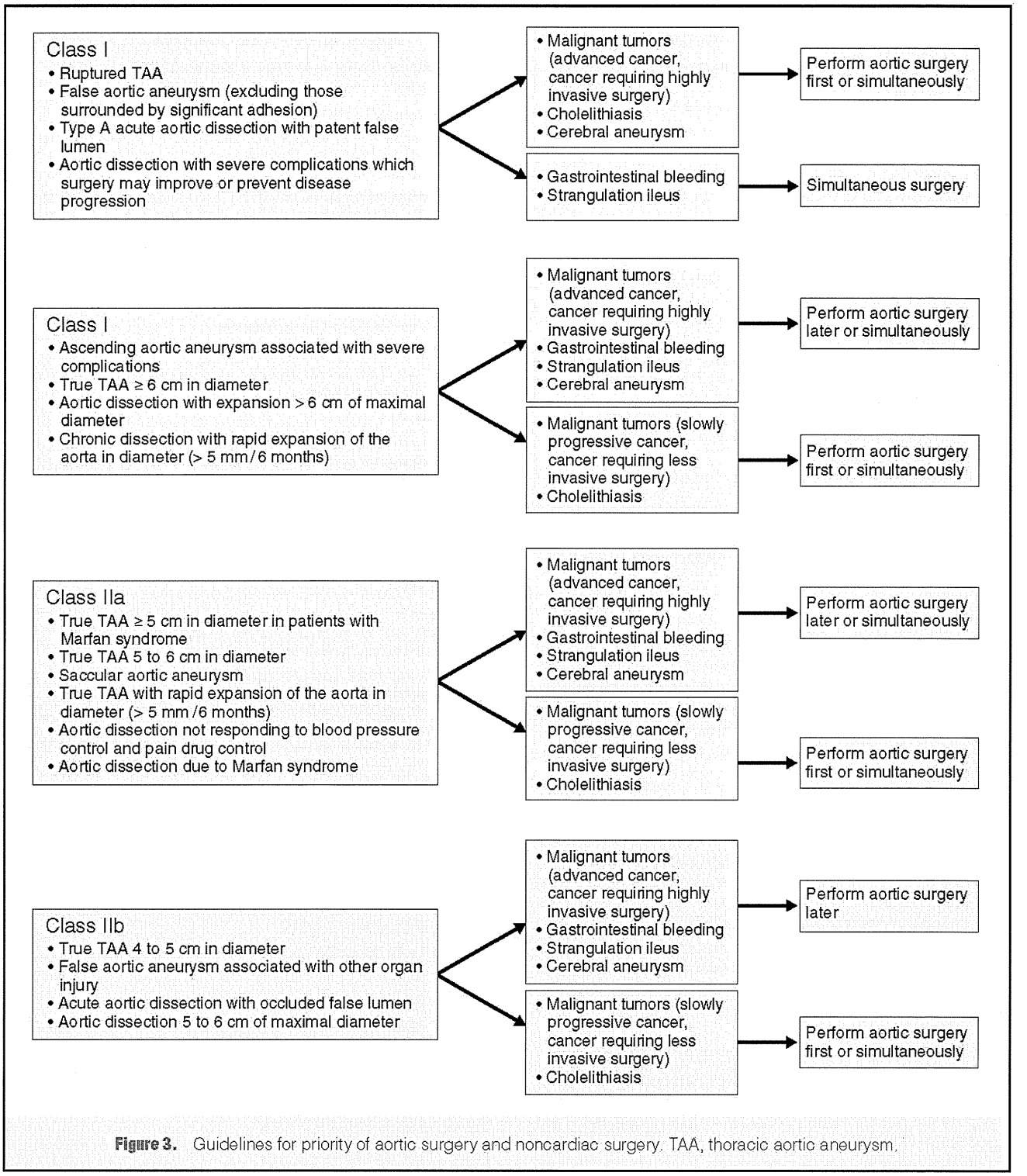

Figure 3. Guidelines for priority of aortic surgery and noncardiac surgery. TAA, thoracic aortic aneurysm.

Patients suspected to have acute aortic dissection should undergo contrast CT to confirm the diagnosis under strict blood pressure control. Treatment of type A acute aortic dissection should be prioritized even when noncardiac surgery is planned. Antihypertensive therapy is the treatment of first choice for patients with type B acute aortic dissection.

(2) Management of Aortic Aneurysm During Noncardiac Surgery

During noncardiac surgery, patients with aortic aneurysms should be carefully observed for ischemic heart disease and severe hypertension, that frequently co-exist. Although there have been few reports about aortic aneurysm rupture during the perioperative period of noncardiac surgery, perioperative blood pressure control has been reported to be effective in preventing rupture of aortic aneurysms.[69–71] When hyper-