UNIVERSITE BRETAGNE LOIRE

UNIVERSITÉ DE NANTES

Thèse de Doctorat

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Mémoire présenté en vue de l'obtention du
grade de Docteur de l'Université de Nantes
sous le sceau de l'Université Bretagne Loire

École doctorale : Biologie-Santé

Discipline : *Biomolécules, pharmacologie, thérapeutique*
Spécialité : *Biologie des organismes*
Unité de recherche : EA4275

Soutenue le *28 Novembre 2016*
Thèse N° :

Etude de la détérioration valvulaire structurelle des prothèses valvulaires biologiques cardiaques

Validation d'une méthodologie adaptée pour estimer son incidence, ses facteurs de risque et son impact sur la survie des patients

1. JURY

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Valorisation scientifique :

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Introduction:

Les maladies valvulaires désignent l'ensemble des maladies touchant les valves cardiaques. Les valves cardiaques sont au nombre de quatre et séparent les différentes cavités. Elles assurent un sens unidirectionnel au passage intracardiaque du sang. La valve aortique est une de ces quatre valves, située à la sortie du ventricule gauche. En cas de dysfonctionnement de la valve, il peut apparaitre un rétrécissement valvulaire ou une insuffisance valvulaire. Des symptômes à type de dyspnée, angor ou syncope peuvent alors apparaitre, avec un pronostic spontané sombre pour le patient, 50% de mortalité à 2 ou 3 ans [1]. Le rétrécissement valvulaire aortique est la deuxième cause de décès aux États-Unis. Il est marqué par une rigidification et/ou une calcification des valvules. C'est la plus fréquente des valvulopathies de l'adulte. A partir d'études échographiques portant sur plus de 5000 patients âgés de 65 ans et plus, Stewart et al. [2] estiment sa prévalence à 2% et près de 4% au-delà de 85 ans.

Selon l'état de santé du patient, la prise en charge en cas de dysfonctionnement sévère consiste en la réalisation d'une intervention chirurgicale pour effectuer la réparation ou l'implantation d'une nouvelle valve prothétique. La mortalité opératoire du remplacement valvulaire aortique isolé est estimée à moins de 4% [3]. Le nombre de RVA réalisés annuellement au niveau mondial est estimé à plus de 200 000 [4].

Depuis le premier remplacement valvulaire aortique en 1960, de nombreuses prothèses valvulaires ont vu le jour. Il en existe principalement deux types: les valves entièrement synthétiques (valves mécaniques) et celles composées en partie par du tissu humain ou animal (valves biologiques). Le titane et/ou le carbone composent la majorité des valves mécaniques, en raison de leur propriété physique et de leur durabilité. Les valves biologiques incluent les xénogreffes (fabrication des valves à l'aide de tissu animal, principalement péricarde de veau et valve native de porc), et les allogreffes (à partir tissus humains) [5]. Les valves biologiques animales, ou bioprothèses, sont préservées dans du glutaraldéhyde, qui en réduit l'antigénicité, stérilise le tissu, fixe les structures histologiques et les protège de la dégradation enzymatique. Les bioprothèses péricardiques bovines sont les prothèses les plus utilisées actuellement en France.

Les complications valvulaires ont un impact important sur le pronostic postopératoire et à long-terme des patients. Les principales sont les complications thrombo-emboliques (incluant les thromboses et les complications liées aux anticoagulants nécessaires pour éviter ces thromboses), les infections de prothèses, les détériorations structurelles, et les dysfonctions non structurelles (fuite paraprothètique et « pannus » sous-valvulaire responsable de sténose). Les taux de complications sont identiques pour les deux types de valves, avec cependant des spécificités en fonction du type de valve. La principale raison est le risque thrombo-embolique associé aux prothèses mécaniques, les patients ont besoin d'une anticoagulation au long cours, avec le risque hémorragique associé à un tel traitement. La survie à long-

terme est cependant meilleure chez les sujets jeunes [6, 7]. Les valves biologiques ne nécessitent pas de traitement anticoagulant mais sont exposées au risque de détérioration valvulaire survenant généralement après 10-15 ans. Les recommandations actuelles pour le choix du substitut valvulaire sont en faveur d'une valve biologique après 65 ans [8]. Depuis une dizaine d'années, le choix du type de prothèse a évolué au profit des prothèses biologiques plutôt que mécaniques en raison du vieillissement de la population et de performances hémodynamiques améliorées [4].

Une prothèse valvulaire fonctionnelle peut cependant être responsable d'une sténose fonctionnelle en cas d'inadéquation entre la taille de la prothèse implantée et la surface du patient. On parle alors de mismatch patient-prothèse (*prosthesis-patient mismatch* ou PPM), survenant principalement pour les petites tailles de prothèses. Toutes les prothèses valvulaires sont responsables d'un certain degré de sténose et donc d'un gradient de pression amont-aval, en raison 1) du coussinet de suture de la valve, 2) du stent métallique sous-jacent et/ou 3) des valvules qui s'effacent plus ou moins complètement pour laisser passer le sang.

Un PPM sévère est défini par une surface fonctionnelle de l'orifice de la valve indexée sur la surface corporelle inférieure à 0,65 cm2/m2 [9]. Bien que les conséquences cliniques restent débattues dans la littérature [9, 10], les conséquences hémodynamiques pourraient avoir une influence délétère sur la durabilité de la bioprothèse. Ainsi, Flameng *et al.* [2010] ont montré qu'une détérioration valvulaire structurelle (SVD) était plus fréquente chez les patients avec un PPM modéré avec une surface inférieure à 0,85 cm2/m2.

Toutes les bioprothèses biologiques sont soumises à un risque de dégénérescence valvulaire (SVD) à moyen ou long terme, variable selon le type de prothèse étudiée [11]. Cette SVD peut se présenter sur un mode sténosant reproduisant le rétrécissement valvulaire préexistant, ou par l'apparition d'une insuffisance valvulaire intra-prothétique par rigidité et/ou rupture d'une cusp (ou valvule) prothétique. Selon les recommandations des sociétés savantes [12], la définition d'une SVD inclut un dysfonctionnement ou une détérioration de la prothèse, déterminé par une ré-intervention chirurgicale, une autopsie, ou une investigation clinique.

Parmi les prothèses biologiques, la valve Mitroflow® (Groupe Sorin, Milan, Italie), disponible depuis 1982 [13], a été conçue pour permettre une ouverture optimale de l'orifice prothétique afin d'améliorer les performances hémodynamiques de la prothèse. Le modèle 12A, introduit en 1992 [14], présente pour principal avantage théorique un profil hémodynamique particulièrement adapté pour les anneaux aortiques de petit calibre grâce à un encombrement moindre [15]. L'efficacité de cette bioprothèse est controversée dans la littérature : si plusieurs études ont présenté des résultats à long terme satisfaisants [16, 17], d'autres plus récentes ont émis des réserves sur sa réelle durabilité avec notamment une possible détérioration structurelle précoce dès la quatrième année [18].

Malgré les recommandations des sociétés savantes, évaluer l'incidence de SVD reste en effet difficile. Tout d'abord, sa définition a longtemps été basée sur la ré-intervention chirurgicale, dont le risque opératoire fait récuser de nombreux patients jugés trop âgés pour affronter une nouvelle chirurgie. De plus, beaucoup d'études présentent une durée de suivi trop faible pour évaluer cette complication, sa survenue étant décrite en moyenne entre la 8ème et la 10ème année postopératoire [11]. Enfin, en cas d'évaluation échographique, l'absence de critères précis recommandés a conduit à l'utilisation de définitions différentes selon les équipes.

L'implantation d'une bioprothèse conduit à une situation clinique évolutive. Les patients peuvent connaître une succession d'états de santé plus ou moins rapidement et de manière plus ou moins prévisible, avec parfois une complication liée à la valve comme la SVD. Pour améliorer la prise en charge des patients porteurs d'une bioprothèse, l'étude des facteurs influençant le passage d'un état clinique à un autre est donc importante. La méthode la plus largement utilisée en analyse de survie est le modèle à risques proportionnels de Cox. Cependant, ce modèle permet d'étudier le délai d'apparition d'un seul événement. De plus, il suppose une censure non-informative. Ces hypothèses ne semblent pas acceptables dans l'analyse des prothèses valvulaires biologiques. Le risque de SVD est en effet en compétition avec le risque de décès du patient. Enfin, entre deux échographies cardiaques, la date d'apparition précise de la SVD reste inconnue, avec l'existence d'une censure par intervalle.

L'objectif de cette thèse est de mieux décrire l'histoire naturelle de l'évolution de patients porteurs d'une bioprothèse. Le manuscrit est présenté sous la forme d'articles, et est composé de cinq parties principales. Dans le chapitre 1, nous commençons par la présentation de la base de données Cordabase®, base de soins créée en 2009 et permettant l'implémentation des patients opérés d'une valve cardiaque au CHU de Nantes. Le chapitre 2 regroupe les concepts statistiques utilisés dans ce travail. Dans le chapitre 3, nous présentons une modélisation classique du risque de SVD : i) un modèle de Cox évaluant l'impact de la survenue d'une SVD, covariable dépendante du temps et définie par des critères échographiques, sur le temps entre la chirurgie et le décès du patient, et ii) un modèle de Cox avec pour variable aléatoire le temps entre la chirurgie et la SVD. Le chapitre 4 présente ensuite l'intérêt des scores de propension et d'une approche multi-états pour obtenir une meilleure estimation de l'évolution de patients porteurs d'une bioprothèse et de l'effet marginal du PPM. Le chapitre 5 montre enfin l'intérêt d'un modèle multi-états multivarié pour analyser plus précisément l'incidence, l'effet conditionnel des facteurs de risque et l'impact de la SVD sur la mortalité. En dernière partie, nous proposons une conclusion et les perspectives possibles à ce travail.

Chapitre 1

La base de données Cordabase

Pour tout service de soin clinique, l'évaluation régulière de son activité et de ses résultats est un élément essentiel. Elle permet d'améliorer la qualité des soins apportés et est indispensable à la production scientifique. Dans cette optique, depuis 2007, nous avons cherché à mettre en place une base de données axée sur la chirurgie cardiaque et permettant d'évaluer les résultats à court et à long-terme des patients opérés. Nous avons alors décidé de créer un logiciel permettant de constituer de façon simple et exhaustive cette base de données. Afin d'obtenir une exhaustivité optimale, ce logiciel devait pouvoir être utilisé en pratique quotidienne et aider à la réalisation de l'activité administrative du service.

CordaBase a été créé à l'aide d'un logiciel de programmation appelé Visual Studio. Le langage de programmation est le vb.net. CordaBase permet d'interagir avec des bases de données de type Office® Access pour l'enregistrement des données. Il interagit également avec les logiciels Office® Word et Excel pour créer des comptes rendus médicaux et des tableurs, favorisant ainsi l'exploitation statistique des données enregistrées. Afin d'être accessible par l'ensemble des ordinateurs d'un service, CordaBase est sous la forme d'une application.exe qui permet d'être utilisable sur un réseau hospitalier sécurisé.

Les données administratives et morphologiques du patient sont renseignées prospectivement mais également l'ensemble des données préopératoires, interventionnelles et postopératoires. Ces données sont utilisées pour la création automatisée des comptes rendus opératoire et d'hospitalisation, ainsi que les ordonnances de sortie et le compte-rendu de l'échographie réalisée systématiquement avant la sortie du patient. Très prochainement, une aide à la revalorisation du séjour sera proposée en listant de façon automatique les codes PMSI correspondants aux données saisies. Toutes ces aides apportées à la réalisation de l'activité administrative du service ont pour but de favoriser l'exhaustivité des données enregistrées.

Pour chaque intervention réalisée, le logiciel offre également la possibilité de rentrer les données médicales concernant le suivi du patient à distance de l'intervention, sous forme de données cliniques, para-cliniques (ECG et échographie cardiaque), et d'éventuelles complications. Le statut décédé ou non ainsi que la cause de décès à distance peuvent également être enregistrés pour la réalisation d'études scientifiques. Toutes les données stockées à l'aide de ce logiciel sont accessibles en permanence à travers un second logiciel convivial nommé « LogUse », dédié spécifiquement à l'exploitation des bases de données et à la réalisation d'analyses statistiques sous différentes formes (graphiques, tableaux avec moyennes…). Il propose ainsi en quelques clics la réalisation du bilan d'activité d'un service, la

vérification de l'exhaustivité des données en s'assurant que la sortie de tous les patients enregistrés ait bien été saisie, ou encore la possibilité de réaliser des tableaux Excel avec un nombre sélectionné d'items.

CordaBase s'est également révélé avoir un rôle pédagogique pour les internes de chirurgie qu'ils soient ou non de la spécialité, par la responsabilité qui leur incombent à réaliser les comptes rendus médicaux. Il permet d'avoir accès facilement à un certain nombre de classifications et recommandations concernant l'activité de chirurgie cardiaque.

Depuis Mars 2009, le logiciel CordaBase est utilisé prospectivement pour tout patient opéré dans le service de chirurgie cardiaque du CHU de Nantes. De plus, toutes les études rétrospectives réalisées depuis ont contribué à l'implémentation des données. Il y a actuellement plus de 14000 interventions répertoriées et complètes.

Avec un recul d'utilisation de plus de 6 ans, le logiciel CordaBase a démontré au quotidien son intérêt dans l'activité du service de chirurgie cardiaque du CHU de Nantes. Ce logiciel a permis ainsi la création des comptes rendus opératoires et d'hospitalisations pour la quasi-totalité des patients opérés dans le service, en dehors de quelques rares situations (ex : hospitalisation sans intervention). Immédiatement disponibles pour le secrétariat, le logiciel a permis que les patients quittent le service avec leurs comptes rendus en main, ainsi qu'avec leurs ordonnances. Les médecins traitants et cardiologues sont informés sans délai de la sortie de leurs patients. Un lien vers d'autres bases de données comme la base nationale de la société Française de Chirurgie Thoracique et Cardiovasculaire (logiciel Epicard) a été également créé pour permettre de la renseigner de manière exhaustive tout en permettant d'éviter la double saisie informatique.

La base de données Cordabase a fait l'objet d'une déclaration à la CNIL (Commission Nationale Informatique Libertés) en tant que base de soins (accord #1456630v1), et a été l'objet d'une publication en Septembre 2012 [19].

Chapitre 2

État des connaissances

I. Modèle de Cox

L'analyse de survie s'intéresse au délai d'apparition d'un évènement au cours du temps. La spécificité des données de survie est l'existence d'observations incomplètes. Par exemple, si l'évènement d'intérêt est le décès, certains individus peuvent être encore vivants au moment de l'analyse. La durée de vie, aussi appelée temps de survie, correspond à la durée jusqu'à l'apparition de l'évènement. Il s'agit d'une variable aléatoire réelle positive, généralement considérée continue et à distribution dissymétrique. Soit T cette variable aléatoire d'intérêt correspondant au délai entre la date d'origine et la date d'évènement étudié. Par souci de clarté et de simplicité, nous considérons comme date d'origine $t = 0$ (baseline).

1. Définitions des fonctions de survie

La distribution de la variable T peut être définie à partir de l'une des cinq fonctions suivantes :

- La fonction de survie, notée $S(t)$, est la probabilité que l'évènement ne se produise pas avant un temps t. Elle est définie par :

$$S(t) = P(T > t) \quad (1.1)$$

- La fonction de répartition, notée $F(t)$. C'est la probabilité que l'événement se produise avant un temps t. Elle est définie par :

$$F(t) = P(T \leq t) = 1 - S(t) \quad (1.2)$$

Notons que la fonction de répartition est également appelée fonction d'incidence cumulée (*Cumulative Incidence Function,* CIF) dans la mesure où elle est spécifique à un évènement parmi plusieurs en compétition.

- La fonction de densité de probabilité, notée $f(t)$. Elle représente la probabilité que l'évènement se produise juste après un temps t. Elle est définie par:

$$f(t) = \lim_{\Delta t \to 0+} \left(\frac{P\ (t \leq T < t + \Delta t)}{\Delta t} \right) \tag{1.3}$$

- La fonction de risque (instantané), notée $\lambda(t)$, représente la probabilité que l'évènement se produise juste après un temps t, conditionnellement au fait que l'évènement n'a pas eu lieu jusqu'à t. Elle est définie par :

$$\lambda(t) = \lim_{\Delta t \to 0+} \left(\frac{P(t \leq T < t + \Delta t \mid T > t)}{\Delta t} \right) = \frac{f(t)}{S(t)} \tag{1.4}$$

- La fonction de risque cumulé, notée $\Lambda(t)$, est la somme de la fonction de risque instantané (1.4) entre 0 et t. Elle est définie par :

$$\Lambda(t) = \int_0^t \lambda(u)\, du = \log(-S(t)) \tag{1.5}$$

2. Modèles semi-paramétrique à risques proportionnels

Le modèle de survie le plus rencontré est le modèle de Cox, basé sur la régression de la fonction de risque $\lambda(t)$. Les paramètres d'intérêt sont les coefficients de régression. L'effet des covariables est alors multiplicatif de la fonction de risque et indépendant du temps. Soit un échantillon constitué de n individus indicés par h, $h = 1, ..., n$. Posons $z_h = (z_{h,1}, z_{h,2}, ..., z_{h,p})$ le vecteur des p covariables observées pour l'individu h et $\beta = (\beta_1, \beta_2, ..., \beta_p)$ le vecteur des coefficients de régression associés. Alors, la fonction de risque est définie par :

$$\lambda(t, z_h) = \lambda_0(t) \exp(\beta_k z_h) \tag{1.6}$$

où $\lambda_0(t)$ est la fonction de risque de base (pour la population de référence, c'est-à-dire dans le cas où toutes les covariables sont nulles) au temps t_i. Celle-ci n'est pas spécifiée. Le modèle possède ainsi l'avantage de ne faire aucune hypothèse sur cette fonction de risque de base puisqu'elle n'est pas estimée.

En considérant tous les sujets indépendants, la vraisemblance partielle VP d'un échantillon de taille n est :

$$VP = \prod_{h=1}^{n} \left\{ \frac{\exp(\beta z_h)}{\sum_{r:t_r \geq t_h} \exp(\beta z_r)} \right\}^{\delta_h} \tag{1.7}$$

où (δ_h , t_h) sont respectivement l'indicatrice de survenue ou non de l'évènement et le temps de participation de l'individu *h*, et *r* les individus encore à risque au temps t_h. Cette vraisemblance partielle est indépendante de la fonction de risque de base $\lambda_0(t)$. L'estimation des paramètres β est obtenu par maximisation de la *VP* (1.7).

Soit une covariable supplémentaire et binaire (égale à 0 si le patient est non exposé et 1 sinon) et $\acute{o}$ son coefficient de régression associé. Alors le Hazard Ratio (*HR*) associé à cette variable est :

$$HR = \frac{\lambda_0(t_h)\exp(\beta_k z_h + \acute{o})}{\lambda_0(t_h)\exp(\beta_k z_h)}$$

$$= \exp(\acute{o})$$

(1.8)

HR correspond au rapport des risques instantanés entre un patient exposé et un patient non-exposé, ces deux patients ne diffèrant que sur leur statut d'exposition. Les autres covariables de ces deux patients doivent être identiques pour pouvoir interpréter ce HR. L'effet de cette variable explicative est donc conditionnel à un profil de patient particulier : il s'agit d'un effet dit spécifique à un sujet (subject-specific). En d'autres termes, il s'agit de l'effet relatif pour un patient de passer du statut d'exposé à non-exposé.

3. Hypothèses

Le modèle de survie semi-paramétrique est basé sur l'hypothèse de proportionnalité, c'est-à-dire un rapport des risques instantanés constant au cours du temps. Cette hypothèse peut être vérifiée graphiquement par la fonction Log[-Log[S(t)]] selon plusieurs modalités de la variable. En l'absence de proportionnalité vérifiée, on peut stratifier la fonction de risque de base du modèle de Cox en fonction de cette variable, ou introduire cette variable comme dépendante du temps (voir sous-section suivante).

En cas de variable quantitative, l'hypothèse de log-linéarité doit être vérifiée (le *HR* est constant pour toute augmentation d'une unité de la variable, voir équation 1.8). Celle-ci peut également être vérifiée graphiquement en découpant la variable en classes d'effectifs équivalents (comme les quartiles) puis en représentant graphiquement les HR des différentes classes ainsi obtenues. En cas d'alignement de ces HR, on peut raisonnablement accepter une relation log-linéaire et la variable est garder en variable continue dans le modèle, sinon, elle peut être transformée en variable qualitative.

4. Prise en compte des variables temps-dépendantes

Il peut s'agir d'une variable dont l'effet dépend du temps (hypothèse de proportionnalité non vérifiée), ou dont la valeur change au cours du temps. Par exemple, la SVD est une variable qui peut être associée au temps de décès mais elle n'existe pas à la baseline t=0, avec une valeur qui change donc au cours du temps.

En cas de variable z_1 dont la valeur change après un temps t, la contribution individuelle d'un sujet h est divisée en deux parties : i) un sujet fictif h' présentant la variable $z_1 = u$ et à la baseline ($t_{0,h'} = 0$) un suivi égal à $t_{1,h'}$ avec censure à droite ($\delta_{h'} = 0$), et ii) un second sujet h'' avec $z_1 = v$ entrant dans l'étude au temps $t_{0,h''} = t_{1,h'}$ et suivi jusqu'au temps $t_{1,h'} = t_h$, avec $\delta_{h''} = \delta_h$. Au sein de ces deux intervalles de temps, la variable z_1 ne change pas, et le modèle se rapproche alors d'un modèle de Cox classique.

La fonction de risque est alors définie par :

$$\lambda(t|z_{h,1}(\mathrm{t}), \dots, z_h) = \lambda_0(t) \exp\left(\beta_1 z_{h,1}(\mathrm{t}) + \sum_{k=2}^{p} \beta_k z_{h,k}\right) \quad (1.9)$$

L'approche par vraisemblance partielle peut toujours être utilisée.

$$VP = \prod_{h=1}^{n} \left\{ \frac{\exp\left(\beta_1 z_{1,h} + \sum_{k=2}^{p} \beta_k z_{h,k}\right)}{\sum_{r:\{t_{1,r} \geq t_{1,h} \cap t_{0,r} < t_{1,h}\}} \exp\left(\beta_1 z_{1,r} + \sum_{k=2}^{p} \beta_k z_{h,k}\right)} \right\}^{\delta_h} \quad (1.10)$$

II. Modèles multi-états

Ils sont de plus en plus utilisés en analyse de survie. Il est possible alors de modéliser différents états occupés par les patients au cours du temps et donc de représenter l'évolution du patient à travers différents états successifs. Le modèle maladie-décès (illness-death) est un modèle particulier, avec la modélisation de trois états: sain, malade et décédé. L'état décédé est dit absorbant, avec la probabilité de rester dans cet état égale à 1. Les patients transitent de l'état sain à l'état décédé directement ou en passant par l'état transitoire malade.

Dans notre étude, un modèle illness-death composé des états "vivant sans SVD", "vivant avec SVD" et "décédé" parait approprié (Figure 1). Deux trajectoires sont ainsi possibles pour un sujet qui décède avec un état décrit comme non-SVD à la dernière consultation: une transition directe de l'état "vivant sans SVD" à l'état "décédé", ou une transition par l'état intermédiaire "vivant avec SVD". Cette censure par intervalle peut être prise en compte.

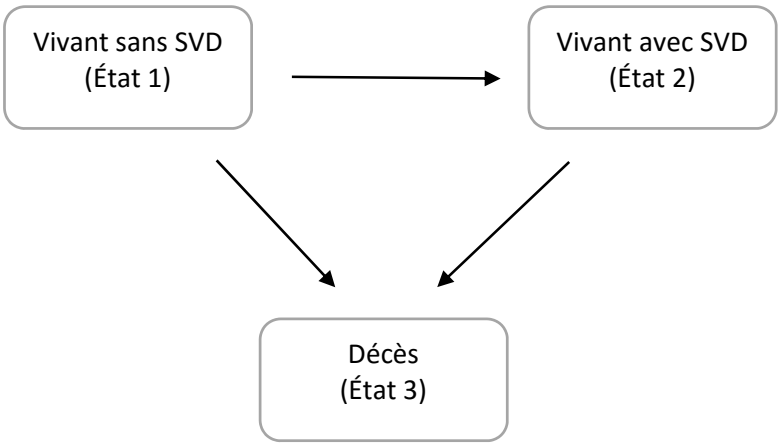

Figure 1: Structure multi-état décrivant l'évolution clinique des patients porteurs d'une bioprothèse aortique

1. Définitions

Un modèle dit semi-Markovien est un modèle multi-états où la transition entre les états prend en compte le temps passé dans l'état en cours [20]. Soit T_m le temps chronologique (depuis l'origine de l'étude) avant passage à l'état Y_m. Le risque instantané de transition de l'état $Y_m = i$ vers l'état $Y_{m+1} = j$ après une durée $t = T_{m+1} - T_m$, sachant les caractéristiques observées du patient z_h est défini par :

$$\lambda_{ij}(t|Z) = \lim_{\Delta t \to 0+} \left(\frac{P(t \leq T_{m+1} - T_m < t + \Delta t,\ Y_{m+1} = j \mid T_{m+1} - T_m > t, Y_m = i, z_h)}{\Delta t} \right) \quad (2.1)$$

Notons que par soucis de simplification, nous avons choisi d'écrire que le vecteur des covariables est identique pour toutes les transitions ($z_{h,ij} = z_h, \forall ij$). Ce ne sera pas le cas dans les applications.

La fonction de survie globale, notée $S_{i.}(t|Z)$ est la probabilité de ne faire aucune transition depuis le temps t et l'état i:

$$S_{i.}(t|z_h) = P(T_{m+1} - T_m > t \mid Y_m = i, z_h)$$

$$= \prod_j \exp\left(- \int_0^t \lambda_{ij}(u|z_h)du \right) \quad (2.2)$$

La fonction de densité spécifique de la transition $i \rightarrow j$ après une durée t dans l'état i est définie par :

$$f_{ij}(t|z_h) = \lim_{\Delta t \to 0+} \left(\frac{P\ (t \leq T_{m+1} - T_m < t + \Delta t\ ,\ Y_{m+1} = j \mid Y_m = i\ , z_h)}{\Delta t} \right)$$

$$= \lambda_{ij}(t|z_h) * S_{i.}(t|z_h) \quad (2.3)$$

La probabilité de transiter de l'état i vers l'état j avant une durée t est définie par :

$$F_{ij}(t|z_h) = P(T_{m+1} - T_m \leq t\ , Y_{m+1} = j \mid Y_m = i\ , z_h\ )$$

$$= \int_0^t f_{ij}(u|z_h)du \quad (2.4)$$

2. Estimation des paramètres par maximum de Vraisemblance

Soit d_0 le temps entre l'opération et la dernière échographie cardiaque sans SVD, v le temps entre l'opération et la date des dernières nouvelles, et d_1 le temps entre l'opération et la date de l'échographie diagnostiquant la SVD (lorsque le diagnostic de SVD est posé). Les contributions individuelles à la vraisemblance peuvent être exprimées comme suit :

- Le patient est toujours vivant à la date de dernières nouvelles, sans diagnostic de SVD. Le patient peut alors être porteur d'une SVD non diagnostiquée. Les deux bornes de l'intervalle où une SVD a pu réellement survenir sont les temps d_0 et v.

$$S_{1.}(v|z_h) + \int_{d_0}^{v} S_{1.}(u|z_h)\ \ \lambda_{12}(u|z_h)\ \ S_{2.}(v-u|z_h)\, du \quad (2.5)$$

- Le patient est décédé à la date de dernières nouvelles, sans diagnostic de SVD. Le patient pouvait alors être porteur d'une SVD non diagnostiquée lors de son décès. Les deux bornes de l'intervalle où une SVD a pu réellement survenir sont les temps d_0 et v.

$$S_{13}(v|z_h)\ \ \lambda_{13}(v|z_h) + \int_{d_0}^{v} S_{1.}(u|z_h)\ \ \lambda_{12}(u|z_h)\ \ S_{23}(v-u|z_h)\ \ \lambda_{23}(v-u|z_h)\, du \quad (2.6)$$

- Le patient est vivant à la date de dernières nouvelles, avec un diagnostic de SVD. Les deux bornes de l'intervalle où une SVD a pu réellement survenir sont les temps d_0 et d_1.

$$\int_{d_0}^{d_1} S_{1.}(u|z_h) \quad \lambda_{12}(u|z_h) \quad S2.(v-u|z_h)\, du \tag{2.7}$$

- Le patient est décédé à la date de dernières nouvelles, avec un diagnostic de SVD. Les deux bornes de l'intervalle où une SVD a pu réellement survenir sont les temps d_0 et d_1.

$$\int_{d_0}^{d_1} S_{1.}(u|z_h) \quad \lambda_{12}(u|z_h) \quad S2.(v-u|z_h) \quad \lambda_{23}(v-u|z_h) \quad du \tag{2.8}$$

3. Choix paramétriques

Parallèlement au principe utilisé par Cox, la fonction de risque propre à la transition de *i* vers *j* peut s'écrire :

$$\lambda_{ij}(t|z_h) = \lambda_{0,ij}(t) \quad \exp(\beta_{ij} z_h) \tag{2.9}$$

où $\lambda_{0,ij}(t)$ est la fonction de risque de base, quand toutes les covariables sont nulles. Au sein de chaque transition, $\exp(\beta_{ij})$ représentent les *HR* conditionnels (subject-specific).

La distribution de Weibull généralisée [21] a été choisie pour modéliser les fonctions de risque de base $\lambda_{0,ij}(t)$. C'est une distribution flexible à 3 paramètres : $\sigma_{ij} > 0$, $\nu_{ij} > 0$, et $\theta_{ij} > 0$. Le risque instantané
évolue de manière non-monotone (en forme de ∩ ou ∪) :

$$\lambda_{0,ij}(t) = \quad (\theta_{ij})^{-1} \quad (1 + (t/\sigma_{ij})^{\nu_{ij}})^{1/(\theta_{ij}-1)} \quad \nu_{ij} \quad (1/\sigma_{ij})^{\nu_{ij}} \quad t^{(\nu_{ij}-1)} \tag{2.10}$$

Si θ_{ij} est égal à 1, la fonction de risque est celle du modèle de Weibull avec une évolution monotone du risque. De plus, si ν_{ij} est égal à 1, il s'agit alors d'une fonction exponentielle avec un risque constant au cours du temps.

4. Hypothèses

L'hypothèse de proportionnalité des risques au sein de chaque transition doit également être vérifiée. Pour une covariable, la vérification peut être graphique en représentant le logarithme des fonctions de risque instantané au sein de plusieurs strates d'une même covariable. L'espacement entre les deux courbes doit être constant pour valider cette proportionnalité.

Afin de choisir la loi de distribution de la fonction de risque, un modèle paramétrique sans covariable a été utilisé. La CIF de décès ainsi obtenue était proche de la courbe obtenue via l'estimateur non-paramétrique de Kaplan-Meier, permettant de valider (même indirectement) l'utilisation de la distribution des fonctions de risque de base choisie :

$$\int_0^t \left(f_{13}(u|z_h) + \int_0^u f_{23}(u-v|z_h) f_{12}(v|z_h) dv \right) du$$

Enfin, le test de rapport de vraisemblance a permis de sélectionner des distributions paramétriques plus simples que la loi de Weibull Généralisée, allant toujours dans le sens d'un modèle assez flexible pour être correctement adapté aux données.

III. Les méthodes de score de propension

1. Définition

Les méthodes de score de propension permettent de minimiser les effets des facteurs de confusion dans l'estimation de l'effet marginal d'un facteur d'exposition [22]. Le score de propension se définit par la probabilité qu'un individu h du groupe exposé (Z_h =1) appartienne à ce groupe conditionnellement aux facteurs de confusion potentiels (notés X_h) [22] :

$$p_h = P(Z_h = 1 | X_h = x_h) \quad (3.1)$$

Ce score est généralement estimé par un modèle de régression logistique. Quatre méthodes d'utilisation du score de propension ainsi obtenu sont possibles :

i) la stratification, qui divise la population d'étude en strates basées sur des seuils prédéfinis du score de propension [23] ;

ii) l'appariement, qui consiste à former des paires d'individus exposés et non-exposés ayant des valeurs du logit du score de propension les plus proches selon une distance appelée *caliper* (recommandée égale à 0,2 fois l'écart-type du logit du score de propension [23]) ;

iii) l'ajustement par un modèle ayant comme covariable le score de propension estimé ;

iv) et la pondération « Inverse Probability Weighting (IPW) », où les observations de l'échantillon sont pondérées en fonction du score de propension.

Austin et al. [23] ont montré que l'appariement, la stratification, et l'ajustement sur le score de propension sont moins performants. En 2010, Austin et al. [24] ont comparé les différentes méthodes de score de propension en analyse de survie. Les auteurs suggèrent d'utiliser l'appariement avec la distance *caliper* quand la prévalence du traitement est faible (5% ou 10%) et la méthode IPW quand celle-ci est élevée (25%). En revanche, Le Borgne et al. [25] ont montré les avantages de la méthode IPW devant l'appariement, toujours en analyse de survie. Nous avons donc choisi de nous intéresser ici plus particulièrement à la méthode IPW adaptée aux modèles semi-Markoviens.

2. Méthode de pondération IPW

La méthode consiste à pondérer les contributions individuelles à la vraisemblance (équations 2.5 à 2.8) par des poids inversement proportionnels à la probabilité d'appartenance de l'individu à son groupe (exposé ou non exposé) en fonction des covariables observées. La seule variable explicative dans le modèle multi-états est alors le facteur d'exposition d'intérêt. L'objectif est d'équilibrer ces covariables entre les deux groupes. Des poids élevés sont attribués aux individus avec des profils sous-représentés dans leur groupe, et inversement des poids faibles sont attribués aux individus avec des profils sur-représentés dans leur groupe. Une méthode proposée par Robins et al. [26, 27] est d'utiliser des poids dits stabilisés (stabilized weight, sw), qui incluent au numérateur la probabilité d'appartenir au groupe observé:

$$w_h = Z_h \, \mathrm{P}(Z_h = 1) \, p_h^{-1} + (1 - Z_h) \, (1 - \mathrm{P}(Z_h = 1)) \, (1 - p_h)^{-1} \tag{3.2}$$

où w_h est le poids de l'individu h.

L'avantage est d'obtenir un pseudo-échantillon où les covariables des patients exposés sont distribuées de la même manière que les patients non-exposés, situation se rapprochant des essais cliniques randomisés où l'exposition est tirée au sort. En utilisant les poids (3.2), la distribution des covariables est identique à celle observés dans tout l'échantillon initial, quel que soit l'exposition. En comparant ces deux groupes, on estime ainsi l'impact marginal si tout l'échantillon passe du statut exposé à non-exposé. On parle aussi d'effet moyen en population (population-average) ou ATE (Average Treatment Effect).

3. Hypothèses

Positivité : L'hypothèse de positivité est la présence de patients exposés et non exposés sur l'ensemble des niveaux du facteur de confusion (chevauchement des distributions dans les deux groupes). Cette hypothèse peut être volontairement impossible (par exemple si l'exposition est un traitement avec contrindications pour certains patients) ou aléatoirement non vérifiée [28]. Une séparation complète des distributions entre exposés et non exposés indique des différences majeures entre les groupes et la possibilité que les méthodes de propension n'apportent pas de résultat satisfaisant.

Equilibre : Une fois la positivité validée, il est alors nécessaire de vérifier que les patients exposés et non exposés ont des caractéristiques comparables dans le nouvel échantillon pondéré. L'approche recommandée est l'examen des différences standardisées pour chacune des variables du score [29]. Il s'agit de la différence moyenne entre les groupes exposés et non exposés divisée par l'écart type dans l'échantillon total.

Examen des poids : Pour les méthodes de pondération, il est important de vérifier que la somme des poids stabilisés est proche de la taille de l'échantillon d'origine. Si ce n'est pas le cas, ceci peut indiquer une violation de l'hypothèse de positivité ou une mauvaise spécification du modèle. Les poids stabilisés que nous utilisons couvrent cette égalité.

Chapitre 3

Modélisation de l'évolution des prothèses valvulaires biologique par un modèle semi-paramétriques de Cox

I. Résumé

La détérioration valvulaire aortique (SVD) reste le problème majeur des bioprothèses valvulaires. Cependant, en raison d'une méthodologie inadaptée, son incidence est probablement sous-estimée. Ainsi, la prothèse SORIN Mitroflow® (modèles LX/12A) semble poser problème avec plusieurs cas décrits de SVD précoces. Son incidence reste cependant incertaine. Nous avons pour cela utilisé un modèle de Cox étendue, modèle le plus souvent utilisé dans la littérature. Cette première analyse a été réalisé pour i) évaluer l'incidence de SVD après implantation d'une bioprothèse SORIN Mitroflow® (modèles 12A/LX), ii) valider la nécessité de critères échographiques pour définir la SVD, iii) chercher les facteurs de risque influençant le temps de survie sans SVD, et iv) estimer l'impact de la survenue d'une SVD sur la survie du patient porteur de cette bioprothèse.

Dans ce papier, nous avons analysé l'évolution de 617 patients ayant bénéficié d'un remplacement valvulaire aortique à l'aide d'une bioprothèse SORIN Mitroflow® entre 2002 et 2007 au CHU de Nantes. Les résultats montrent un taux inattendu de SVD précoce, avec un impact très significatif sur la survie du patient. Parmi les facteurs de risque retrouvé, le mismatch patient-prothèse semble augmenter significativement le risque d'apparition de SVD.

II. Article

Early Structural Valve Deterioration of Mitroflow Aortic Bioprosthesis

Mode, Incidence, and Impact on Outcome in a Large Cohort of Patients

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Background—Structural valve deterioration (SVD) is a major flaw of bioprostheses. Early SVD has been suspected in the last models of Mitroflow bioprosthesis. We sought to assess the incidence, mode, and impact of SVD on outcome in a large series of Mitroflow aortic valve replacement.

Methods and Results—Six hundred seventeenconsecutive patients (aged 76.1±6.3 years) underwent aortic valve replacement with a Mitroflow prosthesis (models 12A/LX) between 2002 and 2007. By echocardiography, 39 patients developed early SVD (1.66% per patient-year), with stenosis as the main mode (n=36). Mean delay to SVD was only 3.8±1.4 years, and 5-year SVD-free survival was 91.6% (95% confidence interval [CI], 88.7–94.7) for the whole cohort and 79.8% (95% CI, 71.2–89.4) and 94.0% (95% CI, 90.3–97.8) for 19- and 21-mm sizes, respectively. Among the 39 patients with SVD, 13 patients (33%) had an accelerated SVD once the mean gradient exceeded 30 mm Hg. Valve-related death was 46.2% in this SVD subgroup. Five-year overall survival was 69.6% (95% CI, 65.7–73.9). In multivariable analysis, SVD was the strongest correlate of overall mortality (hazard ratio=7.7; 95% CI, 4.4–13.6).

Conclusions—Early SVD is frequent in Mitroflow bioprosthesis (models 12A/LX), especially for small sizes (19 and 21 mm), and reduces overall survival. An unpredictable accelerated pattern of SVD constitutes a life-threatening condition. In view of the large number of Mitroflow valves implanted worldwide, one can expect an epidemic of SVD and valve-related deaths, which represents a major public health issue, especially in the elderly. Hence, a close follow-up with yearly echocardiography after Mitroflow implantation is advisable. An urgent reoperation should be discussed in patients with severe SVD even though they are still asymptomatic. **(*Circulation*. 2014;130:2012-2020.)**

Key Words: aortic stenosis ■ bioprosthesis ■ cardiac valves ■ echocardiography ■ survival analysis

The number of aortic valve replacements (AVRs) performed yearly is estimated at >200 000 worldwide.[1] For the past 10 years, the choice regarding the type of prosthesis has evolved to the advantage of biological over mechanical prostheses because of an aging population and improved hemodynamic performances of the commercially available bioprostheses.[1]

Editorial see p 1997
Clinical Perspective on p 2020

Among bovine pericardial prostheses, the Mitroflow valve, available since 1982,[2] was designed to improve prosthesis hemodynamic performance. Results of the first Mitroflow (Sorin Group Inc) models (11A) have nevertheless been marked by the occurrence of pericardial tears due to leaflet abrasion through abnormal contact with the polyester (Dacron)-covered frame, eliciting severe intraprosthetic aortic insufficiency.[3,4] The subsequent prosthesis model, the Mitroflow 12A, introduced in 1992, rectified this flaw but did not integrate any anticalcification treatment in its fabrication. The main theoretical advantage of the 12A model relies on its hemodynamic profile, which is particularly adapted to a small aortic annulus because of its lesser bulk.[5] However, the absence of anticalcification treatment is an intrinsic weakness and has been associated with early structural failure in other type of bioprostheses.[6] More recently, in 2006, the LX model replaced the 12A model. The LX model is a variation of the 12A model with minor manufacturing modifications; the material components remain the same. These manufacturing process improvements for the LX model did not substantially

Received March 31, 2014; accepted September 18, 2014.

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affect the design or performance of the prosthesis.[7] Therefore, both models can be considered the same bioprosthesis.[8]

The major flaw of biological prostheses is the occurrence of structural valve deterioration (SVD) at mid or long term, which is variable depending on the type of prosthesis.[6,9] The Mitroflow aortic bioprosthesis has been implanted in >100 000 patients worldwide.[10] Although some studies have presented satisfactory mid- and long-term results,[11–13] recent studies have expressed reservation about the durability of the Mitroflow bioprosthesis, with reports of early SVD within 4 years after implantation.[14] Nevertheless, SVD diagnosis often has been based on surgical reintervention reports, leading to underestimation of its current prevalence and its impact on patient survival. In fact, numerous elderly patients are denied surgery because of the high risk of major adverse events related to repeat surgery.[15,16]

In view of the potential impact of early SVD in elderly patients, the present study was thus designed (1) to assess in a large cohort of patients the incidence of SVD for Mitroflow aortic pericardial bioprosthesis (12A/LX) based on echocardiography; (2) to characterize the pattern and the temporal course of SVD; and finally (3) to assess the correlates of SVD and its impact on patient prognosis.

Methods

Patients

Between January 2002 and December 2007, 617 consecutive patients who underwent AVR with the use of a Sorin Mitroflow bioprosthesis (12A and LX models) in the cardiac surgery department of the University Hospital of Nantes were included in the study. During the same period, 2113 bioprostheses were implanted in the aortic position: 621 Mitroflow (in 617 patients), 1173 Carpentier-Edwards PERIMOUNT, 206 Medtronic Mosaïc, and 113 miscellaneous bioprostheses. Baseline characteristics were recorded prospectively. For this observational study, the operating techniques and the choice of cardioplegia were left to the operating surgeon's discretion. In all patients, a surgical approach via median sternotomy was used. The Mitroflow valve was preoperatively prepared according to the directives of the Sorin instruction manual,[17] with successive rinses of physiological saline solution.

The postoperative anticoagulant treatment consisted of 3 months of therapeutic anticoagulation for nonoctogenarian patients or because of associated risk factors (treatment by fluindione). Octogenarians without associated risk factors were discharged with antiplatelet treatment (aspirin).

Echocardiography and SVD Definition

SVD of the bioprosthesis was defined according to the latest recommendations[17] and according to precise echocardiographic criteria: progression of aortic transprosthetic gradient ≥30 mm Hg associated with a decreased effective orifice area ≤1 cm^2 or intraprosthetic aortic regurgitation >2/4. Each case of supposed SVD was carefully assessed and validated after review of medical reports. A severe prosthesis-patient mismatch (PPM) was defined as an effective orifice index area of the aortic prosthesis ≤0.65 cm^2/m^2.

Follow-Up

A postoperative echocardiography was performed before patient discharge. Long-term follow-up was ensured through controls performed by the patients' personal cardiologists. Clinical and echocardiographic data obtained from personal physicians and cardiologists were collected by the clinical investigation center of the University Hospital of Nantes after authorization by the local ethics committee (institutional review board) and were recorded in a computerized database (Commission nationale de l'informatique et des libertés authorization No.1456630v1). Informed consent was obtained.

Morbidity and mortality were analyzed with the recommendations of the American Association for Thoracic Surgery/Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery taken into account.[18] Cardiac and valve-related deaths were recorded following these recommendations. In case of suspicion of SVD by echocardiography, patients were referred to our university center. The last available cardiac echocardiography performed in our institution or outside before repeat surgery or death was taken into account for echocardiographic follow-up.

Statistical Analysis

Quantitative data are expressed as mean±SD. Nonparametric 2-sided tests such as the Fisher exact test and the Mann-Whitney test were used as appropriate. A P value ≤0.05 was considered significant.

The main outcome of this study was the time between surgery and patient death. For this analysis, the few SVD patients (n=4) who underwent a new operation were censored. The second outcome was the time between surgery and SVD (death censored). The analyses of long-term outcomes were performed with the use of the Kaplan-Meier estimator. A first selection of covariates was performed with the log-rank test (P<0.20). Then a Cox model was estimated with a backward procedure performed manually variable by variable with the use of a Wald test (P<0.05). This procedure allows the identification of possible confounding factors (variation of regression coefficients >20%). Hazards proportionality was checked by plotting log-minus-log survival curves and by testing the scaled Schoenfeld residuals. Time-dependent coefficients were used for nonproportional covariates. In the analysis of time to death, SVD was considered a time-dependent covariate with the use of an extended Cox model.

The association between covariates and death was tested. The following preoperative data were considered as possible correlates of death: operative age (years), sex, body mass index, family history, high blood pressure history, diabetes mellitus, dyslipidemia, obesity, history of use of tobacco, aortic valve disease (stenosis, insufficiency, mixed disease, endocarditis, prosthetic endocarditis), New York Heart Association class, pulmonary edema, syncope, atrial fibrillation, chronic obstructive pulmonary disease, forced expiratory volume in 1 second <50%, peripheral vascular disease, renal failure (creatinine >200 μmol/L or Cockcroft-Gault creatinine clearance <60 mL/min), preoperative dialysis, cerebral vascular accident, carotid stenosis >50%, myocardial infarction <30 days, coronary stenosis >50%, left ventricular ejection fraction (<50% and <30%), systolic pulmonary arterial pressure >60 mm Hg, aortic insufficiency >2/4, elective cases, urgent or emergency case, and, finally, SVD.

The proportional hazards assumption was violated for chronic obstructive pulmonary disease, which was analyzed as a time-dependent variable. The related hazard ratio (HR) was assumed different for the first 3 years and afterward.

The following possible correlates of SVD were considered: dyslipidemia, PPM, sex, high blood pressure, diabetes mellitus, operative age >70 years, chronic renal failure, and thyroid disorder.

Statistical analyses were performed with the use of version 2.15.0 of R software.

Results

Demographic and Surgical Characteristics

The preoperative characteristics of the cohort are detailed in Table 1. Mean age of the 617 patients was 76.1±6.3 years; 54.1% (n=334) of the patients were aged between 70 and 80 years, and 32.2% (n=199) were octogenarians. In regard to sex, 54.8% (n=338) of the patients were female. The indication for surgery was aortic valve stenosis in 82.3% of patients, and 30.5% (n=188) of patients presented with New York Heart Association class III or IV dyspnea. The proportion of repeat surgery was 6.0% (n=37). An isolated AVR was performed in 391 patients (63.4%). The associated procedures were coronary artery bypass surgery in 30.8% (n=190), mitral or tricuspid valve surgery in

Table 1. Baseline Characteristics of the Population (n=617)

Clinical data	
Female, n (%)	338 (54.8)
Age, y	76.1±6.3
Body surface area, m^2	1.76±0.2
Atrial fibrillation, n (%)	95 (15.4)
High blood pressure, n (%)	380 (61.6)
Diabetes mellitus, n (%)	121 (19.6)
Dyslipidemia, n (%)	270 (43.8)
Obesity, n (%)	138 (22.4)
Tobacco use history, n (%)	108 (17.5)
NYHA class 3–4, n (%)	188 (30.5)
Comorbidities	
Peripheral vascular disease, n (%)	78 (12.6)
Preoperative renal failure, n (%)	47 (7.6)
Stroke, n (%)	25 (4.1)
Myocardial infarction history, n (%)	42 (6.8)
Coronary angioplasty, n (%)	31 (5)
Echocardiographic data	
LVEF, %	57±12
LVEF <50%, n (%)	107 (17.3)
Aortic surface area, cm^2	0.64±0.17
Mean aortic gradient, mm Hg	54±16
Systolic PAP >60 mm Hg, n (%)	38 (6.2)
Aortic stenosis, n (%)	508 (82.3)
Aortic insufficiency, n (%)	16 (2.6)
Surgical data	
Elective surgery, n (%)	534 (86.5)
Urgent or emergency surgery, n (%)	83 (13.5)
Logistic Euroscore	10.5±10.1

Values are mean±SD unless indicated otherwise. LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; and PAP, pulmonary artery pressure.

6.3% (n=39), and an ascending aorta procedure in 1.6% (n=10). A Cox-Maze IV procedure was performed in 4.4% of interventions (n=27). Cardiopulmonary bypass and aortic cross-clamping times were 92±39 and 70±30 minutes, respectively.

Postoperative Complications

The early postoperative mortality was 4.2% (n=26). The main cause of death was cardiogenic shock (n=6). Mean postoperative hospital stay was 14.6±10.3 days, of which a mean of 4.2±7.5 days was spent in the intensive care unit. The proportion of neurological complications was 12.1%, consisting of 2.3% (n=14) cerebral vascular accident, 0.6% (n=4) seizure, and 9.8% (n=61) confusion episodes. Transfusion was needed in 49.6% of patients (n=306). The proportion of postoperative renal failure was 14.1% (n=87), with transient dialysis being necessary in 4.7% of the cases (n=29). Inotropic support was used in 18.5% (n=114) of the patients. The proportion of reoperation was 9.4% (n=58), mainly for pericardial effusion or uncontrolled bleeding. Postoperative atrial fibrillation occurred in 36.3% (n=224) of patients. Finally, 11.7% (n=72) of the patients presented a second- or third-degree atrioventricular block, and 4.9% (n=30) required a pacemaker.

Implanted Bioprostheses

The different sizes of implanted bioprostheses are reported in Table 2. A small-diameter prosthesis (19 or 21 mm) was implanted in 64.2% of patients (n=396), and 9.6% (n=59) received a larger prosthesis (25 or 27 mm). The 19-mm prosthesis was more frequently implanted in the octogenarian compared with the nonoctogenarian population (27.6% versus 18.7%; *P*=0.016). Table 2 shows the postoperative gradients and orifice areas according to the size of the implanted prosthesis. Based on the in vivo effective orifice area values given by the manufacturer of the Sorin Mitroflow valve, 23.5% of the patients (n=145) had severe PPM. Severe PPM was observed primarily with sizes 19 and 21 mm (Table 2).

Structural Valve Deterioration

Overall mean follow-up was 3.8±2.0 years, with a median of 4.1 years. During follow-up, 39 cases of SVD occurred according to echocardiographic criteria. Two failure modes were observed: The main mode was calcified prosthetic stenosis (Figure 1) in 36 patients (92.0%), whereas moderate to severe intraprosthetic regurgitation was found in 3 patients (8.0%). Aortic regurgitation was caused by a cusp tear and prolapse in 2 patients and by cusp retraction and calcification in 1 patient. Figure 2 illustrates the progressive evolution of mean transprosthetic gradients from surgery to the end of follow-up or death for all patients. The 1-, 2-, and 5-year cumulative probability values of SVD were 0.2% (95% confidence interval [CI], 0.0–0.6), 0.8% (95% CI, 0.0–1.6), and 8.4% (95% CI, 5.3–11.3; Figure 3). The first SVD was diagnosed only 14 months after surgery in a patient with a 23-mm prosthesis. Univariable analysis demonstrated that small-sized prostheses (19 or 21 mm) were significantly associated with the occurrence of SVD (Figure 4; *P*<0.001), with 20% and 5% of SVD at 5 years for the sizes 19 and 21 mm, respectively. In multivariable analysis (Table 3), age at the time of surgery was not found to be a significant correlate of SVD. PPM was a significant correlate of SVD (HR=1.95; *P*=0.047). Female sex (HR=2.16; *P*=0.044) and preoperative dyslipidemia (HR=2.01; *P*=0.037) were also found to be correlates of SVD.

Accelerated SVD

Among the 39 cases of SVD, 13 patients had an accelerated or "explosive" SVD, defined by an increase >25 mm Hg of the mean transprosthetic gradient over a short period of time of 12 months (Figure 2). In these patients, the mean gradient increased from 22±11 to 61±16 mm Hg in only 1 year. The

Table 2. Echocardiographic Parameters at Discharge According to Prosthesis Size

	n (%)	LVEF, %	Mean Gradient, mm Hg	Prosthesis Valve Area, cm^2	PPM, n (%)
19 mm	133 (22)	56.4	15.70±7.5	1.14±0.45	46 (35)
21 mm	263 (43)	55.8	14.04±5.32	1.31±0.33	87 (33)
23 mm	162 (26)	55.4	12.08±4.44	1.57±0.51	12 (7)
25 mm	47 (8)	53.8	9.21±3.52	1.57±0.33	0
27 mm	12 (2)	41.4	9.86±3.67	1.86±0.51	0

Values are mean±SD unless indicated otherwise. LVEF indicates left ventricular ejection fraction; and PPM, prosthesis-patient mismatch.

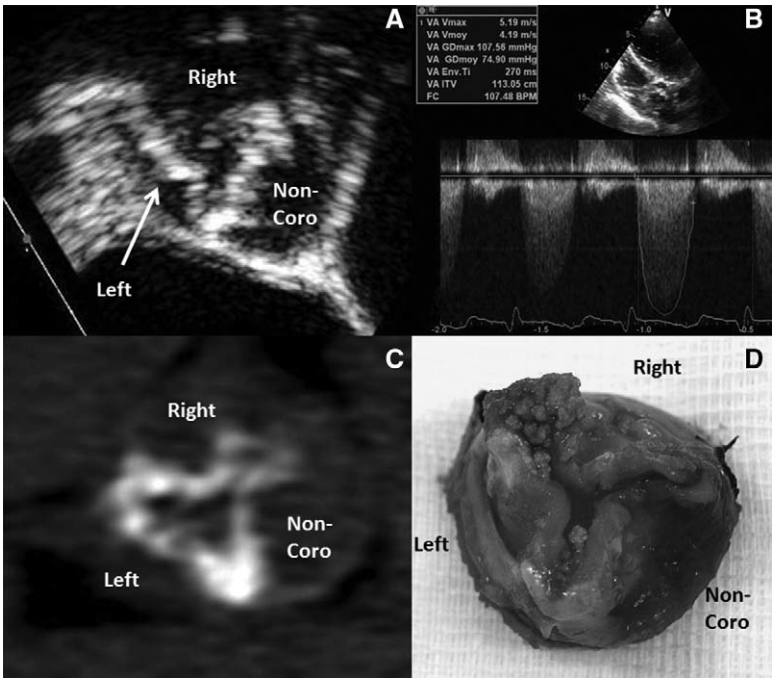

Figure 1. Mitroflow bioprosthesis (21 mm) structural failure characterized by commissural calcified nodules and global thickening and stiffening of the 3 cusps just before reoperation. The Mitroflow was implanted in a 75-year-old woman for severe aortic stenosis. Five years later, the patient had symptomatic calcified structural valve deterioration with a mean gradient of 75 mm Hg and an orifice of 0.7 cm^2.

A, Transesophageal echocardiography showing calcification of the bioprosthesis. **B**, Transvalvular Mitroflow gradients. **C**, Diffuse calcification of the Mitroflow bioprosthesis by computed tomographic scan. **D**, Mitroflow after explantation showing calcified nodules, particularly in the commissural regions, and diffuse cusp infiltration, thickening, and stiffening. Images in **A**, **C**, and **D** are placed roughly in the same orientation for comparison. Left indicates left cusp; Non-coro, noncoronary cusp; and Right, right cusp.

mean age of this subgroup of patients was 73.7±7.8 years, and 30.8% were male, with a prosthesis diameter of 19 or 21 mm in 76.9% of the cases. The evolution was marked by a valve-related death in 46.2% (n=6) of this subgroup of patients. A mean transprosthetic gradient threshold of 30 mm Hg seems to be a divergent point between patients who are developing accelerated and more progressive stenotic SVD. This accelerated form of SVD could be similar to those described by the Boston Children's Hospital and the Harvard Medical School, with several cases of rapid life-threatening valve deterioration with the Mitroflow prosthesis in young adults.[19]

Long-Term Survival and Impact of SVD on Mortality

Table 4 shows the causes of death (n=159), dominated by cancer (n=25; 15.7%) and congestive heart failure (n=23;

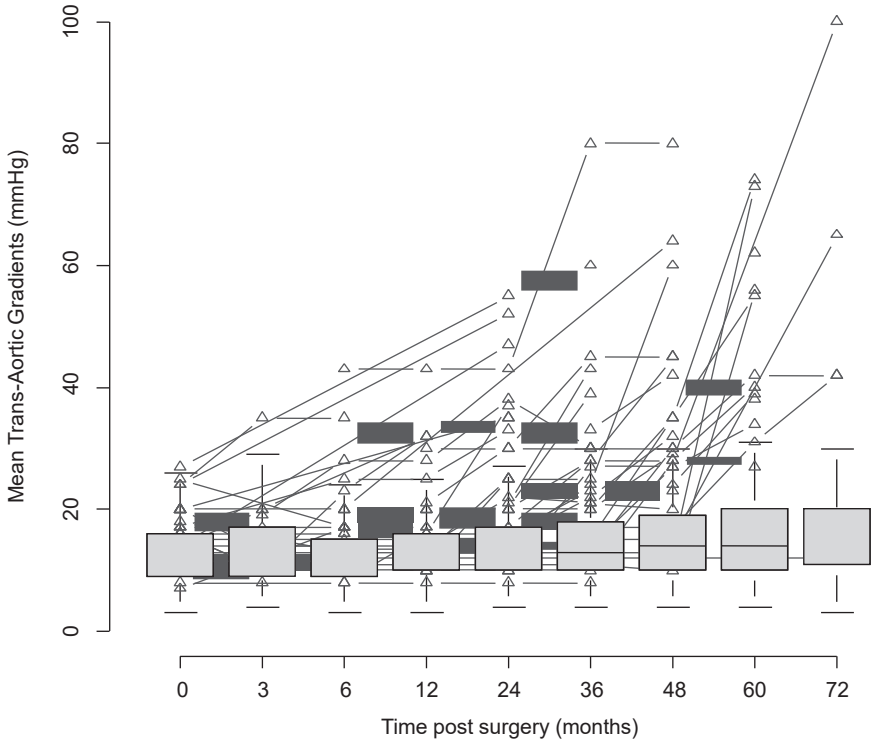

Figure 2. Mean transprosthetic gradient changes of patients with no structural valve deterioration during follow-up (box plots) and representation of each transvalvular gradient change of patients with structural valve deterioration (gray lines).

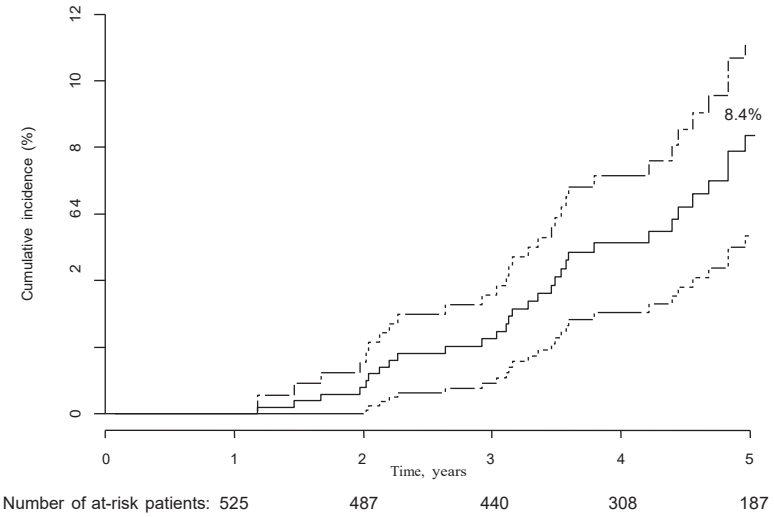

Figure 3. Cumulative incidence of structural valve deterioration (Kaplan–Meier method). Note the early occurrence of structural valve deterioration from 1 year after surgery and the high 5-year rate of structural valve deterioration.

14.5%). In the SVD group, 16 patients (41.1%) died, and SVD was considered the direct cause of death in 12 patients (11 cases of untreatable heart failure and 1 death after reoperation). Four patients with SVD (10.3%) underwent a second AVR. The 35 other patients did not undergo any surgery at the date of data extraction (main reason: patient not referred to surgery [51.4%], patient's refusal of treatment [14.3%], death while on the waiting list [11.4%], and sudden death soon after SVD diagnosis [11.4%]).

The 5-year overall survival rate was 69.6% (95% CI, 65.7–73.9; Figure 5). At 5 years, valve-related and cardiovascular-related survival rates were 88.3% (95% CI, 85.3–91.4) and 81.8% (95% CI, 78.4–85.4), respectively (Figure 5). The 5-year survival rates without stroke or without endocarditis were 93.4% (95% CI, 91.1–95.8) and 94.3% (95% CI, 92.1–96.6), respectively. Thirty-two cases (5.2%) of prosthetic endocarditis were observed (8 of them required a second AVR).

The multivariable Cox model for mortality is shown in Table 5. The final model retained several significant preoperative factors: chronic obstructive pulmonary disease (only the HR after the third year was significant: HR=3.91; *P*=0.001), preoperative respiratory insufficiency (HR=2.75; *P*=0.006), New York Heart Association class III to IV (HR=1.51; *P*=0.007), repeat surgery (HR=1.85; *P*=0.014), and myocardial infarction in the previous 3 months (HR=2.76; *P*=0.008). Elderly patients (aged ≥80 years), diabetes mellitus, and preoperative poor left ventricular function were not found to be significant correlates. SVD emerged as the strongest correlate of mortality, with an increased risk of death of 7.7 after diagnosis of SVD (95% CI, 4.4–13.6). No interaction was found statistically between SVD and PPM.

Discussion

SVD remains a concern for the use of bioprostheses.[6,12–14] The objectives of the present study were to assess the incidence of SVD, the mode of SVD, and its impact on outcome in aortic Mitroflow models 12A/LX. Despite satisfactory early hemodynamics results after implantation,[20] SVD rates in our study reached 8.4% (95% CI, 5.3–11.3) only 5 years after surgery. SVD is therefore an early and frequent finding in patients implanted with a Mitroflow bioprosthesis in the aortic position. SVD consists mainly of progressive stenosis with an

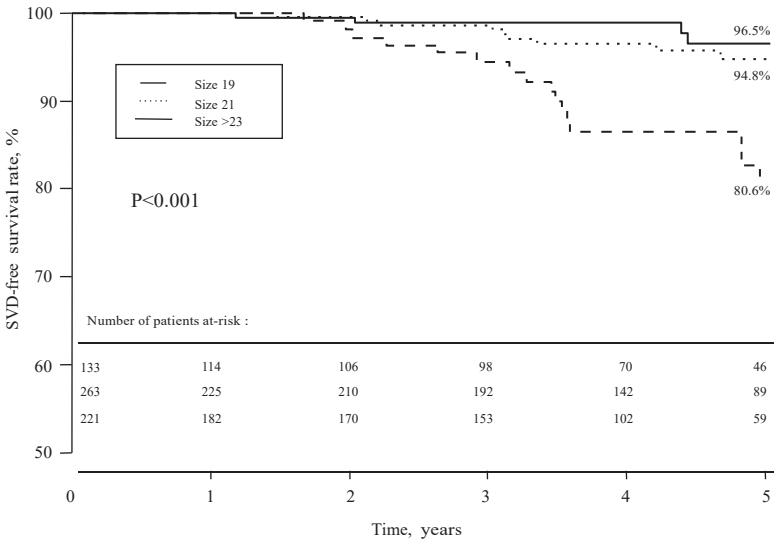

Figure 4. Structural valve deterioration (SVD)–free survival curves according to prosthesis size.

Table 3. Correlates of SVD in Multivariable Analysis

Variable	Hazard Ratio	95% CI	P Value
Female sex	2.162	1.021–4.577	0.044
Dyslipidemia	2.014	1.045–3.880	0.037
Prosthesis-patient mismatch	1.945	1.010–3.743	0.047

CI indicates confidence interval.

Table 4. Long-Term Causes of Death

Causes of Death	n	%
Cancer	25	15.7
Congestive heart failure	23	14.5
Sepsis	19	11.9
Sudden death	13	8.2
Endocarditis	12	7.5
Structural valve deterioration	12	7.5
Respiratory failure	8	5.0
Cerebral vascular accident	6	3.8
Myocardial infarction	5	3.1
Cardiogenic shock	2	1.3
Bleeding	2	1.3
Mesenteric ischemia	2	1.3
Multiorgan failure	2	1.3
Thromboembolic event	1	0.6
Other	27	16.9
Total	159	100

unexpected and unpredictable life-threatening accelerated pattern in one third of SVD patients. The occurrence of SVD (particularly the accelerated pattern) has a significant impact on patient outcome and translates to a reduced overall survival in patients developing SVD (HR for mortality=7.7). With respect to the large use of Mitroflow bioprostheses (>100 000 implantation worldwide), one can expect an epidemic of SVD requiring reoperation or leading to death in these patients. Hence, early SVD in the Mitroflow bioprosthesis necessitates annual echocardiography from the first year after implantation in all patients and an even closer follow-up once the mean gradient reaches 30 mm Hg. Owing to the life-threatening accelerated pattern of SVD in one third of patients, urgent reoperation should be considered once bioprosthesis stenosis is severe, even in asymptomatic patients.

Mitroflow Durability

Apart from specific situations, current guidelines recommend bioprosthesis use in the aortic position in patients older than 65 years.[21] However, with 5-year SVD-free survival of 79.8±4.6% and 94.0±1.9% for sizes 19 and 21 mm, respectively, our present study demonstrates that the Mitroflow bioprosthesis presents an abnormal risk of premature SVD. Up to 8.4% of patients in our series would develop SVD only 5 years after surgery despite the absence of specific factors favoring early degeneration such as young age or renal failure. Primary modes of bioprosthesis failure are calcification, noncalcific degeneration, fibrosis, or cusp tear.[22] Progressive cusp stiffening and calcification eliciting stenosis are the main modes of SVD in the present study, as reported previously in Mitroflow[14,23–25] or other types of commercially available bioprostheses.[6,22]

Echocardiographic Assessment of SVD

Several studies have presented satisfactory results with the Mitroflow bioprosthesis and have alleged a low SVD rate, but the SVD rate nevertheless frequently reached 20% after 10 years.[12,26–29] For instance, in a series of 1516 patients, 5- and 10-year SVD-free survival rates were 99% and 82%, respectively.[12] Moreover, SVD diagnosis was determined in most studies only at reoperation, excluding de facto patients denied for repeat surgery. This definition of SVD, based exclusively on macroscopic assessment in the operating department and on histological examination, leads to an underestimation of this complication. In our cohort, only 10% (4/39) of patients with SVD were reoperated during the study period, which represents only 0.3% of the overall cohort. Fear of repeat surgery with a high operating risk in elderly patients as well as the occurrence of severe and rapid heart complications in SVD patients partly explains the low rate of reoperation. Our results thus confirm the work of Alvarez et al,[14] which found, in a cohort of 491 patients with Mitroflow 12A implantation, a 5-year SVD-free survival rate of 95% based on histological diagnosis compared with only 85% by echocardiography. In the same way, Flameng et al[30] reported a 10-year SVD-free survival rate of 86% based on ultrasound diagnosis compared with 96% SVD-free survival when histological diagnosis was considered in different biological valves. Hence, echocardiography should be the reference method for diagnosing and reporting SVD in series of bioprosthetic patients rather than only reoperation, which is a less accurate approach and a clear factor in underestimation, especially in elderly patients.

Life-Threatening Accelerated Pattern of SVD

We observed an accelerated pattern of SVD in approximately one third of patients with SVD, portending a poor outcome. Those patients had a rapid progression of bioprosthesis stenosis leading to severe aortic stenosis in a few months. In native aortic valve stenosis, the annual rate of worsening is normally ≈0.1 cm^2, with an increase in mean gradient of 8 mm Hg,[31] but some patients have a more rapid rate of progression of the disease.[32] In our cohort of patients, beyond the threshold of 30 mm Hg, the rate of increase in mean gradient through the Mitroflow bioprosthesis was >25 mm Hg per year in those who developed accelerated SVD. This accelerated pattern should be known by clinicians and taken into account in the clinical management of these patients. Although the absolute number of patients with an accelerated pattern was relatively small (n=13; 33% of SVD), the high mortality rate of this subgroup is a subject of concern and is an incentive to propose a closer follow-up for patients with a Mitroflow bioprosthesis and to refer patients promptly to surgery once stenosis is severe.

Correlates of SVD

Age is a well-known risk factor for SVD[9,21] and has been linked to SVD in Mitroflow bioprostheses.[14] In the present

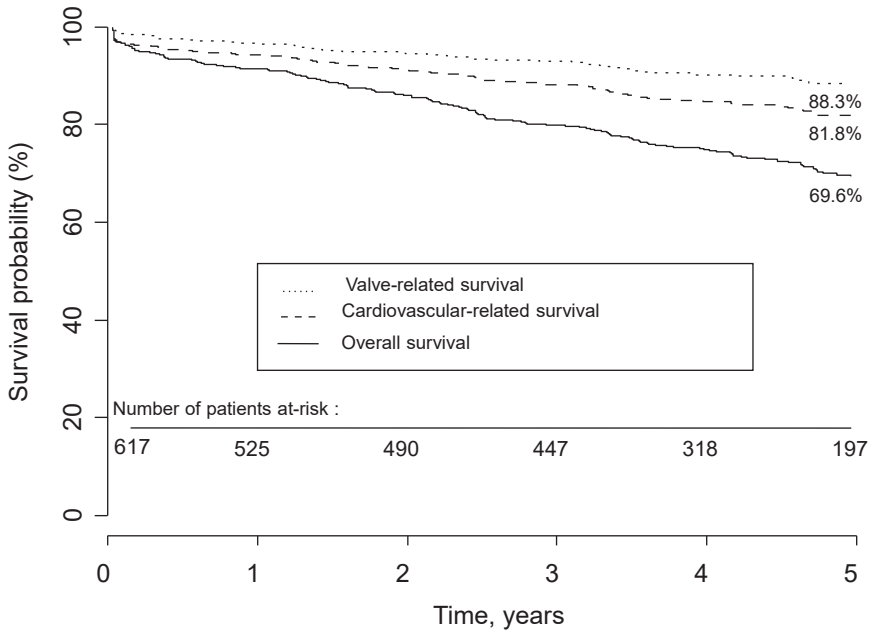

Figure 5. Overall, cardiovascular-related, and valve-related survival curves.

study, multivariable analysis identified female sex, dyslipidemia, and PPM as statistically significant correlates of SVD. However, patient age did not emerge as a significant predictor because most patients are older than 65 years. Dyslipidemia and metabolic syndrome have been associated previously with native aortic valve stenosis development but also with progressive SVD of bioprostheses.[33,34] In our cohort, SVD occurred preferentially in small-sized bioprostheses (19 and 21 mm) with higher postoperative gradients and was associated with PPM. Although the clinical consequences of PPM on morbidity and mortality after AVR remain a matter of debate,[35,36] the hemodynamic consequences of PPM could have a deleterious influence on bioprosthetic duration. Indeed, Flameng et al[30] demonstrated that SVD was more frequent in patients with PPM defined by an actual surface area <0.85 cm^2/m^2. In contrast to other types of bioprostheses, Mitroflow 12A/LX was not prepared with a specific anticalcification treatment. Abnormal mechanical constraints related to PPM and the absence of anticalcification treatment could explain the Mitroflow 12A/LX tendency toward early stiffening and calcification. Indeed, according to experimental work by Cunanan et al,[25] the Mitroflow valve is particularly prone to calcification. Ninety-day subcutaneous valvular prosthetic tissue implants in rats demonstrated a tissue calcium content up to 214 μg/mg for the Mitroflow but only 2.13 μg/mg (P<0.001) for the porcine Carpentier-Edwards and the pericardial PERIMOUNT bioprostheses. Besides patient characteristics and PPM, the early and high rates of SVD in Mitroflow 12A/LX are therefore likely linked to structural characteristics of bioprosthesis and especially the absence of anticalcification treatment during tissue preparation and fixation.

Table 5. **Multivariable Cox Model Analysis of Midterm Survival**

Variable	Hazard Ratio	95% CI	P Value
Structural valve deterioration*	7.7	4.36–13.61	<0.0001
COPD (after year 3)	3.91	2.02–7.55	0.001
Myocardial infarction within 3 mo before surgery	2.76	1.31–5.81	0.008
Preoperative respiratory insufficiency	2.75	1.33–5.67	0.008
Repeat surgery	1.85	1.13–3.03	0.014
NYHA class 3–4	1.51	1.12–2.03	0.007

CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; and NYHA, New York Heart Association.

*Structural valve deterioration is modeled as a time-dependent covariate.

Impact of SVD Occurrence on Patient Survival

Beyond the classic factors of postoperative survival such as respiratory or coronary disease and symptoms, SVD emerged as a strong predictive factor of survival after AVR with a Mitroflow 12A/LX bioprosthesis. Indeed, SVD was found to be the strongest correlate of mortality in multivariable analysis (HR=7.7; P<0.001), overwhelming other pejorative prognosis factors. The deleterious effect of SVD on survival was highlighted previously in the Veterans Affairs study,[37] making the high rate of SVD with the Mitroflow a concern. The present study highlights the short durability of Mitroflow 12A/LX bioprostheses in some patients. Because SVD portends a poor prognosis, patients need to be followed closely after surgery and referred promptly to surgery according to the severity of SVD.

Clinical Implications

Patients with a Mitroflow bioprosthesis (models 12A/LX) thus must face an unusual and quite unpredictable structural and hemodynamic deterioration, with an accelerated worsening in one third of SVD portending a poor outcome under conventional management and a high mortality rate. Because premature SVD risk was considered to be low for all biological valves[9] including the Mitroflow valve,[12,27] European

recommendations advise yearly ultrasound monitoring only after the fifth year. However, early SVD and the accelerated pattern of SVD in some Mitroflow bioprostheses advocate for a closer monitoring from the first postoperative year. On the basis of mean gradient evolution, one would recommend a careful monitoring at least every 6 months when mean gradient is ≈30 mm Hg. Surgical replacement seems to be the most adapted solution in cases of SVD with small prostheses because the Mitroflow valve is not completely favorable to the "valve in valve" concept. The internal diameter of the size 19 Mitroflow is only 15.4 mm, which does not currently allow the smallest available percutaneous valve to be implanted properly. Furthermore, the Mitroflow prosthesis design, with the pericardial leaflet located outside of the stent, exposes the coronary ostia to an obstruction by the transcatheter valve.[38]

Limitation of this Study

The main limitation of this study relies on the relatively short follow-up, which averaged 3.8 years. Further studies are thus warranted to confirm our results regarding early SVD and to extend our findings to long-term durability. Although the absence of anticalcification treatment is the main hypothesis for Mitroflow SVD, we cannot rule out the hypothesis of a sporadic structural defect. In the first hypothesis, SVD rate might continue to grow in an exponential way, whereas it might grow slowly in the second hypothesis. Echocardiographic follow-up, although in overall agreement with current recommendations, was performed by personal cardiologists with some variations in data reporting and with various intervals of time between the 2 follow-ups. Data were thus interval-censored survival data. We chose the middle of the interval between the 2 follow-ups to define the time of SVD. Such an approach may be associated with an underestimation of SVD incidence regarding the possible absence of echocardiography before the death of the patient.

Conclusions

Despite satisfactory hemodynamic results early after implantation, SVD is an early and frequent finding in patients implanted with a Mitroflow 12A/LX bioprosthesis in the aortic position, particularly for small diameters (19 and 21 mm). SVD consists mainly of progressive aortic stenosis, with cusp stiffening and calcification likely related to the absence of anticalcification treatment of the prosthesis. Approximately one third of patients with SVD experienced an unexpected and unpredictable life-threatening accelerated hemodynamic and structural deterioration of the bioprosthesis. Early SVD, particularly the accelerated pattern, has a strong impact on patient outcome, with a reduced overall survival rate. In view of the large volume of implanted Mitroflow bioprostheses, we can expect an epidemic of SVD requiring reoperation in elderly patients. Our findings advocate for yearly echocardiography from the first year after Mitroflow 12A/LX implantation and careful monitoring once the mean gradient reaches 30 mm Hg. Owing to the life-threatening accelerated pattern of SVD in one third of patients, urgent reoperation should be considered once stenosis is severe, even in asymptomatic patients. The replacement of the Mitroflow models 12A/LXA by a new model (DLA with PRT [phospholipid reduction treatment]), which benefits from an anticalcification treatment, offers better perspectives for the durability of the prosthesis.

Sources of Funding

Dr Le Tourneau was supported by INSERM (INSERM translational research grant 2012–2016).

Disclosures

Dr Le Tourneau received speaker fees from Edwards (general educational meeting focused on native valve disease). The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Structural valve deterioration (SVD) remains a major flaw of bioprostheses. Current recommendations advise yearly echocardiography from the fifth year after surgery with the assumption that SVD would not occur earlier. We retrospectively assessed 617 consecutive patients (aged 76.1±6.3 years) who underwent an aortic valve replacement with a Mitroflow bioprosthesis (12A/LX models) between 2002 and 2007 to evaluate the incidence, mode, and impact of SVD on outcome. The diagnosis of SVD was based not only on reoperation but also on echocardiography. During a follow-up of 3.8±1.4 years, we ascertained 39 cases of SVD (1.66% per patient-year), with stenosis as the main mode (n=36; 92%). The first SVD was diagnosed only 14 months after surgery. The 5-year cumulative probability of SVD was up to 8.4% (95% confidence interval, 5.3–11.3), with a higher risk in small-sized bioprostheses (19 and 21 mm). An unpredictable accelerated pattern of SVD was identified in 13 patients (33%) once the mean gradient exceeded 30 mm Hg. In this subgroup, valve-related death reached 46.2%. In multivariable analysis, SVD was the strongest correlate of overall mortality (hazard ratio, 7.7; 95% confidence interval, 4.4–13.6). To conclude, early SVD is an unexpected but frequent finding in Mitroflow bioprosthesis (12A/LX), especially for small sizes (19 and 21 mm), and reduces overall survival. In view of the large number of Mitroflow valves implanted worldwide, one can expect an epidemic of SVD and valve-related deaths. Hence, close follow-up with yearly echocardiography on surgery is advisable in patients with Mitroflow bioprostheses. An urgent reoperation should be discussed in patients with severe SVD in view of the risk of rapid progression and death.

III. Conclusion

En dehors de situations cliniques particulières, il est aujourd'hui recommandé d'implanter une prothèse biologique en cas de remplacement valvulaire aortique chez un patient de plus de 65 ans [8] en raison du faible risque de SVD chez le sujet plus âgé. Cependant, notre étude retrouve un taux de SVD de 8,4% (IC95% de 5,3 à 11,3) à 5 ans, sans facteurs favorisant spécifique. De plus, la survenue d'une SVD est associée à un risque de décès multiplié par 7,7 (IC95% de 4,4 à 13,6). Cette surmortalité associée à une incidence non négligeable de SVD va à l'encontre donc des recommandations actuelles. Un suivi annuel dès la première année nous semble nécessaire pour la surveillance de patients porteurs d'une bioprothèse SORIN Mitroflow®. En regard du nombre de patients porteurs dans le monde d'une prothèse SORIN Mitroflow® (modèles LX/12A), cette étude a permis pour la première fois d'attirer l'attention sur un véritable problème de santé publique.

Parmi les facteurs de risque principaux, le PPM sévère est associé à un risque multiplié par deux de SVD dans notre étude. Ces résultats sont controversés dans la littérature mais sont en accord avec ceux de Flameng et al. [30] qui ont démontré une incidence de SVD plus fréquente en cas de PPM (défini alors comme modéré : $<0,85 cm^2/m^2$). Il a été démontré que le PPM s'associait à une perturbation des flux et des régimes de pression au niveau du culot aortique [30], pouvant peut-être expliquer cette incidence de SVD importante en cas de prothèse sans traitement anti-calcique comme la prothèse SORIN Mitroflow®. En se basant sur les surfaces fonctionnelles données par le constructeur [14], plus d'un tiers des patients porteurs d'une prothèse 19 ou 21 mm présentaient un PPM sévère dans notre cohorte.

Chapitre 4

Modélisation de l'évolution des prothèses valvulaires biologiques par un modèle multi-états utilisant les scores de propension

I. Résumé

Dans le chapitre précédent, nous avons décrit un problème de santé publique concernant la prothèse SORIN Mitroflow®. Le PPM y est retrouvé comme facteur de risque important de SVD. La question de l'impact réel ou non de ce mismatch est encore actuellement débattue dans la littérature [31]. Le modèle de Cox utilisé dans ce précédent chapitre ne permet cependant pas de conclure avec certitude sur le rôle du PPM. En effet, le risque compétitif avec le décès et la censure par intervalle propre au diagnostic échographique de SVD étaient ignorés au sein de ce type de modèle. Une autre modélisation est possible par une approche multi-états de type illness-death, en prenant en compte la censure par intervalle du diagnostic de SVD. Parallèlement aux essais randomisés, les méthodes d'analyse par score de propension permettent d'évaluer l'effet marginal d'une covariable sur la survenue d'un évènement en mimant un essai randomisé contrôlé, effet plus adéquat en terme de santé publilque contrairement à l'effet conditionnel que nous avons estimé par le modèle mutlivarié de Cox dans le chapitre 3.

Notre objectif ainsi a été d'évaluer précisément l'effet marginal PPM sur le risque de survenue de SVD en utilisant les scores de propension au sein d'un modèle multi-états. Dans le cadre de sa thèse [32], Florence Gillaizeau a ainsi proposé pour la première fois un modèle semi-Markov de type illness-death pour données censurées par intervalle avec pondération par la méthode IPW (Inverse Probability Weighting), appliqué à la même cohorte que celle utilisée dans le chapitre 2. Ce travail s'inscrit ainsi donc en complémentarité dans deux thèses.

II. Article

Research Article

Statistics
in Medicine

Received XXXX

(www.interscience.wiley.com) DOI: 10.1002/sim.0000

Inverse Probability Weighting to control confounding in an illness-death model for interval-censored data

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Multistate models with interval-censored data, such as the illness-death model, are still not used to any considerable extent in medical research regardless of the significant literature demonstrating their advantages compared to usual survival models. A possible explanation is their uncommon availability in classical statistical software or, when they are available, by the limitations related to multivariable modelling to take confounding into consideration. In this paper, we propose a strategy based on propensity scores that allows population causal effects to be estimated: the Inverse Probability Weighting in the illness semi-Markov model with interval-censored data. Using simulated data, we validated the performances of the proposed approach. We also illustrated the usefulness of the method by an application aiming to evaluate the relationship between the inadequate size of an aortic bioprosthesis and its degeneration or/and patient death. We have updated the R package *Multistate* to facilitate the future use of this method.

Keywords: Confounding factors; Multistate models; Semi-Markov process; Propensity score; Inverse Probability Weighting (IPW).

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Abbreviations: APO, Acute Pulmonary Oedema; ARR, Absolute Risk Reduction, AVR, Aortic Valve Replacement; BMI, body mass index; CPB, Cardio-Pulmonary Bypass; CI, confidence interval; CIF, Cumulative Incidence Function, COPD, Chronic Obstructive Pulmonary Disease; HR, hazard ratio; IPW, Inverse Probability Weighting; LVEF, Left Ventricular Ejection Fraction; NTT, Number Needed to Treat, NYHA, New York Heart Association; PH, proportional hazard; PPM, Patient-Prosthesis Mismatch; ROC, Receiver Operating Characteristic; RMSE, Root Mean Square Error; SE, Standard Error; SM, Semi-Markov; SVD, Structural Valve Deterioration.

1. Introduction

The management of chronic diseases involves addressing the modifiable risk factors that contribute to the progression of the disease towards different stages [1]. Multistate models allow precise study of the relationship between a set of covariates and multiple times-to-event [2]. As an example, the illness-death model is a three-state model commonly used to describe the chronic diseases process with an initial state, an intermediate state representing a disease-related nonfatal event, and a final state representing a terminal event such as death. The time of occurrence of the intermediate event may be interval-censored if patients are periodically assessed and, consequently, the nonfatal event status may be unknown at the end of follow-up. In this context, the illness-death model for interval-censored data provides more accurate effect estimates of exposures than standard cause-specific analyses where competing events are treated as censoring events [3].

The illness-death model and more generally the multistate models have been tried and tested over many years according to the biostatistic litterature [4, 5]. Nevertheless, they are still not used to any considerable extent in clinical epidemiology for interval-censored data. This may be due to their uncommon availability in classical statistical software or, when they are available, the limitations related to the multivariable modelling as the only method to take confounding into consideration. In observational studies, confounding is a source of bias in estimating causal association [6]. However, biostatisticians may be reluctant to jump into a regression analysis in the multistate setting because the modelling strategy is difficult and time-consuming, especially because: i) one variable may influence different transitions multiplying the numbers of parameters to estimate, ii) different assumptions such as log-linearity and proportionality of hazards (PH) have to been evaluated for each variable on each transition, iii) the adjustment on confounders is complex when the PH assumption does not hold, and iv) the variable selection must be performed for each transition. In addition, and perhaps more importantly, multivariable models allow estimates of conditional subject-specific effects whereas many epidemiological studies are planned to examine the population causal effect of some exposure [7]. Similar to randomized control trials, propensity score methods allow the estimation of marginal (or population-average) effects [8, 9]. The propensity score is the probability of exposure conditional on observed baseline characteristics [10]. Four propensity score methods can be distinguished [9]: matching on the propensity score, stratifying on the propensity score level, adjusting on the propensity score, and Inverse Probability Weighting (IPW). The IPW appears to be an efficient method for estimating marginal effects for survival data analysis in the presence of confounding [11, 12]. The principle of IPW is to create a pseudo dataset by weighting each observation by a function of the inverse propensity score in order to balance observed baseline covariates between groups [13, 14]. To our knowledge, this approach has not yet been assessed in the context of multistate models with interval-censored data.

Our work was motivated by the analysis of a French cohort of patients who underwent heart surgery for an Aortic Valve Replacement (AVR) with a bioprosthesis [15]. Proper functioning of the bioprothesis may be altered by a Strutural Valve Deterioration (SVD) at mid- or long-term [16], this failure being diagnosed during follow-up echographies. An emerging question for physicians is the relationship between an excessively small inserted prosthesis in relation to the patient's body size, namely the Patient-Prosthesis Mismatch (PPM), and progression to SVD or patient death. A possible representation

of the disease evolution is an illness-death model, some patients dying before being diagnosed with the SVD. Applying a multivariable death-censored Cox model to this cohort, Sénage *et al.* [15] found a significant increased risk of SVD for patients with a severe PPM (HR=1.95 [95%CI: 1.01-3.74]). However, this estimation was conditional (subject-specific) and ignored the competing risk with patient death and the interval-censoring of time-to-SVD. Our objective was therefore to estimate the population causal effect of PPM by using an illness-death model for interval-censored data with the issue of possible confounders such as the body mass index (BMI) or the patient age at surgery.

In this paper, we propose a semi-Markov illness-death model for interval-censored data with IPW estimators. Section 2 presents the IPW method and its use in a semi-Markov framework. Section 3 presents our motivating example for the prognosis of patients who underwent AVR replacement. Section 4 details the simulation design and corresponding results to assess the performances of the proposed model. Section 5 presents an analysis strategy of the motivating example and shows the results. Finally, section 6 offers discussions and conclusions.

2. The IPW semi-Markov model

2.1. Notations

Let T be the chronological time from baseline and S the duration (or sojourn time) in a state. Let $\mathcal{Y}$ be the set of possible clinical states. The stochastic process under consideration is $\{Y_m, T_m, m \in \mathbb{N}\}$, where Y_m is the state of the patient after the m-th transition occurring at time T_m with $T_0 < T_1 < ... < T_m$ ($T_0 = 0$ and $Y_0 = 1$ by convention). Let ϵ be the set of possible transitions ij with $(i, j) \in (\mathcal{Y}, \mathcal{Y})$, where i represents a transient state with j distinct from i. We use δ_{ij} to denote the indicator function of a transition ij: $\delta_{ij} = 1$ if the transition ij is observed (with the duration time s_{ij} in state i before transition to state j), and $\delta_{ij} = 0$ otherwise. Let Z be the binary exposure variable under interest at baseline ($Z = 0$ for unexposed and $Z = 1$ for exposed patients). X is the vector of patient characteristics at baseline (except Z), and X_{ij} the subvector of characteristics specifically associated to the transition ij.

In the context of the illness-death model, $\mathcal{Y} = \{1, 2, 3\}$ with $\{Y = 1\}$ the healthy stage, $\{Y = 2\}$ the illness stage, and $\{Y = 3\}$ the death. $[t_{\text{inf}};t_{\text{sup}}]$ refers to the interval of censoring for the time-to-illness from baseline and $t_{\max}$ the last time of follow-up from baseline. If the disease is diagnosed during the follow-up, t_{sup} corresponds to the illness diagnosis time and t_{inf} corresponds to the last examination time where the diagnosis was negative. If the disease is not diagnosed during the follow-up, t_{sup} corresponds to $t_{\max}$.

2.2. Multivariable semi-Markov model

The semi-Markov (SM) model considers that the transition intensities between two states depend on the time already spent in the current state [17]. This assumption appeared relevant in many medical applications, for instance in renal transplantation [18, 19] or in AIDS [20, 21]. The hazard function for transition from state $Y_m = i$ to the state $Y_{m+1} = j$ after a duration s, given patient characteristics $X_{ij} = x_{ij}$ and $Z = z$ is therefore defined by:

$$\lambda_{ij}(s|x_{ij}, z) = \lim_{\Delta s \to 0^+} P(s \leq T_{m+1} - T_m < s + \Delta s, Y_{m+1} = j | T_{m+1} - T_m > s, Y_m = i, x_{ij}, z)/\Delta s \qquad (1)$$

The probability for a patient to spend at least some time s in state i, given its exposure $Z = z$ and other characteristics $X = x$ at baseline, can be defined as:

$$S_i(s|x, z) = \exp\left(- \sum_{j:ij \in \epsilon} \int_0^s \lambda_{ij}(u|x_{ij}, z)\, \mathrm{d}u \right) \qquad (2)$$

The corresponding density function specific to transition ij after duration s can therefore be deduced from equations (1) and (2): $f_{ij}(s|x,z) = \lambda_{ij}(s|x_{ij},z)S_i(s|x,z)$.

In the multivariable SM model, the exponential of the regression coefficients associated to covariates are estimates of the conditional (subject-specific) Hazard Ratios (HRs).

In this work, we studied parametric proportional-hazards (PH) models with fixed time covariates at baseline and parameters were estimated by maximizing the log-likelihood. Take a sample of N independent subjects ($h = 1, ..., N$). Let l_h be the individual contribution to the likelihood for a subject h. In the illness-death context, time-to-illness is often interval-censored. In this case, $l_h = S_1(t_{max}|x,z) + \int_{t_{inf}}^{t_{max}} f_{12}(u|x,z)S_2(t_{max}-u|x,z)du$ for an individual h not observed in state $Y = 2$ during his/her follow-up and still alive at time t_{max}, $l_h = f_{13}(t_{max}|x,z) + \int_{t_{inf}}^{t_{max}} f_{12}(u|x,z)f_{23}(t_{max}-u|x,z)du$ for an individual h not observed in state $Y = 2$ during his/her follow-up and who died at time t_{max}, $l_h = \int_{t_{inf}}^{t_{sup}} f_{12}(u|x,z)S_2(t_{max}-u|x,z)du$ for an individual h observed in state $Y = 2$ during his/her follow-up and still alive at time t_{max}, and $l_h = \int_{t_{inf}}^{t_{sup}} f_{12}(u|x,z)f_{23}(t_{max}-u|x,z)du$ for an individual h observed in state $Y = 2$ during his/her follow-up and who died at time t_{max}.

2.3. *Semi-Markov model with Inverse Probability Weighting*

The propensity score p_h is defined as the probability that an individual h belongs to the exposed group given the possible confounding factors [10]: $p_h = P(Z_h = 1|X_h)$. The principle of IPW is to create a pseudo dataset by weighting each observation by a function of the inverse of the probability of being in the actual exposition group given the patient's characteristics in order to balance observed baseline covariates between groups. Higher weights are assigned to individuals with under-represented profiles in their group of exposure, and conversely lower weights are assigned to individuals with over-represented profiles. The weight w_h may correspond to the inverse of the predicted probability that an individual h belongs to his or her own observed group [22, 23]: $w_h = Z_h p_h^{-1} + (1 - Z_h)(1 - p_h)^{-1}$. This approach, so-called non-stabilized IPW, has two main limits: i) high weights can be assigned to a few individuals and ii) the sample size doubles in the pseudo dataset resulting in an inflated type I error [24]. A solution proposed by Robins *et al.* is to use stabilized weights, where the numerator is the marginal probability of being in the observed group [13, 14, 25]: $w_h = Z_h P(Z_h = 1)p_h^{-1} + (1 - Z_h)P(Z_h = 0)(1 - p_h)^{-1}$. It can be easily demonstrated that using stabilized IPW results in a pseudo dataset with a similar sample size to that of the original data [24], leads to a better estimation of variances. In this work, we were interested in this latter method.

With the IPW approach, the hazard functions (1) and survival functions (2) are only modelled according to the exposure factor Z. The exponential of the regression coefficients associated to Z are estimates of the marginal (population-averaged) HRs, as if the entire population moved from unexposed to exposed. Parameters of the IPW SM model are estimated by maximizing the weighted log-likelihood, i.e. $\sum_{h=1}^{N} w_h \log l_h$.

2.4. *Statistical computation*

We used the R statistical software [26] version 3.0.1 with *optim()* to maximize the weighted log-likelihood function of the IPW SM model and to compute the corresponding Hessian matrix (Nelder and Mead algorithms [27]). The complete methodology has been implemented in the *Multistate* R package available at www.divat.fr and is also available from the authors upon request.

3. Motivating example

3.1. Context

The original sample consisted of 617 adults who underwent surgery for AVR with implantation of a Mitroflow® bioprosthesis at Nantes University Hospital (France) between 2002 and 2007. A detailed description of the design of the cohort and characteristics of the sample was published previously [15]. The "Comité National Informatique et Liberté" approved the data collection (N° 910300) and written information was given to participants. A severe PPM was defined as an effective orifice index area of the aortic prosthesis ≤ 0.65 cm^2/m^2. The SVD of the bioprosthesis was defined according to the following echocardiographic criteria [28]: progression of aortic transprosthetic gradient $\geq$ 30 mmHg associated with a decreased effective orifice area $\leq$1cm^2, or severe intraprosthetic aortic regurgitation (grade III/IV).

Applying a multivariable death-censored Cox model to this sample, Sénage *et al.* [15] found a significant increased risk of SVD for females (HR=2.16, 95%CI: 1.02 to 4.58), patients with preoperative dyslipidemia (HR=2.01, 95%CI: 1.02 to 4.58) and patients with a severe PPM (HR=1.95, 95%CI: 1.01 to 3.74). Contrary to published findings [29], age did not emerge as a significant predictor for SVD since most patients were over 65 years old. In the final multivariable model retaining six binary covariates, SVD was the strongest correlate of overall mortality (HR=7.70, 95%CI: 4.36 to 13.61). Other several significant preoperative factors were chronic obstructive pulmonary disease (COPD) (HR=3.91, 95%CI: 2.02 to 7.55), myocardial infarction in the previous 3 months (HR=2.76, 95%CI: 1.31 to 5.81), preoperative respiratory insufficiency (HR=2.75, 95%CI: 1.33 to 5.67), New-York Heart Association (NYHA) class III-IV (HR=1.51, 95%CI: 1.12 to 2.03), and redo surgery (HR=1.85, 95%CI: 1.13 to 3.03).

In this new work, our objective was to assess whether adjusting the size of the bioprothesis in patients who underwent an AVR trigger changes in the clinical course, by using an illness-death SM model for interval-censored data with the stabilized IPW method. The population of adults with low BMI were not at risk of severe PPM because the existing bioprostheses were always large enough in relation to their body. Therefore, we excluded patients with a BMI lower than 20 kg/m^2 (n=37).

3.2. Dataset

Among the 580 patients studied, 144 patients (25%) had a severe PPM and 150 patients (26%) were obese (BMI greater than 30 kg/m^2). The mean age of patients at surgery was 76 years (min-max: 48-94 years). Other baseline characteristics are described in Table 1. The estimated median follow-up time, as calculated by the reverse Kaplan-Meier method [30], was 4.9 years. The median time between two echocardiographies was 374 days (min-max: 5-2394 days). At the end of the follow-up, 384 patients (66%) survived without diagnosed SVD, 158 patients (27%) died without previously diagnosed SVD, 22 patients (4%) were still alive after a diagnosed SVD, and 16 patients (3%) died after a diagnosed SVD.

4. Simulations

4.1. Design

Simulation studies were conducted to assess the performance of the stabilized IPW estimators for estimating marginal HRs in an illness-death SM model with interval-censored data in the case of different sample sizes, right-censoring rates, exposure prevalences and effect sizes. The design was guided by the real data of patients with an aortic bioprosthesis.

Two covariates were simulated: i) a binary covariate $X1$ (describing obesity) following a binomial distribution with 24% of events; ii) a continuous covariate $X2$ (describing age at surgery) following a truncated normal distribution with $X2 \sim \mathcal{N}(\mu = 76.2; \sigma = 6.5; \min = 45; \max = 95)$ for $X1 = 0$ and $X2 \sim \mathcal{N}(\mu = 75.5; \sigma = 5.6; \min = 45; \max = 95)$ for $X1 = 1$. The binary exposure Z was then simulated as a binomial distribution with a proportion equal to $\{1 + \exp[-(\phi_0 + 1.790X1 - 0.036X2)]\}^{-1}$. The parameter ϕ_0 allowed us to consider scenarios with different exposure prevalences. Three different PH models with exponential baseline hazard functions were considered to simulate duration times: $\lambda_{12}(s|Z, X1, X2) = 0.007 \times \exp(\beta_{12}Z + 0.262X1 + 0.016X2)$, $\lambda_{13}(s|Z, X1, X2, U) = 0.074 \times \exp(\beta_{13}Z - 0.156X1 - 0.002X2 + U)$, and $\lambda_{23}(s|Z, X1, X2, U) = 2.138 \times \exp(\beta_{23}Z - 0.552X1 - 0.024X2 + U)$, with $U \sim \mathcal{N}(\mu = 0, \sigma = 0.5)$. The parameters $\{\beta_{12}, \beta_{13}, \beta_{23}\}$ allowed us to consider scenarios with different conditional effect sizes for Z on each transition. Interval-censoring for time-to-illness was generated by assuming a left-truncated Weibull distribution for the duration between two medical examinations (scale parameter: 692, shape parameter: 1.14, minimum of 5 days between two medical examinations). Right-censored times were simulated with exponential distributions of parameter θ, allowing us to consider scenarios with different censoring rates.

Five hundred datasets were independently generated according to 16 scenarios combining two sample sizes (N=600, N=2000), two right-censoring rates (30% and 65%), two exposure prevalences (12% and 24%), and two conditional effect sizes for Z: a high effect with $(\beta_{12}, \beta_{13}, \beta_{23}) = (0.597, 0.381, -0.462)$ and a moderate effect with $(\beta_{12}, \beta_{13}, \beta_{23}) = (0.182, 0.182, -0.182)$.

Since the marginal and conditional HRs may differ [31], the theoretical value of the marginal log-HRs was asymptotically estimated. Firstly, we simulated a broad sample of one million individuals (covariates only) considering that the first half of the individuals in the sample was exposed and the second half was not [32]. The sojourn times were then simulated and the marginal HRs were estimated from the SM illness-death model for interval-censored data including the exposure factor as only covariate on each transition. The theoretical marginal log-HRs associated with transitions 12, 13, and 23 were $(0.601, 0.375, -0.427)$ when the conditional log-HRs of exposure were high, and $(0.184, 0.175, -0.168)$ when moderate.

Several criteria were reported: the mean absolute bias, the mean relative bias, the root mean square error (RMSE), the estimated asymptotic standard error obtained from the Hessian matrix, the empirical standard error estimated as the standard deviation of estimations, the empirical coverage rate of the nominal 95% confidence intervals (95% CIs), and the empirical power.

4.2. Results

Table 2 presents the results obtained without any adjustment and with the stabilized IPW model from scenarios with a sample size of 600 patients and high exposure effect. The upper part of the Table corresponds to the scenario closest to our application: right-censoring rate at 65% and exposure prevalence at 24%. Not surprisingly, the estimations without any adjustment for confounding were very biased, especially for transitions from state $Y = 1$ to state $Y = 2$ (mean absolute bias of 0.110, corresponding to a relative bias of 18%) and from state $Y = 2$ to state $Y = 3$ (mean absolute bias of 0.230, corresponding to a relative bias of -54%). IPW estimations were associated with absolute biases lower than 0.032, relative biases lower than 8% and coverage rates close to 90%. The empirical powers were fairly low ($< 60\%$), especially for transition from state $Y = 2$ to $Y = 3$ ($< 20\%$) where the number of transitions was small (22 on average). For a similar right-censoring rate but lower exposure prevalence (12% instead of 24%), stabilized IPW performance was slightly lower with higher biases in most transitions, lower coverage rates, and lower empirical powers. For a similar exposure prevalence but lower right-censoring rate (30% instead of 65%), the biases and coverage rates were rather similar whereas the empirical power was higher. Overall, for these four scenarios, IPW estimations were associated with absolute biases lower than 0.07, relative biases lower than 18%, and coverage rates higher than 79%.

Table 3 presents the results obtained from scenarios with a similar sample size of 600 patients but moderate exposure effect. Stabilized IPW performance was slightly lower than that for high exposure effect, especially for power. Similar results were observed with a sample size of 2000 patients (Table S1 and Table S2 in Supplemental Material) regarding the effects of right-censoring rate and exposure prevalence. The bias increased and the coverage rates decreased with either the decrease of exposure proportion or the effect of the exposure factor. The censoring rate had little impact on bias and reasonably decreased the coverage rates. The power was logically higher with the sample size of 2000 patients.

5. Application in cardiac surgery

5.1. Modelling strategies and checking of assumptions

Austin *et al.* have suggested that it is preferable to include either the prognostic covariates (those related to outcomes) or the confounding covariates (those related to exposure and outcomes) in the propensity score model [33]. In our context where investigating covariates related to outcomes requires the use of several univariable multistate models, this would make the IPW approach much more complex to implement while one of its values is precisely to simplify the consideration of confounding factors in multistate modelling. Therefore, we decided to estimate the propensity score by a multivariable logistic regression including known prognostically important factors for time-to-SVD and time-to-death (age, gender, history of smoking, preoperative dyslipidemia, COPD, myocardial infarction in the previous 3 months, NYHA class III-IV, redo surgery) and covariates differently distributed according to the presence of a severe PPM ($p < 0.05$ in Table 1). Log-linearity assumption was checked for quantitative covariates.

Causal inference using the propensity score requires several assumptions [33, 34]. Positivity assumption, that is all individuals have a non-zero probability to be exposed and unexposed [8], was examined in two ways: i) graphically by checking the overlap of the distributions of the propensity scores for the two groups of patients, and ii) numerically by checking that the sample size was not far from the original dataset (this can also indicate a propensity score model misspecification). We used the standardized differences to assess the balance in measured baseline covariates between individuals with and without severe PPM in the pseudo dataset [33]. As a rule of thumb, a standardized difference greater than 10% indicates an imbalance of the covariate between groups that might require further investigation [33, 34].

The sojourn time distributions and PH assumptions for severe PPM were analysed in a SM illness-death model for interval-censored data without covariates. We assumed a Weibull distribution for the baseline hazard functions. This distribution was simplified into the exponential distribution when there was no evidence of lack of fit according to the likelihood ratio statistic. The PH assumption was checked on each transition by plotting the baseline hazards estimated separately in each group with the SM model.

In addition to marginal HRs associated with SVD, we also estimated the marginal Cumulative Incidence Function (CIF) for SVD depending on the presence or absence of severe PPM, and the corresponding Absolute Risk Reduction (ARR) and Number Needed to Treat (NTT) functions, two statistical indicators easy to interpret and communicate to guide clinical practice [35]. The marginal CIFs of SVD at time t in both groups were calculated as $\int_0^t f_{12}(u|z)du$ for $z = 0, 1$. The ARR function was defined as the absolute difference in the CIFs for SVD between the presence and absence of severe PPM and the NNT function was defined as the reciprocal of the ARR function. The NNT at time t represents the number of patients for whom an adjustment of the size of the bioprosthesis (absence of severe PPM) prevents the occurence of one SVD at time t (the higher the NNT, the less effective the adjusted size of the bioprosthesis). The 95%CIs were estimated by taking the 2.5% and 97.5% percentiles of the empirical distributions calculated from 10,000 parametric simulations of the model

parameters (multivariate normal distribution) [36]. We did not report the 95%CIs for the NTT functions when the ARR contained zero [35].

5.2. *The propensity score model*

The final propensity score model contained 16 parameters (Table 4). The corresponding area under the ROC curve was 0.81 [95%CI: 0.76 to 0.85], indicating a considerable imbalance of these characteristics between patients with and without severe PPM.

There was a substantial overlap of the two distributions of the propensity score in patients with and without severe PPM (Figure S1 in Supplemental Material), making the positivity assumption acceptable. The sample size of the pseudo-dataset with the stabilized weights was close to the sample size of the original sample (584 versus 580). The stabilized IPW method fairly balanced the covariates included in the propensity score with standardized differences lower than 10% for 12 covariates and between 10% and 15% for 4 covariates (gender, history of hypertension, COPD, redo surgery) (Table S3 in Supplemental Material).

5.3. *Results of the different semi-Markov models*

Based on likelihood ratio tests, the Weibull distribution was retained to model the time-to-SVD and the time-to-death, while the exponential distribution was retained to model the time from SVD to death. Table 5 presents the results of the SM illness-death model when no adjustment was performed and with stabilized IPW. Comparison of the marginal effects of severe PPM obtained with both approaches illustrated the important confounding biases, especially on the transitions related to death. Based on the confounder-adjusted model, we did not not demonstrate a significant association between a severe PPM and the risk of death with or without previous SVD. However, the association between a severe PPM and the risk of SVD was at the limit of statistical significance after adjustment with the stabilized IPW (HR=1.78, 95%CI: 0.99 to 3.18).

The Figure 1 presents the marginal CIFs of SVD according to presence of a severe PPM and the corresponding ARR and NNT functions. At 5 years post-surgery, the probabilities of SVD for patients with and without severe PPM were estimated to be respectively 26.0% [95%CI: 16.7% to 38.1%] versus 16.5% [95%CI: 11.3% to 23.5%] when no adjustment was performed, and 27.1% [95%CI: 17.0% to 41.2%] versus 16.6% [95%CI: 11.0% to 23.9%] with the stabilized IPW SM model. These results corresponded respectively to an ARR of SVD without severe PPM and a NNT to prevent one SVD at 5 years post-surgery of: 9.5% [95%CI: -1.5% to 21.7%] and 10.6 when no adjustment was performed, and 10.5% [95%CI: -1.2% to 24.8%] and 9.5 with the stabilized IPW SM model. These latter results indicated that, absence of severe PPM was estimated to prevent, on average, one additional SVD per 9.5 patients.

6. Discussion

In the context of observational studies with interval-censored data, the implementation of a multistate model can be complex because it requires confounder-adjusted estimations to correctly describe the relationship between a specific exposure and time-to-events. In this work, we assessed the performances of IPW, a propensity score method, to estimate the marginal effects in an illness-death model with interval-censored data. Results from simulations seemed to validate the adaptation of the stabilized IPW method in semi-Markov modelling. The method gave little biased estimations of the marginal effects of exposure and coverage rates close to 90% when one or more of the following conditions were present: large sample, high exposure effect, absence of major imbalance in the ratio of exposed/unexposed patients.

A main advantage of the IPW is its ease-of-use with a two-step procedure: firstly a logistic model has to be fitted to estimate the probability of belonging to the exposure group according to confounding factors, and secondly a univariable multistate model is considered for the relationships between the exposure and time-to-events by maximising the corresponding weighted likelihood. Finally, the use of a parsimonious multistate model such as that achieved by IPW may be particularly interesting in the context of chronic diseases when the follow-up is relatively short to observe large numbers of transitions.

In accordance with the initial study proposed by Sénage *et al.* [15], which was based on the Kaplan-Meier estimator and Cox model, our confounder-adjusted semi-Markovian illness-death model confirmed that the PPM was an important risk factor for SVD (HR=1.78, 95%CI: 0.99 to 3.18) and we did not report any significant association with death regardless of the previous occurrence of a severe SVD. These latter non-significant results may be due to lack of effect or lack of statistical power as the simulation study suggested. In contrast with the study proposed by Sénage *et al.* [15], we estimated the cumulative probability of SVD at 5 years post-surgery at 27.1% [95%CI: 17.0% to 41.2%] for patients with severe PPM and 16.6% [95%CI: 11.0% to 23.9%] for patients without. In the initial study, the overall cumulative probability of SVD at 5 years post-surgery was estimated to be 8.4% [95%CI: 5.3% to 11.3%], a percentage probably underestimated by ignoring the interval-censoring of time-to-SVD and the competing risk with patient death [37].

Our study has several limitations. Firstly, we proposed a PH parametric illness-death semi-Markov model. These assumptions may be not suitable for other applications, but one can reasonably expect that the IPW framework we proposed can be extended to other multistate models. Secondly, we did not investigate whether the IPW estimators were sensitive to the misspecification of the propensity score model. In our simulation study, we only considered two confounding factors associated with both the exposure and the three times-to-events. In our application, we modelled the propensity score according to covariates significantly associated with exposure and to known prognostically important covariates for times-to-events. We chose to force the latter instead of investigating their associations with each time-to-event. In our context, it would have required the use of several univariable multistate models while the use of IPW was precisely to simplify the consideration of confounding factors.

To note, we did not compare the HRs obtained from the stabilized IPW SM model and from a multivariable SM model because marginal and conditional HRs may differ [31]. However, in our application data, we may think that both effects were close. Indeed, in our simulation study where the times-to-event were generated to represent approximately the conditional HRs observed in the real data, the theoretical marginal HRs were close to conditional HRs. It is however possible, with a multivariable SM model, to indirectly estimate the marginal CIF according to the exposure factor (and the corresponding ARR and NTT functions), by assuming a situation in which every patient would appear both as exposed and unexposed.

In conclusion, we encourage greater use of the stabilized IPW approach to analyze data from cohorts in a multistate framework such as the illness-death model for interval-censored data. This method solves a major issue related to multivariable multistate models that are complex to implement. Both approaches do not estimate the same effects but population-averaged effects provided by IPW-based methods are often the estimated areas of interest for health policy-makers. We hope the *Multistate* R package we updated will support the use of IPW-based methods in SM models.

Acknowledgments

The authors would like to thank A.D.T. International company for proofreading the English manuscript.

Conflict of Interest Statement

None declared.

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Table 1. Pre-operative and surgical characteristics of the 580 patients undergoing a surgery for the implantation of a Mitroflow® aortic bioprosthesis valve according to the presence of a severe Patient-Prosthesis Mismatch (PPM).

Characteristics[1] (missing data)	All (N=580)		Severe PPM absent (N=436)		Severe PPM present (N=144)		p-value	Standardized difference (%)
Female	309	(53.3)	229	(52.5)	80	(55.6)	0.5270	6.1
Age, years	75.9	±6.4	76.2	±6.4	74.9	±6.3	0.0270	21.3
Body Mass Index, kg/m^2	27.1	±4.5	26.0	±3.6	30.6	±5.2	<0.0001	102.5
NYHA class 3-4	171	(29.5)	125	(28.7)	46	(31.9)	0.4550	7.1
Logistic Euroscore	10.4	±10.1	10.1	±9.0	11.2	±12.9	0.3540	9.7
Medical history								
Obesity (BMI > 30 kg/m^2)	150	(25.9)	74	(17.0)	76	(52.8)	<0.0001	81.1
Diabetes mellitus	120	(20.7)	77	(17.7)	43	(29.9)	0.0020	29.0
Hypertension	360	(62.1)	260	(59.6)	100	(69.4)	0.0350	20.6
Dyslipidemia	252	(43.4)	183	(42.0)	69	(47.9)	0.2120	12.0
Smoking	103	(17.8)	72	(16.5)	31	(21.5)	0.1720	12.8
Thyroid dysfunction	27	(4.7)	18	(4.1)	9	(6.2)	0.2950	9.6
Previous dialysis	3	(0.5)	2	(0.5)	1	(0.7)	0.5759	3.1
Renal failure	42	(7.2)	32	(7.3)	10	(6.9)	0.8740	1.5
Neoplasia	48	(8.3)	32	(7.3)	16	(11.1)	0.1540	13.1
Acute pulmonary oedema	82	(14.1)	58	(13.3)	24	(16.7)	0.3150	9.4
Blood cardioplegia (18)	501	(89.1)	380	(90.3)	121	(85.8)	0.1420	13.7
Previous shock	19	(3.3)	13	(3.0)	6	(4.2)	0.5885	6.4
Myocardial infarction <90 days	11	(1.9)	6	(1.4)	5	(3.5)	0.1517	13.7
History of stroke	24	(4.1)	13	(3.0)	11	(7.6)	0.0150	20.9
COPD	35	(6.0)	30	(6.9)	5	(3.5)	0.1360	15.4
Peripheral vascular disease	73	(12.6)	55	(12.6)	18	(12.5)	0.9710	0.3
Family history of CVD	54	(9.3)	38	(8.7)	16	(11.1)	0.3910	8.0
Echocardiography								
LVEF, % (145)	57.6	±12.4	57.7	±12.4	57.2	±12.4	0.7330	3.9
Aortic insufficiency≥ 2	81	(14.0)	62	(14.2)	19	(13.2)	0.7580	3.0
Endocarditis	23	(4.0)	13	(3.0)	10	(6.9)	0.0350	18.3
Surgical characteristics								
Elective procedure	490	(84.5)	378	(86.7)	112	(77.8)	0.0100	23.5
Bypass surgery	177	(30.5)	144	(33.0)	33	(22.9)	0.0220	22.7
Redo surgery	36	(6.2)	24	(5.5)	12	(8.3)	0.2230	11.2
Isolated aortic valve replacement	370	(63.8)	268	(61.5)	102	(70.8)	0.0430	19.9
CPB time, minutes (4)	91.9	±37.9	90.9	±35.2	95.1	±45.1	0.3150	10.3
Aortic clamping time, minutes (4)	70.0	±29.4	69.1	±27.1	72.8	±35.3	0.2500	12.8

[1] n (%) or mean±SD, as appropriate

BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, CPB: Cardio-Pulmonary Bypass, CVD: Cardiovascular Disease, LVEF: Left Ventricular Ejection Fraction, NYHA: New York Heart Association, PPM: Patient-Prosthesis Mismatch.

Table 2. Estimations of the marginal exposure effect in illness-death SM models without any adjustment and with stabilized IPW (500 simulated samples of 600 patients with a high exposure effect).

Censoring rate	Exposure prevalence	Model	Transition	Theoretical value	Mean estimate	Absolute bias	Relative bias (%)	RMSE	Empiric SE	Asymptotic SE	Coverage rate (%)	Power (%)
65%	24%	No adjustment	12	0.601	0.711	0.110	18.29	0.358	0.341	0.332	93.00	59.80
			13	0.375	0.301	−0.074	−19.75	0.212	0.199	0.197	96.00	36.00
			23	−0.427	−0.197	0.230	−53.90	0.557	0.508	0.472	90.40	6.80
		Stabilized IPW	12	0.601	0.632	0.032	5.25	0.387	0.386	0.338	91.80	51.60
			13	0.375	0.346	−0.028	−7.50	0.225	0.224	0.194	93.60	46.20
			23	−0.427	−0.433	−0.007	1.57	0.620	0.621	0.504	89.20	15.80
	12%	No adjustment	12	0.601	0.709	0.108	17.99	0.456	0.443	0.425	93.80	45.20
			13	0.375	0.294	−0.081	−21.64	0.273	0.261	0.266	96.40	24.20
			23	−0.427	−0.141	0.286	−67.03	0.725	0.667	0.602	85.40	7.00
		Stabilized IPW	12	0.601	0.604	0.003	0.52	0.550	0.550	0.447	91.20	39.80
			13	0.375	0.307	−0.067	−17.99	0.344	0.337	0.269	89.40	30.60
			23	−0.427	−0.376	0.051	−11.85	0.893	0.893	0.701	87.80	11.40
30%	24%	No adjustment	12	0.601	0.695	0.094	15.67	0.247	0.228	0.220	92.20	84.80
			13	0.375	0.321	−0.053	−14.23	0.158	0.149	0.145	93.40	61.00
			23	−0.427	−0.197	0.230	−53.89	0.356	0.273	0.242	81.00	14.60
		Stabilized IPW	12	0.601	0.629	0.028	4.66	0.253	0.252	0.222	92.00	75.80
			13	0.375	0.361	−0.013	−3.53	0.171	0.171	0.143	90.40	67.40
			23	−0.427	−0.410	0.017	−3.98	0.319	0.319	0.249	86.80	41.60
	12%	No adjustment	12	0.601	0.696	0.096	15.92	0.311	0.296	0.281	93.00	70.60
			13	0.375	0.322	−0.053	−14.10	0.210	0.203	0.193	93.20	39.20
			23	−0.427	−0.159	0.267	−62.68	0.461	0.376	0.311	80.00	13.00
		Stabilized IPW	12	0.601	0.616	0.016	2.58	0.354	0.354	0.289	90.80	56.80
			13	0.375	0.357	−0.018	−4.76	0.247	0.247	0.189	87.00	47.00
			23	−0.427	−0.369	0.058	−13.55	0.503	0.500	0.329	79.80	30.60

IPW: Inverse Probability Weighting, RMSE: Root Mean Square Error, SE: Standard Error

Table 3. Estimations of the marginal exposure effect in illness-death SM models without any adjustment and with stabilized IPW (500 simulated samples of 600 patients with a moderate exposure effect).

Censoring rate	Exposure prevalence	Model	Transition	Theoretical value	Mean estimate	Absolute bias	Relative bias (%)	RMSE	Empiric SE	Asymptotic SE	Coverage rate (%)	Power (%)
65%	24%	No adjustment	12	0.184	0.297	0.112	61.02	0.386	0.369	0.379	94.60	12.80
			13	0.175	0.102	−0.073	−41.65	0.212	0.199	0.206	96.60	7.80
			23	−0.168	0.083	0.251	−149.57	0.579	0.523	0.511	90.60	5.40
		Stabilized IPW	12	0.184	0.208	0.024	13.07	0.443	0.443	0.389	92.60	13.00
			13	0.175	0.144	−0.031	−17.56	0.222	0.220	0.203	93.80	16.20
			23	−0.168	−0.134	0.033	−19.83	0.644	0.644	0.546	90.80	8.20
	12%	No adjustment	12	0.184	0.310	0.126	68.25	0.532	0.518	0.500	90.20	15.60
			13	0.175	0.072	−0.103	−58.74	0.316	0.299	0.293	97.20	7.00
			23	−0.168	0.177	0.345	−205.52	0.806	0.729	0.658	86.40	10.20
		Stabilized IPW	12	0.184	0.187	0.002	1.35	0.639	0.640	0.542	90.80	14.20
			13	0.175	0.081	−0.094	−53.51	0.401	0.390	0.307	91.40	15.40
			23	−0.168	−0.032	0.136	−81.01	0.958	0.949	0.779	87.40	11.60
30%	24%	No adjustment	12	0.184	0.262	0.078	42.25	0.265	0.254	0.243	91.80	21.20
			13	0.175	0.121	−0.054	−30.60	0.157	0.147	0.145	95.80	15.20
			23	−0.168	0.058	0.226	−134.63	0.371	0.295	0.262	82.40	8.60
		Stabilized IPW	12	0.184	0.197	0.013	6.82	0.288	0.288	0.246	90.20	20.00
			13	0.175	0.161	−0.014	−7.86	0.169	0.169	0.143	89.00	24.60
			23	−0.168	−0.156	0.012	−7.25	0.348	0.348	0.269	87.00	17.40
	12%	No adjustment	12	0.184	0.259	0.075	40.85	0.346	0.338	0.319	92.20	19.40
			13	0.175	0.122	−0.053	−30.26	0.210	0.203	0.193	94.00	11.80
			23	−0.168	0.097	0.264	−157.64	0.484	0.406	0.343	83.20	10.40
		Stabilized IPW	12	0.184	0.175	−0.010	−5.27	0.407	0.407	0.328	90.80	17.60
			13	0.175	0.155	−0.019	−11.13	0.251	0.250	0.190	87.20	21.20
			23	−0.168	−0.106	0.062	−36.83	0.535	0.532	0.364	83.80	18.20

IPW: Inverse Probability Weighting, RMSE: Root Mean Square Error, SE: Standard Error

Table 4. Multivariable logistic regression used to calculate the propensity score in patients undergoing a surgery for the implantation of a Mitroflow® aortic bioprosthesis valve (N=580).

Variable (unit)	Estimate	SE	OR	[95%CI]	p-value
Female	0.434	0.256	1.54	[0.93 ; 2.55]	0.090
Age (for 1 year increase)	−0.016	0.019	0.98	[0.95 ; 1.02]	0.386
BMI (for 1 kg/m^2 increase)	0.257	0.029	1.29	[1.22 ; 1.37]	0.000
NYHA class 3-4	−0.182	0.253	0.83	[0.51 ; 1.37]	0.472
Diabetes mellitus	0.390	0.271	1.48	[0.87 ; 2.51]	0.150
Hypertension	0.001	0.264	1.00	[0.60 ; 1.68]	0.997
Dyslipidemia	0.215	0.243	1.24	[0.77 ; 2.00]	0.376
Smoking	0.533	0.315	1.70	[0.92 ; 3.16]	0.090
Myocardial infarction <90 days	1.660	0.749	5.26	[1.21 ; 22.82]	0.027
History of stroke	1.321	0.488	3.75	[1.44 ; 9.74]	0.007
COPD	−0.723	0.572	0.49	[0.16 ; 1.49]	0.206
Endocarditis	0.856	0.577	2.35	[0.76 ; 7.30]	0.138
Elective procedure	−0.439	0.329	0.64	[0.34 ; 1.23]	0.182
Bypass surgery	−0.099	0.561	0.91	[0.30 ; 2.72]	0.861
Redo surgery	0.011	0.465	1.01	[0.41 ; 2.51]	0.982
Isolated aortic valve replacement	0.362	0.514	1.44	[0.52 ; 3.93]	0.481

BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, NYHA: New York Heart Association, SE: Standard Error. Model intercept: -7.483 (SE=1.683).

Table 5. Estimation of the marginal effects of a severe Patient-Prosthesis Mismatch (PPM) in illness-death SM models without any adjustment and with stabilized IPW (N=580).

Model[1]	Transition	Estimate	Standard Error	HR	[95%CI]	p-value
No adjustment	12	0.597	0.282	1.82	[1.05 ; 3.16]	0.034
	13	0.258	0.264	1.38	[0.83 ; 2.28]	0.218
	23	−0.295	0.361	0.74	[0.37 ; 1.51]	0.414
Stabilized IPW[2]	12	0.575	0.298	1.78	[0.99 ; 3.18]	0.053
	13	0.034	0.286	1.03	[0.59 ; 1.81]	0.906
	23	−0.396	0.366	0.67	[0.33 ; 1.38]	0.279

[1] Weibull distribution for the baseline hazards of transitions 12 and 13 and exponential distribution for the baseline hazard of transition 23.
[2] IPW: Inverse Probability Weighting.

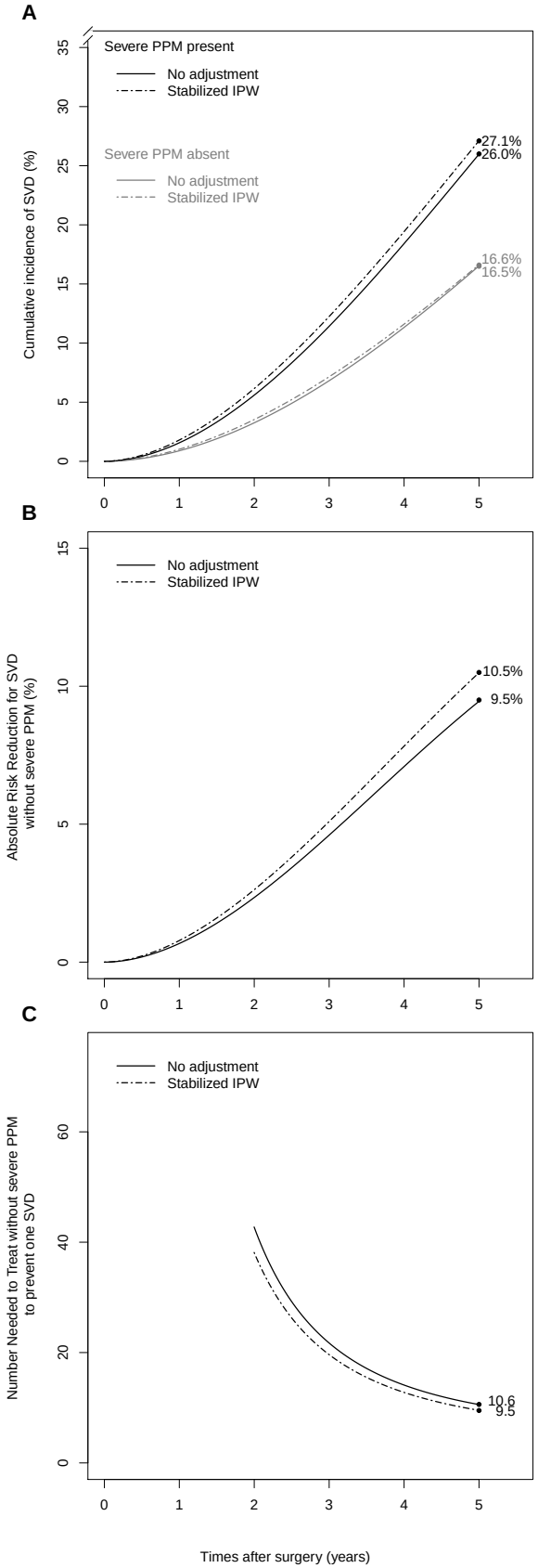

Figure 1. Estimations of the marginal effects of a severe Patient-Prosthesis Mismatch (PPM) in illness-death SM models without any adjustment and with stabilized IPW: A) Cumulative Incidence Function (CIF), B) Absolute Risk Reduction (ARR), and C) Number of patients Needed to Treat (NTT).

Supplemental Material

Table S1. Estimations of the marginal exposure effect in illness-death SM models without any adjustment and with stabilized IPW (500 simulated samples of 2000 patients with a high exposure effect).

Censoring rate	Exposure prevalence	Model	Transition	Theoretical value	Mean estimate	Absolute bias	Relative bias (%)	RMSE	Empiric SE	Asymptotic SE	Coverage rate (%)	Power (%)
65%	24%	No adjustment	12	0.601	0.681	0.081	13.41	0.198	0.181	0.179	91.80	94.40
			13	0.375	0.317	−0.057	−15.34	0.117	0.102	0.105	92.00	84.40
			23	−0.427	−0.200	0.226	−53.06	0.339	0.253	0.250	84.80	12.20
		Stabilized IPW	12	0.601	0.613	0.012	2.06	0.197	0.197	0.181	93.00	87.80
			13	0.375	0.362	−0.013	3.48	0.113	0.112	0.103	92.40	90.40
			23	−0.427	−0.424	0.003	−0.61	0.302	0.302	0.262	90.80	35.60
	12%	No adjustment	12	0.601	0.675	0.074	12.35	0.245	0.234	0.226	92.40	81.40
			13	0.375	0.312	−0.063	−16.77	0.155	0.142	0.138	94.00	61.60
			23	−0.427	−0.194	0.233	−54.54	0.416	0.346	0.317	85.00	10.00
		Stabilized IPW	12	0.601	0.600	−0.000	−0.04	0.271	0.272	0.230	90.20	68.60
			13	0.375	0.353	−0.021	−5.68	0.168	0.167	0.134	88.80	70.60
			23	−0.427	−0.432	−0.005	1.24	0.451	0.452	0.346	86.40	26.40
30%	24%	No adjustment	12	0.601	0.675	0.075	12.42	0.144	0.123	0.120	90.20	100.00
			13	0.375	0.326	−0.049	−12.96	0.096	0.083	0.079	87.40	97.60
			23	−0.427	−0.199	0.228	−53.34	0.275	0.154	0.132	60.20	35.20
		Stabilized IPW	12	0.601	0.612	0.011	1.83	0.140	0.140	0.121	91.20	99.40
			13	0.375	0.365	−0.010	−2.57	0.091	0.090	0.077	89.60	99.40
			23	−0.427	−0.416	0.011	−2.61	0.183	0.183	0.135	85.20	81.60
	12%	No adjustment	12	0.601	0.681	0.080	13.29	0.183	0.165	0.152	89.60	98.00
			13	0.375	0.329	−0.046	−12.23	0.119	0.110	0.103	92.00	83.00
			23	−0.427	−0.184	0.242	−56.82	0.307	0.189	0.167	67.20	22.20
		Stabilized IPW	12	0.601	0.605	0.005	0.77	0.192	0.192	0.154	88.00	91.60
			13	0.375	0.367	−0.007	−1.99	0.131	0.131	0.101	87.40	88.40
			23	−0.427	−0.410	0.017	−3.95	0.256	0.256	0.174	81.40	62.80

IPW: Inverse Probability Weighting, RMSE: Root Mean Square Error, SE: Standard Error

Table S2. Estimations of the marginal exposure effect in illness-death SM models without any adjustment and with stabilized IPW (500 simulated samples of 2000 patients with a moderate exposure effect).

Censoring rate	Exposure prevalence	Model	Transition	Theoretical value	Mean estimate	Absolute bias	Relative bias (%)	RMSE	Empiric SE	Asymptotic SE	Coverage rate (%)	Power (%)
65%	24%	No adjustment	12	0.184	0.259	0.075	40.50	0.213	0.199	0.204	93.20	26.20
			13	0.175	0.123	−0.052	−29.55	0.118	0.106	0.109	92.00	20.80
			23	−0.168	0.061	0.228	−136.20	0.360	0.278	0.270	84.60	6.20
		Stabilized IPW	12	0.184	0.190	0.006	3.19	0.214	0.214	0.206	93.20	18.20
			13	0.175	0.167	−0.008	−4.38	0.116	0.115	0.107	93.00	37.40
			23	−0.168	−0.151	0.017	−10.19	0.328	0.328	0.282	91.60	11.80
	12%	No adjustment	12	0.184	0.246	0.062	33.51	0.284	0.278	0.266	91.80	18.40
			13	0.175	0.114	−0.061	−34.71	0.161	0.149	0.144	94.80	15.00
			23	−0.168	0.073	0.241	−143.71	0.459	0.391	0.352	83.80	9.60
		Stabilized IPW	12	0.184	0.166	−0.018	−9.88	0.328	0.328	0.272	90.00	17.20
			13	0.175	0.154	−0.021	−11.74	0.179	0.178	0.141	90.00	29.20
			23	−0.168	−0.144	0.024	−14.12	0.513	0.513	0.382	86.20	13.00
30%	24%	No adjustment	12	0.184	0.246	0.062	33.73	0.149	0.136	0.132	91.20	45.40
			13	0.175	0.127	−0.048	−27.22	0.096	0.083	0.079	87.20	38.80
			23	−0.168	0.057	0.225	−134.16	0.281	0.169	0.142	61.40	13.00
		Stabilized IPW	12	0.184	0.185	0.001	0.29	0.150	0.150	0.133	90.60	30.40
			13	0.175	0.166	−0.008	−4.86	0.089	0.089	0.077	90.00	56.60
			23	−0.168	−0.158	0.010	−5.85	0.202	0.202	0.145	84.20	26.60
	12%	No adjustment	12	0.184	0.251	0.067	36.13	0.195	0.184	0.171	91.40	33.80
			13	0.175	0.130	−0.045	−25.83	0.117	0.108	0.103	92.80	27.20
			23	−0.168	0.074	0.242	−144.08	0.318	0.207	0.183	71.60	10.60
		Stabilized IPW	12	0.184	0.175	−0.010	−5.26	0.210	0.210	0.174	89.60	25.40
			13	0.175	0.170	−0.005	−2.80	0.126	0.126	0.101	87.20	42.20
			23	−0.168	−0.155	0.013	−7.65	0.278	0.278	0.190	83.80	23.20

IPW: Inverse Probability Weighting, RMSE: Root Mean Square Error, SE: Standard Error

Table S3. Pre-operative and surgical characteristics of patients undergoing surgery for the implantation of a Mitroflow® bioprosthesis in the pseudo-dataset with stabilized weights (N=584).

Characteristics[1] (missing data)	All (N=584)		Severe PPM absent (N=436)		Severe PPM present (N=148)		Standardized difference (%)
Female	295	(50.4)	227	(52.1)	67	(45.6)	13.0
Age, years	76.0	±6.5	75.9	±6.5	76.4	±6.4	7.8
Body Mass Index, kg/m^2	27.2	±4.6	27.2	±4.7	27.2	±4.4	0.2
NYHA class 3-4	182	(31.2)	136	(31.2)	46	(31.1)	0.2
Logistic Euroscore	10.3	±9.7	10.1	±9.4	10.8	±10.6	6.5
Medical history							
Obesity (BMI $>$ 30 kg/m^2)	151	(25.9)	116	(26.7)	35	(23.6)	7.0
Diabetes mellitus	121	(20.6)	92	(21.2)	28	(19.1)	5.2
Hypertension	377	(64.6)	276	(63.3)	101	(68.3)	10.6
Dyslipidemia	257	(43.9)	192	(44.0)	65	(43.7)	0.7
Smoking	107	(18.2)	80	(18.3)	27	(18.0)	0.7
Thyroid dysfunction	24	(4.1)	17	(4.0)	7	(4.6)	3.0
Previous dialysis	3	(0.5)	2	(0.4)	1	(0.7)	3.6
Renal failure	55	(9.3)	30	(7.0)	24	(16.4)	29.6
Neoplasia	53	(9.0)	32	(7.3)	21	(14.0)	21.7
Acute pulmonary oedema	88	(15.1)	64	(14.6)	24	(16.3)	4.7
Blood cardioplegia (17)	515	(90.9)	383	(91.1)	132	(90.3)	2.9
Previous shock	19	(3.2)	16	(3.6)	3	(2.3)	7.4
Myocardial infarction $<$90 days	9	(1.5)	7	(1.6)	2	(1.3)	2.3
History of stroke	23	(4.0)	17	(3.9)	6	(4.3)	2.1
COPD	45	(7.6)	29	(6.6)	16	(10.6)	14.2
Peripheral vascular disease	69	(11.8)	53	(12.1)	16	(11.0)	3.3
Family history of CVD	65	(11.1)	45	(10.4)	19	(13.0)	8.2
Echocardiography							
LVEF, % (134)	56.6	±12.9	57.9	±12.1	53.1	±14.7	35.4
Aortic insufficiency$\geq$ 2	92	(15.8)	59	(13.5)	33	(22.6)	23.9
Endocarditis	19	(3.3)	14	(3.3)	5	(3.4)	0.7
Surgery characteristics							
Elective procedure	501	(85.7)	372	(85.2)	129	(87.2)	5.6
Bypass surgery	179	(30.7)	135	(30.9)	44	(29.9)	2.3
Redo surgery	36	(6.2)	24	(5.5)	12	(8.2)	10.8
Isolated aortic valve replacement	369	(63.1)	277	(63.5)	92	(62.0)	3.1
CPB time, minutes (4)	94.0	±41.1	90.8	±35.3	103.2	±54	27.3
Aortic clamping time, minutes (4)	71.4	±31.7	68.7	±27.4	79.1	±41.2	29.5

[1] n (weighted %) or weighted mean±weighted SD, as appropriate

BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, CPB: Cardio-Pulmonary Bypass, CVD: Cardiovascular Disease, LVEF: Left Ventricular Ejection Fraction, NYHA: New York Heart Association, PPM: Patient-Prosthesis Mismatch.

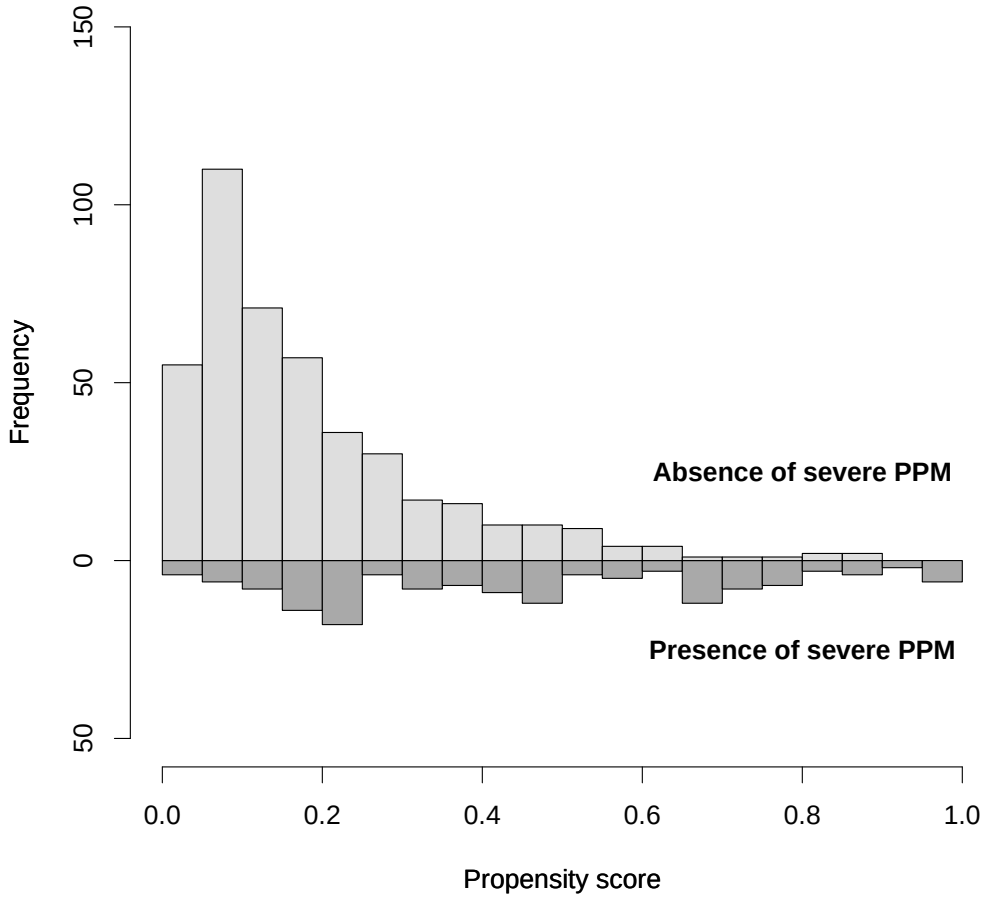

Figure S1. Distribution of the propensity score according to the presence of a severe Patient-Prosthesis Mismatch (PPM) in patients undergoing surgery for the implantation of a Mitroflow® aortic bioprosthesis valve (N=580).

III. Conclusion

Les résultats confirment ceux obtenus à partir du modèle de Cox (chapitre 2). A 5 ans post-chirurgie, les incidences cumulées marginales de SVD avec et sans PPM sévère étaient estimées respectivement à 28,0% (IC95% de 17,2% à 43,4%) et 19.9% (IC95% de 13,4% à 28,2%). Autrement dit, il s'agit respectivement des incidences si toute la population était porteuse ou non d'un PPM.

Il existe cependant quelques limites. Tout d'abord, le suivi réduit, rendant plus difficile l'estimation du taux de SVD et de son impact sur la mortalité à long-terme. Ensuite, il est difficilement envisageable que l'ensemble des patients puissent être porteurs d'un PPM, en particulier les sujets à faible IMC. L'effet ATE estimé est donc discutable, correspondant à des populations contre-factuelles difficilement envisageables. De plus, l'approche IPW ne permet pas l'exploration des facteurs de risque conditionnant l'évolution de la pathologie. Enfin, ce travail de recherche en Biostatistique propose une nouvelle approche méthodologique difficilement acceptable à court termes dans une revue de spécialité à destination des cliniciens.

Chapitre 5

Modélisation de l'évolution des prothèses valvulaires biologiques par un modèle multi-états pour données censurées par intervalle

I. Introduction

Dans le chapitre 3 et l'analyse du temps de survenu de SVD par un modèle de Cox, le décès est alors considéré comme une censure à droite. Il est cependant difficile d'accepter l'indépendance entre la survenue d'une SVD et le décès du patient. Un modèle qui modéliserait conjointement les deux évènements serait plus approprié. Il existe par ailleurs une censure par intervalle dans cette analyse du temps de survenu de SVD, qui conduit à une sous-estimation du taux réel de SVD, du fait de la possible absence d'échocardiographie avant le décès du patient.

Dans le chapitre 4, le rôle du PPM sur le risque de survenue de SVD a été évalué au sein d'une approche originale avec la mise en œuvre des scores de propension associés à un modèle multi-états. Elle ne permet d'évaluer que l'effet marginal en population du PPM. Nous avons discuté quatre limites à ce travail : i) le manque de recul de la cohorte, ii) l'approche ATE discutable, iii) la non exploration des autres facteurs de risque, et iv) l'utilisation d'un modèle nouveau ayant moins de chance d'être accepté dans une revue de spécialité médicale.

Dans ce 5ème chapitre, après une mise à jour du suivi des patients de la cohorte, un modèle illness-death multivarié a ainsi été réalisé. Nous montrons néanmoins comment ce modèle permet également de retrouver une estimation marginale de l'effet d'une exposition. Plus précisément, nous proposons ici d'estimer un effet de type ATT (Average Treatment effect on the Treated), c'est-à-dire l'effet marginale si les exposés ne l'avaient pas été.

II. Article

Structural valve deterioration of the SORIN Mitroflow® aortic valve: a cohort study to assess the true incidence, risk factors and impact on patient survival.

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Number of words: 3418

Abstract word count: 273

Abbreviations:

AVR: Aortic Valve Replacement

COPD: Chronic Obstructive Pulmonary Disease

EAO: Effective Orifice Area

NYHA: NewYork Heart Association

PPM: Patient-Prosthesis Mismatch

SVD: Structural Valve Deterioration

TAVI: Transcatheter Aortic Valve Implantation

Abstract

Background: Structural valve deterioration (SVD) recently emerged as a major problem with the Mitroflow® valve (SORIN group, Model LX/12A). The real incidence of the SVD risk is still unclear, often due to methodological pitfalls. In this report we sought to precisely assess SVD incidence, associated risk factors, and impact on patient survival.

Methods: This study included 561 patients who underwent aortic valve replacement with the aortic SORIN Mitroflow® valve between 2002 and 2007 and were followed-up after the first year of surgery. For the first time in this field, we used an illness-death model for interval-censored data in order to solve the methodological pitfalls observed in the current literature.

Results: Median follow-up was 6.6 years after the first year of surgery: 103 cases of SVD were diagnosed, 81 (79%) with stenosis as the main mode. The 5-year and 8-year SVD cumulative incidences after surgery were 15.2% (95% CI from 11.9 to 19.1) and 31.0% (95% CI from 25.8 to 37.2) respectively. Female gender (HR=1.6; 95% CI 1.1-2.4), dyslipidemia (HR=1.6; 1.1-2.3), Chronic Obstructive Pulmonary disease (COPD) and severe patient-prosthesis mismatch were significant risk factors of SVD (HR=2.9, 95% CI from 1.6 to 5.4, and HR=1.7, 95% CI from 1.1 to 2.5, respectively). The occurrence of SVD was associated with a 2-fold increase in the risk of death (HR=2.0, 95% CI from 1.3 to 2.9). Although the first post-operative year was censored, the observed survival in the SORIN Mitroflow® cohort was clearly lower than the expected survival in the general population (63.5% versus 72.7%).

Conclusions: Appropriate statistical models should be used to assess bioprostheses in order to avoid underestimating the dreadful SVD complication associated with worse long-term survival. In this Mitroflow series (model LX/12A), early and frequent SVD is associated with impaired survival compared to the general population. Finally, in addition to classical factors, COPD emerged as a new risk factor for SVD.

Keywords

Biologic aortic valve replacement; structural valve deterioration; patient survival; illness-death model;

Introduction

More than 200,000 aortic valve replacement (AVR) procedures are performed yearly worldwide [1]. Due to enhanced tissue durability, the choice of prosthesis has changed in favor of biological prostheses. Structural valve deterioration (SVD) remains however a major bioprosthesis-related complication, with significant heterogeneity between the types of prosthesis [2, 3]. It is reasonable to assume that SVD incidence is highly underestimated at the present time. The main reason for this is the macroscopic or histological definition of SVD often used in the literature [4, 5]: high-risk octogenarian patients are referred to surgery less frequently following SVD diagnosis [6, 7] and histological evidence is therefore missing. Among the bovine pericardial prostheses, the SORIN Mitroflow® valve, available since 1982, was designed to improve prosthesis hemodynamic performance, especially in small aortic roots thanks to its lesser bulk [8]. More than 100,000 AVR procedures have been performed with this valve worldwide since its first implantation.

In agreement with recent recommendations [9], we latety assessed SVD based on echocardiographic criteria in a monocentric cohort study of patients [10] who underwent an AVR with the SORIN Mitroflow® bioprosthesis (12A/LX models). We estimated the 5-year cumulative incidence of diagnosed SVD at 8.4% (95% CI from 5.3 to 11.3). In addition, by using an extended Cox model for time-dependent covariates, we found that the risk of death was increased 7.7-fold after SVD diagnosis (95% CI from 4.4 to 13.6). Our study was one of the first to report this issue public health issue. However, we believe that the true incidence of SVD was still underestimated. Firstly, regarding the echocardiograms performed at various times, the event date for patients with SVD was known to have happened between the diagnostic echocardiogram and the previous one recorded without the disease. The time-to-SVD was interval-censored between the two echocardiograms and was therefore overestimated when considering only the dates of the SVD diagnosis, leading therefore to an underestimation of SVD diagnosis. Secondly, patients who died without SVD diagnosis may have developed the SVD after their last normal echocardiogram. Ignoring this interval-censored process by considering death as right-censoring may also be linked to an overestimation of the mean time-to-SVD and an incorrect estimation of the relationship between SVD incidence and the risk of death [11]. Thirdly, the median follow-up time was 4.1 years whereas SVD is normally a long- term process: its cumulative incidence could continuously rise and quantification of this magnitude is of primary importance.

The aim of the present study was thus to estimate more accurately the incidence of SVD for patients who underwent an AVR with SORIN Mitroflow® bioprosthesis and its impact on patient mortality. For that purpose, we updated the patients' follow-up from our previous study [10] to have a better idea of long-term outcomes and applied an original statistical method, i.e. a semi-Markov illness-death model, to deal with interval censoring.

Material and Methods

Patients

Between January 2002 and December 2007, 617 consecutive patients underwent AVR with a SORIN Mitroflow® bioprosthesis (12A and LX models) in the Department of Cardiac Surgery at the Nantes University Hospital (France). The SORIN Mitroflow® valve was prepared preoperatively as indicated in the SORIN User Manual

[12]. SVD is unlikely to occur within the first year post-surgery, we observed no event during this period. In order to accurately study SVD occurrence, the baseline of our study was therefore the first anniversary of the surgery. Five hundred sixty-one patients alive at this time were thus included (26 patients died in hospital and 30 patients were discharged from hospital but died before the first anniversary of surgery).

Data Collection

Per-operative data were collected prospectively while echocardiograms and vital signs were retrospectively collected. The long-term follow-up was ensured by the personal physicians and cardiologists. Clinical and echocardiographic data were collected by the Clinical Investigation Center at the Nantes University Hospital after authorization by the local ethics committee (institutional review board) and the CNIL (Commission Nationale Informatique Libertés –, authorizations #1456630v1 and #910300). Morbidity and mortality were analyzed taking into account the recommendations of the AATS-STS-EACTS (American Association for Thoracic Surgery, the Society of Thoracic Surgery and European Association for Cardio-Thoracic Surgery) [9].

The following preoperative data were collected: age, sex, body mass index (BMI), family history, high blood pressure history, diabetes mellitus, dyslipidemia, obesity, history of smoking, aortic valve disease (stenosis, insufficiency, mixed disease, endocarditis, prosthetic endocarditis), New York Heart Association (NYHA) classification, pulmonary edema, syncope, atrial fibrillation, chronic obstructive pulmonary disease (COPD), 1 second forced expiratory volume <50%, peripheral vascular disease, renal failure (creatinine >200 µmol/L or Cockcroft-Gault creatinine clearance <60 mL/min), preoperative dialysis, sroke, carotid stenosis >50%, myocardial infarction <30 days, coronary stenosis >50%, left ventricular ejection fraction (<50% and <30%), systolic pulmonary arterial pressure >60 mm Hg, elective, urgent or emergency procedure. Severe prosthesis-patient mismatch (PPM) was defined as an effective orifice index area of the aortic prosthesis ≤0.65 cm^2/m^2 [13].

SVD Definition

The SVD was defined according to international recommendations [14]: progression of aortic transprosthetic gradient ≥30 mmHg associated with a decrease in effective orifice area ≤1 cm^2 and aortic cusp alteration, or intra-prosthetic aortic regurgitation >2/4. Each case of supposed SVD was carefully assessed and validated following a review of medical reports. In cases where SVD was suspected on echocardiography but not ascertained, patients were referred to our institution. The last available cardiac echocardiography carried out within our institution or outside, before repeat surgery or death, was taken into account for echocardiographic follow-up.

Statistical Analysis

The study time scale ran from the date of the first anniversary of the surgery. The median follow-up time was estimated using the reverse Kaplan-Meier method [15]. We used a semi-Markov illness-death model which allowed us to study SVD as an interval-censored transient state before death [16, 17]. Patients who underwent repeat aortic valve replacement not related to valve deterioration were right-censored at the time of the new surgery (n=7). The assumption of proportional hazards was graphically assessed. Risk factors were initially selected from univariable models (Wald test, $p<0.25$). A multivariable model was then estimated with a backward procedure performed manually, variable by variable, for each transition (Wald test, $p<0.05$).

The illness-death model was used to estimate: i) the cumulative incidence of SVD, ii) the Hazard Ratio (HR) of death related to SVD incidence by combining bootstrapping and simulations (for each bootstrap sample, the times-

to-event were simulated according to the final multivariable model and the observed baseline characteristics of the patients, and the HR was estimated from a time-dependent Cox model), and iii) the marginal effect of the main risk factors on the risk of SVD (average exposure effect in the exposed patients) [18].

We also used relative survival model with additive hazards to estimate excess mortality in this cohort compared to the general population, i.e. a very large cohort from the general French population comprising the same individuals in terms of age, gender, and birthdate. Statistical analyses were performed with R software (version 3.1.1), and the *Multistate* [19] and the *relsurv* packages [20].

Results

Baseline cohort characteristics

The preoperative characteristics of the 561 patients are presented in Table 1. The mean age was 76.4 (SD=6.0) years old. Fifty seven per cent (n=321) of the patients were between 70 and 80 years old and 29% (n=162) were octogenarians. Females represented 56% (n=314) of the patients. The indication for surgery was aortic valve stenosis in 83.6% (n=469) of patients. The proportion of repeat surgery was 5.5% (n=31). An isolated AVR was performed in 362 patients (64.5%). The associated procedures were mainly coronary artery bypass surgery in 30.3% of patients (n=170). A small diameter prosthesis (19 or 21 mm) was implanted in 64.9% of patients (n=364) and 23.4% of patients (n=131) had severe PPM.

Description of the patient outcomes

The median follow-up time was 6.6 years (ranging from 0 to 10.6) after the first anniversary of surgery. Two thousands one hundred sixty four echocardiographies were collected. At the end of follow-up, 298 patients were still alive without SVD diagnosis, 160 patients died without previous SVD diagnosis, 73 patients were still alive after SVD diagnosis, and 30 patients died following SVD diagnosis. Structural valve deterioration was diagnosed in 103 patients. Two SVD modes were observed: the main was calcified prosthetic stenosis in 81 patients (78.6%), while moderate to severe intra-prosthetic regurgitation was found in 22 patients (21.4%). Among the patient diagnosed with SVD, 35.0% (n=36) were not referred by cardiologists, 38.8% (n=40) underwent a repeat AVR (n=31) or TAVI (n=9), 15.5% (n=16) were denied surgery and TAVI after clinical work-up, and 3.9% (n=4) refused the clinical work-up. Four patients (3.9%) died while waiting for repeat surgery. Among the 190 deaths, SVD was one of the main reported causes of death in 10.0% of cases (n=19). The other reported causes were congestive heart failure (17.9%, n=34), cancer (12.6%, n=24) and sepsis (9.5%, n=18). Cardiac-related deaths represent 54.2% (n=103) of all causes.

Cumulative incidence of SVD

Figure 1 shows the cumulative incidence function of SVD. The first SVD was diagnosed 2 months after the first year of surgery (14 months after surgery). The 2-, 5- and 8-year incidences were 1.8% (95% CI from 1.0 to 3.2), 15.2% (95% CI from 11.9 to 19.1), and 31.0% (95% CI from 25.8 to 37.1), respectively surgery.

As listed in Table 2, the multivariable illness-death model indicated that significant baseline risk factors for the development of SVD were female gender (HR=1.6, 95% CI from 1.1 to 2.4), dyslipidemia (HR=1.6, 95% CI from 1.1 to 2.3), severe PPM (HR=1.7, 95% CI from 1.1 to 2.5) and COPD (HR=2.9, 95% CI from 1.6 to 5.4).

Among these risk factors, some are probably modifiable in terms of prevalence (severe PPM by implanting the adequate prosthesis size), or in terms of effect on SVD (COPD and dyslipidemia by using alternative medical therapies). Figure 2 illustrates the marginal effect of these factors by considering the counterfactual situation where the exposed patients would have not been exposed. More precisely, the cumulative incidence of SVD at 7 years after the first year of surgery was estimated to be 26.5% (95% CI from 14.8 to 32.0) for the 33 patients with COPD versus 11.9% (95% CI from 9.3 to 21.5) if these patients were COPD-free (Figure 2A). Similarly, the cumulative incidence was 25.3% (95% CI from 12.7 to 26.7) for the 257 patients with dyslipidemia versus 11.8% (95% CI from 10.9 to 23.9) if these patients were dyslipidemia-free (Figure 2B). Finally, we estimated the cumulative incidence at 24.9% (95% CI from 18.3 to 27.2) for the 131 patients with severe PPM versus 16.7% (95% CI from 15.1 to 22.7) if these patients were PPM-free (Figure 2C).

Patient survival

Figure 3 draws a comparison between the observed patient survival in our cohort and the corresponding expected survival in the French general population with similar age, birthdate, and gender. The 2-, 5- and 8-year observed survival rates were 94.7% (95% CI from 92.8 to 96.5), 78.7% (95% CI from 75.4 to 82.3), and 63.5% (95% CI from 59.1 to 68.3), respectively. In contrast, the expected survival rates were 95.9%, 85.4% and 72.7%, respectively (theoretical values from lifetime tables without confidence interval). Since the multivariable illness-death model indicated that patients with SVD had a 2-fold increased risk of death (95% CI from 1.3 to 2.9), these results confirmed the hypothesis that excessive mortality in patients with the SORIN Mitroflow® bioprosthesis is partially attributable to the valve-related complications, including the SVD.

Discussion

The aims of the present study were to accurately estimate the incidence of SVD and its relationship with the risk of death in patients who underwent an AVR with SORIN Mitroflow® models 12A/LX. In our previous study [10], the cumulative incidence of SVD reached 8.4% (95%CI from 5.3 to 11.3) at 5 years post-surgery. Moreover, the SVD diagnosis was associated with a significant 7.7-fold increase in the risk of death (95% CI from 4.4 to 13.6). But, as pointed out by Grunkemeier and Wang [21], the usual methods we used did not handle several specific issues relating to the SVD risk assessment. In the present study, we observed major differences by using an original and more relevant statistical approach dealing with the interval censoring of SVD: the 5-year cumulative incidence of SVD was estimated to be up to 15.2% (95% CI from 11.9 to 19.1), underlying an important underestimation of the SVD incidence in our previous study. We also described a cumulative incidence of SVD up to 31.0% (95% CI from 25.8 to 37.2) at 8 years post-surgery and reported that this cumulative incidence of SVD is still increasing 13 years after surgery. We further explored baseline determinants of SVD and found for the first time that COPD is associated with a large increase in the risk of SVD. Finally, the present the present study sheds light on outcomes up to 8 years post-surgery, thanks to an extended follow- up and a comparison to the expected survival in the general population.

These results are highly contrasting in comparison to the studies which described a very low percentage of SVD with the SORIN Mitroflow® valve [4, 5, 22, 23]. These differences are likely related to the methodological pitfalls

of current AVR literature. Firstly, it should be noted that SVD is often only considered on repeat surgery, leading to a significant underestimation of the true incidence of SVD in this particular age group [4, 5, 10, 22, 24, 25]. One can estimate that the proportion of patients who benefits for redo intervention is as low as 1 to 2 out of 10 patients [10]. Secondly, interval-censoring and/or competition between SVD and patient death were not processed [10, 23, 26, 27]. We therefore hope that the methodological framework we propose in this study, i.e. the definition of SVD based on echocardiograms and the illness-death model for interval-censored data, will be further considered in future AVR-related studies.

In addition to this public health issue, the present study highlights for the first time (as far as we know), that COPD could be a risk factor of SVD. Its prevalence was observed in 5.9% (n=33) of the cohort. The mechanism seems unclear but inhalation exposures, as in COPD, can lead to local and general inflammatory responses, which increase with disease severity. Moreover, respiratory infections are more frequent in patient with COPD and can also increase the systemic inflammatory response. Thus, repetitive inflammatory responses could increase the immune response, which has been reported to potentially increase the SVD process [28]. This hypothesis needs to be confirmed, but it could pave the way for improving our understanding and prevention of SVD.

Other risk factors were significantly linked to SVD incidence. In accordance with the literature, we found that dyslipidemia [29, 30] and PPM [27, 31] were associated with an increased risk of SVD. Flameng et al. [31] assumed that the role of PPM could be due to disturbed flow patterns. Annulus enlargement is thus currently recommended by some authors in patients with predictable severe PPM [25], but with an increased risk of procedure-related surgical complications. The PPM prevalence we observed in our study was quite different from those typically found in the literature. For example, some authors [32] reported only 2.9% of severe PPM cases for the 19-mm SORIN Mitroflow®, and 0.5% overall. However, the in-vivo Effective Orifice Area (EAO) used was validated from a small number of patients and was clearly greater than that the pre-specified information provided by the company: for instance, an in-vivo EOA of 1.4 cm^2 for the 19-mm SORIN Mitroflow® versus 1.1 cm^2 from the SORIN data [33]. With similar values, the severe PPM rates in our cohort would have been 0% and 2.4% (n=7) for the 19 mm and 21mm dimensions, respectively.

We additionnally proposed a precise appraisal of SVD impact on patient survival. We estimated a 2-fold higher risk of death after SVD occurrence (95% CI from 1.3 to 2.9). In contrast, we previously reported a 7.7-fold higher risk (95% CI from 4.4 to 13.6) [10]. To confirm this result, we assume that we could expect to observe a mortality rate close to that reflected in the general population in a counterfactual world where the risk of SVD would be very low and/or its impact negligible on mortality. Nevertheless, we observed that patient survival 7 years after the first anniversary of surgery was 63.5% (95% CI from 59.1 to 68.3), almost an absolute decrease of 10 points than that expected in the general population, which can be considered as a reference cohort with complication-free bioprostheses. In contrast, Sharabiani et al [34] did not find any difference between observed and anticipated survival rates in the United Kingdom.

As it is always the case for this kind of observational studies of this kind, limitations have to be underlined. Firstly, even if we updated the follow-up of this cohort, the follow-up period still does not allow a precise estimation of long-term SVD cumulative incidence (the curve is still increasing at this maximum time in Figure 1), and therefore its consequence on the risk of death. Secondly, the echocardiograpy procedures were not planned as in a clinical trial, but were implemented by personal cardiologists as in real medical practice. The main consequence is

probably the link between the frequency of echocardiographies and the patient's clinical status. For instance, a patient presenting with increased dyspnea or cardiac symptoms would be more likely to visit his/her cardiologist. Consequently, the incidence of SVD may still be underestimated by omitting infra-clinic SVD. Thirdly, we did not compare the outcomes of this SORIN Mitroflow® bioprosthesis (models 12A and LX) with another bioprosthesis. A comparison of the efficacy of different bioprostheses is beyond the aim of the present study, even if the results we reported appeal for future randomized or at least comparative clinical trials to evaluate bioprostheses. Alternatively, we proposed a comparison with the mortality of the general population as a control group, i.e. the expected survival rate in the absence of valve-related mortality.

In conclusion, our study confirms the unexpected high incidence of SVD for one aortic bioprosthesis type (SORIN Mitroflow®, models 12A and LX). The SVD risk related to this valve is a public health issue given the number of implantations world-wide. This issue has been considerably underestimated due to methodological pitfalls, particularly the SVD definition based on histological criteria, the too short follow-up, and the use of usual statistical models such as Cox regression. Our results have an immediate impact for patients implanted with the SORIN Mitroflow® valve: we highly recommend annual follow-up, especially for patients with SVD risk factors such as severe PPM, dyslipidemia or COPD (in contrast to the international guidelines proposing an initial echocardiogram 5 years post-surgery). We also hope that our results will encourage comparative clinical trials, based on the same methodology we proposed, in order to evaluate bioprotheses. This literature is crucial in order to avoid this kind of public health issue in the future.

Table 1: Baseline characteristics of the monocentric cohort comprising 561 patients who underwent an AVR with a SORIN Mitroflow® bioprosthesis.

Clinical data	
Female, n (%)	314 (56.0)
Age, years (mean ± SD)	76.4±6.0
Body Mass Index, Kg/m² (mean ± SD)	26.7±4.8
Atrial fibrillation, n (%)	86 (15.3)
High blood pressure, n (%)	352 (62.8)
Mellitus diabetes, n (%)	111 (19.8)
Dyslipidemia, n (%)	257 (45.8)
Obesity, n (%)	129 (23.0)
History of smoking, n (%)	91 (16.2)
NYHA classification 3-4, n (%)	167 (29.8)
Comorbidities	
Peripheral vascular disease, n (%)	71 (12.7)
Preoperative renal failure, n (%)	37 (6.6)
Chronic Obstructive Pulmonary Disease, n (%)	33 (5.9)
Stroke, n (%)	18 (3.2)
Myocardial infarction history, n (%)	30 (5.3)
Coronary angioplasty, n (%)	29 (5.2)
Echocardiography	
Left ventricular ejection fraction, percentage (mean ± SD)	58±12
Left ventricular ejection fraction < 50%, n (%)	68 (12.1)
Systolic pulmonary artery pressure > 60 mmHg, n (%)	16 (2.9)
Aortic stenosis, n (%)	469 (83.6)
Aortic insufficiency, n (%)	16 (2.6)
Surgical data	
Elective surgery, n (%)	486 (86.6)
Implanted bioprostheses ≤ 21 mm, n (%)	364 (64.9)
Severe PPM, n (%)	131 (23.4)
Logistic Euroscore (mean ± SD)	10.0±10.1

Table 2: Significant SVD risk factors after the first anniversary of surgery in the illness-death model multivariable (forced age adjustment).

	HR	**[95%CI]**	**p-value**
Severe Patient-Prosthesis Mismatch (PPM)	1.68	[1.13 – 2.49]	0.010
Female	1.59	[1.06 – 2.38]	0.026
Dyslipidemia	1.56	[1.07 – 2.27]	0.019
Chronic Obstructive Pulmonary Disease (COPD)	2.91	[1.56 – 5.44]	0.001
Under 70 at the time of surgery	1.00		
between 70 and 80 years old	1.05	[0.62 – 1.78]	0.867
Over 80 years old	0.90	[0.47 – 1.72]	0.751

Figure 1: Cumulative incidence of SVD after the first anniversary of surgery. The curve was estimated from the illness-death model handling interval censoring for time-to-SVD.

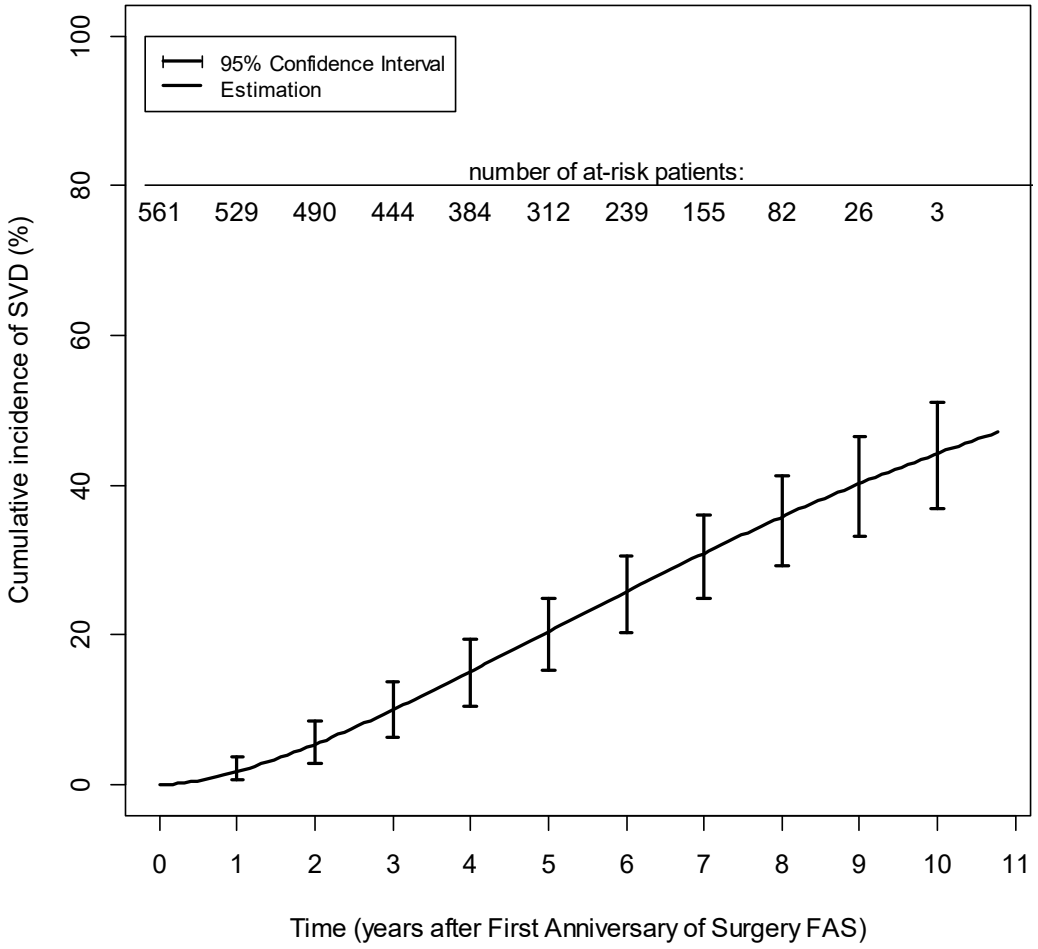


Figure 2: Marginal effects on the cumulative incidence of SVD by considering the counterfactual situation where the exposed patients would not have been exposed (average exposure effect in the exposed patients). **A:** COPD (n=33 patients), **B:** Dyslipidemia (n=257 patients) and **C:** severe Patient-Prosthesis Mismatch (n=131 patients).

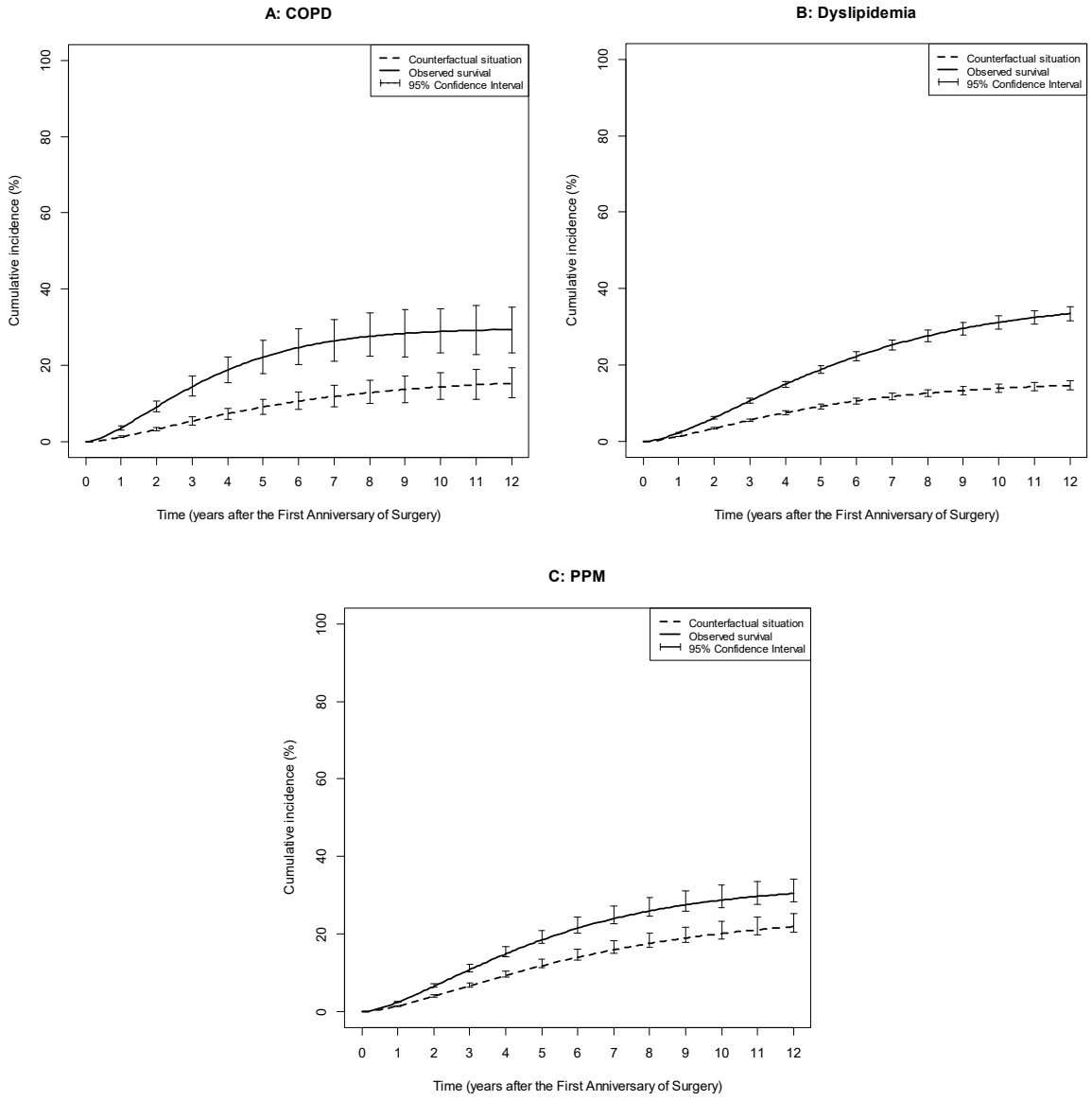
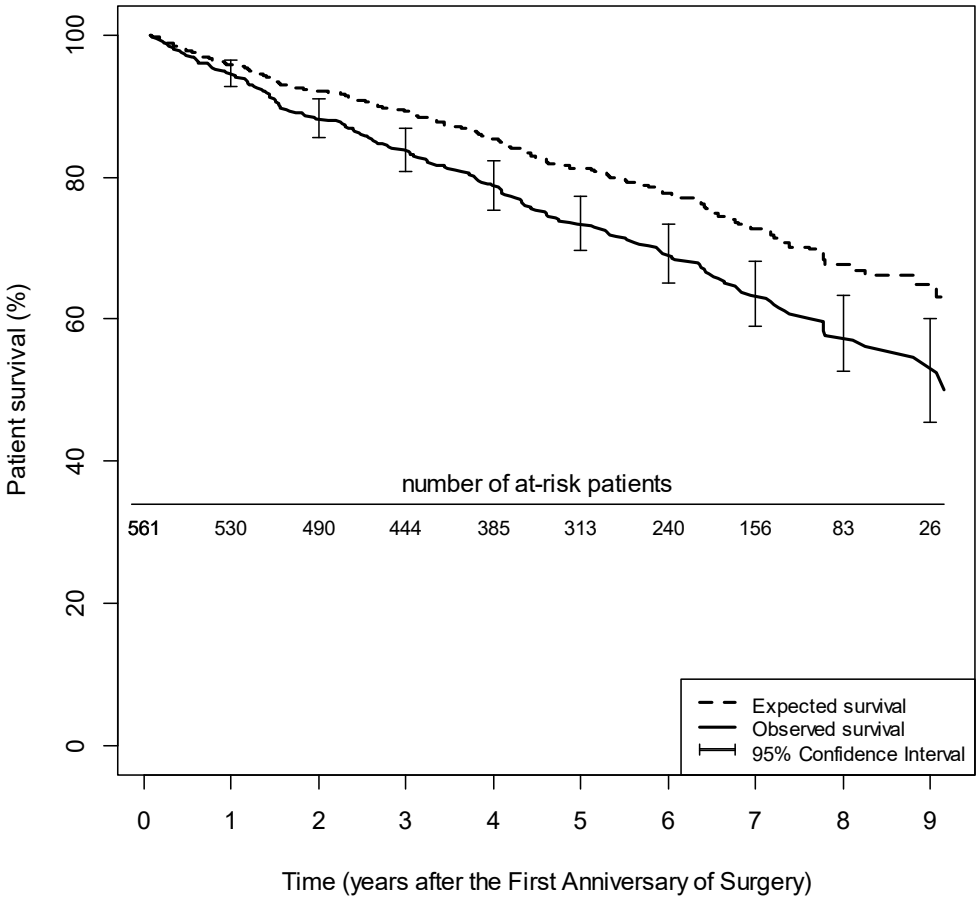


Figure 3: Expected versus observed patient survival rate after the first anniversary of surgery. Observed survival was recorded using the Kaplan-Meier estimator. The expected rate was obtained from the French mortality table, for a cohort with the same age, gender, and birthdate.



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III. Conclusion

En comparaison avec celle du chapitre 3, cette étude propose une meilleure estimation de l'incidence réelle de SVD, évaluée à 15.2% (IC95% de 11,9 à 19,1) à 5 ans de la chirurgie. Avec un recul plus important, il est également possible d'estimer cette incidence à 31.0% (IC95% de 25,8 à 37,2) à 8 ans de la chirurgie. Ces résultats sont en opposition avec plusieurs études publiées [16, 17, 33, 34], probablement en lien avec les avancées méthodologiques utilisées.

Dans cette étude nous avons également représenté l'effet marginal de type ATT associé aux principaux facteurs de risque identifiés de SVD, à savoir le PPM, la dyslipidémie et la broncho-pneumopathie obstructive (BPCO). Cette représentation graphique est intéressante pour présenter aux cliniciens cet impact autrement que par un rapport de risque.

En prenant la population générale française comme référence, nous avons aussi pu faire apparaitre un excès de mortalité dans notre cohorte de patients porteurs d'une bioprothèse SORIN Mitroflow®, en partie lié à la pathologie valvulaire et son risque de SVD. Il s'agit de près de 10% de survie en moins à 8 ans de la chirurgie. Cette comparaison nous apparait comme un moyen alternatif de juger de la qualité d'une bioprothèse.

Conclusion et Perspectives

I. Conclusion

L'objectif de cette thèse était d'estimer l'incidence de SVD et son impact sur la survie des patients porteurs d'une bioprothèse SORIN Mitroflow®, suite à de récentes publications mettant en question la durabilité et la fiabilité de cette prothèse.

Dans un premier temps, un modèle de Cox a donc été modélisé et l'incidence cumulée de SVD avait été estimée à 8,4% à 5 ans (IC95% de 5,3% à 11,3%) selon l'estimateur de Kaplan-Meier. Ce travail avait permis alors d'alerter le milieu médical sur le risque sous-estimé et méconnu de détérioration valvulaire de cette prothèse [35]. La survenue d'une SVD ressortait comme le principal facteur de risque de décès au cours du temps avec un risque de décès multiplié par 7,7 après diagnostic posé (IC95% de 4,4 à 13,6). En regard du nombre considérable de prothèses déjà implantées déclaré par le constructeur [36], il s'agit d'un réel problème de santé publique, qui a été décrit pour la première fois dans notre étude.

Il existait cependant de nombreuses limites à l'utilisation d'un modèle de Cox sur ces données. Les principales étaient l'absence de prise en compte de la compétition existante entre le risque de décès et celui de SVD d'une part, et l'existence d'une censure par intervalle dans l'analyse du temps de survenue de SVD, qui pouvait conduire à une sous-estimation de l'incidence de cette complication sévère, comme démontré préalablement par Joly et al. [37] et bien discuté par Leffondré et al. [38].

Considérant ces limites intrinsèques à l'utilisation de modèles de Cox, le choix d'un modèle multi-états semblait donc intéressant, en prenant en compte la censure par intervalle présente lors du diagnostic de SVD et la compétition entre SVD et décès. Le rôle du mismatch patient-prothèse pouvait ainsi également être évalué plus précisément. La stratégie de pondération par le score de propension simplifie grandement la mise en œuvre des modèles multi-états en la résumant à deux étapes : un modèle logistique est construit pour estimer les probabilités d'appartenir au groupe exposé selon les possibles facteurs de confusion, puis un modèle multi-états univarié est estimé par pondération des contributions individuelles. Les résultats issus de ce modèle original semblent valider le rôle du PPM dans la survenue d'une SVD avec un HR marginal (ATE) estimé à 1,78 (IC95% de 0,99 à 3,18). Ce résultat a deux conséquences en pratique clinique. D'une part, il nous parait important de ne pas sous-estimer sa prévalence. Il est nécessaire de se baser sur la surface valvulaire *in vivo* des prothèses données par le constructeur. En effet, les données *in vitro* auraient conduit à estimer un taux de PPM de 0% et 2,4% (n=7) respectivement pour les tailles 19 et 21, contre 35% et 33% avec les données *in vivo*. D'autre part, ce phénomène pourrait parfois être évité, par l'implantation d'une prothèse ayant une surface valvulaire

fonctionnelle adaptée à la surface du patient et/ou un élargissement de l'anneau avec les risques inhérents à cette technique chirurgicale plus lourde. En regard de l'estimation de l'effet marginale du PPM, la prévention de ce mismatch permettrait une réduction du risque de SVD (Absolute Risk Reduction) de 10,5% (IC95% de -1,2 à 24,8) à 5 ans, passant de 27,1% (IC95% de 17,0 à 41,2) à 16,6% (IC95% de 11,0 à 23,9).

Les résultats complémentaires du modèle multi-états multivarié après extension du suivi ont confirmé cette hypothèse de sous-estimation de l'incidence de SVD chez les patients porteurs d'une bioprothèse SORIN Mitroflow®, avec une incidence à 5 ans estimée à 15,2% (IC95% de 11,9 à 19,1) contre 8,4% (IC95% de 5,3% à 11,3%) dans notre premier travail [35]. Ces résultats vont cependant à l'encontre de ceux publiés encore récemment [16, 17, 33, 34]. Ils militent pour une méthodologie adaptée lors de la réalisation d'étude sur les prothèses biologiques valvulaires cardiaques : utiliser des critères échographiques de SVD, prendre en compte la censure par intervalle et la compétition entre décès et SVD, et accorder une attention particulière à l'ajustement. Un modèle multi-états n'a que rarement été utilisé pour évaluer le devenir de patients porteurs de valve cardiaque prothétique. La censure par intervalle et le diagnostic échographique n'étaient pas pris en compte dans ces études [39, 40].

Le rôle du mismatch sur le risque d'apparition de la SVD a été encore une fois confirmé dans cette analyse multivariée, avec un risque conditionnel (subject-specific) multiplié par 1,7 (IC95% de 1,1 à 2,5). Par ailleurs, la BPCO est retrouvée pour la première fois comme facteur de risque de SVD, avec un risque multiplié par 2,9 (IC95% de 1,6 à 5,4). Il est cependant nécessaire de confirmer son rôle sur la survenue d'une SVD par d'autres analyses axées spécialement sur ce facteur, le mécanisme physiopathologique n'étant pas évident. En cas de confirmation, il est important de savoir si une prise en charge thérapeutique optimale de ce facteur de risque diminuerait ou non le risque de survenue d'une SVD.

Ce modèle mulit-états multivarié nous a enfin permis d'obtenir une meilleure estimation du risque de décès associé à la survenue d'une SVD (HR=2,0 - IC95% de 1,3 à 2,9). En comparaison, le modèle de Cox semble inapproprié et surestime grandement ce risque (HR=7,7 - IC95% de 4,4 à 13,6) en ne prenant pas en compte la censure par intervalle et le risque compétitif de décès. En comparant avec la survie de la population générale française (âge, sexe et année de naissance similaires), la survie à 8 ans après la chirurgie est près de 10% plus faible dans notre cohorte (63,5% contre 72,7%). Ceci va à l'encontre de ce qui est habituellement admis et décris dans la littérature. Sharabiani et al. [41] retrouvaient une survie comparable entre leur cohorte de 1815 patients de plus de 65 ans porteurs d'un RVA et la population générale anglaise.

Au terme de ce travail, l'impact clinique de nos résultats nous apparait immédiat pour la prothèse SORIN Mitroflow®. Les patients porteurs de cette bioprothèse sont exposés à un risque inhabituel et

précoce de SVD, qui impacte directement leur espérance de vie. Un suivi échographique débutant à 5 ans, recommandé actuellement en raison du risque estimé faible de SVD pour toutes les bioprothèses, semble inadapté pour ces patients. Nous recommandons un suivi annuel dès la première année, échographique et clinique. Il est d'autant plus important de renforcer ce suivi chez les patients ayant au moins un des facteurs de risque suivants : PPM, dyslipidémie ou BPCO. Même si cette prothèse n'est actuellement plus implantée, il existe un nombre encore important de patients vivants porteurs de cette valve qui pourraient bénéficier de ces nouvelles recommandations.

Concernant les autres prothèses biologiques actuellement disponibles sur le marché, cette étude ne permet bien évidement pas de prédire leur risque de SVD. Cependant nos études montrent que ces autres prothèses doivent être évaluées selon une méthodologie comparable afin de ne pas sous-estimer l'incidence des complications associées. Il est en effet important de ne pas reproduire les évaluations biaisées réalisées pour la prothèse SORIN Mitroflow® qui ont conduit à plus de 100000 implantations dans le monde. L'analyse de ces autres prothèses permettra également de les comparer entre elles et de proposer aux patients les plus fiables.

II. Perspectives

Nous avons comme projet de compléter la cohorte initiale en incluant des patients opérés après 2007, et d'inclure des patients contrôles opérés avec une autre bioprothèse utilisée dans la même période de temps. Le suivi moyen sera plus long et la comparaison avec d'autres prothèses permettra notamment : i) d'estimer l'incidence globale définitive dans la cohorte des prothèses SORIN Mitroflow®, ii) de rechercher un taux inattendu de SVD pour d'autres prothèses biologiques, et iii) de proposer un suivi adapté en fonction du type de prothèse implantée. Nous envisageons également de modéliser le risque de SVD conditionnellement aux comorbidités du patient pour proposer au clinicien une estimation du risque de SVD propre à son patient.

Notre objectif principal est cependant plus large : la base de soins Cordabase doit évoluer et aboutir à la création d'une base de recherche. La création d'une cohorte fermée de patient porteur de la valve SORIN Mitroflow® a montré ses limites. En particulier, les patients ne sont pas suivis de façon prospective. Pour des raisons évidentes de faisabilité, cette cohorte ouverte ne peut concerner les 1400 patients annuels opérés au sein du CHU de Nantes. Nous envisageons donc de limiter cette cohorte aux patients qui vont bénéficier d'une prothèse valvulaire aortique, mécanique ou biologique. Plus

précisément, en regard des 600 patients implantés chaque année, seul un pourcentage de ces patients sera inclus après obtention de leur consentement (1 patient sur trois). Les prothèses biologiques implantées par voie trans-cathéter (Transcatheter Aortic Valve Implantation - TAVI) seront également prises en compte dans la conception de cette cohorte, avec pour objectif une collaboration potentielle avec le registre France TAVI, rempli systématiquement après chaque intervention. Les 200 patients inclus chaque année seront suivis annuellement avec recueil et enregistrement des données collectées. Un attaché de recherche clinique aura pour rôle de saisir et mettre à jour les données. Il sera alors possible de limiter la censure par intervalle propre au diagnostic de SVD en planifiant les échographies. Le financement du poste de cet attaché de recherche passera par des collaborations avec les principaux laboratoires constructeurs de valve et par la valorisation scientifique des données.

La création d'une base de recherche nécessite également l'évolution de la base de soins vers un logiciel professionnel pour une optimisation de la saisie, du stockage et de l'analyse des données. Pour ce faire, le projet Labcom RISCA (Recherche en Informatique et en Statistique pour l'Analyse de Cohortes) entre l'équipe d'accueil EA4275-SPHERE (MethodS for Patients-centered outcomes and HEalth REsearch, www.sphere-nantes.fr, Université de Nantes) et la société IDBC-A2COM (www.a2com.fr, Rennes) débutera dès octobre 2016. Son objectif est de proposer, en lien direct avec les données collectées, une interface ergonomique et intuitive pour pouvoir réaliser des requêtes ou des analyses statistiques adaptées aux pathologies étudiées. Ce logiciel permettra ainsi i) d'éliminer les étapes longues, coûteuses, et sources d'erreurs liées aux transferts des données vers le logiciel statistique en automatisant cette étape ; et ii) d'éviter l'utilisation de modèles statistiques peu adaptés à la pathologie étudiée en développant et en intégrant des modèles adaptés. Le projet est partiellement financé par l'ANR (Agence Nationale de la Recherche) pour couvrir le recrutement d'un ingénieur informatique et d'un doctorant en biostatistique.

Cette transition vers une base de recherche et un groupe de recherche en épidémiologie de la chirurgie valvulaire nous parait indispensable pour améliorer nos connaissances sur les prothèses actuellement implantées avec pour finalité de fournir au patient une prise en charge optimale.

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UNIVERSITE BRETAGNE LOIRE

UNIVERSITÉ DE NANTES

Thèse de Doctorat

Thomas SÉNAGE

Etude de la détérioration valvulaire structurelle des prothèses biologiques cardiaques

Structural valve deterioration of bioprosthetic heart valves

Résumé

Avec une prévalence de plus de 2% des patients âgés de plus de 65 ans, la maladie valvulaire aortique est la principale maladie valvulaire de l'adulte, avec plus de 200000 remplacements valvulaires réalisés chaque année dans le monde. La détérioration valvulaire aortique (SVD) reste le problème majeur des bioprothèses implantées. Cependant, en raison d'une méthodologie inadaptée, son incidence peut parfois être sous-estimée. Ainsi, la prothèse SORIN Mitroflow® (modèles LX/12A) semble poser problèmes avec plusieurs cas décrits de SVD précoces. Son incidence reste cependant incertaine. Nous avons cherché ici à estimer son incidence réelle, les facteurs de risque de SVD, et l'impact de la SVD sur la survie des patients. Nous avons tout d'abord utilisé un modèle de Cox étendue, modèle le plus souvent utilisé dans la littérature, et nous avons reporté une incidence anormale de SVD qui était retrouvé comme un facteur important de mortalité. Le Mismatch Patient-Prothèse restant débattu dans la littérature comme facteur de risque potentiel de SVD, un modèle original utilisant les scores de propension au sein d'un modèle multi-état, a été proposé pour confirmer ou non cette hypothèse. Enfin, après une extension du suivi, nous proposons une analyse multivariée au sein d'un modèle multi-états de type illness-death pour une estimation moins biaisée de l'incidence et de l'impact de la SVD dans notre cohorte.

Mots clés

Maladie valvulaire aortique ; remplacement valvulaire aortique biologique ; détérioration valvulaire structurelle ; survie ; modèle illness-death ; modèle semi-Markov ; Modèle de Cox ; Scores de propension

Abstract

With a prevalence of 2% of patients older than 65 years old, the aortic valve stenosis is the main valvular heart disease with more than 200000 aortic valve replacement worldwide. The structural valve deterioration (SVD) remains the major flaw of implanted bioprostheses. However, due to methodological pitfalls observed in the current literature, its incidence may be underestimated. As an example, a true concern appeared lately concerning the Mitroflow® valve (SORIN group, Model LX/12A), with very early SVD observed in serval centers. Indeed, the true incidence of SVD for this valve remained unclear in the literature. We sought here to assess precisely the SVD incidence, the associated risk factors, and its impact on the patient survival. First, we used a extended Cox model, as the more frequent model used in published studies, and we reported an unusual and early SVD rate. Secondly, the Patient-Prosthesis Mismatch is still debated as a risk factor of SVD and we carried out an original model using propensity scores (IPW: Inverse probability weighting) in a multistate model to answer this question. At last, with an updated follow-up, we handled the interval-censoring and competing risk through a multivariable illness-death model for interval censored data in order to get a better estimation of the true incidence of SVD and its impact in our cohort.

Key Words

Valvular heart disease ; Biologic aortic valve replacement; structural valve deterioration; patient survival; illness-death model; semi-Markov ; Cox model ; propensity scores ; Inverse probability weighting